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The Association Between High CHA_2DS_2-VASc Scores and Short and Long-Term Mortality for Coronary Care Unit Patients

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Abstract

Background: The CHA_2DS_2-VASc score has been associated with the prognosis of cardiovascular diseases. This study aimed to explore the association between the CHA_2DS_2-VASc score and all-cause mortality in coronary care unit (CCU) patients.

Methods: The study was based on the Medical Information Mart for Intensive Care (MIMIC) III database. CCU patients were divided into two groups according to CHA_2DS_2-VASc score: 0-3 (low risk), 4-9 (intermediate and high risk). The primary outcome was 30-day mortality, and the secondary endpoints included in-hospital, 1-year, and 5-year mortality. Propensity score matching (PSM) and sensitivity analyzes for the confounders were also performed. The restricted cubic splines flexibility model was used to demonstrate the relation between red blood cell volume distribution width (RDW), blood urea nitrogen (BUN), platelet, white blood cell (WBC), hemoglobin, phosphorus, glucose, potassium, sodium and 30-day mortality in the 0-3 score versus the 4-9 score groups after PSM.

Results: Among 4491 eligible patients, 988 patients with low CHA_2DS_2-VASc scores and 988 patients with intermediate and high CHA_2DS_2-VASc scores had similar propensity scores and were included in the analyzes. In the survival analysis, the patients with intermediate and high CHA_2DS_2-VASc scores were associated with higher 30-day mortality [hazard ratio (HR): 1.11; 95% confidence interval (CI), 1.02–1.20, $P = .014$], 1-year mortality [HR: 1.13; 95%CI, 1.06–1.19, $P < .001$], and 5-year mortality [HR: 1.13; 95%CI, 1.07–1.18, $P < .001$]. The interaction for 30-day mortality among subgroups was not significant between the 0-3 score versus the 4-9 score groups. The restricted cubic splines for 30-day mortality demonstrated an L-shaped trajectory for platelets and hemoglobin, a J-shaped trajectory for WBC, glucose and potassium, and a U-shaped trajectory for sodium, respectively (all nonlinear $P < .001$).

Conclusions: A high CHA_2DS_2-VASc score was an independent risk for 30-day, 1-year, and 5-year mortality for CCU patients.

Keywords

CHA_2DS_2-VASc score, Propensity score matching, Coronary care unit, Mortality

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Introduction

Originating in the 1960s, the coronary care unit (CCU), which is now a comprehensive system designed for patients with advanced cardiovascular disease, has undergone tremendous evolution. Although mortality rates in CCU have declined remarkably from 30-40% to approximately 5% over the past 50 years,[1] cardiovascular disease remains the leading cause of mortality all over the world. Thus, a simple and practical scoring system is required to facilitate prognostic stratification and develop preventive strategies for CCU patients.

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All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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The CHA_2DS_2-VASc score was published in 2010[2] and accounts for congestive heart failure, hypertension, age 65–74 years, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral artery disease, or aortic plaque], and female [1 point each]; and age ≥75 years and prior stroke/transient ischemic attack (TIA)/thromboembolism [2 points each]. It was initially widely employed to predict the risk of thromboembolism in patients with non-valvular atrial fibrillation (AF) and to guide the need for anticoagulant therapy.[3] Additionally, AF and other cardiovascular diseases share common risk factors, which are part of the components of the CHA_2DS_2-VASc score. Thus, several studies explored the predictive value of the CHA2DS2–VASc score in patients with cardiovascular diseases such as heart failure,[4,5] acute coronary syndrome[6] (ACS), valvular heart disease[7] (VHD) and thromboembolic events[8] (TE). However, the prognostic value of this score in CCU patients remains unclear. The purpose of the present study is to evaluate the association between CHA_2DS_2-VASc and all-cause mortality in a large real-world cohort of CCU patients.

Method

Data Source and Extraction

The data presented in this study was extracted from Medical Information Mart for Intensive Care III[9,10] (MIMIC-III, version 1.4), which is comprised of identified health-related data from over 50 000 patients who stayed in critical care units of the Beth Israel Deaconess Medical Center from 2001 to 2012.[10] In order to protect the privacy of patients, all personal information was deleted. The study data, including patient demographics, common coexisting conditions, birth and death, CCU admission and discharge information, laboratory data, and medication, were extracted by author L.C. The author had passed an online training course from the National Institutes of Health (certification number : 9046642) and obtained permission to access the MIMIC-III database. The study protocol conformed to the 1975 Declaration of Helsinki. Data extraction was performed using pgAdmin4 PostgreSQL 9.6.

