



Predictive Value of the CHA₂DS₂-VASC Score for Mortality in Hospitalized Acute Coronary Syndrome Patients With Chronic Kidney Disease

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Background: Chronic kidney disease (CKD) patients have a high prevalence of coronary artery disease and a high risk of cardiovascular events. The present study assessed the value of the CHA₂DS₂-VASC score for predicting mortality among hospitalized acute coronary syndrome (ACS) patients with CKD.

Methods: This was a retrospective cohort study that included CKD patients who were hospitalized for ACS from January 2015 to May 2020. The CHA₂DS₂-VASC score for each eligible patient was determined. Patients were stratified into two groups according to CHA₂DS₂-VASC score: <6 (low) and ≥6 (high). The primary endpoint was all-cause mortality.

Results: A total of 313 eligible patients were included in the study, with a mean CHA₂DS₂-VASC score of 4.55 ± 1.68. A total of 220 and 93 patients were assigned to the low and high CHA₂DS₂-VASC score groups, respectively. The most common reason for hospitalization was unstable angina (39.3%), followed by non-ST-elevation myocardial infarction (35.8%) and ST-elevation myocardial infarction (24.9%). A total of 67.7% of the patients (212/313) received coronary reperfusion therapy during hospitalization. The median follow-up time was 23.0 months (interquartile range: 12–38 months). A total of 94 patients (30.0%) died during follow-up. The high score group had a higher mortality rate than the low score group (46.2 vs. 23.2%, respectively; *p* < 0.001). The cumulative incidence of all-cause death was higher in the high score group than in the low score group (Log-rank test, *p* < 0.001). Multivariate Cox regression analysis indicated that CHA₂DS₂-VASC scores were positively associated with all-cause mortality (hazard ratio: 2.02, 95% confidence interval: 1.26–3.27, *p* < 0.001).

Conclusion: The CHA₂DS₂-VASc score is an independent predictive factor for all-cause mortality in CKD patients who are hospitalized with ACS. This simple and practical scoring system may be useful for the early identification of patients with a high risk of death.

Keywords: chronic kidney disease, acute coronary syndrome (ACS), CHA₂DS₂-VASc score, prognosis, mortality

INTRODUCTION

Chronic kidney disease (CKD) is an important contributor to morbidity and mortality from non-communicable diseases and has become a considerable public health issue (1–3). Patients with CKD have a high prevalence of coronary artery disease, and many of these patients die from cardiovascular disease, especially those with acute coronary syndrome (ACS) (4, 5). The early identification of high-risk ACS patients is important for assessing prognosis and guiding treatment. Current international guidelines recommend Global Registry of Acute Coronary Events (GRACE) scores to predict the cumulative risk of death and myocardial infarction (6, 7). However, derivations of GRACE scores are based on unselected and generalizable patients, and the calculation of GRACE scores is relatively complicated (8), which may limit its application in CKD patients, especially those with end-stage renal disease. The CHA₂DS₂-VASc score is used to assess the combination of congestive heart failure, hypertension, diabetes, prior stroke, vascular disease, and age. It is an easily calculated scoring system that can assess the risk of stroke in patients with atrial fibrillation (9, 10). All of these risk factors have been proven to be associated with cardiovascular prognosis. Recent studies also used CHA₂DS₂-VASc scores to predict poor prognosis in patients with cardiovascular disease, regardless of atrial fibrillation (11–13). The risk factors that are included in this scoring system are also common in CKD patients with coronary artery disease (5, 14). The objective of the present study was to evaluate the predictive value of CHA₂DS₂-VASc scores in hospitalized ACS patients with CKD.

