The Association Between High CHA2DS2-VASc Scores and Short and Long-Term Mortality for Coronary Care Unit Patients

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Abstract

Background: The CHA2DS2-VASc score has been associated with the prognosis of cardiovascular diseases. This study aimed to explore the association between the CHA2DS2-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 CHA2DS2-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 CHA2DS2-VASc scores and 988 patients with intermediate and high CHA2DS2-VASc scores had similar propensity scores and were included in the analyzes. In the survival analysis, the patients with intermediate and high CHA2DS2-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 after PSM. 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 CHA2DS2-VASc score was an independent risk for 30-day, 1-year, and 5-year mortality for CCU patients.

Keywords
CHA2DS2-VASc score, Propensity score matching, Coronary care unit, Mortality

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The CHA2DS2-VASc score was published in 2010 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. Additionally, AF and other cardiovascular diseases share common risk factors, which are part of the components of the CHA2DS2-VASc score. Thus, several studies explored the predictive value of the CHA2DS2–VASc score in patients with cardiovascular diseases such as heart failure, acute coronary syndrome (ACS), valvular heart disease (VHD) and thromboembolic events (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 CHA2DS2-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 (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. 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 CHA2DS2-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 χ² 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. After PSM, survival analysis was performed to estimate whether the CHA2DS2-VASc score predicted 30-day mortality. The effect of the CHA2DS2–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 CHA2DS2–VASc score. A stratification analysis was conducted to explore whether the association between the CHA2DS2–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, BUN, platelet, WBC, hemoglobin, phosphorus, glucose, potassium, sodium 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. The Wald test was used to estimate the presence of nonlinearity. All analyses 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 CHA₂DS₂-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, SAMS, SOFA except for psychoses, liver disease, alcohol and drug abuse. In addition, patients with intermediate and high-risk CHA₂DS₂-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 CHA₂DS₂-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 CHA₂DS₂-VASc score and 30-day mortality was consistent across the subgroups. There was no statistically significant heterogeneity between the CHA₂DS₂-VASc score and the 30-day mortality across the subgroups (\( P \) for interaction≥.05 for all).

Restricted Cubic Spline Plots
Based on the stratification of the CHA₂DS₂-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 phosphate 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 sodium and 30-day mortality. Serum sodium levels around 135mEq/L 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 CHA₂DS₂-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≥.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 CHA₂DS₂-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.
Table 1. Baseline Characteristics Before and After Propensity-Score Matching.