Participants and Definitions

As shown in Figure S1, all adult patients (≥18 years) and only the first admitted to CCU were analyzed from the MIMIC-III database. Exclusion criteria: (1) more than 89 years old, (2) duration of CCU stay < 24 h. The CHA_2DS_2-VASc score was calculated by assigning 2 points for age≥75 and history of stroke, transient ischemic attacks, or thromboembolism and 1 point for congestive heart failure, hypertension, diabetes mellitus, age 65–75 years, vascular disease and female sex. The components of this score were collected from materialized views, including views/summaries of the data in MIMIC-III, eg, demographics, organ failure scores, the severity of illness scores, durations of treatment, etc The relevant information was extracted on the PostgreSQL software. The sum of all items resulted in a final score between 0 and 9 points. Patients were divided into 2 groups based on their CHA2DS2-VASc scores: 0–3 score (low risk, n = 3206), 4–9 score (intermediate and high risk, n = 1285). The follow-up was started from the date of admission. In addition, laboratory data were calculated as the average values of data collected on the first day of admission after admission. The primary outcome was 30-day mortality, and the secondary outcomes included in-hospital, 1-year, and 5-year mortality . All human studies have been approved by the appropriate ethics committee and were performed in accordance with the ethical standards laid down in the 1964 Declaration of Helsinki and its later amendments.

Statistical Analysis

For the baseline characteristics, continuous variables with normal distribution were presented as mean ± standard deviation (SD). The means of continuous variables were compared using an independent-sample t-test. Variables with skewed distribution were expressed as median and interquartile range and the Mann-Whitney test was used for comparison. Categorical variables were expressed as proportions or percentages and were tested using the χ^2 or fisher's exact test. The continuous variables with more than 2% missing data were excluded.

To minimize bias between the two groups, propensity score matching (PSM) was performed without replacement and with a caliper width of 0.2 in the pooled SD of the logit of the propensity score according to baseline factors at a 1:1 ratio. An absolute standardized difference (ASD)<20% for the measured covariate suggests an appropriate balance between groups. For the matched cohort, sensitivity analyzes were performed by assuming unmeasured confounders that might result in different magnitudes of bias and exploring their effects on 30-day mortality.[11] After PSM, survival analysis was performed to estimate whether the CHA_2DS_2-VASc score predicted 30-day mortality. The effect of the CHA_2DS_2-VASc score was presented as a hazard ratio (HR) with a 95% confidence interval (CI). Kaplan–Meier curves with the log-rank test were used to compare survival according to the CHA_2DS_2-VASc score. A stratification analysis was conducted to explore whether the association between the CHA_2DS_2-VASc score and 30-mortality differed across various subgroups classified by sepsis, AF/ AFL, ethnicity, comorbidities, vasoactive drug use, diuretic use, proton pump inhibitor (PPI) use and so on. Moreover, the restricted cubic splines (RCS) were used to visualize the association between RDW,[12] BUN,[13] platelet,[14] WBC,[15] hemoglobin,[16,17] phosphorus,[18] glucose,[19] potassium,[20] sodium[21] and 30-day mortality in the 0-3 score versus the 4-9 score groups after PSM. The number of knots was set to four, located at the fifth, 35th, 65th, and 95th percentiles according to both Harrell recommendations.[22,23] The Wald test was used to estimate the presence of nonlinearity. All analyzes were performed using STATA MP Version 16.0 (Stata-Corp, College Station, TX) and 2-side $P < .05$ was considered statistically significant.

Results

Clinical and Laboratory Characteristics

A total of 4491 participants were ultimately included in the analysis after screening the inclusion and exclusion criteria. Vital signs, laboratory results and comorbidities were summarized based on the CHA_2DS_2-VASc score and presented in Table 1. Before PSM, the low-risk score and intermediate and high-risk score groups comprised 3206 (71.38%) patients and 1285 (28.62%) patients, respectively. As expected, the patients in the intermediate and high-risk score group were older (61.92 vs 77.97; $P < .001$) and included more females (30.47% vs 66.61%; $P < .001$). Compared with the low-risk group, the intermediate and high-risk group had higher rates of comorbidity, including diabetes, hypertension, AF/AFL, coronary heart disease (CHD), respiratory failure, hyperlipidemia, congestive heart failure (CHF), valvular heart disease (VHD), cardiac arrhythmias, anemia, prior stroke or TIA or TE, chronic obstructive pulmonary disease (COPD), renal failure, hypothyroidism, depression, rheumatoid arthritis, sepsis, OASIS, SAPSII, SOFA except for psychoses, liver disease, alcohol and drug abuse. In addition, patients with intermediate and high-risk CHA_2DS_2-VASc scores had significantly higher BUN (23.98 vs 34.29; $P < .001$), RDW (14.57 vs 15.18; $P < .001$), and glucose (138.33 vs 151.82; $P < .001$). Conversely, the hemoglobin level was higher in the low-risk group. There were no statistically significant differences in obesity, ethnicity, white blood cell count, and platelet count. After PSM, the difference between the two groups was significantly reduced.

Pharmacological Therapy

Detailed data regarding pharmacological therapy in hospitalized patients are shown in Table 2. Except for angiotensin-converting enzyme inhibitors (ACEI)/ angiotensin receptor blocker (ARB) and digoxin, specific CCU treatment was more frequently used in patients with intermediate and high-risk CHA_2DS_2-VASc scores.

After PSM, similar patterns regarding the use of medications were observed between the two groups.