METHODS

Study Design and Population

This was a retrospective cohort study that included CKD patients who were hospitalized for ACS from January 2015 to May 2020. We consecutively enrolled patients in the Cardiology Department, China-Japan Friendship Hospital. Cases were identified using International Classification of Diseases-Clinical Modification code 9. All enrolled patients were confirmed to have at least one major coronary artery with more than 50% stenosis, determined by coronary angiography. Data on demographics, medical history, and laboratory tests were abstracted from electronic medical records. The glomerular filtration rate was estimated according to serum creatinine and the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI). Chronic kidney disease was defined by an estimated glomerular filtration rate <60 ml/min/1.73 m², including dialysis. Coronary reperfusion therapy included percutaneous

transluminal coronary angioplasty (PTCA) ± stenting, PTCA alone, or coronary artery bypass grafting. The study conformed to the Declaration of Helsinki and was approved by the Research Ethical Review Committee of China-Japan Friendship Hospital (2020-112-K71).

CHA₂DS₂-VASc Score

For each patient, the CHA₂DS₂-VASc score was calculated at admission based on the following scoring system: (1) point for congestive heart failure, hypertension, 65–74 years of age, diabetes mellitus, vascular disease, and female sex and (2) points for ≥75 years of age and prior stroke or transient ischemia attack. We performed a receiver operating characteristic analysis that showed that the best cut-off value of the CHA₂DS₂-VASc score to predict mortality was ≥6 with 45.7% sensitivity and 77.2% specificity [area under curve: 0.64; 95% confidence interval (CI): 0.58–0.71, *p* < 0.001; **Supplementary Material**]. Therefore, the CHA₂DS₂-VASc score was classified as <6 and ≥6. The patients were not further divided into more than these two groups because of the relatively small sample size.

Follow-Up and Outcome

The primary outcome of the study was all-cause mortality, which was the rate of death from any cause from the date of admission until the occurrence of endpoint events or until the latest follow-up date (June 1–July 1, 2021). Clinical events were ascertained by longitudinally tracking patients' medical records or through telephone interviews.

Statistical Analysis

Continuous variables are expressed as the mean ± standard deviation or median and interquartile range and compared using *t*-tests or the Mann-Whitney *U*-test when appropriate. Categorical variables are expressed as frequencies and percentages and were compared using the χ^2 -test or Fisher's exact test. Univariate and multivariate Cox regression analyses were performed to determine risk factors for all-cause death, and the hazard ratio (HR) and 95% CI were calculated. Variables with values of *p* < 0.10 in the univariate analysis were included in the multivariate analysis. Time-dependent survival between groups was evaluated using Kaplan-Meier curves and the Log-rank test. Stratified analyses were performed using the following variables: age (≥65 vs. <65 years), sex, hyperlipidemia, diabetes, prior myocardial infarction, hemodialysis, main diagnosis, left ventricular ejection fraction (≥50 vs. <50%), and reperfusion therapy. Multiplicative interactions were calculated in each subgroup. All statistical analyses were performed using SPSS 27.0 software (IBM Corp., Armonk, NY, USA). Two-tailed values of *p* < 0.05 were considered statistically significant.

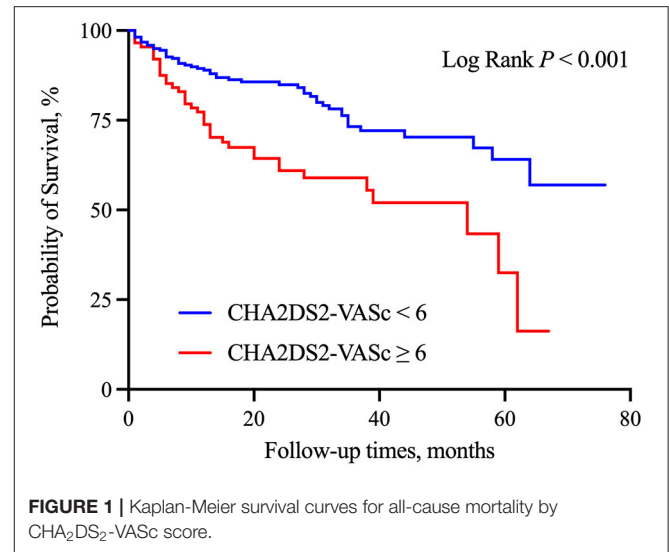
TABLE 1 | Baseline characteristics in CKD patients hospitalized with ACS by CHA₂DS₂-VASC score.

