Research Article

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Association of aggregate index of systemic inflammation with mortality in coronary artery disease patients without sepsis and application of a nomogram model

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Abstract

Objectives: To investigate the association between the aggregate index of systemic inflammation (AISI) and short- and long-term all-cause mortality in coronary artery disease (CAD) patients without sepsis, and to develop and internally validate an AISI-based nomogram for predicting 30-day mortality.

Methods: This retrospective study included 2,386 CAD patients without sepsis. Cox proportional hazards models evaluated associations between AISI and 30-, 90-, 180-, and 365-day mortality. Kaplan-Meier curves compared survival across AISI quartiles. Restricted cubic spline analyses assessed linearity, and receiver operating characteristic curves evaluated discrimination. A nomogram incorporating AISI and clinical variables was developed using LASSO and multivariate logistic regression and validated with discrimination, calibration, and decision curve analysis.

Results: Higher AISI was associated with increased mortality risk. Survival differed significantly across AISI quartiles (Log-rank $p<0.05$). The relationship between AISI and mortality was linear across time points (p for nonlinearity >0.05), with moderate discrimination. The nomogram including AISI, age, lymphocyte count, creatinine, SOFA, cerebrovascular disease, and respiratory failure showed strong performance (AUC 0.870 training; 0.848 testing) and clinical utility.

Conclusions: AISI independently predicted all-cause mortality in non-septic CAD patients, and an AISI-based nomogram may improve risk stratification.

Keywords: AISI; coronary artery disease; non-sepsis; mortality; nomogram

Introduction

Coronary artery disease (CAD) remains the leading cause of morbidity and mortality worldwide, accounting for approximately 40 % of all cardiovascular deaths [1]. It is characterized by the accumulation of atherosclerotic plaques within the arterial wall, resulting in luminal narrowing or occlusion of the coronary arteries [2]. Compelling evidence has established that inflammation within the arterial wall plays a central role in the formation, progression, and rupture of atherosclerotic plaques [3]. Both innate and adaptive immune responses are critical drivers of plaque evolution [4]. Therefore, identifying specific inflammatory biomarkers holds considerable promise for preventing disease progression and optimizing clinical outcomes in patients with CAD.

Several inflammatory indices have been recognized as predictors of poor prognosis in CAD, including the systemic inflammatory response index [5], neutrophil-to-lymphocyte ratio (NLR) [6], and systemic immune-inflammation index (SII) [7]. The aggregate index of systemic inflammation (AISI), which integrates neutrophil, lymphocyte, monocyte, and platelet counts, has emerged as a novel biomarker reflecting immune activation and adverse cardiovascular outcomes. In patients with congestive heart failure, elevated AISI levels have been associated with increased risks of all-cause, cardiovascular, and cardio-cerebrovascular mortality [8]. Additionally, AISI has demonstrated a nonlinear association with prevalent cardiovascular disease (CVD) in the general adult population [9]. In patients with ischemia and non-obstructive coronary arteries, AISI independently predicted the slow coronary flow phenomenon and showed superior predictive

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performance compared with individual counts of neutrophils, lymphocytes, monocytes, and platelets [10]. Nevertheless, the association between AISI and mortality in CAD patients without sepsis remains unclear.

In recent years, risk predictive models have been increasingly utilized and have shown robust performance in the risk stratification for CAD patients [11]. Inflammation indices, such as white blood cell and neutrophil counts, have been incorporated into clinical models for assessing CAD risk in patients with chest pain [12], as well as for predicting motoric cognitive risk syndrome [13] and acute kidney injury [14] in CAD populations. However, existing nomograms developed to predict all-cause mortality in CAD patients have primarily focused on specific subgroups with concomitant sepsis [15], diabetes mellitus [16], or chronic kidney disease [17]. The prognostic performance of nomograms incorporating AISI in this context remains unexplored.

To address this knowledge gap, the present study hypothesized that elevated AISI levels are independently associated with increased short- and long-term all-cause mortality in critically ill CAD patients without sepsis, and that incorporating AISI into a predictive model would improve risk stratification. Therefore, we aimed to (1) investigate the association between AISI and 30-, 90-, 180-, and 365-day all-cause mortality in CAD patients without sepsis, and (2) develop and validate a novel nomogram incorporating AISI and other readily available clinical variables to predict 30-day mortality in this population.