Outcomes

After matching, 30-day mortality was 18.32% among patients with intermediate and high-risk scores compared to 14.78% for patients with low-risk scores ($P = .037$) (Table 3). Similarly, the intermediate and high-risk score group had a significantly higher 1-year mortality (29.45% vs 33.81%, $P = .035$) and 5-year mortality (42.71% vs 49.60%, $P = .006$). However, the incidence of in-hospital mortality did not show a statistically significant difference. To further investigate the relationship between CHA2DS2-VASc score and all-cause mortality, a survival analysis was performed. As shown in Figure 1, the intermediate and high-risk score group was associated with the improved 30-day (HR: 1.11; 95% CI, 1.02-1.20, Log-rank $P = .014$), 1-year (HR: 1.13; 95% CI, 1.06-1.19, Log-rank $P < .001$) and 5-year mortality (HR: 1.13; 95% CI, 1.07-1.18, Log-rank $P < .001$).

Subgroup Analyses

The results of subgroup analyzes for 30-day mortality are shown in Figure 2. The association between the CHA_2DS_2-VASc score and 30-day mortality was consistent across the subgroups. There was no statistically significant heterogeneity between the CHA_2DS_2-VASc score and the 30-day mortality across the subgroups (P for interaction$\geq .05$ for all).

Restricted Cubic Spline Plots

Based on the stratification of the CHA_2DS_2-VASc score, the RCS model was used to simulate the relationship between several laboratory results and HR for 30-day mortality (Figure 3). After PSM, the trend of 30-day mortality for these laboratory parameters was similar between the two groups except for WBC. The risk of 30-day mortality was relatively flat at the low end of the serum phosphorus levels but increased rapidly after 3mg/dL. A typical J-type curve was observed for the association between serum phosphorus and 30-day mortality (Figure 3F). A similar non-linear shape was observed for serum potassium (Figure 3H). Patients demonstrated the lowest risk of 30-day mortality with serum sodium levels around 140mEq/L. Both lower and higher values were associated with increased risks of 30-day mortality, illustrated by a U-shaped curve (Figure 3I). Similarly, a pronounced U-shape was also found between serum glucose and 30-day mortality. Serum glucose levels around 120mg/dL demonstrated the lowest risk for 30-day mortality (Figure 3G). Moreover, results from the RCS model suggested that higher platelet (Figure 3C) and hemoglobin (Figure 3E) levels had higher 30-day mortality in both groups, especially in the intermediate and high-risk CHA_2DS_2-VASc score group. The relationship was characterized by a typical L-curve. At the 30-day follow-up, higher levels of RDW (Figure 3A) and BUN (Figure 3B) were associated with increased risk of mortality in both groups. Furthermore, the HR for 30-day mortality increased in parallel from the first to the fourth quartiles of RDW [HRs: 0.699 (95%CI:0.422,1.159), 0.919 (95%CI:0.643,1.314), 0.967(95% CI:0.914,1.023), 1.451 (95%CI:1.101,1.913)] and BUN [HRs: 0.592 (95%CI: 0.318,1.103), 2.100 (95%CI:1.538,2.868), 3.882 (95% CI:2.649, 5.649), 8.233 (95%CI:4.649,14.579)], respectively. In all these subgroup analyzes, no significant differences were observed between the 0-3 score group versus 4-9 score group (all P for interaction≥ 0.05). Collectively, HRs of WBC for 30-day mortality in both groups were lower at the lower levels, then increased rapidly between 9 and 16 K/μL. Notably, the association was more pronounced in individuals with a low CHA_2DS_2-VASc score group (Figure 3D) for WBC values over 27K/μL. Detailed data on knots (fifth,35th,65th,95th), HRs and 95%CI are presented in Table S1 and Table S2.

Table1. Baseline Characteristics Before and After Propensity-Score Matching.

