Original Article

Effect of Metabolic Syndrome on Risk Stratification for Left Atrial or Left Atrial Appendage Thrombus Formation in Patients with Nonvalvular Atrial Fibrillation

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Abstract

Background: Metabolic syndrome (MS) is a risk factor for stroke and thromboembolism event. Left atrial or LA appendage (LA/LAA) thrombus is a surrogate of potential stroke. The relationship between MS and atrial thrombus remains unclear. In this study, we sought to investigate the effect of MS on risk stratification of LA/LAA thrombus formation in patients with nonvalvular atrial fibrillation (NVAF).
Methods: This cross-sectional study enrolled 294 consecutive NVAF patients without prior anticoagulant and lipid-lowering therapies. LA/LAA thrombus was determined by transesophageal echocardiography. Risk assessment of LA/LAA thrombus was performed using the $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS scores. Logistic regression analyses were performed to determine which factors were significantly related to LA/LAA thrombus. Odds ratio (*OR*) including 95% confidence interval was also calculated. The predictive powers of different scores for the risk of LA/LAA thrombus were represented by C-statistics and compared by receiver operating characteristic (ROC) analysis.
Results: LA/LAA thrombi were identified in 56 patients (19.0%). Logistic analysis showed that MS was the strongest risk factor for LA/LAA thrombus in NVAF patients ($OR = 14.698$, $P < 0.001$). ROC curve analyses revealed that the C-statistics of $CHADS_2$-MS and CHA_2DS_2-VASc-MS was significantly higher than those of $CHADS_2$ and CHA_2DS_2-VASc scores ($CHADS_2$-MS vs. $CHADS_2$, 0.807 vs. 0.726, $P = 0.0019$). Furthermore, MS was helpful for identifying individuals with a high risk of LA/LAA thrombus in the population with a low risk of stroke ($CHADS_2$ or CHA_2DS_2-VASc score = 0).
Conclusions: MS is associated with LA/LAA thrombus risk in patients with NVAF. In addition to the $CHADS_2$ and CHA_2DS_2-VASc scores, the $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores provide additional information on stroke risk assessment.

Key words: Left Atrial Appendage Thrombus; Left Atrial Thrombus; Metabolic Syndrome; Nonvalvular Atrial Fibrillation; Risk Stratification; Transesophageal Echocardiography

Introduction

The prevalence of atrial fibrillation (AF) will increase rapidly in the next few decades due to population aging and longer survival. AF confers a 5-fold increase in stroke risk and 2-fold increase in cardiac mortality.[1,2] Moreover, the risk of stroke is high in any type of AF.[3] To identify the risk for stroke in patients with nonvalvular AF (NVAF), the $CHADS_2$ and CHA_2DS_2-VASc scores are commonly used in clinical practice.[4,5] However, their predictive powers remain limited in patients with low $CHADS_2$ or CHA_2DS_2-VASc score.[6]

Metabolic syndrome (MS) is a cluster of common clinical disorders, including obesity, insulin resistance, glucose intolerance, hypertension, and dyslipidemia, which is a risk factor of cardiovascular disease. MS can lead to

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vascular endothelial dysfunction, activation of coagulatory and inflammatory reactions, and subclinical damage in various organs, which are more severe than the harm caused by conventional risk factors.[7] Recently, a study indicated that MS was associated with thromboembolic risk of AF, and $CHADS_2$-MS score was superior to $CHADS_2$ score in predicting the risk of AF-related stroke.[8] Hence, MS may be a supplement of $CHADS_2$ score for predicting AF-related stroke.

Clinically, left atrial or LA appendage (LA/LAA) thrombus provides objective evidence of AF-related stroke in several studies,[9,10] and it is used as a surrogate marker of potential stroke for the NVAF patients.[6] However, it is uncertain whether MS is also linked to LA/LAA thrombus in patients with low $CHADS_2$ and CHA_2DS_2-VASc scores. In this study, we sought to investigate the effect of MS on risk stratification of LA/LAA thrombus formation in NVAF patients.