Methods

Study design and populations

This retrospective observational study was conducted using a large, de-identified cohort of patients admitted to intensive care units from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database (version 3.0) [18]. The database contains de-identified health information from patients admitted to the Beth Israel Deaconess Medical Center between 2008 and 2022. Patients diagnosed with CAD, including myocardial infarction, ischemic heart disease, or acute coronary syndrome (ICD-9 codes 410-414 and ICD-10 codes I20-I25), were included. To minimize confounding by infection-related systemic inflammation on the AISI, patients with sepsis were explicitly excluded according to the Sepsis-3 criteria [19]: suspected or confirmed infection accompanied by an acute increase in the Sequential Organ Failure Assessment (SOFA) score of ≥2 points attributable to the infection. For patients with multiple ICU admissions, only data from the first admission were analyzed. Exclusion criteria comprised: (1) age < 18 years; (2) stay in ICU <24 h (to ensure sufficient first-day data prior to major interventions or discharge/death); (3) missing data for neutrophil, lymphocyte, monocyte, or platelet counts on the first day of ICU admission; and (4) presence of sepsis as defined above. Ultimately, 2,386 patients were included in the final analysis.

Primary endpoint and secondary endpoints

The primary endpoint was 30-day mortality, and secondary endpoints included 90-day mortality, 180-day mortality and 365-day mortality.

Data collection and definitions

Baseline characteristics were extracted from the database, including sex, age, race, SOFA score, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), respiratory rate (RR) and body temperature. Comorbidities, including hypertension, diabetes mellitus, cerebrovascular disease, congestive heart failure (CHF), atrial fibrillation (AF) and respiratory failure, were identified. Laboratory parameters collected included white blood cell, neutrophil, lymphocyte, monocyte, and platelet counts, as well as hemoglobin, fasting plasma glucose (FPG), and creatinine levels. Candidate variables were pre-specified based on clinical relevance. Variables with missing values ≤5 % were imputed using multiple imputation. Variables with missing values >5 % – including alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, lactic dehydrogenase, albumin, partial pressure of arterial carbon dioxide ($PaCO_2$), partial pressure of arterial oxygen (PaO_2), and oxygen saturation – were excluded from subsequent analyses to minimize potential bias associated with excessive imputation.

The AISI was calculated as follows: AISI=(neutrophil count × platelet count × monocyte count)/lymphocyte count [20]. AISI quartile: G1:≤315.49; G2: 315.49–579.94; G3:579.94–1,168.81; G4:>1,168.81.

Statistical analysis

Statistical analyses were performed using SPSS Statistics version 25.0 and R version 4.4.1. Normally distributed continuous variables were expressed as mean ± standard deviation (SD) and compared among groups using one-way analysis of variance (ANOVA). Non-normally distributed continuous variables were compared using the Kruskal–Wallis test. Categorical data were expressed as frequency (percentages), and

compared using the chi-square test. Kaplan-Meier survival curves and Cox proportional hazard models were used to evaluate the association between AISI and clinical outcomes, with results reported as hazard ratio (HR) with 95 % confidence intervals (CIs). Model 1 was unadjusted; Model 2 was adjusted for age, sex and race; and Model 3 was adjusted for age, sex, race, hypertension, cerebrovascular disease, CHF, AF, respiratory failure, hemoglobin, creatinine, FPG and SOFA. The predictive performance of AISI was assessed by receiver operating characteristic (ROC) curves. Restricted cubic spline (RCS) analyses were conducted to explore potential nonlinear associations between AISI (log-transformed) and mortality outcomes.

Least absolute shrinkage and selection operator (LASSO) regression with 10-fold cross-validation, combined with forward stepwise multivariate logistic regression, was used to identify significant predictors of 30-day mortality and to develop the prediction model in the training cohort. Results were expressed as odds ratios (ORs) with 95 % CIs. Variance Inflation Factors (VIFs) were calculated to evaluate potential multicollinearity among the predictors. A nomogram model for predicting 30-day mortality in non-septic patients with CAD was constructed using R 4.4.1. Patients were randomly divided into a training cohort (n=1,670) and a testing cohort (n=716) at a 7:3 ratio. The discriminatory performance of the nomogram was assessed using ROC curves in both cohorts. Calibration was evaluated using calibration curves, and clinical utility was determined through decision curve analysis (DCA). A two-sided p value<0.05 was considered statistically significant.

Ethics approval and informed consent

The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology. The MIMIC-IV database contains fully de-identified patient information; therefore, the requirement for informed consent was waived. Access to the database was granted after completion of the required training and certification by the study investigators.