	Before matching			After matching		
Item	Low Risk 0-3 (n = 3206)	Intermediate and High Risk 4-9 (n = 1285)	*P* value	Low Risk 0-3 (n = 988)	Intermediate and High Risk 4-9 (n = 988)	*P* value
CHA_2DS_2-VASc score, (x ± s)	1.81 ± 1.01	4.57 ± 0.81	<.001	2.23 ± 0.90	4.45 ± 0.73	<.001
Age (years)	61.92 ± 14.48	77.97 ± 7.61	<.001	66.98 ± 13.00	77.78 ± 7.78	<.001
Female, n(%)	977(30.47)	856(66.61)	<.001	381(38.56)	670(67.81)	<.001
Admission type, n(%)			.037			.701
Elective	183(5.71)	70(5.45)		58(5.87)	50(5.06)	
Emergency	2830(88.27)	1162(90.43)		888(89.88)	893(90.38)	
Urgent	193(6.02)	53(4.12)		42(4.25)	45(4.55)	
Race/ethnicity, n(%)			.254			.780
White	2201(68.65)	899(69.96)		679(68.72)	677(68.52)	
Black	216(6.74)	87(6.77)		66(6.68)	73(7.39)	
Asian	57(1.78)	16(1.25)		12(1.21)	10(1.01)	
Hispanic/Latino	70(2.18)	17(1.32)		18(1.82)	12(1.21)	
Other	662(20.65)	266(20.70)		213(21.56)	216(21.86)	
Obesity, n(%)	155(4.83)	49(3.81)	.137	41(4.15)	37(3.74)	.644
SBP (mm Hg)	115.39 ± 16.27	117.42 ± 18.17	<.001	116.27 ± 17.18	115.99 ± 17.78	.726
DBP (mm Hg)	62.78 ± 10.96	56.47 ± 10.06	<.001	58.97 ± 11.17	57.57 ± 10.00	.003
Pluses (beats per minute)	80.14 ± 16.39	78.58 ± 15.53	.023	80.36 ± 16.72	79.08 ± 15.89	.079
Urine output (mL)	2203.55 ± 1327.90	1733.71 ± 1077.25	<.001	1908.97 ± 1188.56	1807.95 ± 1093.15	.049
Diabetes mellitus, n(%)	660(20.59)	679 (52.84)	<.001	247(25.00)	507(51.32)	<.001
Hypertension, n(%)	180(5.61)	413(32.14)	<.001	120(12.15)	221(22.37)	<.001
Active smokers, n(%)	162(5.05)	100(7.78)	<.001	73(7.39)	67(6.78)	.599
Alcohol abuse, n(%)	159(4.96)	11(0.86)	<.001	25(2.53)	11(1.11)	.019
Drug abuse, n(%)	89(2.78)	6(0.47)	<.001	14(1.42)	6(0.61)	.072
AF/AFL, n(%)	818(25.51)	481(37.43)	<.001	315(31.88)	352(35.62)	.087
CHD,n(%)	1484(46.29)	863(67.16)	<.001	433(43.83)	674(68.22)	<.001
Respiratory failure, n(%)	321(10.01)	158(12.30)	.025	131(13.26)	106(10.73)	.083
Hyperlipidemia, n(%)	711(22.18)	409(31.83)	<.001	275(27.83)	292(29.55)	.398
CHF, n(%)	163(5.08)	257(20.00)	<.001	70(7.09)	171(17.31)	<.001
VHD, n(%)	61(1.90)	75(5.84)	<.001	35(3.54)	34(3.44)	.902
Cardiac arrhythmias, n(%)	191(5.96)	171(13.39)	<.001	97(9.82)	102(10.32)	.709
Anemia, n (%)	466(14.54)	350(27.24)	<.001	213(21.56)	214(21.66)	.956
Prior stroke or TIA or TE, n(%)	71(2.21)	209(16.26)	<.001	12(1.21)	175(17.71)	<.001
COPD, n(%)	560(17.47)	300(23.35)	<.001	213(21.56)	228(23.08)	.418
Renal failure, n(%)	285(8.89)	436(33.93)	<.001	212(21.46)	228(23.08)	.387
Hypothyroidism, n(%)	247(7.70)	200(15.56)	<.001	124(12.55)	132(13.36)	.592
Depression, n(%)	203(6.33)	86(6.69)	.656	69(6.98)	67(6.78)	.859
Psychoses, n(%)	109(3.40)	25(1.95)	.010	24(2.43)	22(2.23)	.765
Rheumatoid arthritis, n(%)	68(2.12)	45(3.50)	.008	28(2.83)	32(3.24)	.600
Liver disease, n(%)	112(3.49)	25(1.95)	.006	34(3.44)	22(2.23)	.104
Sepsis, n(%)	86(2.68)	57(4.44)	.002	37(3.74)	39(3.95)	.815
PTCA, n(%)	550(17.16)	280(21.79)	<.001	180(18.22)	194(19.64)	.421
DES/ non-DES, n(%)	1075(33.53)	427(33.23)	.847	316(31.98)	333(33.70)	.415
Coronary arteriography, n(%)	1561(48.69)	630(49.03)	.838	462(46.76)	493(49.90)	.163
Severity scores						
OASIS	27.99 ± 8.61	31.85 ± 8.88	<.001	29.70 ± 8.97	31.47 ± 8.76	<.001
SAPSII	31.05 ± 13.41	39.92 ± 13.14	<.001	34.74 ± 13.58	39.24 ± 13.12	<.001
SOFA	3.05 ± 2.74	3.94 ± 2.89	<.001	3.66 ± 2.92	3.72 ± 2.86	.651
Blood urea nitrogen (mg/dL)	23.98 ± 17.10	34.29 ± 21.01	<.001	29.80 ± 20.89	30.94 ± 18.59	.199
Hemoglobin (g/dL)	11.86 ± 1.79	10.77 ± 1.36	<.001	11.13 ± 1.62	10.97 ± 1.39	.019
White blood cell count (K/μL)	10.37 ± 4.19	10.56 ± 5.16	.545	10.42 ± 4.68	10.50 ± 5.46	.699
RDW(%)	14.57 ± 1.83	15.18 ± 1.73	<.001	15.06 ± 2.03	15.05 ± 1.68	.927
Glucose (mg/dL)	138.33 ± 49.38	151.82 ± 53.52	<.001	143.69 ± 55.90	150.77 ± 54.56	.004

(continued)

Table1. (continued)

Item	Before matching			After matching		
	Low Risk 0-3 (n = 3206)	Intermediate and High Risk 4-9 (n = 1285)	*P* value	Low Risk 0-3 (n = 988)	Intermediate and High Risk 4-9 (n = 988)	*P* value
Platelet count (K/μL)	233.90 ± 90.55	230.58 ± 90.97	.268	229.43 ± 88.80	231.01 ± 90.47	.696

Abbreviations: SBP, systolic blood pressure; DBP, diastolic blood pressure; AF, atrial fibrillation; AFL, atrial flutter; CHD, coronary heart disease; CHF, congestive heart failure; VHD, valvular heart disease; TE, thromboembolism; COPD, chronic obstructive pulmonary disease; PTCA, percutaneous transluminal coronary angioplasty; DES, drug-eluting stent; OASIS, oxford acute severity of illness score; SAPSII, simplified acute physiology score II; SOFA, sequential organ failure assessment; WBC, white blood cell; RDW, red blood cell volume distribution width.