Methods

Study population

This study included 400 consecutive patients with symptomatic NVAF in the Sun Yat-Sen Memorial Hospital of the Sun Yat-Sen University from 2007 to 2014, and finally, 294 patients were enrolled according to the inclusion and exclusion criteria. AF was diagnosed by 12-lead electrocardiogram or 24-h dynamic electrocardiogram. All the patients underwent transesophageal echocardiography (TEE) examination to detect LA/LAA thrombi. Exclusion criteria included acute myocardial infarction within previous 6 months, rheumatic heart disease or valvular heart disease, a history of cardiac surgery (e.g., coronary artery bypass graft and heart valve replacement), hyperthyroidism, cancer, end-stage renal disease, and gastroesophageal diseases, which are contraindications to TEE examination. As medicine may affect the thrombus formation and the diagnosis of MS, anyone who had received antiplatelet or anticoagulation agents (e.g., aspirin, clopidogrel, warfarin, dabigatran, rivaroxaban, and apixaban) and lipid-lowering drugs (e.g., statins, fibrates, nicotinic acid, bile acid sequestrants) were also excluded from the study. The study was approved by the hospital's Ethics Committee, and informed consent was obtained from all patients.

Metabolic syndrome definition

MS was defined according to the 2009 MS harmonizing definition and the guidelines issued by the Chinese Diabetes Society of the Chinese Medical Association as having three or more of the following: (1) body mass index (BMI) ≥28 kg/m^2, (2) fasting triglyceride (TG) ≥150 mg/dl, (3) fasting high-density lipoprotein cholesterol (HDL-C) <40 mg/dl, (4) systolic blood pressure ≥130 mmHg/diastolic blood pressure ≥85 mmHg and/or a history of hypertension treatment, and (5) fasting glucose ≥100 mg/dl or a history of diabetes (or on diabetes medication).[11,12]

Transthoracic echocardiography and transesophageal echocardiography examination

All patients underwent transthoracic echocardiography with a GE VIVID 7 ultrasonograph and a 2.5-MHz transducer in a left lateral decubitus position before TEE examination. The LA diameter (LAD) and left ventricular end-diastolic diameter were obtained from M-mode tracing, and the left ventricular ejection fraction (LVEF) was calculated. TEE was performed with a 5-MHz multiplane probe, and live images were analyzed by an experienced physician who was blind to lipid levels. Continuous images of the LA and LAA were assessed to determine the presence or absence of thrombus. LA/LAA thrombus was defined as a well-circumscribed echogenic mass with a unique echotexture contrasting with the adjacent myocardium.

$CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, CHA_2DS_2-VASc-MS scores, and clinical evaluation

In this study, both $CHADS_2$ and CHA_2DS_2-VASc scores were used as the same in the 2010 ESC guideline.[6] Patients with $CHADS_2$ or CHA_2DS_2-VASc score of 0, 1, and ≥2 were divided into low-, moderate-, and high-risk stroke groups, respectively. In addition, the MS score was calculated as the number of abnormal items in the MS criteria, and the total score ranged from 0 to 5. $CHADS_2$ score and MS score overlapped in high blood pressure (HBP) and diabetes mellitus (DM); therefore, $CHADS_2$-MS score was the combination of $CHADS_2$ score and additional MS score which removed HBP and DM components. Similarly, CHA_2DS_2-VASc-MS was composed of CHA_2DS_2-VASc score and additional MS score which removed HBP and DM components.

Clinical data consisted of clinical status (e.g., age, gender, BMI, type of AF, HBP, DM, previous stroke/transient ischemic attack [TIA], vascular disease, and MS), medication history, electrocardiograms, echocardiograms, TEE, and blood sample results. Hypertension was defined as systolic blood pressure >140 mmHg or diastolic blood pressure >90 mmHg. DM was defined as the use of diabetic medications or fasting blood glucose >126 mg/dl. Chronic heart failure was defined as systolic heart failure or LVEF <40%. Previous and current stroke was confirmed by brain computed tomography and magnetic resonance imaging. Vascular disease was defined as atherosclerotic disease (diagnosed by vascular angiogram or ultrasonography).

Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (Q_1, Q_3), and categorical variables are presented as numbers and proportions. The differences between two groups were compared using independent samples *t*-test for normal distributed data and Mann–Whitney *U*-tests for non-normal distributed data. Discrete variables between two groups were compared using Chi-square test or Fisher's exact test. Logistic regression analyses were performed to determine which variables were significantly related to LA/LAA thrombus. Results of

the logistic regression were reported as odds ratios (*OR*s) and corresponding 95% confidence intervals. All the variables which were statistically significant at the 0.05 level in univariate analyses were entered into a multivariate logistic regression model with forward step-wise selection. At each step, the variable was entered at the 0.05 level and removed at the 0.10 level. For all scores, the relationships between risk scores or categories and the prevalence of LA/LAA thrombus were examined using Chi-square test. Receiver operating characteristic (ROC) curves were constructed, and C-statistics was measured for each score to compare the predictive powers for the risk of LA/LAA thrombus formation. Youden index (*J*) was calculated using the following formula: J = sensitivity + specificity − 1, and the maximum values of Youden index for each score system were calculated to determine the corresponding optimal cutoff points. PASW Statistics version 18.0 (SPSS Inc., Chicago, Illinois, USA) was used in data analysis. All probability values were two-sided, and $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics of patients with and without left atrial/left atrial appendage thrombi