Results

Baseline characteristics of populations

A total of 2,386 participants with CAD without sepsis were included in the analysis. The mean age was 68.14 ± 11.8 years, and 1,747 (73.22 %) were male. According to Table 1, significant differences across AISI quartile groups were observed in age, SBP, DBP, HR, RR, body temperature, SOFA, white blood cell, neutrophil, lymphocyte, monocyte, platelet, FPG and creatinine (all p<0.05). Patients in the highest AISI quartile exhibited higher prevalence of cerebrovascular disease, CHF, respiratory failure; as well as lower proportions of male sex and hypertension (all p<0.05). In addition, elevated AISI levels were associated with significantly higher all-cause mortality rates at 30, 90, 180, and 365 days compared with lower AISI quartile groups (all p<0.05). No significant differences were observed for the other characteristics (p>0.05).

Association between AISI and clinical outcomes

Multivariate Cox proportional hazards regression analyses were conducted to explore the association between AISI and all-cause mortality in CAD patients without sepsis. In the unadjusted model (Model 1), the highest AISI quartile (G4) was correlated with substantially increased risks of 30-day mortality (HR 8.50, 95 % CI 4.25–17.00), 90-day mortality (HR 4.96, 95 % CI 3.10–7.96), 365-day mortality (HR 3.50, 95 % CI 2.47–4.98) and 180-day mortality (HR 4.05, 95 % CI 2.74–6.13). After full adjustment for potential confounders in Model 3, the HRs of the G4 group were 5.13 (95 % CI: 2.51–10.48) for 30-day mortality, 2.88 (95 % CI: 1.76–4.69) for 90-day mortality, 2.33 (95 % CI: 1.53–3.54) for 180-day mortality, and 1.95 (95 % CI: 1.35–2.81) for 365-day mortality respectively. Kaplan–Meier survival curves further illustrated clear separation across AISI quartiles, with the highest quartile (G4) exhibiting markedly lower survival probabilities at all four time points (log-rank p<0.001, Figure 1). These findings indicated a strong graded relationship between elevated systemic inflammation and poorer short- and long-term survival (Table 2).

Predictive performance and linearity of AISI

RCS analysis, using log (AISI) as the continuous exposure, revealed a linear positive relationship between AISI and all-cause mortality at 30, 90, 180 and 365 days in CAD patients without sepsis (p for nonlinearity >0.05 for all time points, Figure 2), with no evidence of a threshold effect. ROC curves were presented in Figure 3. The AISI demonstrated moderate predictive accuracy for all-cause mortality, with AUC values of 0.744 for 30-day mortality, 0.698 for 90-day mortality, 0.683 for 180-day mortality and 0.659 for 365-day mortality respectively. In comparison, the SOFA score revealed lower predictive performance across all time points, with AUC values of 0.601 for 30-day mortality, 0.578 for 90-day mortality, 0.547 for 180-

Table 1: Baseline characteristics of the study population.