Table 2. Drug Therapy for Discharged Study Patients Before and After PSM, n (%).

Item	Before matching			After matching		
	Low Risk 0-3 (n = 3206)	Intermediate and High Risk 4-9 (n = 1285)	*P* value	Low Risk 0-3 (n = 988)	Intermediate and High Risk 4-9 (n = 988)	*P* value
Aspirin （n%）	2143(66.84)	1056(82.18)	<.001	760(76.92)	778(78.74)	.330
Clopidogrel （n%）	1288(40.17)	614(47.78)	<.001	444(44.94)	455(46.05)	.619
Beta-blocker （n%）	2132(66.50)	936(72.84)	<.001	705(71.36)	700(70.85)	.804
ACEI/ARB （n%）	1517(47.32)	612(47.63)	.869	463(46.86)	483(48.89)	.368
ARNI (n%)	125(3.90)	71(5.53)	.016	53(5.36)	50(5.06)	.761
Statins （n%）	1783(55.61)	822(63.97)	<.001	604(61.13)	612(61.94)	.711
CCB （n%）	530(16.53)	299(23.27)	<.001	189(19.13)	198(20.04)	.610
Nitrates （n%）	261(8.14)	206(16.03)	<.001	127(12.85)	129(13.06)	.893
Diuretics （n%）	1482(46.23)	793(61.71)	<.001	565(57.19)	579(58.60)	.524
MRA (n%)	204(6.36)	80(6.23)	.864	77(7.79)	68(6.88)	.437
Digoxin （n%）	281(8.76)	136(10.58)	.061	111(11.23)	107(10.83)	.774
Amiodarone （n%）	579(18.06)	270(21.01)	.022	199(20.14)	202(20.45)	.867
Anticoagulant （n%）	2355(73.46)	989(76.96)	.015	754(76.32)	754(76.32)	1.000
PPI （n%）	1637(51.06)	705(54.86)	.023	528(53.44)	534(54.05)	.787
Vasopressin use(n%)	549(17.12)	303(23.58)	<.001	221(22.37)	217(21.96)	.828

Abbreviations: PSM, propensity score matching; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; ARNI, angiotensin receptor/neprilysin inhibitor; MRA, aldosterone receptor antagonist including spironolactone eplerenone; CCB, calcium channel blocker; PPI, proton pump inhibitors; Diuretics including furosemide torsemide nimetani etaneric acid hydrochlorothiazide indapamide metolazone spironolactone eplerenone methotrexate amilori tolvaptan acetazolamide; Anticoagulant drugs including warfarin heparin calcium low molecular weight heparin dabigatran ester argatroban bivalirudin lepirudin rivaroxaban apixaban fondaparin sodium.

Table 3. Clinical Outcomes of the Study Patients Before and After PSM, n (%).

Item	Before matching			After matching		
	Low Risk 0-3 (n = 3206)	Intermediate and High Risk 4-9 (n = 1285)	*P* value	Low Risk 0-3 (n = 988)	Intermediate and High Risk 4-9 (n = 988)	*P* value
All-cause mortality	1195(37.27)	740(57.59)	<.001	478(48.38)	554(56.07)	.001
In hospital	289 （9.01）	174(13.54)	<.001	119(12.04)	132(13.36)	.380
30-day	350(10.92)	218(16.96)	<.001	146(14.78)	181(18.32)	.037
1-year	667(20.80)	438(34.09)	<.001	291(29.45)	334(33.81)	.035
5-year	1027(32.03)	672(52.30)	<.001	422(42.71)	490(49.60)	.006

IQR, interquartile range.

