

The Value of the CHADS₂ and CHA₂DS₂-VASc Score for Predicting the Prognosis in Lacunar Stroke with or without Atrial Fibrillation Patients

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Background: The CHADS₂ and CHA₂DS₂-VASc scoring systems have been proved efficacy to stratify stroke and thromboembolism risk in patients with atrial fibrillation (AF). Whether CHADS₂ and CHA₂DS₂-VASc score has predictive value for the prognosis in lacunar stroke (LS) patients remains unclear. **Methods:** A total of 763 consecutive patients with LS (mean age: 66 ± 12 years; 464 male) were enrolled in this study between January 2013 and December 2014. Patients were divided into LS without AF (LS; n = 679) and LS with AF (LS-AF; n = 84) groups. Measures of performance for the risk scores were evaluated at predicting mortality and restroke in LS-AF and LS without AF patients. All patients were evaluated with respect to clinical features and in-hospital clinical results. **Results:** During the mean follow-up period of 20 ± 5.8 months, 29 patients (3.8%) experienced all-cause death, 105 patients (13.8%) experienced recurrence of ischemic stroke. Multivariate analysis revealed that CHADS₂ and CHA₂DS₂-VASc score were independently associated with all-cause death (all *P* < .05). On receiver operating characteristic curve analysis, area under the curve (AUC) for CHADS₂ score was .942 with a similar accuracy of the CHA₂DS₂-VASc score (AUC: .908) in predicting mortality in LS-AF patients. Kaplan-Meier curves were conducted according to the cut-off value of CHA₂DS₂-VASc score. When CHADS₂ score greater than or equal to 4 point or CHA₂DS₂-VASc score greater than or equal to 5 point, the mortality in LS-AF patients was significantly higher compared with those CHADS₂ score less than 4 point or CHA₂DS₂-VASc score less than 5 point. However, after adjusting for clinical covariates, CHADS₂ and CHA₂DS₂-VASc score could not predict both mortality and restroke in LS without AF patients. **Conclusions:** The CHADS₂ and CHA₂DS₂-VASc score have excellent predictive value for mortality in LS-AF patients but could not predict both mortality and restroke in LS without AF patients.

Key Words: Atrial fibrillation—lacunar stroke—predict—prognosis

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Introduction

Atrial fibrillation (AF) is a key risk factor for cardioembolic stroke and is associated with a high mortality and disability rate.^{1,2} AF is often associated with large, cortically based infarcts, which have a 30-day mortality rate as high as 24% among patients not taking any antithrombotic therapy.¹ Lacunar stroke (LS) is a small (<2cm) infarction that accounts for approximately 25% of ischemic strokes.³ In terms of disease progression and prognosis, LS patients have slightly lower rates of stroke recurrence and mortality in the short term (1-2 years) compared to those with non-LS.⁴ Several studies have reported higher case fatality and morbidity after an acute ischemic stroke among AF patients compared with

patients in sinus rhythm.^{5,6} Both mortality and recurrence rate of acute ischemic stroke with AF patients are higher than that of ischemic stroke without AF.⁷ Risk stratification in ischemic stroke with AF patients of high risk of mortality and recurrence is necessary.

Various clinical scoring systems have been developed for the risk stratification in cardiovascular and stroke diseases. The CHADS₂ and CHA₂DS₂-VASc scores are the widely recommended clinical risk prediction tools used to evaluate the risk of thromboembolism, as well as in the decision to use preventive antithrombotic agents in patients with nonvalvular AF (NVAf) because of their simplicity.⁸ CHADS₂ and CHA₂DS₂-VASc scores have also been reported to have a predictive role for cardiovascular and cerebrovascular outcomes.⁹⁻¹¹ However, there is little information available regarding the predictive value of the CHADS₂ and CHA₂DS₂-VASc scores for mortality in LS with or without AF patients.

The aim of this study was to evaluate the value of the CHADS₂ and CHA₂DS₂-VASc score for predicting the prognosis in LS with or without AF patients.

Methods

Study Population

This was a retrospective study based on electronic hospital databases of our hospital. Eligible patients diagnosed with LS at Renmin Hospital of Wuhan University between January 2014 and December 2015 were enrolled in this study. The exclusion criteria were as follows: (1) nonischemic stroke (ie, hemorrhagic stroke); (2) non-LS; (3) lost to follow-up. From the baseline clinical characteristics of each patient, the CHADS₂ and CHA₂DS₂-VASc scores were calculated according to the ESC guidelines for the management of AF.¹² The present study was conducted in accordance with the Declaration of Helsinki and was approved by the ethical committee of our hospital.

Electrocardiogram

Twelve-lead ECG (paper speed 25 mm/s; amplitude 1.0 mV/10 mm) was recorded in all patients soon after their admission to the hospital. Heart rate, QRS complex duration, and QT interval were recorded automatically by the ECG machine. The corrected QT (QTc) was adjusted for the RR interval, using the Bazett formula ($QTc = QT/\sqrt{RR}$).