	Total (n=2,386)	G1 (n=597)	G2 (n=596)	G3 (n=596)	G4 (n=597)	p-Value
Age, years	68.14 ± 11.8	67.21 ± 10.65	67.95 ± 11.48	67.85 ± 12.27	69.55 ± 12.62	0.005
Male sex, %	1,747 (73.22)	448 (75.04)	455 (76.34)	442 (74.16)	402 (67.34)	0.002
Race, %						0.189
White	1,662 (69.66)	395 (66.16)	423 (70.97)	424 (71.14)	420 (70.35)	
Asian	146 (6.12)	47 (7.87)	27 (4.53)	33 (5.54)	39 (6.53)	
Black	53 (2.22)	16 (2.68)	14 (2.35)	15 (2.52)	8 (1.34)	
Hispanic/Latino	45 (1.89)	18 (3.02)	10 (1.68)	8 (1.34)	9 (1.51)	
Other	480 (20.12)	121 (20.27)	122 (20.47)	116 (19.46)	121 (20.27)	
SBP, mmHg	118.64 ± 21.76	115.60 ± 20.14	117.38 ± 20.18	120.25 ± 22.82	121.32 ± 23.26	<0.001
DBP, mmHg	64.20 ± 15.44	61.32 ± 12.80	62.82 ± 13.77	65.11 ± 16.53	67.56 ± 17.48	<0.001
HR (beats/min)	81.72 ± 15.91	78.20 ± 12.99	80.63 ± 14.32	81.41 ± 15.43	86.65 ± 19.06	<0.001
RR (insp/min)	17.77 ± 5.28	16.80 ± 4.99	16.99 ± 4.83	17.70 ± 5.07	19.59 ± 5.73	<0.001
Temperature, °C	36.55 ± 0.56	36.44 ± 0.58	36.50 ± 0.56	36.57 ± 0.54	36.70 ± 0.54	<0.001
SOFA	4.00 (2.00–6.00)	4.00 (3.00–6.00)	4.00 (2.00–6.00)	4.00 (2.00–6.00)	4.00 (2.00–6.00)	0.003
Hypertension, %	1,129 (47.32)	330 (55.28)	314 (52.69)	278 (46.64)	207 (34.67)	<0.001
Diabetes mellitus, %	1,008 (42.25)	264 (44.22)	249 (41.78)	239 (40.10)	256 (42.88)	0.526
Cerebrovascular disease, %	328 (13.75)	77 (12.90)	77 (12.90)	89 (14.93)	85 (14.24)	<0.001
Congestive heart failure, %	864 (36.21)	143 (23.95)	182 (30.54)	232 (38.93)	307 (51.42)	<0.001
Atrial fibrillation, %	1,014 (42.50)	233 (39.03)	248 (41.61)	267 (44.80)	266 (44.56)	0.141
Respiratory failure, %	306 (12.83)	45 (7.54)	37 (6.21)	80 (13.42)	144 (24.12)	<0.001
WBC (10^9/L)	9.70 (7.50–13.10)	8.60 (6.70–11.30)	9.25 (7.28–13.00)	9.70 (7.78–12.53)	11.50 (8.70–14.70)	<0.001
Neutrophil (10^9/L)	9.10 (6.61–12.08)	7.07 (5.20–9.26)	8.56 (6.01–11.01)	9.86 (7.40–12.67)	11.43 (8.88–14.80)	<0.001
Lymphocyte (10^9/L)	1.64 (1.10–2.34)	1.94 (1.43–2.64)	1.89 (1.33–2.49)	1.62 (1.13–2.33)	1.12 (0.77–1.67)	<0.001
Monocyte (10^9/L)	0.62 (0.44–0.88)	0.41 (0.29–0.54)	0.56 (0.42–0.71)	0.72 (0.55–0.93)	0.95 (0.72–1.23)	<0.001
Hemoglobin, g/dL	11.16 ± 2.32	11.07 ± 2.24	11.09 ± 2.28	11.38 ± 2.32	11.09 ± 2.41	0.060
Platelet (10^9/L)	190.00 (149.00–236.00)	160.00 (130.00–197.00)	177.00 (142.00–218.25)	195.00 (160.00–243.00)	225.00 (184.00–284.00)	<0.001
FPG, mmol/L	6.72 (5.72–8.33)	6.61 (5.61–8.00)	6.56 (5.67–7.97)	6.72 (5.72–8.22)	7.14 (5.83–9.10)	<0.001
Creatinine, μmol/L	88.40 (70.72–114.92)	79.56 (70.72–97.24)	88.40 (70.72–106.08)	88.40 (70.72–114.92)	88.40 (70.72–132.60)	<0.001
AISI	579.94 (315.49, 1,168.81)	223.67 (179.94–264.93)	428.58 (372.82–490.83)	809.10 (693.06–943.89)	1,953.39 (1,461.32–2,919.59)	<0.001
Outcomes						
30-day mortality	120 (5.03)	9 (1.51)	12 (2.01)	27 (4.53)	72 (12.06)	<0.001
90-day mortality	191 (8.01)	21 (3.52)	21 (3.52)	52 (8.73)	97 (16.25)	<0.001
180-day mortality	228 (9.56)	30 (5.03)	24 (4.03)	61 (10.24)	113 (18.93)	<0.001
365-day mortality	286 (11.99)	41 (6.87)	41 (6.87)	74 (12.42)	130 (21.78)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SOFA, sequential organ failure assessment; WBC, white blood cell; FPG, fasting plasma glucose; AISI, aggregate index of systemic inflammation.

day mortality, and 0.530 for 365-day mortality (Figure 3). These findings indicated that AISI consistently outperformed the SOFA score in predicting mortality risk among CAD patients without sepsis, highlighting its superior discriminative ability as an inflammation biomarker.