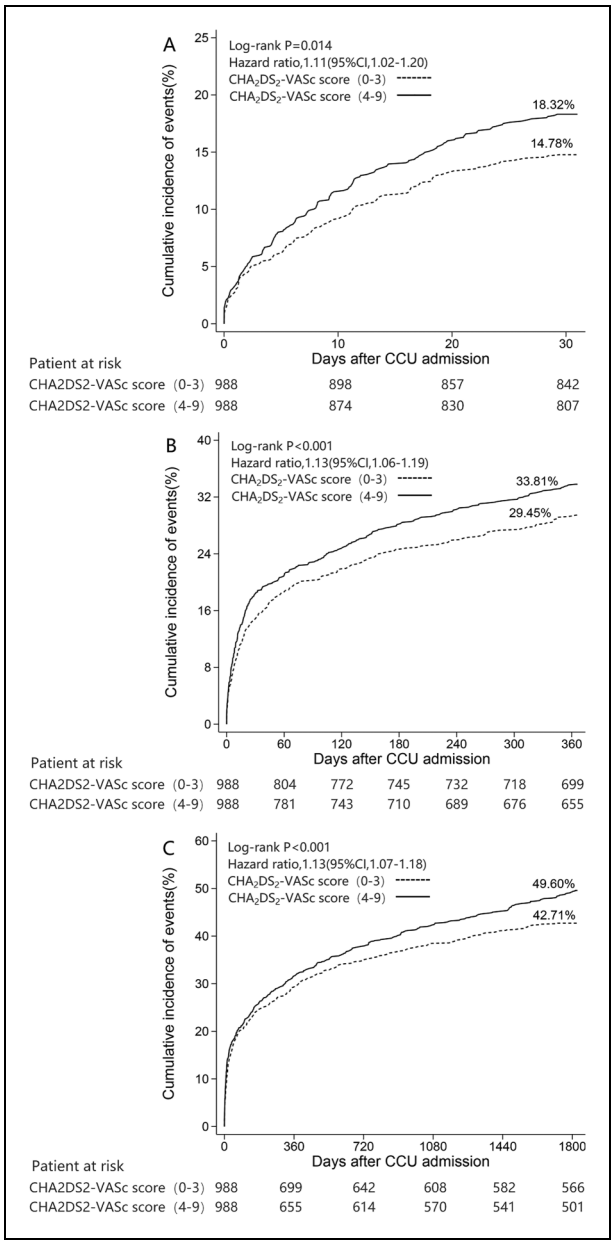

Figure 1. Cumulative incidence of (A)30-day (B)1-year (C)5-year mortality in the 0-3 *versus* the 4-9 group after PSM. CCU, coronary care unit; PSM, propensity score match.

Discussion

The principal findings of the present study included: (1) in a real-world cohort of CCU patients, a high CHA2DS2-VASc score was associated with a higher rate of comorbidity undergoing the balance confounders; (2) a high CHA2DS2-VASc score was associated with a significant risk of short (30-day HR: 1.11, $P = .014$) and long-term (1-year HR: 1.13, $P < .001$; 5-year HR: 1.13, $P < .001$) mortality in CCU patients, irrespective of AF status.

The CHA2DS2VASc score was originally developed to stratify thromboembolic risk in AF patients[24] and determine whether these patients were indicated for antithrombotic treatment according to contemporary guidelines.[25–27] However, in recent years, several studies have demonstrated that this score could also be used to predict outcomes in other cardiovascular diseases, including acute coronary syndrome,[28,29] pulmonary embolism, heart failure,[5,30] and even chest pain.[31] However, it is uncertain whether it can be used as a marker of CCU mortality.

CCU, which was initially established as a separate unit for the early detection and treatment of arrhythmias associated with acute myocardial infarction (AMI),[32] now provides the setting for monitoring and treating a wide variety of critical cardiovascular disease (CVD) states.[33] Jason N. Katz et al[32] reported a decreasing contemporary CCU and in-hospital mortality over time, although this decrease in odds was modest. Although mortality for AMI has steadily decreased among the patients admitted to CCU,[34,35] the prevalence of other cardiovascular diseases and critical illnesses seems to be increasing.[32,36] Additionally, the probability of multiple comorbidities also increases as the average life expectancy increases. Due to the increase in severity and complexity of illnesses, additional resources should be allocated to older patients with multiple co-morbidities. Readily available and commonly used risk scores can support the admission decision for CCU treatment by predicting the severity and the possibility of deterioration.

In such circumstances, several scores have been proposed for predicting the prognosis of severe cases. Although these scores may reflect the severity of the disease to a certain extent, they focus on different conditions, such as the GRACE score, Killip classification, and even some biomarkers. As shown in the 2015 acute coronary syndrome guidelines of the European Society of Cardiology,[37] a GRACE score of 140 or more reasonably indicates intensive care management for non-ST elevated ACS (NSTE-ACS). The Killip classification[38] was established 50 years ago and was originally used for the severity of AMI. Although the in-hospital mortality of AMI has decreased to less than 5%[39] with reperfusion therapy within CCU, the mortality rate of Killip IV is still over 50%. Additionally, the outcome prediction was improved with the combination of GRACE score and brain natriuretic peptide (BNP).[40] Cardiovascular-related patients can be admitted to the CCU by using these biomarkers in combination with various scores, which may be a direction for future research.