Blood Test

Blood test was performed before discharge from the hospital. The blood test included B-type natriuretic peptide (BNP), MB isoenzyme of creatine kinase (CKMB), troponin I (cTnI), homocysteine (Hcy), uric acid (UA), total glyceride (TG), total cholesterol (Tch), and low-density lipoprotein cholesterol (LDL) levels.

Definitions

The definition of AF was in accordance with 2014 AHA/ACC/HRS guideline for the management of patients with AF.¹³ The definition of LS was in accordance with 2018 AHA/ASA guideline.¹⁴ The definition of heart failure was in accordance with 2013 ACCF/AHA guideline for the management of heart failure.¹⁵ Hypertension was defined as a systolic blood pressure greater than or equal to 140 mm Hg, diastolic blood pressure greater than or equal to 90 mm Hg, or treatment with antihypertensive drugs. Diabetes mellitus was considered to be present in patients with diabetes controlled by diet, oral hypoglycemic agents, or insulin, as well as in cases discharged from the hospital with a diagnosis of diabetes mellitus and/or prescription of hypoglycemic agents. In the present study, coronary heart disease included ischemic heart disease that had been diagnosed as acute myocardial infarction (MI), coronary stenosis detected by coronary angiography and treated by percutaneous coronary revascularization, and/or coronary artery bypass grafting, ischemic stroke, hemorrhagic stroke, peripheral artery disease, and history of macrovascular surgery. Hyperlipidemia was defined as the use of lipid-lowering agents, a total serum cholesterol level greater than 240 mg/dL, or a serum triglyceride level greater than 200 mg/dL. LS was classified according to the TOAST system.¹⁶

Follow-Up and End Points

The subjects were followed up until May 31, 2018. Research coordinators and physicians recorded baseline data of all patients at the time of enrollment, including patient demographics, past medical conditions, and current medication. The primary end point of the study was all-cause death. The causes of death were determined from medical records or by direct communication with patients' general practitioners or families. The secondary end point was unplanned rehospitalization for recurrence of ischemic stroke. The secondary end point was determined from medical records.

Statistical Analysis

Data are expressed as the mean \pm SD or percentages. For variables that showed skewed distributions, descriptive statistics are presented as medians with interquartile ranges. Comparisons of continuous variables were performed using the unpaired *t* test. Comparisons of categorical variables were analyzed by the chi-square test. Receiver operating characteristic (ROC) curve analysis was used to identify the value of CHADS₂ and CHA₂DS₂-VASc score predictive of prognosis in LS-AF patients. Area under the curve (AUC) is a rough guide for quantifying the discriminatory capacity of a diagnostic test ranked as: excellent (.9-1), good (.8-.89), fair (.7-.79), poor (.6-.69).¹⁷ The Kaplan-Meier method was used to estimate primary and secondary end point-free

survival, and the differences between the curves were compared using the log-rank test. The prognostic value of each factor was first evaluated by univariate Cox proportional hazard regression analysis. The factors that had *P* values <.05 in the univariate analysis were entered into a multivariate Cox proportional hazards model to identify the independent predictors. Assessing value of CHADS₂ and CHA₂DS₂-VASc scores in prediction all cause death using the AUC, whether AUC were statistically significant was analyzed using the Z test. *P* < .05 was considered to be statistically significant. All statistical analyses were performed using SPSS for Windows version 20 (IBM, New York, NY).

Results

Comparison of Clinical and Laboratory Characteristics in the LS Groups with or without AF

A total of 763 LS patients (464 male and 299 female, mean age 66 ± 12 years) were enrolled in this study.

Among the 763 LS patients, 679 patients (89%) were without AF and 84 (11%) with AF. Table 1 lists the baseline characteristics of patients. Significant differences were noted between the 2 groups in terms of age, percentage of congestive heart failure, coronary heart diseases and diabetes mellitus, heart rate, and TG. LS-AF patients were older, had a higher percentage of congestive heart failure, coronary heart diseases and diabetes mellitus, faster heart rate, and lower TG (all *P* < .05). Compared with LS without AF group, anticoagulation drugs use in LS-AF group were higher (*P* < .05). No significant differences were found between the 2 groups in regard to percentage of female, hypertension, hyperlipidemia, QRS duration, QTc duration, and serum CKMB, UA, cTnI, BNP, Tch, LDL, Hcy levels, and use of statins and antiplatelets.

No significant differences in the NIH Stroke Scale (NIHSS) score were found between the 2 groups (*P* > .05, Table 1). The CHADS₂ score and CHA₂DS₂-VASc score in LS-AF group were significantly higher than LS group (*P* < .05, respectively).