Baseline characteristics of the training and testing cohorts

As shown in Table 3, no significant differences were observed in the distribution of basic characteristics between the training and testing cohorts, confirming successful random splitting and maintained clinical comparability between the two groups.

Table 4 summarized the baseline clinical characteristics of patients in the training cohort, stratified by 30 day-survival status. Compared with survivors, non-survivors exhibited significantly higher age, HR, RR, body temperature, white blood cell, monocyte, creatinine, and AISI, as well as lower levels of hemoglobin and lymphocytes (all $p<0.05$). Additionally, non-survivors had a higher prevalence of cerebrovascular disease, CHF, AF and respiratory failure (all $p<0.05$).

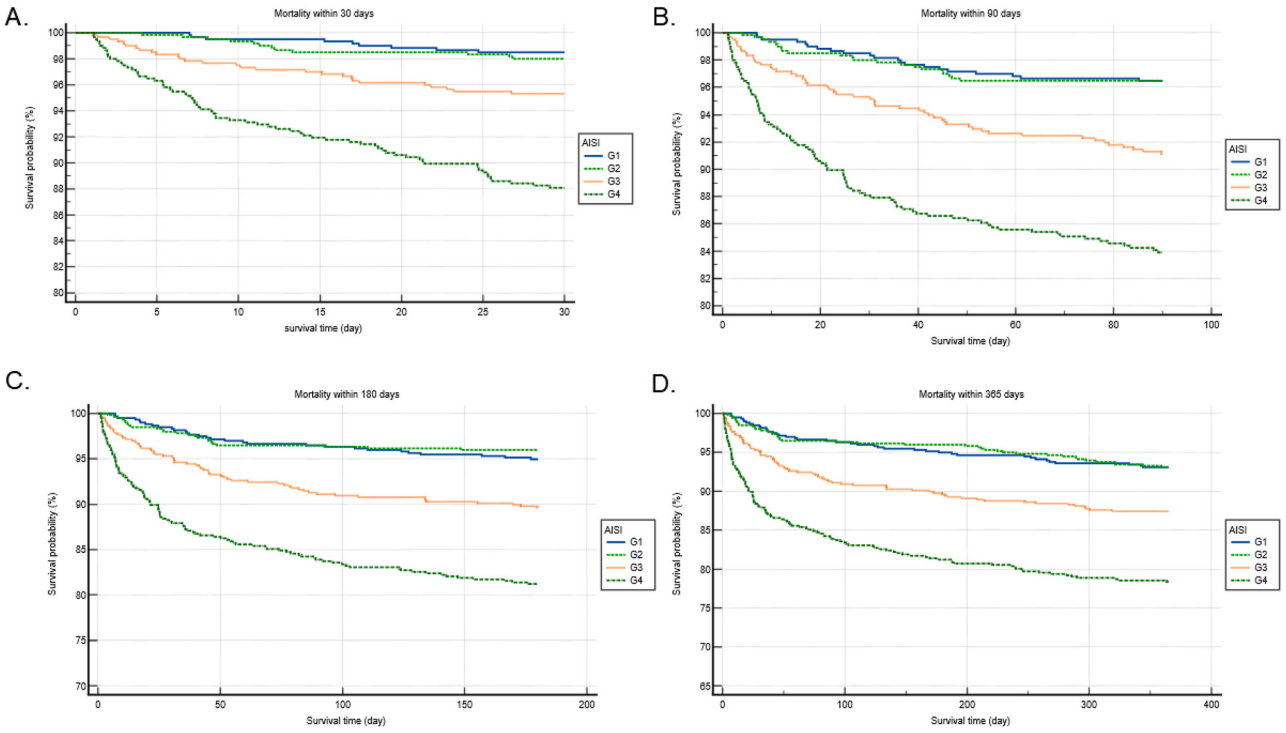

Figure 1: Kaplan-Meier survival curves for all-cause mortality by AISI quartiles.

Table 2: Cox proportional hazard ratios (HR) for outcome events.

