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Clinical Investigation

CHA_2DS_2-VASc Score Is Associated With Prognosis in Patients With Acute Ischemic Stroke Without Atrial Fibrillation

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Abstract

Background: Although the prognostic value of the CHA_2DS_2-VASc (congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, and female sex) scoring system in patients with stroke has been explored in several studies, a research gap exists in its application, especially in patients without atrial fibrillation (AF).

Methods: This study investigated the association between CHA_2DS_2-VASc score and prognosis at 1 year in patients with acute ischemic stroke (AIS) who do not have AF. A total of 993 patients with AIS but without AF were recruited between January 2019 and December 2022. Patients were categorized into high-risk (CHA_2DS_2-VASc score, >2; n = 424), moderate-risk (CHA_2DS_2-VASc score, 2; n = 218), and low-risk (CHA_2DS_2-VASc score, 0-1; n = 351) groups. The primary outcome was major adverse cardiac events (MACE) at 1 year after index AIS. Multivariate Cox regression analyses evaluated the prognostic value of CHA_2DS_2-VASc scores after controlling for potential confounding factors. A sensitivity analysis was performed based on 3 CHA_2DS_2-VASc groups generated using propensity score matching.

Results: The rate of MACE during 12-month follow-up was statistically significantly higher ($P < .01$) in patients with a CHA_2DS_2-VASc score greater than 2 (34.7%) than in patients with a score of 2 (23.9%) or of 0 or 1 (14.8%). Multivariate Cox regression models indicated that, compared with a CHA_2DS_2-VASc score of 0 or 1, the hazard ratio (HR) of MACE occurrence was 3.22 (95% CI, 1.93-5.37; $P < .01$) for a CHA_2DS_2-VASc score greater than 2 and 1.92 (95% CI, 1.24-2.98; $P < .01$) for a CHA_2DS_2-VASc score of 2. When included in the Cox regression model as a continuous variable, the CHA_2DS_2-VASc score remained strongly associated with higher risks of MACE (HR, 1.19 [95% CI, 1.11-1.26]; $P < .01$), all-cause mortality (HR, 1.14 [95% CI, 1.05-1.23]; $P < .01$), and recurrent stroke (HR, 1.15 [95% CI, 1.06-1.256]; $P < .01$). Sensitivity analyses based on populations generated by propensity score matching yielded similar results.

Conclusion: The CHA_2DS_2-VASc score effectively predicts MACE in patients with AIS but without AF, providing more accurate risk stratification.

Keywords: Prognosis; ischemic stroke; cardiovascular diseases; atrial fibrillation

Introduction

Stroke is the most common cause of mortality and disability in China.[1] Although there have been substantial improvements in stroke care in past decades, long-term prognosis is still a challenge. Five years after a stroke, poor outcomes (death or disability) were found in 70.6% of patients with acute ischemic stroke (AIS).[2] Early screening and active treatment are therefore required to improve prognosis.

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The CHA$_2$DS$_2$-VASc (congestive heart failure [HF], hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack [TIA], vascular disease, age 65-74 years, and female sex) scoring system is normally used for the prediction of thromboembolic risk in patients with atrial fibrillation (AF).[3] Considering that many of the individual components included in the CHA$_2$DS$_2$-VASc score have been reported as risk factors for stroke, some studies have explored the predictive value of CHA$_2$DS$_2$-VASc scores in poststroke prognosis.[1,4] There is a research gap, however, when it comes to the application of this predictive value because of short-term follow-up and limited studies, especially in patients with stroke but without AF.

This study evaluated the association of CHA$_2$DS$_2$-VASc score with 1-year major adverse cardiovascular events (MACE) in patients with AIS but without AF.