Table 1. Baseline characteristics

Variable	Total (n = 763)	LS (n = 679)	LS-AF (n = 84)	<i>P</i> Value
Age, years	66.1 ± 12.2	65.4 ± 12.3	71.4 ± 9.7	<.001
Female, n (%)	299 (39.2)	261 (38.4)	38 (45.2)	.229
Congestive heart failure, n (%)	37 (4.8)	24 (3.5)	13 (15.5)	<.001
Coronary heart diseases, n (%)	134 (17.6)	100 (14.7)	34 (40.5)	<.001
Hypertension, n (%)	492 (64.5)	442 (65.1)	50 (59.5)	.314
Diabetes mellitus, n (%)	171 (22.4)	163 (24.0)	8 (9.5)	.003
Hyperlipidemia, n (%)	130 (17.0)	120 (17.7)	10 (11.9)	.185
ECG data				
Heart rate, beat/min	77.1 ± 21.6	75.2 ± 19.3	95.0 ± 31.7	<.001
QRS duration, ms	97.5 ± 20.8	97.1 ± 18.1	100.7 ± 36.8	.150
QTc	433.5 ± 49.0	433.5 ± 46.7	433.2 ± 66.2	.962
Laboratory data				
BNP, pg/mL	369 (103, 1545)	232 (73, 915)	1733 (681, 3645)	.750
cTnI, ng/mL	.02 (.01, .05)	.02 (.01, .05)	.02 (.01, .10)	.509
CKMB, ng/mL	1.29 (.58, 2.42)	1.09 (.54, 2.25)	1.96 (1.20, 2.71)	.485
UA, mmol/L	351.3 ± 113.2	350.6 ± 112.9	356.8 ± 116.3	.642
Tch, mmol/L	4.1 ± 1.0	4.2 ± 1.0	4.0 ± 1.2	.291
TG, mmol/L	1.5 ± .9	1.6 ± 1.0	1.3 ± .7	.018
LDL, mmol/L	2.3 ± 1.1	2.3 ± 1.4	2.3 ± 1.1	.778
Hcy, ng/mL	16.8 ± 8.9	17.0 ± 9.3	15.4 ± 5.9	.257
Medications use				
Statin, n (%)	555 (72.7)	490 (72.2)	65 (77.4)	.311
antiplatelets, n (%)	366 (48.0)	326 (48.0)	40 (47.6)	.946
Anticoagulation, n (%)	136 (23.3)	101 (14.9)	70 (83.3)	<.001
Baseline NIHSS score	3.0 ± 1.0	2.9 ± .9	3.1 ± 1.0	.110
CHADS ₂ score	3.2 ± .9	3.2 ± .8	3.4 ± 1.0	.039
CHA ₂ DS ₂ -VASc score	4.1 ± 1.2	4.1 ± 1.2	4.4 ± 1.2	.010
All-cause death, n (%)	29 (3.8)	22 (3.2)	7 (8.3)	.021
Cardiovascular death, n (%)	11 (1.4)	7 (1.0)	4 (3.6)	.007

Abbreviations: AF, atrial fibrillation; BNP, B-type natriuretic peptide; CKMB, creatine kinase MB; cTnI, troponin I; HCY, homocysteine; LDL, low-density lipoprotein cholesterol; LS, lacunar stroke; NIHSS score, NIH Stroke Scale score; QTc, rate-corrected QT; Tch, total cholesterol; TG, total glyceride; UA, uric acid.

Data are presented as n (%), median (interquartile range), or mean ± standard deviation.

Table 2. Multivariate predictors of primary end event and secondary end event in AIS-AF patients

Variable	Mortality		Restroke	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.013 (.884, 1.161)	.850	-	-
History of congestive heart failure	-	-	2.711 (.730, 10.076)	.136
History of coronary heart diseases	-	-	-	-
History of diabetes mellitus	-	-	-	-
Heart rate	-	-	-	-
TG	1.332 (.799, 2.219)	.272	1.332 (.799, 2.219)	.272
CHADS ₂ score	3.601 (1.314, 9.870)	.013	-	-
CHA ₂ DS ₂ -VASc score	2.880 (1.115, 7.440)	.029	1.451 (.917, 2.297)	.112

Abbreviations: CI, confidence interval; HR, hazard ratio; TG, total glyceride.
Parameters with a *P* value < .05 were entered in the multivariate analysis.

Compared with LS without AF group, LS-AF group had higher all-cause death rate (8.3% versus 3.2%, *P* < .05) and cardiovascular death rate (3.6% versus 1.0%, *P* < .05).

Survival Analysis

During the mean follow-up period of 20.0 ± 5.8 months, 29 patients (3.8%) experienced all-cause death. In addition, 105 patients (13.8%) had a recurrence of ischemic stroke, the secondary end point.

Predictors of Prognosis in LS-AF Patients

Table 2 summarizes the factors predicting all-cause death and restroke. Age, TG, CHADS₂ score, and CHA₂DS₂-VASc score were identified as significant predictors of all-cause death. Multivariate Cox regression analysis revealed that CHADS₂ score (hazard ratio: 3.601, 95% confidence interval [CI]: 1.314-9.870) and CHA₂DS₂-VASc score (hazard ratio: 2.880, 95% CI: 1.115-7.440) were

independent predictors of all-cause death in LS-AF patients.