The associations between the CHA2DS2-VASc score and 30-day mortality for CCU patients with different comorbidities and parameters were revealed in subgroup analyzes. After PSM, the interactions between subgroup factors and the HR for 30-day mortality were modestly significant, except for WBC. In the present study, WBC counts are viewed as a marker of inflammatory status,[41,42] while other inflammatory markers such as C-reactive protein (CRP) were not calculated due to a considerable number of missing values. However, post-hoc analysis from the GLOBAL LEADERS trial[43] and a sub-study of PLATO[41] indicated that WBC count and neutrophil count were independent predictors of the primary endpoint of

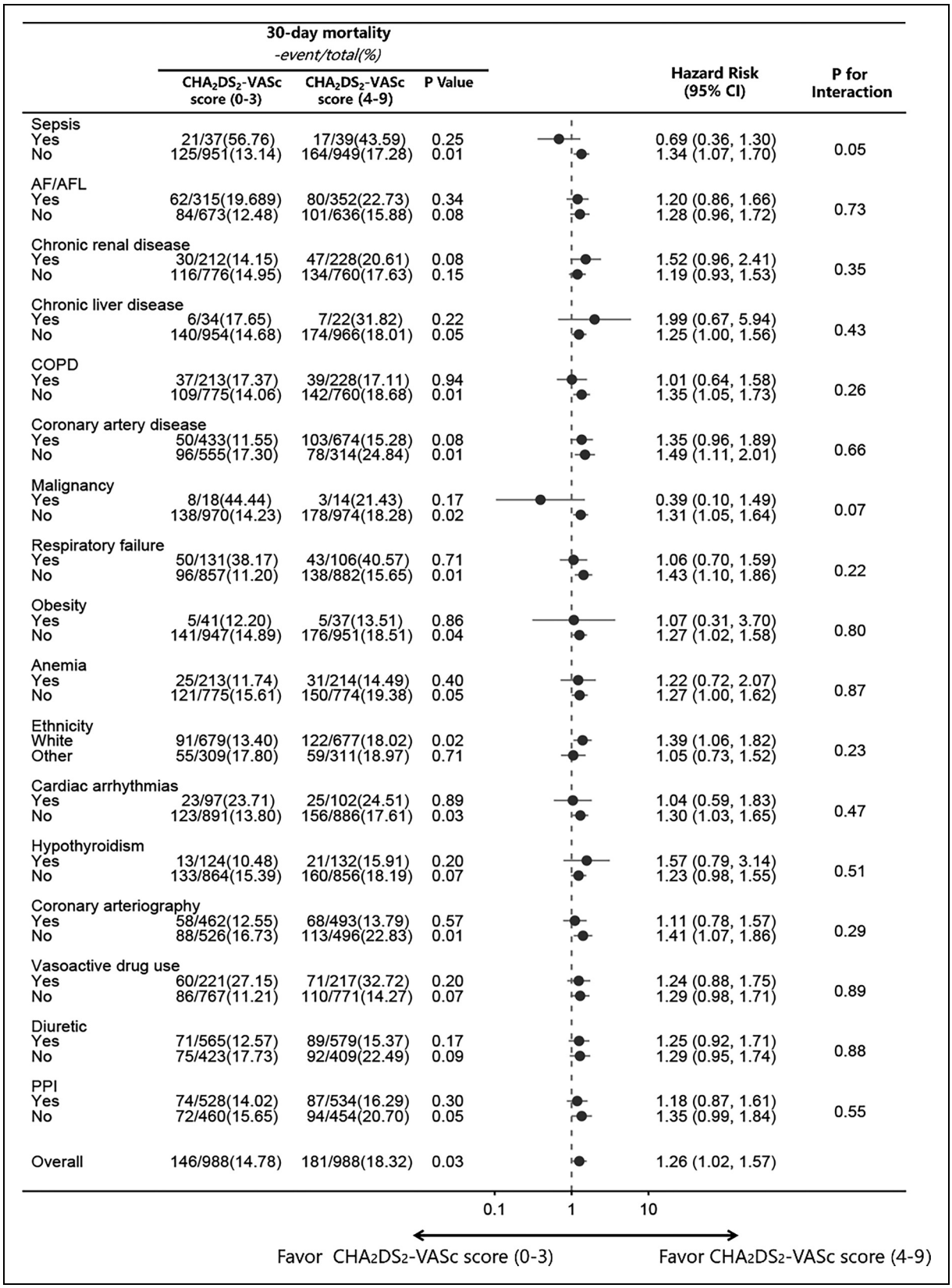

Figure 2. Subgroup analysis of 30-day mortality in the 0-3 vs. the 4-9 group after PSM. CI, indicates confidence interval; AF, atrial fibrillation; AFL, atrial flutter; COPD, chronic obstructive pulmonary disease; PPI, proton pump inhibitors; PSM, propensity score match.