	Model 1		Model 2		Model 3	
	HR (95 % CI)	**p-Value**	**HR (95 % CI)**	**p-Value**	**HR (95 % CI)**	**p-Value**
All-cause mortality within 30 days						
G1	Reference		Reference		Reference	
G2	1.34 (0.56, 3.18)	0.508	1.20 (0.51, 2.85)	0.679	1.12 (0.47, 2.68)	0.796
G3	3.06 (1.44, 6.51)	0.004	2.78 (1.31, 5.89)	0.008	2.32 (1.08, 4.96)	0.031
G4	8.50 (4.25, 17.00)	<0.001	6.60 (3.29, 13.26)	<0.001	5.13 (2.51, 10.48)	<0.001
Log (AISI)	8.00 (5.16, 12.39)	<0.001	6.38 (4.10, 9.93)	<0.001	4.71 (2.94, 7.55)	<0.001
All-cause mortality within 90 days						
G1	Reference		Reference		Reference	
G2	1.00 (0.55, 1.83)	0.997	0.91 (0.50, 1.67)	0.762	0.83 (0.45, 1.52)	0.538
G3	2.59 (1.56, 4.30)	<0.001	2.31 (1.40, 3.84)	0.001	1.87 (1.12, 3.13)	0.017
G4	4.96 (3.10, 7.96)	<0.001	4.02 (2.50, 6.46)	<0.001	2.88 (1.76, 4.69)	<0.001
Log (AISI)	5.38 (3.81, 7.59)	<0.001	4.38 (3.09, 6.19)	<0.001	3.02 (2.09, 4.37)	<0.001
All-cause mortality within 180 days						
G1	Reference		Reference		Reference	
G2	0.80 (0.47, 1.37)	0.415	0.73 (0.43, 1.25)	0.253	0.65 (0.38, 1.12)	0.123
G3	2.13 (1.38, 3.30)	0.001	1.92 (1.24, 2.97)	0.003	1.58 (1.02, 2.46)	0.043
G4	4.05 (2.74, 6.13)	<0.001	3.36 (2.24, 5.05)	<0.001	2.33 (1.53, 3.54)	<0.001
Log (AISI)	4.70 (3.43, 6.44)	<0.001	3.87 (2.81, 5.31)	<0.001	2.58 (1.84, 3.61)	<0.001
All-cause mortality within 365 days						
G1	Reference		Reference		Reference	
G2	1.00 (0.65, 1.54)	0.993	0.91 (0.59, 1.41)	0.679	0.81 (0.52, 1.25)	0.343
G3	1.90 (1.30, 2.78)	0.001	1.72 (1.17, 2.52)	0.005	1.53 (1.04, 2.24)	0.031
G4	3.50 (2.47, 4.98)	<0.001	2.91 (2.04, 4.14)	<0.001	1.95 (1.35, 2.81)	<0.001
Log (AISI)	3.80 (2.87, 5.04)	<0.001	3.16 (2.38, 4.20)	<0.001	2.07 (1.53, 2.80)	<0.001

Model 1: unadjusted. Model 2: adjusted for age, sex, race. Model 3: adjusted for age, sex, race, hypertension, cerebrovascular disease, CHF, AF, respiratory failure, hemoglobin, creatinine, FPG, SOFA.