Key Points

- The prognostic value of the CHA$_2$DS$_2$-VASc score in patients with stroke is unclear, especially in patients without AF.
- The rate of MACE was statistically significantly higher in patients with CHA$_2$DS$_2$-VASc scores greater than 2 than in patients with scores of 0 through 2.
- The risk for MACE in patients with CHA$_2$DS$_2$-VASc scores of at least 2 were 3.22 higher than patients with scores of 0 and 1.92 times higher than patients with scores of 1.
- The CHA$_2$DS$_2$-VASc scoring system provides a simple but very useful way to stratify risk for patients with stroke but without AF.

Abbreviations

AF, atrial fibrillation
AIS, acute ischemic stroke
BMI, body mass index
CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, and female sex
HF, heart failure
HR, hazard ratio
MACE, major adverse cardiovascular events
PSM, propensity score matching
TIA, transient ischemic attack
TOAST, Trial of ORG 10172 in Acute Stroke Treatment

Patients and Methods

This retrospective study included consecutive patients with AIS admitted to the study hospital between January 2019 and December 2022. Patients were included if they (1) were aged 18 years or older, (2) were diagnosed with AIS by computed tomography or magnetic resonance imaging, (3) had no diagnosis of AF, and (4) had complete CHA$_2$DS$_2$-VASc score data at admission. This study was approved by the Ethics Committee of Tinglin Hospital (approval No. 2023026). All procedures involving human participants were performed according to the 1964 Declaration of Helsinki and its later amendments or comparable ethical standards. As this was a retrospective study, the Ethics Committee of Tinglin Hospital waived the need for informed consent. All data were fully anonymized and kept confidential.

Patients' baseline demographic profiles, medical histories, CHA$_2$DS$_2$-VASc scores, Trial of ORG 10172 in the Acute Stroke Treatment (TOAST) categories, and medications at discharge were retrieved by reviewing medical records. Demographic profiles included data for age, sex, body mass index (BMI), and smoking habits. Medical history included diagnoses of hypertension, dyslipidemia, diabetes, stroke or TIA, HF, and vascular disease. The CHA$_2$DS$_2$-VASc score was calculated for all patients during their index hospitalization, and patients were allocated to 1 of 3 groups according to their score: low risk (score, 0-1), moderate risk (score, 2), and high risk (score, >2). This classification has been used in several previous studies to explore the association of CHA$_2$DS$_2$-VASc score with prognosis in populations with and without AF.[5,6]

The primary outcome of this study was the rate of MACE within 12 months of enrollment, a rate that included data for all-cause mortality, myocardial infarction, and recurrent stroke. The secondary outcomes were the occurrences of all-cause mortality and recurrent stroke within 12 months. The outcomes were collected from medical records and telephone interviews.

Statistical Analysis

Continuous and categorical variables were compared by 1-way analysis of variance, and categorical variables were compared by χ^2 test. Multivariate Cox regression analyses were performed to evaluate the prognostic value of the CHA$_2$DS$_2$-VASc groups as categorical variables or CHA$_2$DS$_2$-VASc scores as continuous variables after controlling for potential confounding factors, including age, sex, BMI, smoking habits,

medical history, TOAST category, and medications at discharge.

A sensitivity analysis was performed based on 3 CHA$_2$DS$_2$-VASc groups generated by the propensity score matching (PSM) method, adjusting for age, sex, BMI, smoking habits, medical history, TOAST category, and medications at discharge.

Patients were censored at the time of last follow-up or 1 year after enrollment, depending on their outcome status. Censoring was appropriately accounted for in Kaplan-Meier survival analyses and Cox regression models. For any missing clinical data, multiple imputation methods were used, where applicable, to minimize potential bias.

All tests were 2 sided, and $P < .05$ was considered statistically significant. IBM SPSS Statistics, version 27.0, software (IBM Corp) was used for data analyses.