Table 2 also summarizes the factors predicting recurrence of ischemic stroke. History of congestive heart failure, CHA₂DS₂-VASc score were significantly associated with recurrence of ischemic stroke. However, according to multivariate Cox regression analysis, only CHA₂DS₂-VASc score was independent predictor of recurrence of LS in LS-AF patients.

As seen in Figure 1A, both mortality and ischemic stroke recurrence rate continuously increased as the scores became higher. CHADS₂ score and CHA₂DS₂-VASc score were independent predictors of all-cause death but not recurrence of ischemic stroke in LS-AF patients. So we utilize ROC curve analysis to find the optimal cut-off value of CHADS₂ score and CHA₂DS₂-VASc score to predict the death in LS-AF patients. On ROC curve analysis, the optimal cut-off value of CHADS₂ score for predicting death was 4 (AUC .942, 95% CI: .87-.98) with a sensitivity of 82.7% and specificity of 92.3% (Fig 2A). The optimal

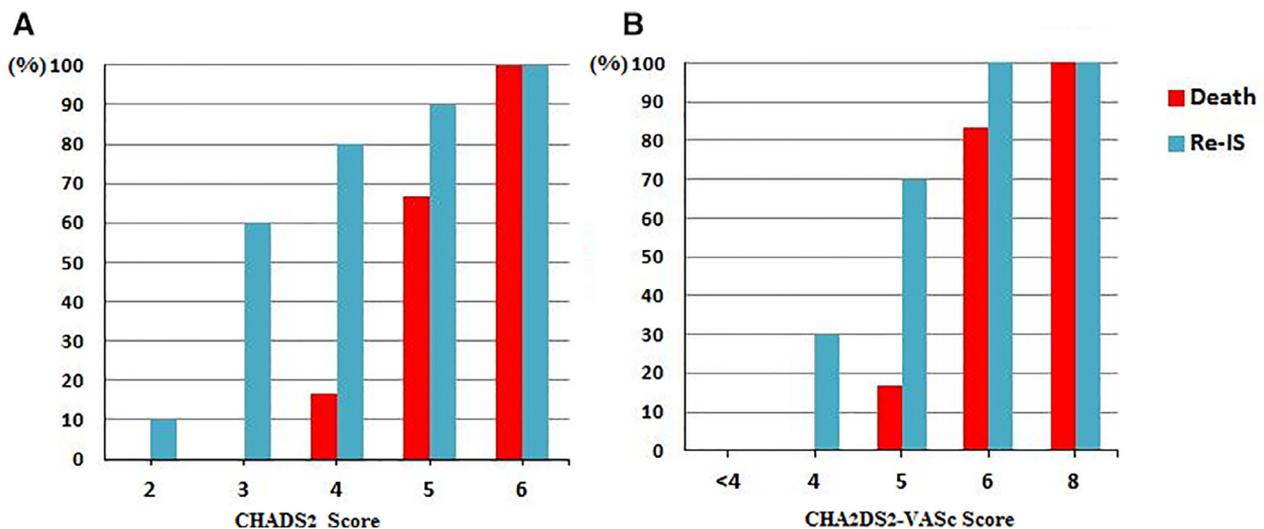


Figure 1. (A) The relation between mortality, recurrence rate of ischemic stroke (Re-IS), and CHADS₂ score in LS-AF patients; (B) the relation between mortality, recurrence rate of stroke (Re-IS), and CHA₂DS₂-VASc score in LS-AF patients.

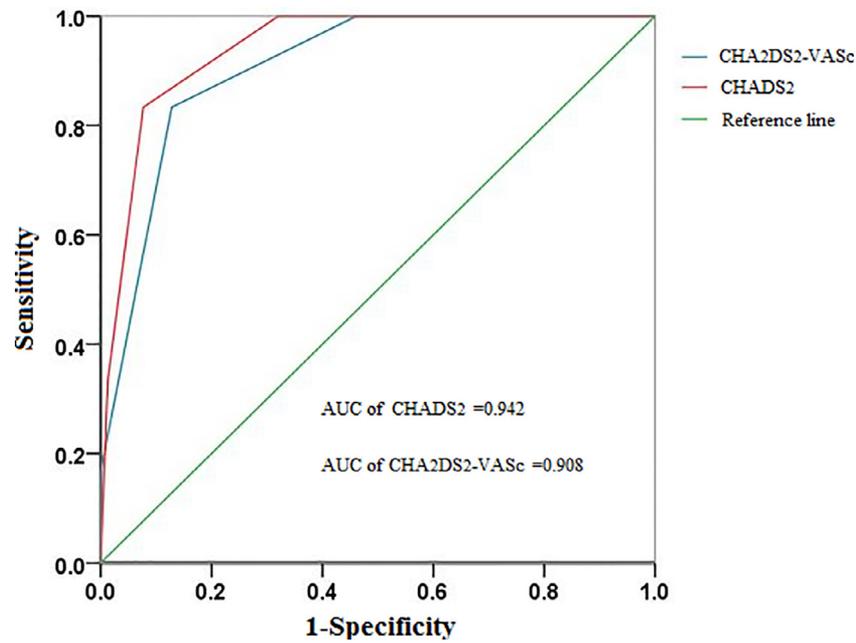


Figure 2. Receiver operating characteristic curves (ROC) for CHADS₂ and CHA₂DS₂-VASC scores for prediction of all-cause death in LS-AF patients.