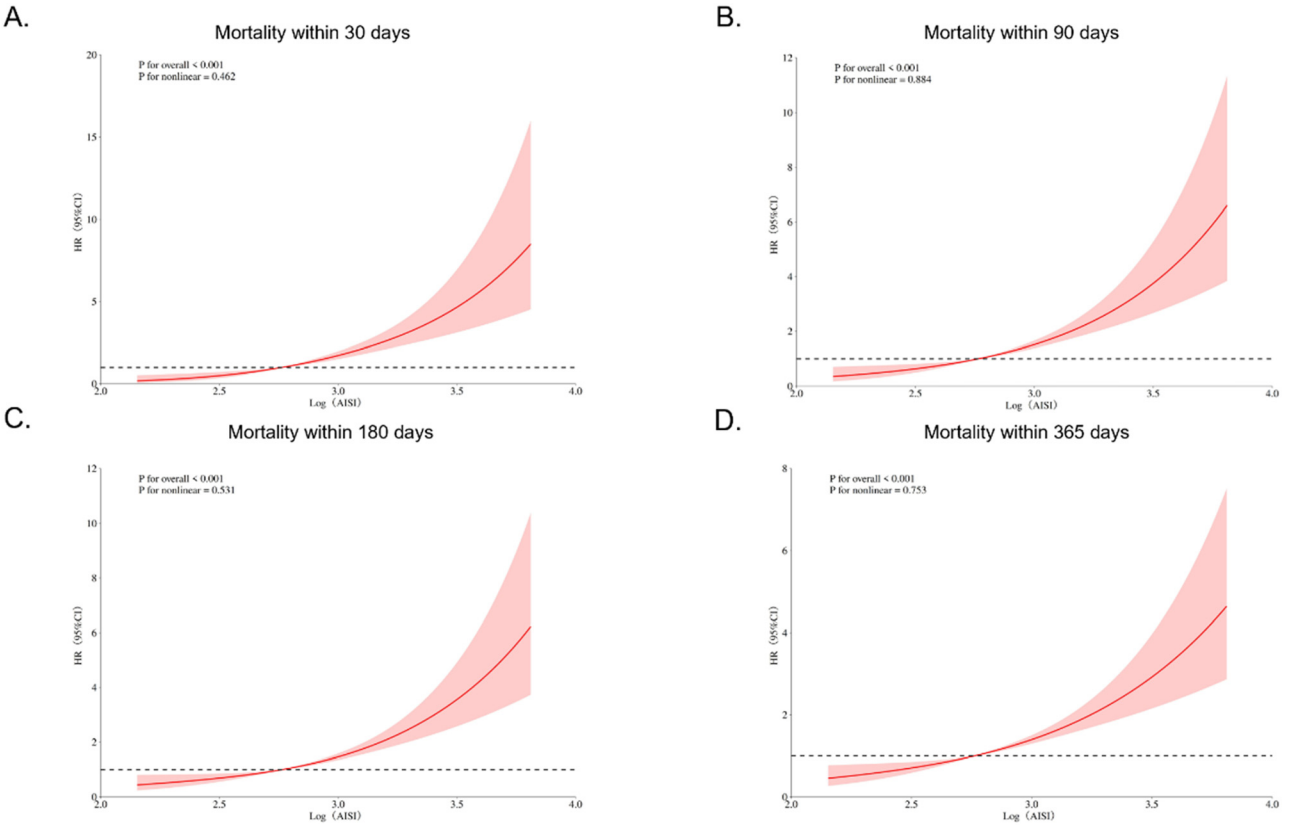

Figure 2: Restricted cubic spline analysis of AISI and mortality risk.

Feature selection and model construction

LASSO regression combined with 10-fold cross-validation was applied for dimensionality reduction and variable selection. All candidate predictors shown in Table 4 were initially entered into the LASSO model. The optimal penalty parameter λ was determined to be 0.0049 according to the minimum mean cross-validated error. At this λ value, eight variables with non-zero coefficients were retained: age, respiratory rate, respiratory failure, cerebrovascular disease, lymphocyte count, creatinine, SOFA score, and log (AISI) (Figure 4). These eight variables were subsequently included in a forward stepwise multivariate logistic regression analysis. The final model identified seven independent predictors of 30-day mortality: age, lymphocyte count, creatinine, SOFA score, respiratory failure, cerebrovascular disease, and log (AISI) (Table 5). A nomogram was then constructed based on these predictors (Figure 5). The total points on the nomogram correspond to the predicted probability of 30-day all-cause mortality in CAD patients without sepsis, with higher scores indicating greater mortality risk.

The performance of the nomogram model was assessed by ROC curves (Figure 6), calibration curves (Figure 7) and DCA (Figure 8). ROC curve analysis demonstrated strong discriminatory ability for 30-day all-cause mortality, with an AUC of 0.870 (95 % CI 0.830–0.909) in the training cohort, and 0.848 (95 % CI 0.774–0.921) in the testing cohort, indicating robust performance without significant overfitting. Calibration curves showed good agreement between predicted and observed probabilities in both cohorts, with points closely distributed along the ideal 45-degree line. DCA further confirmed the clinical usefulness of the nomogram, demonstrating a substantial net benefit compared with “treat-all” or “treat-none” strategies across a wide range of threshold probabilities (0.1–0.7). These results supported the nomogram as a reliable and clinically practical tool for early risk stratification in non-septic CAD patients.