Results

The baseline characteristics of patients in the 3 groups before and after PSM are presented in Table I. Before PSM, a total of 933 patients were included and categorized into high-risk (n = 424), moderate-risk (n = 218), and low-risk (n = 351) groups based on their CHA$_2$DS$_2$-VASc scores. Statistically significant differences were observed in age, sex, BMI, smoking status, medical history (hypertension, dyslipidemia, diabetes, stroke or TIA, HF, and vascular disease), large artery atherosclerosis, and antihypertension agents among the 3 groups (all $P < .01$). After PSM, 159 patients were included in each group, and differences in all baseline characteristics were no longer statistically significant.

The median (IQR) follow-up time was 365 (340-376) days. In the overall population, the rate of MACE during this 12-month follow-up was statistically significantly higher ($P < .01$) in patients with a CHA$_2$DS$_2$-VASc score greater than 2 (34.7%) compared with patients with a score of 2 (23.9%) and with a score of 0 or 1 (14.8%). As shown in Figure 1, the Kaplan-Meier survival curve showed that compared with patients with a CHA$_2$DS$_2$-VASC score of 0 or 1, the risks of MACE, all-cause mortality, and recurrent stroke were statistically significantly higher in patients with a score of at least 2 (all $P < .01$). After PSM, the risks of MACE, all-cause mortality, and recurrent stroke remained statistically significantly higher in patients with a CHA$_2$DS$_2$-VASC score of at least 2 (all $P < .01$).

Multivariate Cox proportional hazard regression analysis was performed to identify prognostic factors associated with the risk of outcomes (Table II). After adjusting for potential confounding factors, compared with a CHA$_2$DS$_2$-VASc score of 0 or 1, the hazard ratio (HR) of MACE occurrence was 3.22 (95% CI, 1.93-5.37; $P < .01$) for a score greater than 2 and 1.92 (95% CI, 1.24-2.98; $P < .01$) for a score of 2. The risks for all-cause mortality (>2 vs 0-1: HR, 3.47 [95% CI, 1.84-6.56], $P < .01$; 2 vs 0-1: HR, 2.04 [95% CI, 1.18-3.53], $P = .01$) and recurrent stroke (>2 vs 0-1: HR, 2.39 [95% CI, 1.25-4.56], $P < .01$; 2 vs 0-1: HR, 1.87 [95% CI, 1.10-3.20], $P = .02$) were also statistically significantly increased for the high-risk and moderate-risk groups. When the CHA$_2$DS$_2$-VASc score was treated as a continuous variable in the Cox regression model, an increase of 1 point in the CHA$_2$DS$_2$-VASc score was associated with a 1.19-fold increase in the risk of MACE (95% CI, 1.11-1.26; $P < .01$), a 1.14-fold increase in the risk of all-cause mortality (95% CI, 1.05-1.23; $P < .01$), and a 1.15-fold increase in the risk of recurrent stroke (95% CI, 1.06-1.256; $P < .01$). Sensitivity analyses based on populations generated by PSM yielded similar results.

Discussion

The present study indicated that CHA$_2$DS$_2$-VASc score was independently related to MACE in patients with AIS but without AF during a 12-month follow-up period. This finding is of clinical relevance as CHA$_2$DS$_2$-VASc score can be easily calculated, thereby offering a simple but reliable tool for risk assessment after stroke.

The CHA$_2$DS$_2$-VASc score was originally developed to refine the assessment of stroke risk in patients with AF.[7] This scoring system has subsequently been associated with poor clinical outcomes in various cardiovascular diseases.[8] Mitchell et al[9] and Koene et al[10] found that CHA$_2$DS$_2$-VASc scores effectively predicted ischemic stroke risk in patients with acute coronary syndrome but without AF and in community-dwelling individuals without AF, respectively. Studies by Perna et al[11] and Harb et al[12] provide additional evidence supporting the value of the CHA$_2$DS$_2$-VASc score. Perna and team's research[11] underscores the broader

TABLE I. Baseline Characteristics of the Study Population According to CHA$_2$DS$_2$-VASc Score Before and After PSM