cut-off value of CHA₂DS₂-VASC score for predicting death was 5 (AUC .908, 95% CI: .81-.98) with a sensitivity of 83.3% and specificity of 87.2% (Fig 2B). The difference between the 2 areas under the curves was not significant ($Z = .695, P > .05$).

The predictive role of CHADS₂ and CHA₂DS₂-VASC score in the prognosis of LS-AF patients were further confirmed when Kaplan-Meier curves were conducted according to the cut-off value of CHADS₂ and CHA₂DS₂-VASC score. When CHADS₂ score greater than or equal to 4 point, the mortality in LS-AF patients was significantly higher compared with those CHADS₂ score less than 4 point (Fig 3A), when CHA₂DS₂-VASC score greater than or equal to 5 point, the mortality in LS-AF patients was significantly higher compared with those CHA₂DS₂-VASC score less than 5 point (Fig 3B). However, CHA₂DS₂-VASC score could not predict the LS recurrence in LS-AF patients, which was consistent with previous results.

Predictors of Prognosis in LS without AF Patients

Table 3 summarizes the results of multivariate Cox analysis of factors predicting all-cause death and recurrence of ischemic stroke. Age and history of coronary heart diseases were significantly associated with all-cause death. Furthermore, history of congestive heart failure, history of coronary heart diseases, and heart rate were significantly predictors of restroke. However, both CHADS₂ score and CHA₂DS₂-VASC score were not independent predictors of all-cause death and recurrence of LS in LS without AF patients.

Discussion

In the present study, we investigated the value of the CHADS₂ and CHA₂DS₂-VASC score for predicting the prognosis in LS with or without AF patients. The main findings are as follows: (1) the CHADS₂ and CHA₂DS₂-VASC score are independent predictors of all-cause death and might be useful for predicting the prognosis in LS-AF patients; (2) the cut-off value of CHADS₂ score for predicting death was 4 with a sensitivity of 82.7% and specificity of 92.3%, CHA₂DS₂-VASC score was 5 with a sensitivity of 85.7% and specificity of 73.4%; and (3) when CHADS₂ score greater than or equal to 4 point, the mortality in LS-AF patients was significantly higher compared with those CHADS₂ score less than 4 point, when CHA₂DS₂-VASC score greater than or equal to 5 point, the mortality in LS-AF patients was significantly higher compared with those CHA₂DS₂-VASC score less than 5 point; (4) both CHADS₂ score and CHA₂DS₂-VASC score were not independent predictors of all-cause death and restroke in LS without AF patients.

AF and ischemic stroke are closely associated. AF is found in 6%-20% of patients with IS.^{18,19} In the present study, AF is found in 11% of the LS patients. LS patients with AF have more risk factors and comorbidities than patients without AF. The data from our study demonstrate that the prevalence of congestive heart failure, coronary heart diseases, and diabetes mellitus among LS patients with AF was higher than patients without AF. Increased risk of stroke and other thromboembolic events related to stroke complicating AF results in significant