For all the 294 patients enrolled in this study, the median of $CHADS_2$ score and CHA_2DS_2-VASc score was 1.2 and 2.3, respectively. Fifty-six patients had LAA thrombi and 64 patients were diagnosed with MS. In 56 patients with LAA thrombus, there were 9, 19, and 28 patients with $CHADS_2$ score of 0, 1, and ≥2, and 3, 11, and 42 patients with CHA_2DS_2-VASc score of 0, 1, and ≥2, respectively. The baseline characteristics of the patients were listed in Table 1. Compared with patients without thrombi, patients with LA/LAA thrombi were elder (63.8 years vs. 60.6 years, $P = 0.042$), and had higher proportions of congestive heart failure (CHF) (10.7% vs. 1.7%, $P = 0.004$), HBP (75.0% vs. 42.4%, $P < 0.001$), DM (35.7% vs. 12.2%, $P < 0.001$), previous stroke/TIA (35.7% vs. 10.5%, $P < 0.001$), vascular disease (46.4% vs. 28.6%, $P = 0.011$), and MS (57.1% vs. 13.4%, $P < 0.001$). In addition, higher BMI, larger LAD, higher serum levels of lipids (TG, total cholesterol [TC], and low-density lipoprotein cholesterol [LDL-C]), lower HDL-C, and estimated glomerular filtration rate were found in patients with LA/LAA thrombi. Furthermore, individuals with thrombi tended to have higher risk scores of $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS ($P < 0.001$ for all).

Risk factors of the left atrial/left atrial appendage thrombus formation

The results of univariate and multivariate logistic regression analyses were shown in Table 2. Age ≥75 years ($OR = 3.882$, $P = 0.002$), BMI ≥28 kg/m^2 ($OR = 3.576$, $P < 0.001$), CHF ($OR = 7.020$, $P = 0.003$), HBP ($OR = 4.069$, $P < 0.001$), DM ($OR = 4.004$, $P < 0.001$), previous stroke/TIA ($OR = 2.176$, $P < 0.001$), LA >35 mm ($OR = 4.335$, $P < 0.001$), TG ≥150 mg/dl ($OR = 2.778$, $P = 0.001$), HDL-C <40 mg/dl ($OR = 2.815$, $P = 0.001$), $CHADS_2$ score ≥2 ($OR = 8.628$, $P < 0.001$), CHA_2DS_2-VASc score ≥2 ($OR = 4.472$, $P = 0.016$), and MS score ≥3 ($OR = 23.000$, $P < 0.001$) were associated with LA/LAA thrombus formation.

Multivariate logistic regression model included age, gender, BMI, CHF, HBP, DM, previous stroke/TIA, vascular diseases, TG ≥150 mg/dl, TC ≥200 mg/dl, HDL-C <40 mg/dl, LDL-C ≥130 mg/dl, MS, and $CHADS_2$ and CHA_2DS_2-VASc categories. The results showed that previous stroke/TIA ($OR = 1.991$, $P = 0.001$), LA >35 mm ($OR = 2.823$, $P = 0.008$), and MS score ≥3 ($OR = 14.698$, $P < 0.001$) were independent risk factors for LA/LAA thrombus formation. Interestingly, traditional high-risk categories of stroke classified by $CHADS_2$ score ≥2 or CHA_2DS_2-VASc score ≥2 were not associated with LA/LAA thrombus formation.

Relationship between the left atrial/left atrial appendage thrombus and risk scores

For the stroke risk stratification of $CHADS_2$, CHA_2DS_2-VASc, and MS scores, the prevalence of LA/LAA thrombus increased with elevated risk scores [Figure 1a, 1c, and 1e], and statistically significant trends were found (all $P < 0.001$). Similar to $CHADS_2$ and CHA_2DS_2-VASc scores, the prevalence of LA/LAA thrombus also increased in line with elevated $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores (both $P < 0.001$). For $CHADS_2$-MS score, the minimum rate of thrombus was 2.9% when $CHADS_2$-MS score = 0 and the maximum was 100% when $CHADS_2$-MS score ranged from 7 to 8 [Figure 1f]. Similarly, the minimum rate of thrombus was 0 when CHA_2DS_2-VASc-MS score = 0 and the maximum was 100% when CHA_2DS_2-VASc-MS score ranged from 9 to 10 [Figure 1g]. The prevalence of LA/LAA thrombus also increased significantly with ascending $CHADS_2$ or CHA_2DS_2-VASc risk categories (both $P \leq 0.001$) [Figure 1b and 1d].