Characteristic	Total (N = 313)	CHA ₂ DS ₂ -VASC score (N = 313)		P-value
		<6 (N = 220)	≥6 (N = 93)	
Age, yrs	69.8 ± 11.2	67.7 ± 11.3	74.6 ± 9.2	<0.001
Male sex	128 (40.9)	90 (34.5)	38 (55.9)	<0.001
BMI (kg/m ²)	24.9 ± 4.8	24.7 ± 3.99	25.2 ± 6.3	0.410
Medical history				
Hypertension	274 (87.5)	185 (84.1)	89 (95.7)	0.004
Diabetes mellitus	179 (57.2)	105 (47.7)	74 (79.6)	<0.001
Hyperlipidemia	173 (55.3)	111 (50.5)	62 (66.7)	0.008
Congestive heart failure	164 (52.4)	96 (43.6)	68 (73.1)	<0.001
Prior stroke or TIA	102 (32.6)	35 (15.9)	67 (72.0)	<0.001
Prior MI	85 (27.2)	56 (25.5)	29 (31.2)	0.300
Prior PCI	80 (25.6)	48 (21.8)	32 (34.4)	0.020
Prior CABG	17 (5.4)	10 (4.5)	7 (7.5)	0.290
Peripheral artery disease	57 (18.2)	29 (13.2)	28 (30.1)	<0.001
Stage of CKD				0.690
Stage 3	136 (43.5)	93 (42.6)	43 (46.2)	
Stage 4	47 (15.0)	32 (14.6)	15 (16.1)	
Stage 5	129 (41.2)	94 (42.9)	43 (46.2)	
Clinical presentation				0.820
STEMI	78 (24.9)	57 (25.9)	21 (22.6)	
NSTEMI	112 (35.8)	78 (35.5)	34 (36.6)	
UA	123 (39.3)	85 (38.6)	38 (40.9)	
Laboratory measures				
Hemoglobin, g/dl	112.6 ± 121.6	114.8 ± 21.8	107.2 ± 20.5	0.004
Platelet count, ×10 ⁹ /l	194 ± 61	194.3 ± 59.7	189.8 ± 63.1	0.520
LDL, mmol/l	2.5 ± 0.9	2.59 ± 0.88	2.33 ± 0.99	0.005
Serum creatinine, mg/dl	4.33 ± 3.73	4.61 ± 3.94	3.66 ± 3.11	0.110
Uric acid	408 ± 134	404 ± 133	419 ± 136	0.380
Homocysteine, μmol/l	23.6 ± 26.3	24.0 ± 21.4	22.7 ± 35.5	0.007
D-dimer, mg/l	1.30 ± 1.78	1.28 ± 1.93	1.33 ± 1.38	0.060
LVEF	55 ± 12	55 ± 11	55 ± 13	0.450
Reperfusion therapy	212 (67.7)	156 (70.9)	56 (60.2)	0.060
Medical therapy at admission				
Aspirin	301 (96.2)	211 (95.9)	90 (96.8)	0.720
P2Y ₁₂ receptor antagonist	297 (94.9)	208 (94.5)	89 (95.7)	0.670
Statin	303 (96.8)	213 (96.8)	90 (96.8)	0.980
β-blockers	286 (91.4)	201 (91.4)	85 (91.4)	0.990

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; CABG, coronary artery bypass grafting; LDL, Low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attacks; UA, unstable angina.