| Item                                      | Before matching | After matching | P value |
|-------------------------------------------|-----------------|----------------|---------|
|                                            | Low Risk 0-3 (n = 3206) | Intermediate and High Risk 4-9 (n = 1285) | P value |
| CHA2DS2-VASc score (x ± s)                | 1.81 ± 1.01     | 4.57 ± 0.81    | <.001   |
| Age (years)                               | 61.92 ± 14.48   | 77.97 ± 7.61   | <.001   |
| Female, n(%)                              | 977(30.47)      | 856(66.61)     | <.001   |
| Admission type, n(%)                      | 183(5.71)       | 70(5.45)       | .37     |
| Elective                                  | 2830(88.27)     | 1162(90.43)    | .002    |
| Emergency                                 | 193(6.02)       | 53(4.12)       | .001    |
| Race/ethnicity, n(%)                      | 220(68.65)      | 899(69.96)     | <.001   |
| White                                     | 1484(46.29)     | 867(67.77)     | <.001   |
| Black                                     | 32(1.78)        | 16(1.25)       | <.001   |
| Hispanic/Latino                           | 70(2.18)        | 17(1.32)       | <.001   |
| Other                                     | 662(20.65)      | 266(20.70)     | <.001   |
| Obesity, n(%)                             | 155(4.83)       | 49(3.81)       | .137    |
| SBP (mm Hg)                               | 115.39          | 87(67.77)      | <.001   |
| DBP (mm Hg)                               | 62.78 ± 10.96   | 56.47 ± 10.06  | <.001   |
| Pluses/beat per minute                    | 80.14 ± 16.39   | 78.58 ± 15.53  | .023    |
| Urine output (mL)                         | 2203.55 ± 1327.90 | 1733.71 ± 1077.25 | <.001 |
| Diabetes mellitus, n(%)                   | 660(20.59)      | 679(52.84)     | <.001   |
| Hypertension, n(%)                        | 180(5.61)       | 413(32.14)     | <.001   |
| Active smokers, n(%)                      | 162(30.05)      | 100(7.78)      | <.001   |
| Alcohol abuse, n(%)                       | 159(4.96)       | 11(0.86)       | <.001   |
| Drug abuse, n(%)                          | 89(2.78)        | 6(0.47)        | <.001   |
| AF/AFL, n(%)                              | 818(25.51)      | 481(37.43)     | <.001   |
| CHD, n(%)                                 | 1484(46.29)     | 863(67.16)     | <.001   |
| Respiratory failure, n(%)                 | 321(10.01)      | 158(12.30)     | <.001   |
| Hyperlipidemia, n(%)                      | 711(22.18)      | 409(31.83)     | <.001   |
| CHF, n(%)                                 | 163(3.08)       | 257(20.00)     | <.001   |
| VHD, n(%)                                 | 61(1.90)        | 75(5.84)       | <.001   |
| Cardiac arhythmia, n(%)                   | 191(5.96)       | 171(13.39)     | <.001   |
| Anemia, n(%)                              | 466(14.54)      | 350(27.24)     | <.001   |
| Prior stroke or TIA or TE, n(%)           | 71(2.21)        | 21(16.26)      | <.001   |
| COPD, n(%)                                | 560(17.47)      | 300(23.55)     | <.001   |
| Renal failure, n(%)                       | 285(8.89)       | 146(33.93)     | <.001   |
| Hypothyroidism, n(%)                      | 247(7.70)       | 200(55.56)     | <.001   |
| Depression, n(%)                          | 203(6.33)       | 86(6.69)       | <.001   |
| Psychoses, n(%)                           | 109(3.40)       | 25(1.95)       | <.001   |
| Rheumatoid arthritis, n(%)                | 68(2.12)        | 45(3.50)       | <.001   |
| Liver disease, n(%)                       | 112(3.49)       | 25(1.95)       | <.001   |
| Sepsis, n(%)                              | 86(2.68)        | 75(4.44)       | <.001   |
| PCTA, n(%)                                | 550(17.16)      | 280(21.79)     | <.001   |
| DES/ non-DES, n(%)                        | 1075(33.53)     | 427(33.23)     | <.001   |
| Coronary arteriography, n(%)              | 1561(48.69)     | 630(49.03)     | <.001   |
| Severity scores                           | 27.99 ± 8.61    | 31.85 ± 8.88   | <.001   |
| OASIS                                     | 31.05 ± 13.41   | 39.92 ± 13.14  | <.001   |
| SAPSII                                    | 3.05 ± 2.74     | 3.94 ± 2.89    | <.001   |
| Blood urea nitrogen (mg/dL)               | 23.98 ± 17.10   | 34.29 ± 21.01  | <.001   |
| Hemoglobin (g/dL)                         | 11.86 ± 1.79    | 10.77 ± 1.36   | <.001   |
| White blood cell count (K/μL)             | 10.37 ± 4.19    | 10.56 ± 5.16   | <.001   |
| RDW (%)                                   | 14.57 ± 1.83    | 15.18 ± 1.73   | <.001   |
| Glucose (mg/dL)                           | 138.33 ± 49.38  | 151.82 ± 53.52 | <.001   |

(continued)
## Table 1. (continued)

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

**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    | Low Risk 0-3   |                          |
|                           | (n = 3206)      | (n = 988)      |                           |
|                           | Intermediate and High Risk 4-9 | Intermediate and High Risk 4-9 |                           |
|                           | (n = 1285)      | (n = 988)      |                           |
| Aspirin (n%)              | 2143 (66.84)    | 760 (76.92)    |                           |
| Clopidogrel (n%)          | 1288 (40.17)    | 463 (46.86)    |                           |
| Beta-blocker (n%)         | 2132 (66.50)    | 53 (5.36)      |                           |
| ACEI/ARB (n%)             | 1517 (47.32)    | 436 (43.60)    |                           |
| ARNI (n%)                 | 125 (3.90)      | 50 (5.06)      |                           |
| Statins (n%)              | 1783 (55.61)    | 604 (61.13)    |                           |
| CCB (n%)                  | 530 (16.53)     | 189 (19.13)    |                           |
| Nitrates (n%)             | 261 (8.14)      | 127 (12.85)    |                           |
| Diuretics (n%)            | 1482 (46.23)    | 565 (57.19)    |                           |
| MRA (n%)                  | 204 (6.36)      | 77 (7.79)      |                           |
| Digoxin (n%)              | 281 (8.76)      | 111 (11.23)    |                           |
| Amiodarone (n%)           | 579 (18.06)     | 199 (20.41)    |                           |
| Anticoagulant (n%)        | 2355 (73.46)    | 754 (76.32)    |                           |
| PPI (n%)                  | 1637 (51.06)    | 528 (53.44)    |                           |
| Vasopressin use (n%)      | 549 (17.12)     | 221 (22.37)    |                           |