Comparisons of the predictive powers for the risk of the left atrial/left atrial appendage thrombus formation among $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS scores

The C-statistics of $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS was 0.726, 0.710, 0.776, 0.807, and 0.792, respectively [Table 3 and Figure 2]. All the risk scores had moderate predictive powers for the risk of LA/LAA thrombus. There were no significant differences among the C-statistics of $CHADS_2$, CHA_2DS_2-VASc, and MS scores in predicting LA/LAA thrombus. However, the C-statistics of $CHADS_2$-MS score was significantly higher than those of $CHADS_2$ score (0.807 vs. 0.726, $P_{CM-C} = 0.0019$), and the C-statistics of CHA_2DS_2-VASc-MS score was also significantly higher than those of CHA_2DS_2-VASc score (0.792 vs. 0.710, $P_{CM-C} = 0.0007$). These results suggested that the predictive power of $CHADS_2$ score for the risk of LA/LAA thrombus was improved after mixing the MS score, and so was the CHA_2DS_2-VASc score.

Table 1: Baseline characteristics of patients with and without LA/LAA thrombus

Variables	Thrombi (+) (n = 56)	Thrombi (−) (n = 238)	Statistics	P
Demographic data				
Age, years	63.8 ± 10.4	60.6 ± 10.5	2.041*	0.042
Male, n (%)	36 (64.3)	146 (61.3)	0.166†	0.761
BMI, kg/m^2	26.3 ± 3.9	24.3 ± 3.4	3.375*	<0.001
Paroxysmal AF, n (%)	44 (78.6)	189 (79.3)	0.019†	1.000
Chronic heart failure, n (%)	6 (10.7)	4 (1.7)	8.678‡	0.004
Hypertension, n (%)	42 (75.0)	101(42.4)	19.242†	<0.001
Diabetes mellitus, n (%)	20 (35.7)	29 (12.2)	18.071†	<0.001
Previous stroke/TIA, n (%)	20 (35.7)	25 (10.5)	22.225†	<0.001
Vascular diseases, n (%)	26 (46.4)	68 (28.6)	6.646†	0.011
Metabolic syndrome, n (%)	32 (57.1)	32 (13.4)	50.830†	<0.001
$CHADS_2$ score	1.5 (1.0,4.0)	1.0 (0,1.0)	5.572§	<0.001
CHA_2DS_2-VASc score	3.0 (1.5,5.0)	2.0 (1.0,3.0)	4.981§	<0.001
MS score	3.0 (1.5,4.0)	1.0 (0,2.0)	6.627§	<0.001
CHA_2DS_2-MS score	3.5 (2.0,4.0)	1.0 (0,2.0)	7.307§	<0.001
CHA_2DS_2-VASc-MS score	5.0 (3.0,6.0)	2.0 (1.0,3.0)	6.892§	<0.001
Clinical data				
LVEF, %	67.5 (61.0,71.0)	67.0 (64.0,71.0)	0.498§	0.620
LA diameter, mm	39.0 (36.0,42.0)	35.0 (32.0,39.0)	5.191§	<0.001
LVEDD, mm	48.5 (45.5,52.0)	48.0 (45.0,50.0)	1.424§	0.155
TG, mg/dl	150.5 (118.7,221.4)	114.7 (87.7,154.1)	4.376§	<0.001
TC, mg/dl	193.9 (167.8,219.7)	176.9 (157.8,202.2)	2.636§	0.008
HDL-C, mg/dl	42.0 (35.0,50.3)	46.8 (41.0,52.6)	2.814§	0.005
LDL-C, mg/dl	127.2 (110.8,144.1)	111.0 (94.4,128.4)	3.664§	<0.001
eGFR, ml/min	62.9 (53.4,70.0)	73.0 (62.2,84.6)	4.625§	<0.001
Medication before TEE, n (%)				
β-blockers	16 (32.7)	69 (28.2)	0.004†	0.950
ACEIs/ARBs	29 (51.8)	60 (25.2)	15.168†	<0.001
CCBs	14 (25.0)	36 (15.1)	3.131†	0.112

Values are present by mean ± standard deviation or median (Q_1, Q_3), or number (percentages). *: Independent samples t-test; †: Chi square test; ‡: Fisher's test, §: Nonparametric test. LA: Left atrial; LAA: Left atrial appendage; BMI: Body mass index; AF: Atrial fibrillation; TIA: Transient ischemic attack; MS: Metabolic syndrome; LVEF: Left ventricular ejection fraction; LVEDD: Left ventricular end-diastolic diameter; TG: Triglyceride; TC: Total cholesterol; HDL-C: High density lipoprotein cholesterol; LDL-C: Low density lipoprotein cholesterol; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: Angiotensin receptor blockers. CCBs: Calcium channel blockers.