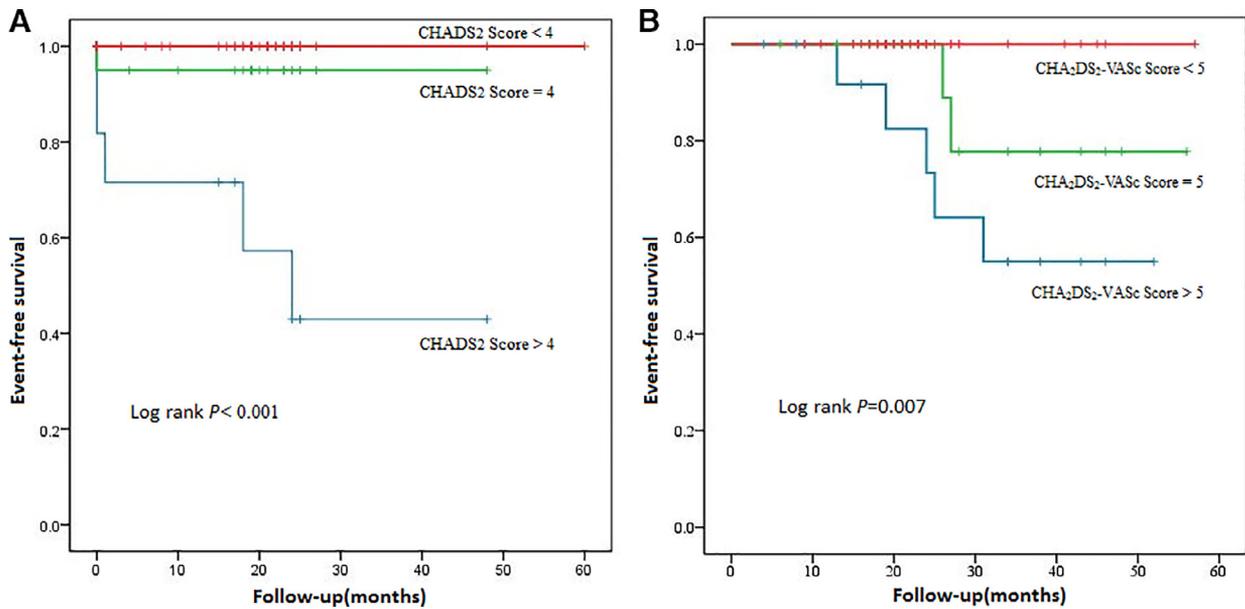


Figure 3. (A) Comparison of the Kaplan-Meier curve of all-cause death-free survival in LS-AF patients among the 3 groups according to cut-off CHADS₂ score value; (B) comparison of the Kaplan-Meier curve of all-cause death-free survival in LS-AF patients among the 3 groups according to cut-off CHA₂DS₂-VASc score value.

degraded quality of life and long-term death. Saxena et al reported that stroke patients with AF have more risk of short-term and long-term recurrence stroke and death.⁷ In the present study, LS patients with AF had a higher risk of LS recurrence and mortality than patients without AF during the mean follow-up period of 20.0 ± 5.8 months ($P < .05$, respectively), indicated that the presence of AF was independent risk factor for recurrence of LS and death in LS patients, which consent with Steger et al reported.²⁰

Clinical scores may help the physicians to identify patients at higher risk of unfavorable events, to establish closer monitoring programs in order to prevent disease progression and negative outcomes; their usefulness will be greater the more they include simply assessable parameters which can be easily combined CHADS₂ and CHA₂DS₂-VASc scales are simple instruments which are able to identify patients at low, medium, and high risk to develop cardioembolic stroke.²¹ CHADS₂ score was developed to identify AF patients at risk for stroke or

thromboembolic event and thus to guide anticoagulation therapy.²² However, patients with an intermediate risk presented a challenge in everyday practice because some of them were at low-intermediate risk and others were at high-intermediate risk. Consequently, CHA₂DS₂-VASc score was introduced to improve predictive value for thromboembolic events in patients at low and intermediate risk. The utility of the score goes beyond the benefits of risk stratification for thromboembolic events.²³ Except for preventing stroke in AF patients, several studies recently have reported that the CHADS₂ and CHA₂DS₂-VASc scores can also predict severity and outcomes of stroke and thromboembolic events in patients with AF and those without AF. Chen et al reported that CHADS₂, CHA₂DS₂-VASc, and R₂CHADS₂ can be used to predict 1-year all-cause mortality in systolic heart failure patients with or without AF.²⁴ In patients with interatrial block without a history of AF, CHADS₂ and CHA₂DS₂-VASc scores can predict the risk of ischemic stroke or transient

Table 3. Multivariate predictors of primary end event and secondary end event in AIS-without AF patients

Variable	Mortality		Restroke	
	HR (95% CI)	P Value	HR (95% CI)	P Value
Age	1.042 (1.003, 1.083)	.035	-	-
History of congestive heart failure	-	-	.468 (.357, .614)	<.001
History of coronary heart diseases	3.354 (1.437, 7.831)	.005	1.897 (1.166, 3.086)	.010
Heart rate	-	-	1.016 (1.006, 1.027)	.002
CHADS ₂ score	1.262 (.800, 1.991)	.316	1.189 (.970, 1.456)	.095
CHA ₂ DS ₂ -VASc Score	1.321 (.891, 1.959)	.166	1.017 (.850, 1.216)	.855

Abbreviation: CI, confidence interval; HR, hazard ratio.