**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 amiloril tolvaptan acetazolamide; Anticoagulant drugs including warfarin heparin calcium low molecular weight heparin dabigatran ester argatobran bivalirudin lepirudin rivaroxaban apixaban fondaparinux sodium.

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

| Item                      | Before matching | After matching |
|---------------------------|-----------------|----------------|
|                           | Low Risk 0-3    | Low Risk 0-3   |                          |
|                           | (n = 3206)      | (n = 988)      |                           |
|                           | Intermediate and High Risk 4-9 | Intermediate and High Risk 4-9 |                           |
|                           | (n = 1285)      | (n = 988)      |                           |
| All-cause mortality       | 1195 (37.27)    | 478 (48.38)    |                           |
| In hospital               | 289 (9.01)      | 119 (12.04)    |                           |
| 30-day                    | 350 (10.92)     | 146 (14.78)    |                           |
| 1-year                    | 667 (20.80)     | 291 (29.45)    |                           |
| 5-year                    | 1027 (32.03)    | 422 (42.71)    |                           |

**Abbreviations:** IQR, interquartile range.

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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 CHA2DS2-VASc score was originally developed to stratify thromboembolic risk in AF patients and determine whether these patients were indicated for antithrombotic treatment according to contemporary guidelines. 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, pulmonary embolism, heart failure, and even chest pain. 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), now provides the setting for monitoring and treating a wide variety of critical cardiovascular disease (CVD) states. Jason N. Katz et al 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, the prevalence of other cardiovascular diseases and critical illnesses seems to be increasing. 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, a GRACE score of 140 or more reasonably indicates intensive care management for non-ST elevated ACS (NSTEMI). The Killip classification 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% 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). 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, 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 and a sub-study of PLATO indicated that WBC count and neutrophil count were independent predictors of the primary endpoint of
| 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. |
|---|
| **30-day mortality** | **Event/Total (%)** | **Risk Ratio (95% CI)** | **P for Interaction** |
| **CHADS 2-VASC Score** | 0-3 | 0-3 | 4-9 | 4-9 | 0-3 vs. 4-9 | 0-3 vs. 4-9 |