ROC curve analyses indicated that the optimal cutoff points of $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores in predicting thrombus were both ≥3 [Table 4]. Compared with $CHADS_2$-MS score, CHA_2DS_2-VASc-MS score ≥3 was more sensitive in predicting LA/LAA thrombus formation (0.877 vs. 0.714) and had a lower negative predictive value (0.23 vs. 0.36). However, it was less specific than $CHADS_2$-MS score (0.555 vs. 0.786) in predicting LA/LAA thrombus. The positive predictive value of CHA_2DS_2-VASc-MS score was also lower (1.96 vs. 3.33).

Additive effect of the metabolic syndrome score on the $CHADS_2$ and CHA_2DS_2-VASc risk categories in predicting the left atrial or left atrial appendage thrombus formation

Since the $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores were superior in predicting LA/LAA thrombus formation, we attempted to investigate whether the thrombotic risk was increased when additional MS components (high BMI, high level of TG, and low level of HDL-C) were added to the $CHADS_2$ and CHA_2DS_2-VASc scores. The prevalence of LA/LAA thrombus for patients with 0–3 additional MS scores in conventional low-stroke risk group ($CHADS_2$ or CHA_2DS_2-VASc scores = 0), moderate-risk group ($CHADS_2$ or CHA_2DS_2-VASc scores = 1), and high-risk group ($CHADS_2$ or CHA_2DS_2-VASc scores ≥2) is shown in Figure 3. In the low-risk group, the thrombotic prevalence of patients who had three additional MS scores was 50.0% for $CHADS_2$ category and 33.3% for CHA_2DS_2-VASc category, which were both higher than the high-risk group without any additional MS score (30.0% for $CHADS_2$ category and 16.5% for CHA_2DS_2-VASc category). In addition, additional MS scores increased the prevalence of LA/LAA thrombus in each conventional risk category. All the patients in the high-stroke risk group with three additional MS scores suffered from LA/LAA thrombi.

Discussion

In this study, we evaluated the additive effect of MS on risk stratification for LA/LAA thrombus formation in patients with NVAF and low $CHADS_2$ and CHA_2DS_2-VASc scores. We found that MS was an independent risk factor for LA/LAA

Table 2: Univariate and multivariate logistic regression model of LA/LAA thrombus with AF

Variables	Univariate		Multivariate	
	OR (95% *CI*)	*P*	*OR* (95% *CI*)	*P*
Age, years				
65–74	1.269 (0.655–2.459)	0.480	–	–
≥75	3.882 (1.661–9.074)	0.002	–	–
Male	1.134 (0.619–2.079)	0.684	–	–
BMI ≥28 (kg/m^2)	3.576 (1.846–6.929)	<0.001	–	–
Chronic heart failure	7.020 (1.910–25.797)	0.003	–	–
Hypertension	4.069 (2.109–7.851)	<0.001	–	–
DM	4.004 (2.048–7.829)	<0.001	–	–
Previous stroke/TIA	2.176 (1.544–3.066)	<0.001	1.991 (1.332–2.977)	0.001
LA >35 (mm)	4.335 (2.216–8.483)	<0.001	2.823 (1.317–6.051)	0.008
TG ≥150 (mg/dl)	2.778 (1.528–5.050)	0.001	–	–
HDL-C <40 (mg/dl)	2.815 (1.531–5.175)	0.001	–	–
$CHADS_2$ score				
1	1.794 (0.713–4.516)	0.214	–	–
≥2	8.628 (3.644–20.429)	<0.001	–	–
CHA_2DS_2-VASc score				
1	1.303 (0.320–5.300)	0.712	–	–
≥2	4.472 (1.315–15.214)	0.016	–	–
MS score				
1–2	3.526 (1.016–12.230)	0.047	2.502 (0.681–9.188)	0.167
≥3	23.000 (6.554–80.720)	<0.001	14.698 (3.907–55.290)	<0.001

OR: Odds ratio; *CI*: Confidence interval; LA: Left atrial; LAA: Left atrial appendage; AF: Atrial fibrillation; TIA: Transient ischemic attack; TG: Triglyceride; TC: Total cholesterol; HDL-C: High-density lipoprotein cholesterol; LDL-C: Low-density lipoprotein cholesterol; MS: Metabolic syndrome; DM: Diabetes mellitus; –: Not available.