	Before PSM				After PSM			
Variable	Low risk (n = 351)	Moderate risk (n = 218)	High risk (n = 424)	*P* value	Low risk (n = 159)	Moderate risk (n = 159)	High risk (n = 159)	*P* value
Age, mean (SD), y	61.4 (7.0)	70.1 (5.3)	76.9 (6.1)	<.01	69.9 (7.0)	70.0 (5.0)	70.9 (5.9)	.23
Sex, No. (%)				<.01				.44
Male	234 (66.7)	117 (53.7)	117 (27.6)		81 (50.9)	84 (52.8)	73 (45.9)	
Female	117 (33.3)	101 (46.3)	307 (72.4)		78 (49.1)	75 (47.2)	86 (54.1)	
BMI, mean (SD)	24.5 (2.7)	24.1 (2.8)	23.9 (2.8)	.02	24.0 (2.7)	24.2 (2.8)	24.1 (2.9)	.84
Smoking status, No. (%)				.04				.67
Smoker	45 (12.8)	36 (16.5)	83 (19.6)		27 (17.0)	25 (15.7)	31 (19.5)	
Nonsmoker	306 (87.2)	182 (83.5)	341 (80.4)		132 (83.0)	134 (84.3)	128 (80.5)	
Medical history,[a] No. (%)								
Hypertension	150 (42.7)	135 (61.9)	342 (80.7)	<.01	103 (64.8)	92 (57.9)	108 (67.9)	.16
Dyslipidemia	89 (25.4)	57 (26.1)	208 (49.1)	<.01	52 (32.7)	43 (27.0)	60 (37.7)	.13
Diabetes	36 (10.3)	31 (14.2)	111 (26.2)	<.01	22 (13.8)	22 (13.8)	25 (15.7)	.86
Stroke or TIA	10 (2.8)	20 (9.2)	87 (20.5)	<.01	10 (6.3)	15 (9.4)	14 (8.8)	.56
Heart failure	1 (0.3)	4 (1.8)	13 (3.1)	<.01	1 (0.6)	1 (0.6)	4 (2.5)	.38
Vascular disease	14 (4.0)	21 (9.6)	74 (17.5)	<.01	14 (8.9)	7 (4.4)	18 (11.3)	.08
TOAST category,[b] No. (%)								
Large artery atherosclerosis	80 (22.8)	55 (25.2)	130 (30.7)	.04	39 (24.5)	39 (24.5)	53 (33.3)	.13
Small vessel occlusion	147 (41.9)	75 (34.4)	147 (34.7)	.08	60 (37.7)	58 (36.5)	53 (33.3)	.70
Cardioembolism	17 (4.8)	9 (4.1)	13 (3.1)	.44	4 (2.5)	6 (3.8)	7 (4.4)	.65
Medications at discharge,[c] No. (%)								
Antiplatelet agents	280 (79.8)	161 (73.9)	330 (77.8)	.26	123 (77.4)	118 (74.2)	121 (76.1)	.80
Antihypertension agents	139 (39.6)	107 (49.1)	227 (53.5)	<.01	78 (49.1)	73 (45.9)	80 (50.3)	.72
Statins	58 (16.5)	43 (19.7)	99 (23.3)	.06	30 (18.9)	33 (20.8)	34 (21.4)	.85

BMI, body mass index; CHA$_2$DS$_2$-VAS, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, and female sex; PSM, propensity score matching; TIA, transient ischemic attack; TOAST, Trial of ORG 10172 in Acute Stroke Treatment.

[a] Some patients had more than 1 comorbidity.

[b] Some data were missing.

[c] Some patients were prescribed more than 1 medication at discharge.

P < .05 was considered statistically significant.

applicability of the score beyond AF, emphasizing its role in predicting cardiovascular events in patients with underlying heart conditions. Findings by Harb and colleagues[12] further validate the CHA$_2$DS$_2$-VASc score as an effective tool for stratifying patients based on future cardiovascular risk, regardless of the presence of AF and anticoagulation status.