| **Sepsis** | Yes | 21/37 (56.76) | 17/39 (43.59) | 0.25 | 0.69 (0.36, 1.30) | 0.74 | 0.05 |
| No | 125/951 (13.14) | 164/949 (17.28) | 1.34 (1.07, 1.70) | 0.33 |
| **AF/AFL** | Yes | 63/315 (19.669) | 80/352 (22.73) | 0.34 | 1.20 (0.86, 1.66) | 0.73 |
| No | 84/673 (12.48) | 101/636 (15.82) | 1.28 (0.96, 1.72) | 0.35 |
| **Chronic renal disease** | Yes | 30/212 (14.15) | 47/228 (20.61) | 0.08 | 1.52 (0.96, 2.41) | 0.35 |
| No | 116/770 (14.95) | 134/760 (17.63) | 1.19 (0.93, 1.53) | 0.35 |
| **Chronic liver disease** | Yes | 6/34 (17.65) | 7/22 (31.82) | 0.22 | 1.99 (0.67, 9.54) | 0.43 |
| No | 140/954 (14.88) | 174/966 (18.01) | 1.25 (1.00, 1.56) | 0.26 |
| **COPD** | Yes | 37/213 (17.37) | 39/228 (17.11) | 0.94 | 1.01 (0.64, 1.58) | 0.66 |
| No | 109/775 (14.06) | 142/760 (18.68) | 1.35 (1.05, 1.73) | 0.55 |
| **Coronary artery disease** | Yes | 50/433 (11.55) | 103/674 (15.28) | 0.08 | 1.35 (0.96, 1.89) | 0.22 |
| No | 96/555 (17.30) | 176/728 (24.84) | 1.49 (1.11, 2.01) | 0.66 |
| **Malignancy** | Yes | 8/18 (44.44) | 3/14 (21.43) | 0.17 | 0.39 (0.10, 1.49) | 0.67 |
| No | 138/970 (14.23) | 178/974 (18.28) | 1.31 (1.05, 1.64) | 0.55 |
| **Respiratory failure** | Yes | 50/131 (38.17) | 43/106 (40.57) | 0.71 | 1.06 (0.70, 1.59) | 0.22 |
| No | 96/657 (14.89) | 138/882 (15.65) | 1.43 (1.10, 1.86) | 0.22 |
| **Obesity** | Yes | 5/41 (12.00) | 5/37 (13.51) | 0.86 | 1.07 (0.31, 3.70) | 0.80 |
| No | 141/947 (14.89) | 176/951 (18.51) | 1.27 (1.02, 1.58) | 0.22 |
| **Anemia** | Yes | 25/213 (11.74) | 31/214 (14.49) | 0.40 | 1.22 (0.72, 2.07) | 0.87 |
| No | 121/775 (15.61) | 150/774 (19.38) | 1.27 (1.00, 1.62) | 0.23 |
| **Ethnicity** | White | 91/679 (13.40) | 122/677 (18.02) | 0.02 | 1.39 (1.06, 1.82) | 0.67 |
| Other | 59/309 (17.80) | 59/311 (18.97) | 1.05 (0.73, 1.52) | 0.29 |
| **Cardiac arrhythmias** | Yes | 23/97 (23.71) | 25/102 (24.51) | 0.89 | 1.04 (0.59, 1.83) | 0.47 |
| No | 123/891 (13.80) | 156/886 (17.61) | 1.30 (1.03, 1.65) | 0.29 |
| **Hypothyroidism** | Yes | 13/124 (10.48) | 21/132 (15.91) | 0.20 | 0.79 (0.31, 2.03) | 0.41 |
| No | 133/864 (15.39) | 160/856 (18.19) | 1.23 (0.98, 1.55) | 0.51 |
| **Coronary arteriography** | Yes | 58/462 (12.55) | 68/493 (13.79) | 0.57 | 1.11 (0.78, 1.57) | 0.55 |
| No | 88/528 (16.73) | 113/486 (22.83) | 1.41 (1.07, 1.86) | 0.29 |
| **Vasoactive drug use** | Yes | 60/221 (27.15) | 71/217 (32.72) | 0.20 | 1.24 (0.88, 1.75) | 0.69 |
| No | 89/767 (11.21) | 110/771 (14.21) | 1.29 (0.98, 1.71) | 0.88 |
| **Diuretic use** | Yes | 71/56S (12.57) | 89/579 (15.37) | 0.17 | 1.25 (0.92, 1.71) | 0.55 |
| No | 75/432 (17.33) | 92/409 (22.49) | 1.29 (0.95, 1.74) | 0.55 |
| **PPI** | Yes | 74/528 (14.02) | 87/534 (16.29) | 0.30 | 1.18 (0.87, 1.61) | 0.55 |
| No | 72/460 (15.85) | 94/454 (20.70) | 1.35 (0.99, 1.84) | 0.55 |
| **Overall** | Yes | 146/988 (14.78) | 181/988 (18.32) | 0.03 | 1.26 (1.02, 1.57) | 0.55 |