Parameters with a P value $< .05$ were entered in the multivariate analysis.

ischemic attack outcomes.²⁵ In a meta-analysis included 8 cohort studies, CHADS₂ score was associated with increased mortality and stroke/TIA incidence in patients without AF.²⁶

In the present study, we sought to investigate the role of the CHADS₂ and CHA₂DS₂-VASc scores in predicting prognosis in LS with or without AF patients. The ROC curve analysis showed that both CHADS₂ and CHA₂DS₂-VASc scores were predictive of death in LS-AF patients, and multivariate analysis showed that CHADS₂ and CHA₂DS₂-VASc were independently associated with death. The CHADS₂ and CHA₂DS₂-VASc scoring systems comprise a cluster of common cardiovascular risk factors such as age,²⁷ diabetes,²⁸ and heart failure²⁹ associated with thromboembolism. So it is reasonable it may identify underlying conditions that may lead to stroke, or death during follow-up. The CHA₂DS₂-VASc scoring system has been proved to be more sensible than the CHADS₂ scale in discriminating between patients really at low risk of cardioembolic events and is indicated,³⁰ in the ESC Guidelines as the preferred instrument to guide the choice of anticoagulant treatment.¹² However, in the present study, we found the AUC for CHADS₂ score was .942 with a similar accuracy of the CHA₂DS₂-VASc score (AUC .908) in predicting death in high-risk LS-AF patients. Both CHADS₂ and CHA₂DS₂-VASc scores showed excellent predictive accuracy (AUC .9-1.0). When CHADS₂ score greater than or equal to 4 and CHA₂DS₂-VASc score greater than or equal to 5 were chosen as the optimal predictive cut-off values, the 2 clinical-based risk scores significantly improved risk classification for death. Taken together, these findings further support the potential role of CHADS₂ and CHA₂DS₂-VASc score in identifying high-risk LS-AF patients. More aggressive therapeutic management and frequent clinical follow-up may be indicated for these patients.

However, when evaluating the potential role of CHADS₂ and CHA₂DS₂-VASc score in LS without AF patients, we found that both CHADS₂ score and CHA₂DS₂-VASc score were not independent predictors of all-cause death and restroke in LS without AF patients. Recently, a study reported that the CHADS₂ and CHA₂DS₂-VASc scores could predict 5-year recurrent stroke and death in non-AF stroke patients,¹¹ which was inconsistent with our results. It was possible that the follow-up period (20.0 ± 5.8 months) in this study is shorter than Ntaios et al reported (5 years). Furthermore, this study focuses on LS, which accounts for only 25% of ischemic strokes, this subtype of stroke has slightly lower rates of stroke recurrence and mortality in the short term (1-2 years) compared to other subtype strokes, so the 2 risk scores may have no predictive role on the prognosis in LS without AF patients. This result needs to be confirmed in the future.

Our study has several limitations. First, our study is a retrospective study, as such, potentially affected by collection and entry bias, and possible residual confounding.

Second, the study population in this study is LS patients the exclusion of patients with other subtype strokes potentially associated with a higher mortality, which may also add bias to obtained results. Third, the mortality of patients with LS is influenced by multiple risk factors; therefore, a comprehensive evaluation, rather than single measurements of CHADS₂ or CHA₂DS₂-VASc score, is necessary to assess an increased mortality risk, making CHADS₂ or CHA₂DS₂-VASc score a useful predictor of clinical events in LS-AF patients. Fourth, short-term follow-ups of this study have been performed. A longer follow-up period may have provided additional data.

Conclusions

In conclusion, both CHADS₂ and CHA₂DS₂-VASc may be predictors of the death in LS with AF but not LS without AF patients and can serve as additive tools in identifying high-risk LS with AF patients that require aggressive management.

Conflicts of Interest

All authors declare no conflicts of interest.

References

1. Hylek EM, Go AS, Chang Y, et al. Effect of intensity of oral anticoagulation on stroke severity and mortality in atrial fibrillation. *N Engl J Med* 2003;349:1019-1026.
2. Longstreth Jr WT, Bernick C, Fitzpatrick A, et al. Frequency and predictors of stroke death in 5,888 participants in the cardiovascular health study. *Neurology* 2001;56:368-375.
3. Sudlow CL, Warlow CP. Comparable studies of the incidence of stroke and its pathological types: results from an international collaboration. *International stroke incidence collaboration. Stroke* 1997;28:491-499.
4. Sacco S, Marini C, Totaro R, et al. A population-based study of the incidence and prognosis of lacunar stroke. *Neurology* 2006;66:1335-1338.
5. Candelise L, Pinardi G, Morabito A. Mortality in acute stroke with atrial fibrillation. The Italian Acute Stroke Study Group. *Stroke* 1991;22:169-174.
6. Harrison MJ, Marshall J. Atrial fibrillation, TIAs and completed strokes. *Stroke* 1984;15:441-442.
7. Saxena R, Lewis S, Berge E, et al. Risk of early death and recurrent stroke and effect of heparin in 3169 patients with acute ischemic stroke and atrial fibrillation in the international stroke trial. *Stroke* 2001;32:2333-2337.
8. Pisters R, Nieuwlaat R, Lane DA, et al. Potential net clinical benefit of population-wide implementation of apixaban and dabigatran among European patients with atrial fibrillation: a modelling analysis from the Euro Heart Survey. *Thromb Haemost* 2013;109:328-336.
9. Kang IS, Pyun WB, Shin GJ. Predictive value of CHADS₂ score for cardiovascular events in patients with acute coronary syndrome and documented coronary artery. *Korean J Intern Med* 2016;31:73-81.
10. Hsu CY, Chen TH, Su YW, et al. Usefulness of the CHADS₂ score for determining risk of seizure in patients with atrial fibrillation. *Am J Cardiol* 2016;118:1340-1344.