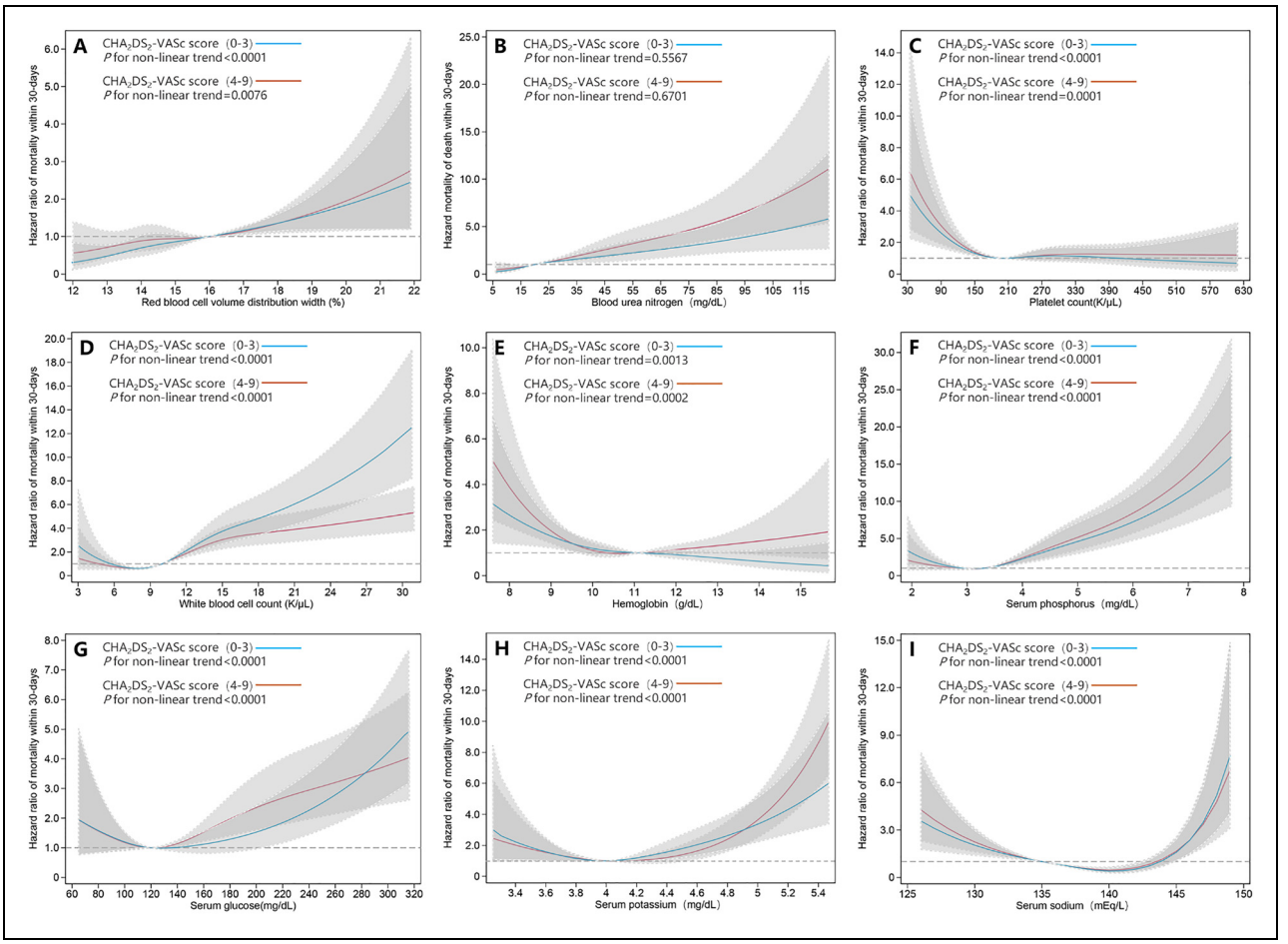

Figure 3. After propensity score match, restricted cubic splines to flexibly model were used to visualize the relation of (A)RDW, (B)BUN, (C) platelet, (D)WBC, (E)hemoglobin, (F)phosphorus, (G)glucose, (H)potassium, (I)sodium within 30-day mortality in the 0-3 vs. the 4-9 group.

cardiovascular mortality, whereas various inflammatory markers including CRP, IL-6, and monocyte count were not. Furthermore, the results from this study[41] demonstrated an increased risk of the primary outcome at WBC levels above approximately 8×10^9/L in patients with NSTE-ACS. In contrast, the risk of primary cardiovascular mortality did not start to increase until approximately12×10^9/L or higher in patients with STE-ACS. Consistent with our study, the risk of 30-day mortality increased when WBC levels exceeded approximately 9×10^9/L in both groups. However, this tendency is mitigated till 15×10^9/L in the intermediate or high-risk score group, while this phenomenon is not observed in the low-risk score group. Therefore, the mortality rate of the low-risk score group is higher than that of the intermediate or high-risk score group at higher WBC levels. This may be attributed to the low-risk score patients exhibiting a substantial temporary increase inflammatory factors due to the disease stress, but patients with intermediate and high-risk scores are chronically inflamed. Therefore, inflammation markers can better reflect the severity of the current disease for low-risk score patients.

Limitation

Several limitations should be considered in the present study. Firstly, due to the nature of retrospective analysis, unadjusted confounders might affect the robustness of our findings. Thus, sensitivity analyzes were performed to evaluate the presence of unmeasured confounders. The results demonstrated that differences in 30-day mortality in CCU patients between the two groups remained statistically significant even under moderate biases. Secondly, data on angiographic variables and admission parameters such as electrocardiogram (ECG) findings were not available for all patients. Thirdly, the clinical endpoint was all-cause mortality rather than cardiovascular mortality due to constraints from public databases. Fourthly, given the possible differences in baseline and treatment characteristics, the findings should be cautiously extrapolated to other patients. Finally, a well-designed prospective study should be conducted to further validate the stratification of the CHA_2DS_2-VASc score, including the relationships between several specific laboratory results and HR for 30-day mortality.

Conclusion

High CHA2DS2-VASc scores were associated with short- and long-term mortality risk in real-world CCU patients.

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Supplemental material

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