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.
cardiovascular mortality, whereas various inflammatory markers including CRP, IL-6, and monocyte count were not. Furthermore, the results from this study demonstrated an increased risk of the primary outcome at WBC levels above approximately $8 \times 10^9/L$ in patients with NSTE-ACS. In contrast, the risk of primary cardiovascular mortality did not start to increase until approximately $12 \times 10^9/L$ or higher in patients with STE-ACS. Consistent with our study, the risk of 30-day mortality increased when WBC levels exceeded approximately $9 \times 10^9/L$ in both groups. However, this tendency is mitigated at 15 $\times 10^9/L$ 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 in 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 CHA2DS2-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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References
1. Fye WB. Resuscitating a circulation abstract to celebrate the 50th anniversary of the coronary care unit concept. Circulation. 2011;124(17):1886-1893.
2. Lip GY, Nieuwlaat R, Pisters R, Lane DA, Crijs HJ. 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(2):263-272.
3. January CT, Wann LS, Alpert JS, et al. 2014 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(21):e1-76.
4. Wu Y, Xie Z, Liang W, et al. Usefulness of CHADS2, R2CHADS2, and CHA2DS2-VASc scores for predicting incident atrial fibrillation in heart failure with preserved ejection fraction patients. ESC Heart Fail. 2021.
5. Shuvy M, Zwas DR, Keren A, Gotsman I. Value of the CHA2DS2-VASc score for predicting outcome in patients with heart failure. ESC Heart Fail. 2020;7(5):2553-2560.
6. Abougroun A, Hassan A, Gaznabi S, et al. Modified CHA2DS2-VASc score predicts in-hospital mortality and procedural complications in acute coronary syndrome treated with percutaneous coronary intervention. Int J Cardiol Heart Vasc. 2020;28:100532.
7. Orvin K, Levi A, Landes U, et al. Usefulness of the CHA(2)-DS(2)-VASc score to predict outcome in patients who underwent transcatheter aortic valve implantation. Am J Cardiol. 2018;121(2):241-248.
8. Onuk T, Karatas MB, Ipek G, et al. Higher CHA2DS2-VASc score is associated with increased mortality in acute pulmonary embolism. Clin Appl Thromb Hemost. 2017;23(6):631-637.
9. Goldberger A. Physiobank, PhysioToolkit, and Physionet : components of a new research resource for complex physiologic signals. Circulation. 2000;101(23):e215-e220.
10. Johnson A, Pollard TJ, Shen L, et al. MIC-MIC-III, a freely accessible critical care database. Sci Data. 2016;3(1):1-9.
11. Rosenbaum PR, Silber JH. Amplification of sensitivity analysis in matched observational studies. J Am Stat Assoc. 2009;104(488):1398-1405.
12. Peng Y, Guan X, Wang J, Ma J. Red cell distribution width is correlated with all-cause mortality of patients in the coronary care unit. J Int Med Res. 2020;48(7):30060520941317.
13. Breen TJ, Padkins M, Bennett CE, et al. Predicting 1-year mortality on admission using the mayo cardiac intensive care unit admission risk score. Mayo Clin Proc. 2021;96(9):2354-2365.
14. Griffin JM, Tariq A, Menez S, et al. Higher prevalence of concurrent thrombocytopenia in patients receiving continuous renal replacement therapy in the cardiac intensive care unit. Blood Purif. 2021;50(6):891-898.
15. Hatmi ZN, Saeid AK, Broumand MA, Khoshkar SN, Danesh ZF. Multiple inflammatory prognostic factors in acute coronary syndromes: a prospective inception cohort study. Acta Med Iran. 2010;48(1):51-57.
16. Gao M, Zhang X, Qin L, et al. Discharge hemoglobin association with long-term outcomes of ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. Cardiovasc Ther. 2020,2020:1-7.
17. Moghaddam N, Wong GC, Cairns JA, et al. Association of anemia with outcomes among ST-segment-elevation myocardial infarction patients receiving primary percutaneous coronary intervention. Circulation Cardiovasc Interventions. 2018;11(12):e007175.
18. Ognibene A, Ciniglio R, Greifenstein A, et al. Ventricular tachycardia in acute myocardial infarction: the role of hypophosphatemia. South Med J. 1994;87(1):65-69.
19. Gustafsson I, Hildebrandt P. Blood glucose in the CCU: time to measure. Eur Heart J. 2001;22(13):1061-1062.
20. Madias JE, Shah B, Chintalapally G, Chalavarya G, Madias NE. Admission serum potassium in patients with acute myocardial infarction: its correlates and value as a determinant of in-hospital outcome. Chest. 2000;118(4):904-913.