11. Ntaios G, Lip GY, Makaritsis K, et al. CHADS₂, CHA₂DS₂-VASc, and long-term stroke outcome in patients without atrial fibrillation. *Neurology* 2013;80:1009-1017.
12. Camm AJ, Lip GY, De CR, et al. Focused update of the ESC guidelines for the management of atrial fibrillation: an update of the 2010 ESC guidelines for the management of atrial fibrillation-developed with the special contribution of the European Heart Rhythm Association. *Europace* 2012;14:1385-1413.
13. January CT, Wann LS, Alpert JS, et al. 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;64:1-76.
14. Powers WJ, Rabinstein AA, Ackerson T, et al. 2018 Guidelines for the early management of patients with acute ischemic stroke: a guideline for healthcare professionals from the American Heart Association/American Stroke Association. *Stroke* 2018;49:46-110.
15. Yancy CW, Jessup M, Bozkurt B, et al. 2013 ACCF/AHA guideline for the management of heart failure: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *J Am Coll Cardiol* 2013;62:147-239.
16. Adams Jr HP, Bendixen BH, Kappelle LJ, et al. Classification of subtype of acute ischemic stroke: definitions for use in a multicenter clinical trial. TOAST: trial of org 10172 in acute stroke treatment. *Stroke* 1993;24:35-41.
17. Wingert NC, Gotoff J, Parrilla E, et al. The ACS NSQIP risk calculator is a fair predictor of acute periprosthetic joint infection. *Clin Orthop Relat Res* 2016;474:1643-1648.
18. Broderick JP, Phillips SJ, O'Fallon WM, et al. Relationship of cardiac disease to stroke occurrence, recurrence, and mortality. *Stroke* 1992;23:1250-1256.
19. Sandercock P, Bamford J, Dennis M, et al. Atrial fibrillation and stroke: prevalence in different types of stroke and influence on early and long term prognosis (Oxfordshire Community Stroke Project). *BMJ* 1992;305:1460-1465.
20. Steger C, Pratter A, Martinekbregele M, et al. Stroke patients with atrial fibrillation have a worse prognosis than patients without: data from the Austrian Stroke registry. *Eur Heart J* 2004;25:1734-1740.
21. Lip GY, Nieuwlaet R, Pisters R, et al. Refining clinical risk stratification for predicting stroke and thromboembolism in atrial fibrillation using a novel risk factor-based approach: the Euro Heart Survey on atrial fibrillation. *Chest* 2010;137:263-272.
22. Gage BF, Waterman AD, Shannon W, et al. Validation of clinical classification schemes for predicting stroke: results from the National Registry of Atrial Fibrillation. *JAMA* 2001;285:2864-2870.
23. Camm AJ, Kirchhof P, Lip GY, et al. Guidelines for the management of atrial fibrillation: the task force for the management of atrial fibrillation of the European Society of Cardiology (ESC). *Eur Heart J*. 2010;31:2369-2429.
24. Chen YL, Cheng CL, Huang JL, et al. Mortality prediction using CHADS₂/CHA₂DS₂-VASc/R₂CHADS₂ scores in systolic heart failure patients with or without atrial fibrillation. *Medicine* 2017;96:e8338.
25. Wu JT, Wang SL, Chu YJ, et al. CHADS₂ and CHA₂DS₂-VASc scores predict the risk of ischemic stroke outcome in patients with interatrial block without atrial fibrillation. *J Atheroscler Thromb* 2017;24:176-184.
26. Zhou X, Cao K, Kou S, et al. Usefulness of CHADS₂ score for prognostic stratification of patients with coronary artery disease: a systematic review and meta-analysis of cohort studies. *Int J Cardiol* 2017;228:906-911.
27. Appelros P, Nydevik I, Viitanen M. Poor outcome after first-ever stroke: predictors for death, dependency, and recurrent stroke within the first year. *Stroke* 2003;34:122-126.
28. Heuschmann PU, Kolominsky-Rabas PL, Misselwitz B, et al. Predictors of in-hospital mortality and attributable risks of death after ischemic stroke: the German Stroke Registers Study Group. *Arch Intern Med* 2004;164:1761-1768.
29. Ois A, Gomis M, Cuadrado-Godia E, et al. Heart failure in acute ischemic stroke. *J Neurol* 2008;255:385-389.
30. Lip GY, Frison L, Halperin JL, et al. Identifying patients at high risk for stroke despite anticoagulation: a comparison of contemporary stroke risk stratification schemes in an anticoagulated atrial fibrillation cohort. *Stroke* 2010;41:2731-2738.