Table 3: Comparisons of C-statistics and 95% *CI*s for the risk of LA/LAA thrombus among $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS scores

Variables	C-statistics	95% *CI*	*P* for C-statistics	P_{CM-C}	P_{CM-M}
$CHADS_2$	0.726	0.671–0.776	<0.001	–	–
CHA_2DS_2-VASc	0.710	0.654–0.761	<0.001	–	–
MS	0.776	0.724–0.822	<0.001	–	–
$CHADS_2$-MS	0.807	0.757–0.851	<0.001	0.0019	0.2827
CHA_2DS_2-VASc-MS	0.792	0.741–0.837	<0.001	0.0007	0.6625

P for C-statistics: *P* value for area under the curve of each score; P_{CM-C}: *P* value for the comparison of C-statistics between the CHADS2-MS score and the $CHADS_2$ score or between the CHA_2DS_2-VASc-MS score and the CHA_2DS_2-VASc score; P_{CM-M}: *P* value for the comparison of C-statistics between the $CHADS_2$-MS score and the MS score or between the CHA_2DS_2-VASc-MS score and the MS score; *CI*s: Confidence intervals; LA: Left atrial; LAA: Left atrial appendage; –: Not available.

Table 4: Sensitivity, specificity, PPV, and NPV of $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores ≥3 for predicting TEE risk factors

Variables	Sensitivity	Specificity	PPV	NPV
$CHADS_2$-MS	0.714	0.786	3.33	0.36
CHA_2DS_2-VASc-MS	0.877	0.555	1.96	0.23

PPV: Positive predictive value; NPV: Negative predictive value; TEE: Transesophageal echocardiography.

thrombus. Both $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores had better predictive powers for the risk of LA/LAA thrombus than $CHADS_2$ and CHA_2DS_2-VASc scores, respectively.

LA/LAA thrombus detected by TEE is considered a risk for stroke in NVAF. The patients with LA/LAA thrombi were associated with 7.8% of the stroke per year and had 2.5-fold increase in thromboembolic events as compared with those without thrombi.[13,14] In comparison with the other conventional risk factors such as HBP, DM, CHF, and previous stroke, LA/LAA thrombus was a visible marker of AF-related stroke and a direct evidence for anticoagulant therapy. The $CHADS_2$ and CHA_2DS_2-VASc scores were recommended for predicting the risk of stroke or thromboembolic events for NVAF patients,[15,16] and both of them were associated with TEE risk factors for thromboembolism.[17]

The vast majority of epidemiological and observational studies suggested that individuals with MS had a greater likelihood of AF than their non-MS counterparts.[18-20] Furthermore, Tsai *et al*.[8] found that MS was also associated with the increased thromboembolic rate of NVAF patients.