An increasing number of studies have explored the predictive value of CHA$_2$DS$_2$-VASc score in prognosis after stroke, but the conclusions are inconsistent. In a study conducted by Lee et al,[1] an increase of each point in the CHA$_2$DS$_2$-VASc score corresponds with a 1.10-times-higher (95% CI, 1.06-1.15) risk of MACE within 1 year in patients with AIS and AF.

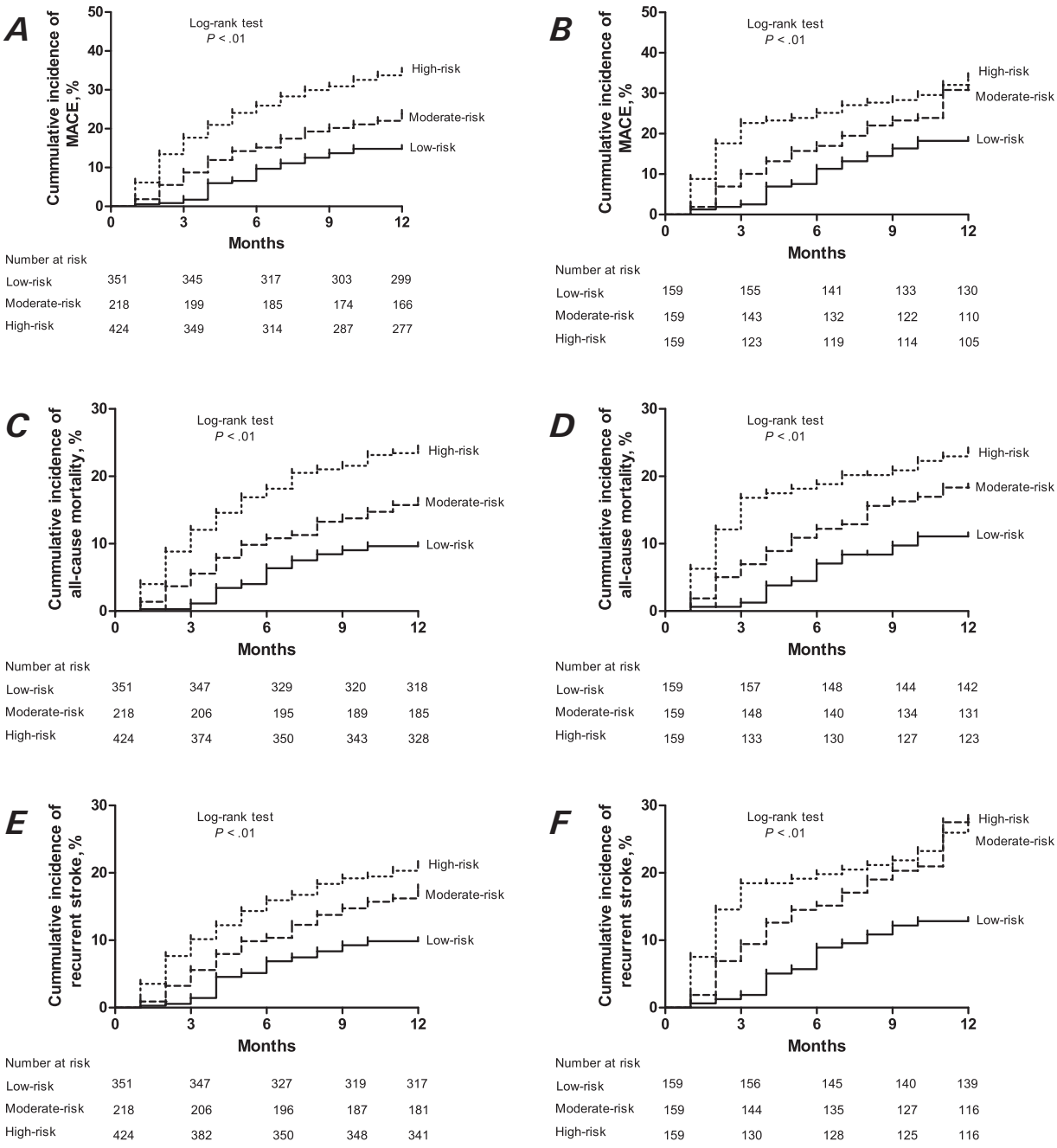

Fig. 1 Kaplan-Meier survival functions (**A**) before and (**B**) after PSM show that in patients with AIS without AF, the 1-year risk for MACE was statistically significantly higher in patients with moderate (score, 2) and high-risk (score, >2) CHA$_2$DS$_2$-VASc scores than in patients with low-risk (score, 0-1) CHA$_2$DS$_2$-VASc scores. Kaplan-Meier survival functions (**C**) before and (**D**) after PSM show that in patients with AIS without AF, the 1-year risk for all-cause mortality was statistically significantly higher in patients with moderate (score, 2) and high-risk (score, >2) CHA$_2$DS$_2$-VASc scores than in patients with low-risk (score, 0-1) CHA$_2$DS$_2$-VASc scores. Kaplan-Meier survival functions (**E**) before and (**F**) after PSM show that in patients with AIS without AF, the 1-year risk of recurrent stroke was statistically significantly higher in patients with moderate (score, 2) and high-risk (score, >2) CHA$_2$DS$_2$-VASc scores than in patients with low-risk (score, 0-1) CHA$_2$DS$_2$-VASc scores.

AF, atrial fibrillation; AIS, acute ischemic stroke; CHA$_2$DS$_2$-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, and female sex; MACE, major adverse cardiovascular events; PSM, propensity score matching.

$P < .05$ was considered statistically significant.