RESULTS

A total of 313 eligible patients were recruited in the study. Baseline characteristics are presented in **Table 1**. Among these patients, the mean CHA₂DS₂-VASC score was 4.55 ± 1.68. A total of 220 patients (70.3%) had a low CHA₂DS₂-VASC score (<6

**FIGURE 1** | Kaplan-Meier survival curves for all-cause mortality by CHA₂DS₂-VASC score.

points), and 93 (29.7%) had a high CHA₂DS₂-VASC score (≥6 points). The high CHA₂DS₂-VASC score group included patients who were older and had a higher prevalence of comorbidities, including diabetes mellitus, heart failure, and cerebrovascular disease. Patients who were diagnosed with non-ST-elevation myocardial infarction (35.8%) and unstable angina pectoris (39.3%) were more common than patients who were diagnosed with ST-elevation myocardial infarction (24.9%). Among the 313 patients, 67.7% (212) received coronary reperfusion therapy, including PTCA ± stenting ($n = 187$), PTCA ($n = 15$), and coronary artery bypass grafting ($n = 10$). Accordingly, in-hospital treatment was comparable between the two groups.

The median follow-up time was 23.0 months (interquartile range: 12–38 months). During the follow-up period, a total of 94 patients (30.0%) died. High CHA₂DS₂-VASC scores were associated with a higher risk of mortality (46.2 vs. 23.2%, $p < 0.001$). Kaplan-Meier curves for patients who were stratified by CHA₂DS₂-VASC scores are presented in **Figure 1**. The cumulative incidence of all-cause mortality (Log-rank test, $p < 0.001$) was higher in the high CHA₂DS₂-VASC score group than in the low CHA₂DS₂-VASC score group. We performed Cox univariate and multivariate analyses using the low CHA₂DS₂-VASC score group as the reference group. The HR for all-cause mortality was 2.49 (95% CI: 1.66–3.74, $p < 0.001$). After adjusting for hypertension, diabetes, prior myocardial infarction, and CKD stage, the HR of all-cause mortality was 2.029 (95% CI: 1.33–3.10, $p = 0.001$). The HR of all-cause mortality was largely unchanged after adding all other variables with $p < 0.10$ in the univariate analysis (HR: 2.027, 95% CI: 1.26–3.27, $p < 0.001$). The univariate analysis of factors that were related to all-cause mortality is presented in **Table 2**. The multivariate analyses between the CHA₂DS₂-VASC score group and outcomes are shown in **Table 3**. A significant between-group difference in outcome was found in the subgroup analyses of sex [HR: 2.94 (95% CI: 1.66–5.21) for men; HR: 1.91 (95% CI: 1.00–3.61) for women; $p = 0.045$]. A similar result was found for death in the subgroup analyses of

TABLE 2 | Cox regression analysis of factors related to all-cause mortality.

Parameter	Univariate (all-cause mortality)	
	HR (95% CI)	P-value
Age ^a	1.02 (1.00–1.04)	0.024
Male sex (vs. Female)	0.98 (0.65–1.47)	0.920
BMI ^b	0.79(0.53–1.19)	0.260
Prior PCI	1.13 (0.72–1.78)	0.590
Prior CABG	1.38 (0.60–3.16)	0.470
Stage of CKD		
Stage 3	1 (ref)	..
Stage 4	1.72 (1.11–2.67)	0.015
Stage 5	2.12 (1.14–4.31)	0.019
Diagnosis		
UA	1 (ref)	..
NSTEMI	1.30 (0.76–2.25)	0.340
STEMI	1.80 (1.12–2.89)	0.015
Hemoglobin, g/dl	0.990 (0.981–0.999)	0.027
Platelet count, ×10 ⁹ /l	0.998 (0.994–1.000)	0.180
LDL, mmol/l	0.87 (0.69–1.10)	0.250
Uric acid, μmol/l	0.999 (0.998–1.001)	0.360
Serum creatinine, mg/dl	1.04 (0.98–1.09)	0.180
Homocysteine, μmol/l	1.004 (0.999–1.010)	0.100
D-dimer, mg/l	1.08 (1.00–1.164)	0.041
LVEF (≥50 vs. <50)	0.74 (0.48–1.13)	0.160
Reperfusion therapy	0.68 (0.45–1.04)	0.070
Aspirin	1.24 (0.39–3.93)	0.710
P2Y12 receptor antagonist	1.55 (0.49–4.88)	0.460
Statin	1.58 (0.38–6.43)	0.520
β-blockers	1.37 (0.60–3.15)	0.450
ACEI/ARB	1.58 (0.39–6.43)	0.520
CHA ₂ DS ₂ -VASC score ^c ≥ 6	2.48 (1.65–3.73)	<0.001

^aPer 1 unit increase.