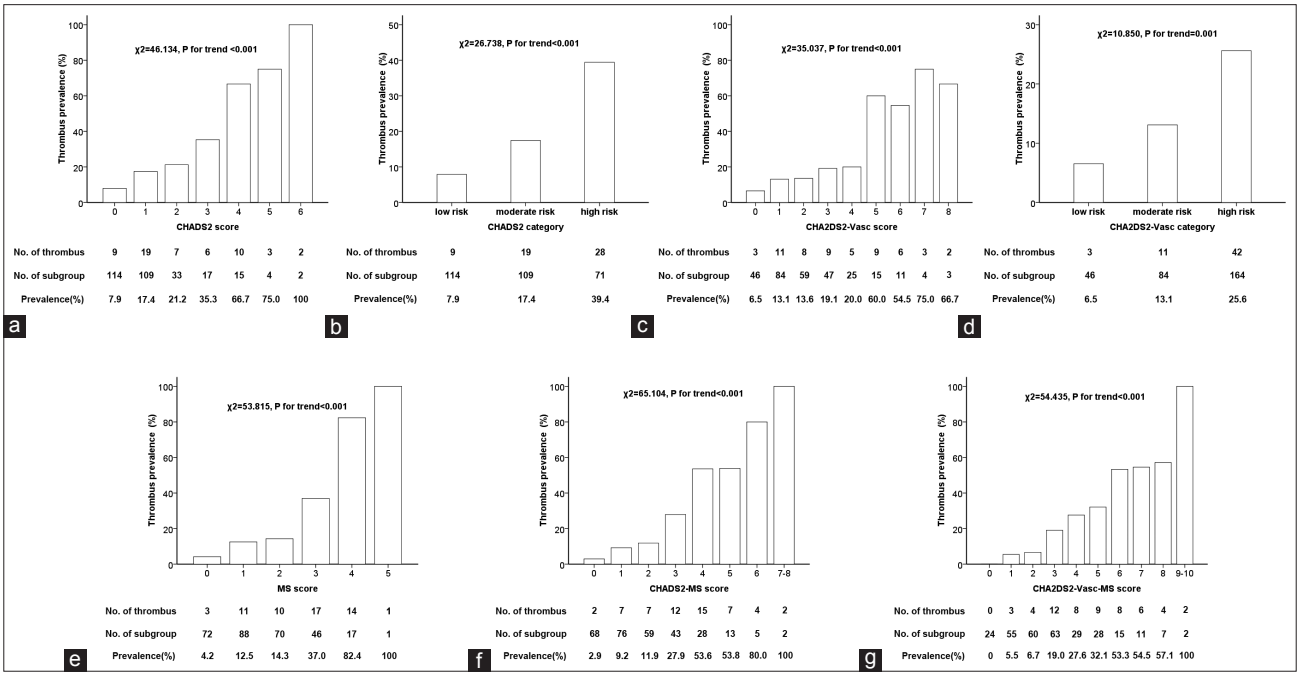

Figure 1: The prevalence (percentage) of the left atrial or left atrial appendage thrombus formation for $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS scores and their corresponding categories. The prevalence (percentage) of the left atrial or left atrial appendage thrombus formation for $CHADS_2$ score (a) and $CHADS_2$ category (b); for CHA_2DS_2-VASc score (c) and CHA_2DS_2-VASc category (d); for MS score (e); for $CHADS_2$-MS score (f); and CHA_2DS_2-VASc-MS score (g).

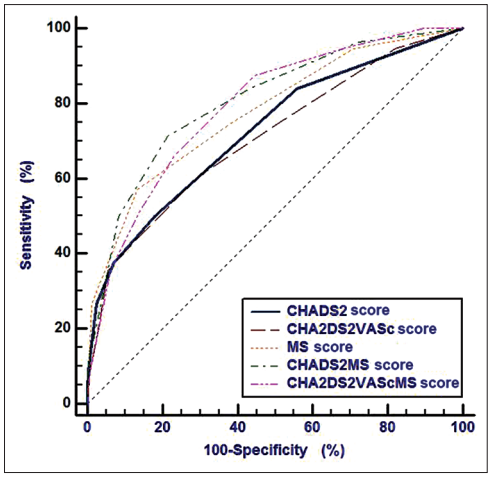

Figure 2: Receiver operating characteristic (ROC) curves of predictive abilities of the risk of the left atrial or left atrial appendage thrombus formation by the $CHADS_2$, CHA_2DS_2-VASc, MS, $CHADS_2$-MS, and CHA_2DS_2-VASc-MS scores.

Our results showed that a graded positive association between the increasing number of MS components and the elevated rate of LA/LAA thrombus was identified, which was similar to the previous outcomes stated above. Previous pathophysiologic findings detected a possible link between MS and thromboembolism due to abnormal fibrinolysis, inflammation, and endothelial dysfunction. In patients with MS, the plasma level of fibrinogen, Factor VII, and Factor VIII was increased and the level of plasminogen activator inhibitor-1 was decreased, which resulted in a prothrombotic or hypercoagulable state.[21] Another possible mechanism was that MS was a state of chronic inflammation with increased inflammatory factors, which induced atrial structural and electrical remodeling.[22] Finally, all the components of MS contributed to the impairment of endothelial function, and AF led to a decreased antithrombotic ability in the damaged atrial endocardium and thus promoting thrombogenesis.[23] In brief, NVAF patients with MS are more prone to developing a prothrombotic state and undergoing thromboembolic events than those without MS. The more components of MS someone has, the higher risk for him/her to have an LA/LAA thrombus.