21. Evans JR, McIntosh JP, McIntosh HJ, Mitchell PE. Hyponatremia in patients admitted to a coronary care unit. Clin Chem. 1990;36(2):322-325.
22. Harrell FE Jr, Lee KL, Pollock BG. Regression models in clinical studies: determining relationships between predictors and response. J Natl Cancer Inst. 1988;80(15):1198-1202.
23. Harrell FE. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis. Regression Modeling Strategies: With Applications to Linear Models, Logistic and Ordinal Regression, and Survival Analysis; 2015.
24. Borre ED, Goode A, Raitz G, et al. Predicting thromboembolic and bleeding event risk in patients with non-valvular atrial fibrillation: a systematic review. *Thromb Haemost*. 2018;118(12):2171-2187.
25. Lip GY. Withdrawn as duplicate: the CHA₂DS₂-VASc score for stroke risk stratification in patients with atrial fibrillation: a brief history. *Eur Heart J*. 2015;36(42):2880-2885.
26. January CT, Wann LS, Alpert JS, et al. 2014 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. *Circulation*. 2014;130(23):e199-e267.
27. Camm AJ, Lip GY, De Caterina R, et al. 2012 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. *Eur Heart J*. 2012;33(21):2719-2747.
28. Scudiero F, Zocchi C, De Vito E, et al. Relationship between CHA(2)DS(2)-VASc score, coronary artery disease severity, residual platelet reactivity and long-term clinical outcomes in patients with acute coronary syndrome. *Int J Cardiol*. 2018;262:9-13.
29. Rozenbaum Z, Elia A, Shuvy M, et al. CHA2DS2-VASc Score and clinical outcomes of patients with acute coronary syndrome. *Eur J Intern Med*. 2016;36:57-61.
30. Yoshihisa A, Watanabe S, Kanno Y, et al. The CHA2DS2-VASc score as a predictor of high mortality in hospitalized heart failure patients. *ESC Heart Fail*. 2016;3(4):261-269.
31. Topaz G, Haisraely O, Shacham Y, et al. CHA(2) DS(2) -VASc score and clinical outcomes of patients with chest pain discharged from internal medicine wards following acute coronary syndrome rule-out. *Clin Cardiol*. 2018;41(4):539-543.
32. Katz JN, Shah BR, Volz EM, et al. Evolution of the coronary care unit: clinical characteristics and temporal trends in healthcare delivery and outcomes. *Crit Care Med*. 2010;38(2):375-381.
33. Nonogi H. The necessity of conversion from coronary care unit to the cardiovascular intensive care unit required for cardiologists. *J Cardiol*. 2019;73(2):120-125.
34. Rogers WJ, Canto JG, Lambrew CT, et al. Temporal trends in the treatment of over 1.5 million patients with myocardial infarction in the US from 1990 through 1999: the national registry of myocardial infarction 1, 2 and 3. *J Am Coll Cardiol*. 2000;36(7):2056-2063.
35. Fox KA, Goodman SG, Klein W, et al. Management of acute coronary syndromes. Variations in practice and outcome; findings from the global registry of acute coronary events (GRACE). *Eur Heart J*. 2002;23(15):1177-1189.
36. Katz JN, Turer AT, Becker RC. Cardiology and the critical care crisis: a perspective. *J Am Coll Cardiol*. 2007;49(12):1279-1282.
37. Roffi M, Patrono C, Collet JP, et al. 2015 ESC guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation: task force for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation of the European society of cardiology (ESC). *Eur Heart J*. 2016;37(3):267-315.
38. Killip T3rd, Kimball JT. Treatment of myocardial infarction in a coronary care unit. A two year experience with 250 patients. *Am J Cardiol*. 1967;20(4):457-464.
39. Yasuda S, Nakao K, Nishimura K, et al. The current status of cardiovascular medicine in Japan - analysis of a large number of health records from a nationwide claim-based database, JROAD-DPC. *Circ J*. 2016;80(11):2327-2335.
40. Ang DS, Wei L, Kao MP, Lang CC, Struthers AD. A comparison between B-type natriuretic peptide, global registry of acute coronary events (GRACE) score and their combination in ACS risk stratification. *Heart*. 2009;95(22):1836-1842.
41. Thomas MR, James SK, Becker RC, et al. Prognostic impact of baseline inflammatory markers in patients with acute coronary syndromes treated with ticagrelor and clopidogrel. *Eur Heart J Acute Cardiovasc Care*. 2021;10(2):153-163.
42. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol*. 2009;54(23):2129-2138.
43. Ono M, Tomanik M, Koenig W, et al. Impact of white blood cell count on clinical outcomes in patients treated with aspirin-free Ticagrelor monotherapy after percutaneous coronary intervention: insights from the GLOBAL LEADERS trial. *Eur Heart J Cardiovasc Pharmacother*. 2022,8(1):39-47