^bBMI ≥ 24 kg/m² vs. BMI < 24 kg/m².

^cCHA₂DS₂-VASC score ≥ 6 score vs. CHA₂DS₂-VASC score < 6 score.

ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; BMI, body mass index; CKD, chronic kidney disease; CABG, coronary artery bypass grafting; LDL, Low-density lipoprotein; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NSTEMI, non-ST-segment elevation myocardial infarction; STEMI, ST-segment elevation myocardial infarction; TIA, transient ischemic attacks; UA, unstable angina.

hemodialysis. No significant interactions were found between the other subgroups and CHA₂DS₂-VASC scores for the prediction of all-cause mortality. The results of the subgroup analyses are shown in **Figure 2**.

DISCUSSION

The present study found that CHA₂DS₂-VASC scores were associated with worse clinical outcome in CKD patients with ACS. High scores (≥6) were an independent predictor of all-cause mortality and may be useful for risk stratification. The subgroup analyses indicated that high scores were a slightly better predictor of all-cause mortality in men than in women and in patients who did not undergo hemodialysis. Compared

TABLE 3 | Adjusted hazard ratios of all-cause mortality by high CHA₂DS₂-VASC score (≥6 points) relative to low CHA₂DS₂-VASC score (<6 points).

Model adjustment	All-cause mortality	
	HR (95% CI)	P-value
Unadjusted	2.49 (1.66–3.74)	< 0.001
Model 1	2.49 (1.66–3.74)	< 0.001
Model 2	2.029 (1.33–3.10)	0.001
Model 3	2.027 (1.26–3.27)	0.004

Model 1, adjusted for age, sex; Model 2, adjusted for age, sex, hypertension, diabetes, prior MI, stage of CKD; Model 3, adjusted for age, sex, hypertension, diabetes, Hyperlipidemia, prior MI, stage of CKD, diagnosis, Cr, LVEF, reperfusion therapy and medication therapy at admission.

HR, hazard ratios; CI, confidence interval.

with patients with low scores, patients with high scores were more often older and women and had a higher prevalence of comorbidities. Additionally, patients with high scores were less likely to receive reperfusion therapy in clinical practice.

Acute coronary syndrome is a common critical cardiovascular disease and primary focus of cardiologists. Benefiting from the application of stents, the mortality rate of ACS has gradually decreased over the past decade (15). Patients with coronary disease and CKD, especially end-stage kidney disease, have a very high risk of cardiovascular events (16, 17). The high rate of all-cause mortality in the present study aligns with the high-risk feature of these patients in previous studies. Despite having worse outcomes after a cardiovascular event, patients with CKD are often excluded from the majority of ACS or heart failure cardiovascular outcome trials (18). The reasons for this are likely multifactorial, such as the potential for diminished effects of medical treatment and coronary intervention in trials, complex pathophysiological mechanisms that contribute to cardiovascular disease, safety concerns, and trial recruitment difficulties (19). Therefore, clinical evidence from the general population may not be suitable for this specific patient population. The Framingham risk score is the most well-validated coronary artery disease risk prediction tool, but it has been shown to have poor overall accuracy in predicting cardiac events in individuals with CKD (20). Data from GRACE indicated that the GRACE risk score underestimates the risk of major events in end-stage kidney disease patients who undergo dialysis (21). Moreover, the inclusion of multiple types of variables and relatively complex calculation significantly limit clinical utility of the GRACE risk score (8).