A new scoring scheme called $CHADS_2$-MS score which was established by Tsai *et al*.[8] has a better predictive power for thromboembolism risk compared to $CHADS_2$ score. In our study, we evaluated the predictive power of this new scoring system for the risk of LA/LAA thrombus formation. In fact, the $CHADS_2$-MS score improved the predictive power of $CHADS_2$ score for the risk assessment of LA/LAA thrombus, and the situation was the same for the CHA_2DS_2-VASc-MS score. In addition, our analysis showed that NVAF patients with $CHADS_2$ or CHA_2DS_2-VASc score of 0 or 1 and three additional MS scores had a significantly higher prevalence of LA/LAA thrombus compared with those who had the same $CHADS_2$ or CHA_2DS_2-VASc score but without MS. All the above-mentioned findings suggested that the additional MS score was complimentary to the $CHADS_2$ or CHA_2DS_2-VASc score. High additional MS score could help identify patients at a high risk of developing stroke in the low-risk group stratified by the $CHADS_2$ or CHA_2DS_2-VASc score.

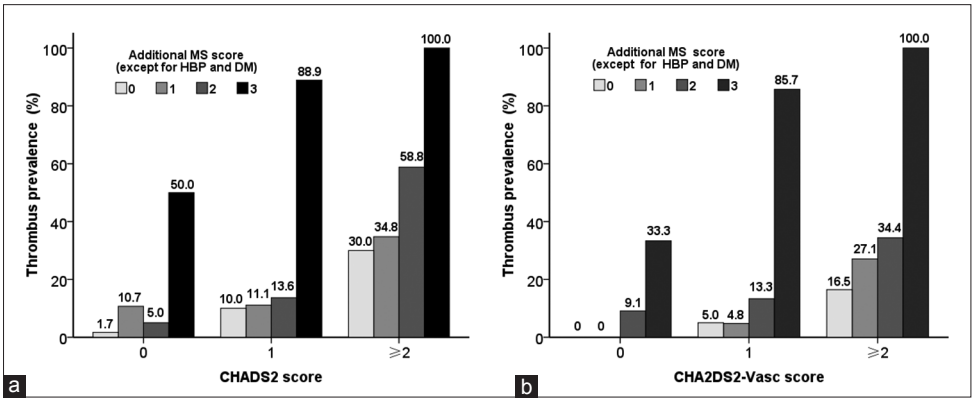

Figure 3: The prevalence (percentage) of the left atrial or left atrial appendage thrombus formation classified by additional MS score in low-, moderate-, and high-risk categories of $CHADS_2$ (a) and CHA_2DS_2-VASc scores (b).

As we know, the key pathogenesis of MS is insulin resistance. All the components of MS are related to each other by insulin resistance. Besides, chronic inflammatory reaction, impairment of endothelial function, and hypercoagulable state related to LA/LAA thrombus are associated with insulin resistance. The more severe the degree of insulin resistance is, the more components of MS the patients will develop. Several studies proved that higher mortality of cerebro-cardiovascular disease was in line with the increasing components of MS,[24,25] and MS was associated with an increased prevalence of AF.[20] Although there was no previous report on the relationship between the number of MS components and LA/LAA thrombus formation, our observation provided novel evidence that there was a positive correlation between MS score and the prevalence of LA/LAA thrombus, and it might be a reasonable explanation for the improvement of predictive power for the risk of LA/LAA thrombus by adding MS scores.

In general, MS not only increases the predictive power of $CHADS_2$ and CHA_2DS_2-VASc scores for the risk of LA/LAA thrombus, but also identifies individuals at a high risk of LA/LAA thrombus in low-stroke risk group classified by $CHADS_2$ or CHA_2DS_2-VASc score. Anticoagulant therapy should be strengthened for the NVAF patients with higher additional MS score.

Our study also had several limitations. First, the sample size of this study was relatively small. In addition, most studies have chosen stroke or thromboembolic event as a major end point. LA/LAA thrombus might be a surrogate marker of stroke or thromboembolic events; however, it could not represent the prevalence of stroke or thromboembolic events completely. Finally, the $CHADS_2$-MS or CHA_2DS_2-VASc-MS scoring system should also be evaluated in Caucasian and other Asian populations. A further follow-up would be needed to assess their actual predictive powers on stroke and thromboembolic events.

MS is an independent risk factor for LA/LAA thrombus formation in NVAF patients. Because the $CHADS_2$-MS and CHA_2DS_2-VASc-MS scores can both identify individuals at a high risk of LA/LAA thrombus in low-stroke risk population classified by $CHADS_2$ and CHA_2DS_2-VASc scores, they are superior to the $CHADS_2$ and CHA_2DS_2-VASc scores in the risk stratification for LA/LAA thrombus formation. The present findings may help identify and control the risk factors for LA/LAA thrombus, thus preventing the occurrence of stroke and thromboembolism events.

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Conflicts of interest

There are no conflicts of interest.

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