TABLE II. Univariate and Multivariate Cox Regression for Exploring the Association of CHA_2DS_2-VASc Score and Prognosis at 12 Months in the Population Before and After PSM

		Before PSM						After PSM					
		Univariate analysis			Multivariate analysis			Univariate analysis			Multivariate analysis		
Variable	**CHA_2DS_2-VASc**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**	**HR**	**95% CI**	***P* value**
MACE	Continuous	1.21	1.15-1.27	<.01	1.19	1.11-1.26	<.01	1.12	1.03-1.21	<.01	1.13	1.04-1.23	<.01
	Categorical												
	Low risk	[Reference]			[Reference]			[Reference]			[Reference]		
	Moderate risk	1.70	1.16-2.49	<.01	1.92	1.24-2.98	<.01	1.78	1.13-2.82	.01	1.76	1.11-2.80	.02
	High risk	2.71	1.97-3.72	<.01	3.22	1.93-5.37	<.01	2.14	1.36-3.36	<.01	2.10	1.32-3.34	<.01
All-cause mortality	Continuous	1.17	1.10-1.25	<.01	1.14	1.05-1.23	<.01	1.13	1.02-1.25	.02	1.15	1.03-1.28	.01
	Categorical												
	Low risk	[Reference]			[Reference]			[Reference]			[Reference]		
	Moderate risk	1.75	1.08-2.82	.02	2.04	1.18-3.53	.01	1.73	0.95-3.17	.07	1.70	0.92-3.12	.09
	High risk	2.78	1.87-4.14	<.01	3.47	1.84-6.56	<.01	2.42	1.36-4.31	<.01	2.50	1.38-4.51	<.01
Recurrent stroke	Continuous	1.17	1.10-1.25	<.01	1.15	1.06-1.25	<.01	1.11	1.01-1.22	.02	1.12	1.01-1.23	.03
	Categorical												
	Low risk	[Reference]			[Reference]			[Reference]			[Reference]		
	Moderate risk	1.85	1.16-2.95	<.01	1.87	1.10-3.20	.02	2.27	1.33-3.85	<.01	2.31	1.35-3.94	<.01
	High risk	2.35	1.57-3.50	<.01	2.39	1.25-4.56	<.01	2.46	1.45-4.19	<.01	2.44	1.41-4.21	<.01

CHA_2DS_2-VASc, congestive heart failure, hypertension, age ≥75 years, diabetes mellitus, prior stroke or transient ischemic attack, vascular disease, age 65-74 years, and female sex; HR, hazard ratio; MACE, major adverse cardiovascular event; PSM, propensity score matching.