The CHA₂DS₂-VASC score is a validated and extensively used score to estimate thromboembolic risk in patients with atrial fibrillation, consisting of several cardiovascular risk factors (9). Among these factors, old age, hypertension, diabetes, and heart failure have been proven to influence the prognosis of cardiovascular disease (4, 5, 22–24). Prior stroke is also associated with a high risk of major adverse cardiovascular and cerebrovascular events (25). Sex differences in the epidemiology, manifestation, pathophysiology, and outcome of cardiovascular disease have been observed in previous studies (26). Therefore, all

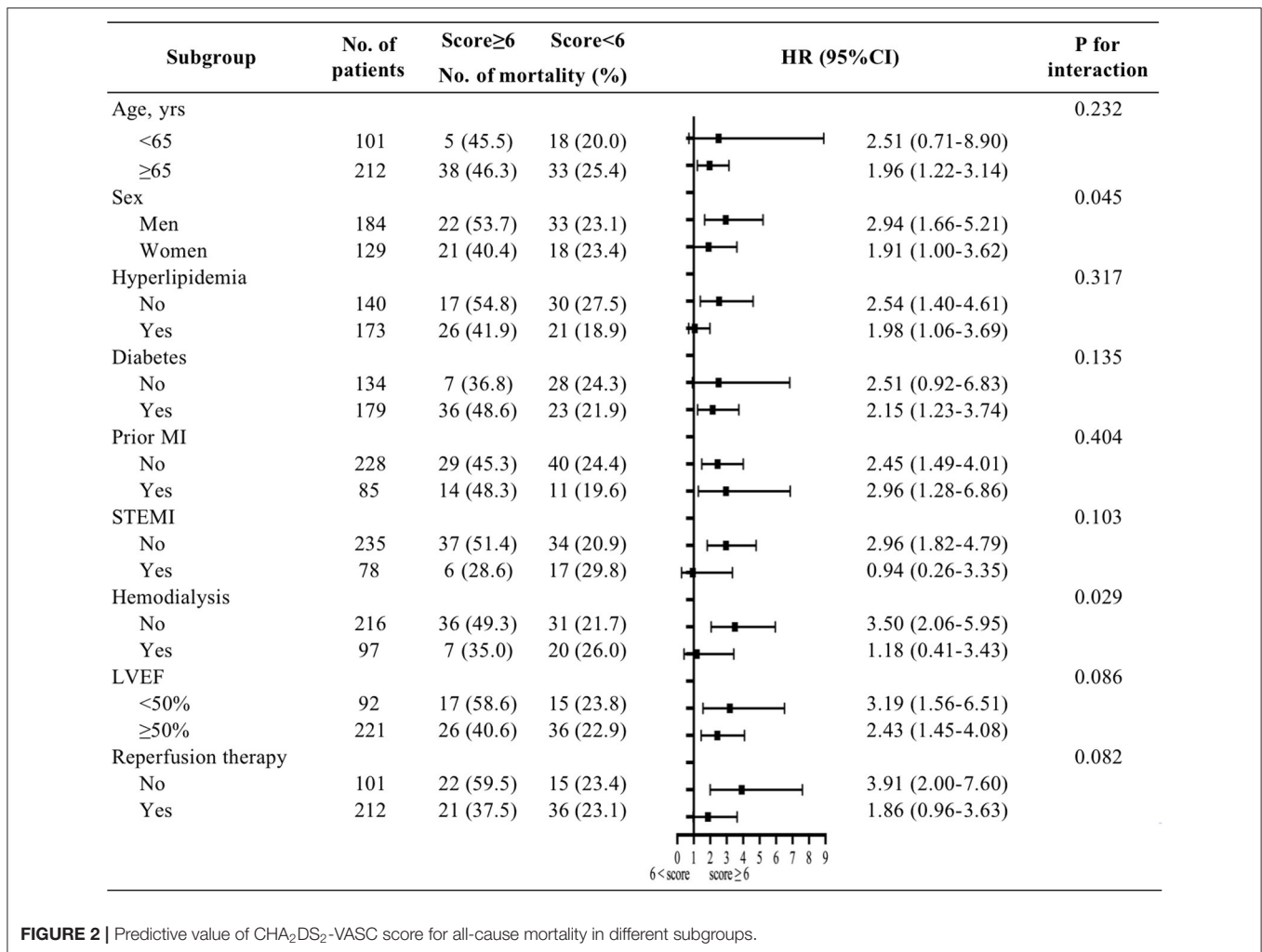


FIGURE 2 | Predictive value of CHA₂DS₂-VASC score for all-cause mortality in different subgroups.