$P < .05$ was considered statistically significant.

In another study involving patients both with and without AF, a CHA$_2$DS$_2$-VASc score of at least 2 was associated with higher risks for death and serious adverse cardiac events after 3 months.[5] Ntaios et al[6] demonstrated that CHA$_2$DS$_2$-VASc scores predict long-term outcomes in patients with stroke but without AF. Their findings indicate that patients in the intermediate-risk and high-risk subgroups faced a 3.56-fold increase in mortality risk, a 2.93-fold increase in the risk for stroke recurrence, and a 2.71-fold increase in the risk for cardiovascular events over a 5-year follow-up period. Yang et al,[13] however, reported that the CHA$_2$DS$_2$-VASc score cannot predict both mortality and recurrent stroke in patients with stroke but without AF. The current study showed that even in patients with stroke but without AF, a higher CHA$_2$DS$_2$-VASc score was still statistically significantly associated with an increased risk for poor outcomes.

A study by Chua et al[14] adds another important layer to this discussion. In their observational study among patients with acute coronary syndrome, the authors demonstrated that both CHADS$_2$ (congestive HF; hypertension; age ≥75 years; diabetes; and stroke, TIA, or thromboembolism) and CHA$_2$DS$_2$-VASc scores were statistically significant predictors of adverse events such as myocardial infarction, stroke, and death within 1 year of discharge. They found that the CHA$_2$DS$_2$-VASc score performed better than the CHADS$_2$ score, with an improvement in the area under the receiver operating characteristic curve from 0.66 to 0.70, which suggests that the CHA$_2$DS$_2$-VASc score is a more accurate tool for predicting cardiovascular outcomes, even in populations without AF.

These studies, including the current one, illustrate the consistent value of the CHA$_2$DS$_2$-VASc score in predicting adverse cardiovascular outcomes. Although traditionally used in populations with AF, its application in broader contexts, such as for patients with acute coronary syndrome and patients with stroke but without AF, is supported by growing evidence. This scoring system offers clinicians a practical, noninvasive method for identifying high-risk patients and potentially optimizing management strategies to reduce the risk of subsequent adverse events.

Study Limitations

This study had several potential limitations. First, because of its retrospective nature, the authors could not evaluate more possible confounding factors (eg, socioeducational status) that may have also influenced outcomes. The duration of and patient adherence to medical treatment after discharge were not ascertained, and these crucial factors can substantially affect long-term outcomes. The current study is furthermore a single-center study, which limits its generalizability. Future research should address these limitations by including multicenter data and tracking medication adherence to provide a more comprehensive understanding of the CHA$_2$DS$_2$-VASc score's impact on prognosis and to optimize management strategies in patients with AIS.

Conclusion

The CHA$_2$DS$_2$-VASc score is a strong and independent risk predictor of 1-year MACE in patients with AIS but without AF. Increased use of the CHA$_2$DS$_2$-VASc scoring system may therefore help improve the holistic clinical assessment of AIS, even in patients without AF.

Article Information

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Author Contributions: M. Song and X. Chen conceived of the study idea and designed the study; M. Song acquired the data and performed the data analysis; M. Song drafted the manuscript; and X. Chen substantially revised the article. All authors agreed on the journal to which the article would be submitted and agree to take responsibility and be accountable for the contents of the article. M. Song and X. Chen contributed equally to this study.

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