components of the CHA₂DS₂-VASC score have a close association with the prognosis of cardiovascular disease. Tufan Cinar et al. evaluated 267 patients with mechanical mitral valve thrombosis and found that a CHA₂DS₂-VASC score ≥ 2.5 was associated with a higher risk of prosthetic valve thrombosis (27). Several recent studies evaluated the predictive value of the CHA₂DS₂-VASC score for clinical outcome. A large real-world cohort study reported that CHA₂DS₂-VASC scores were significantly associated with mortality in heart failure patients (11). Hsu et al. reported the predictive value of CHA₂DS₂-VASC scores for all-cause mortality and cardiovascular mortality in CKD patients without ACS (28). A similar study found that CHA₂DS₂-VASC scores were strongly associated with 1-year mortality and cardiovascular risk in hemodialysis patients (29). Studies that investigated patients with ST-elevation myocardial infarction showed that CHA₂DS₂-VASC scores were an independent predictor of no-reflow and an independent predictor of in-hospital and long-term mortality in patients who underwent primary percutaneous coronary intervention (30–32). Although the association between CHA₂DS₂-VASC score and clinical outcome in ACS patients without CKD or CKD patients without

ACS have been estimated, the value of these scores in ACS patients with CKD is unclear. In the present study, we found a significant association between CHA₂DS₂-VASC scores and all-cause mortality in ACS patients with CKD, which may be useful for the risk stratification of these patients. The mean CHA₂DS₂-VASC score in the present study was significantly higher than in patients without CKD in a previous study, which may help explain the high mortality in ACS patients with CKD. Variables that are included in the CHA₂DS₂-VASC score can be readily found in patients' medical histories. Furthermore, CHA₂DS₂-VASC scores may be useful for quickly identifying very high-risk ACS patients with CKD.

The present study has limitations. This was a single-center, retrospective study. We were unable to control the variables that were included in the analyses given the study's observational design. In addition to traditional cardiovascular risk factors (e.g., diabetes and hypertension), non-traditional CKD-related CVD risk factors (e.g., mineral and bone disease abnormalities, vascular calcification, inflammation, and oxidative stress) may also play an important role in the prognosis of cardiovascular disease (4). However, we focused on the prognostic value of the

CHA₂DS₂-VAsC scoring system in ACS patients with CKD, based on variables that were readily obtained from the patients' medical records. Another limitation was that the sample size was not sufficiently large to evaluate prognostic value in dialysis and non-dialysis populations separately. Future studies should integrate CHA₂DS₂-VAsC scores with non-traditional CKD-related CVD risk factors and develop and validate novel CVD risk prediction scores for the CKD population and dialysis population.

In conclusion, CHA₂DS₂-VAsC scores were an independent predictive factor for mortality in ACS patients with CKD. The CHA₂DS₂-VAsC scoring system is a simple and practical method for identifying very high-risk ACS patients among the CKD population. Further studies are needed to evaluate whether CHA₂DS₂-VAsC scoring can improve the management and outcome of this high-risk population.

DATA AVAILABILITY STATEMENT

The raw data supporting the conclusions of this article will be made available by the authors, without undue reservation.

ETHICS STATEMENT

The studies involving human participants were reviewed and approved by the Research Ethical Review Committee of China-Japan Friendship Hospital. Written informed consent for participation was not required for this study in accordance with the national legislation and the institutional requirements.

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AUTHOR CONTRIBUTIONS

YW, JR, and JZ: study design and manuscript preparation. YG, QL, CW, EX, YT, ZG, ZY, PL, YL, and XY: data collection. YW and YG: data analysis and interpretation. All authors contributed to the article and approved the submitted version.

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SUPPLEMENTARY MATERIAL

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