Discussion

In the present study, we found that higher AISI levels were independently associated with increased risk of all-cause mortality at 30, 90, 180, and 365 days in critically ill CAD patients without sepsis, exhibiting a linear dose-response relationship. Furthermore, we developed and internally validated a nomogram model incorporating AISI, age, lymphocyte

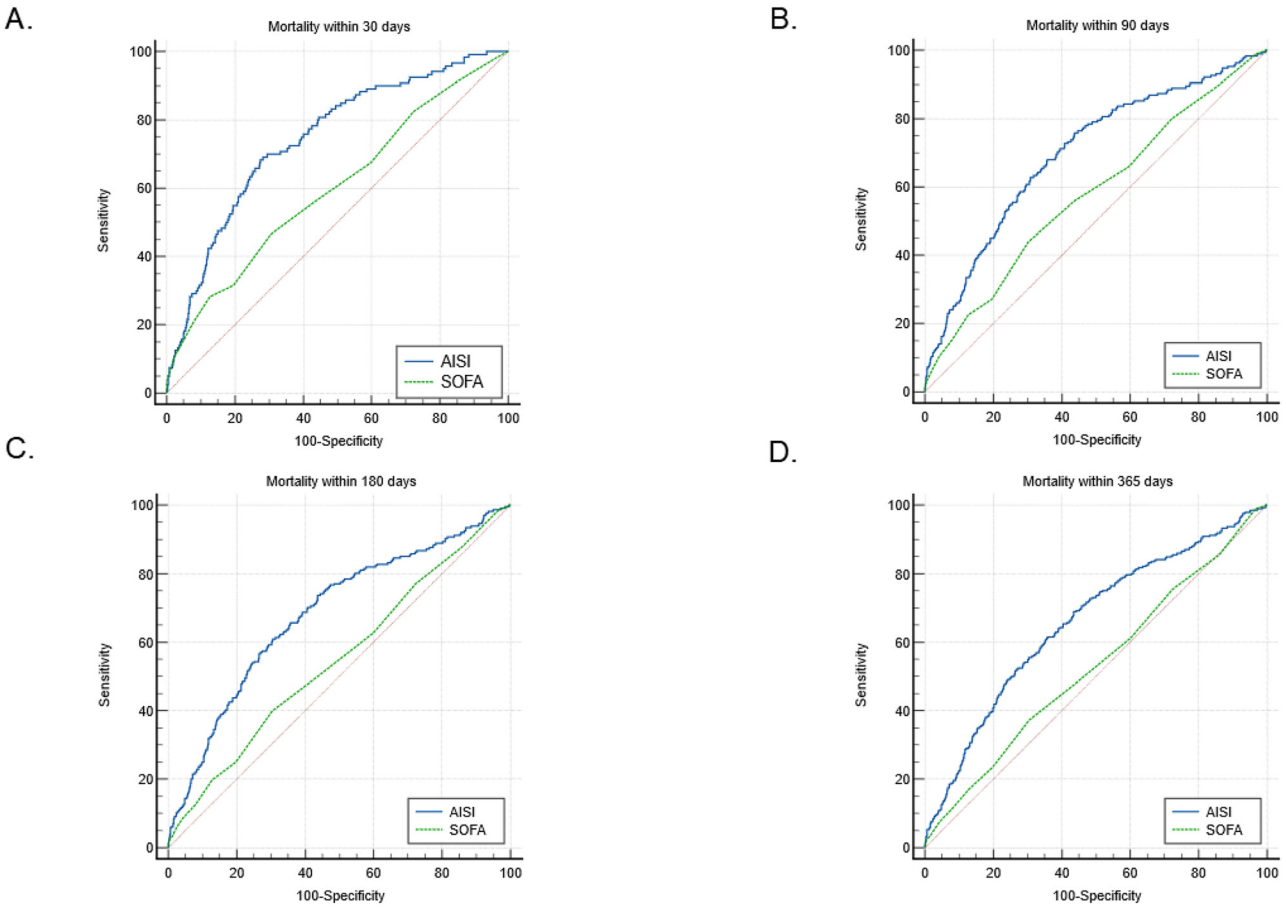

Figure 3: Receiver operating characteristic curves for AISI predictive accuracy.

count, creatinine, SOFA score, cerebrovascular disease, and respiratory failure, which demonstrated excellent discriminatory ability (AUC 0.870 in training and 0.848 in testing cohorts) and good clinical utility. The present findings extend previous evidence by confirming the prognostic value of AISI specifically in the non-septic CAD population and providing a practical tool for early risk stratification upon ICU admission.

Globally, CAD remains a leading cause of mortality and morbidity. Recent evidence highlighting prolonged ICU stays and elevated mortality rates among critically ill CAD patients [21] underscored the need for greater attention to this vulnerable population. The AISI, derived from neutrophil, monocyte, lymphocyte and platelet counts, has exhibited superior diagnostic performance compared with individual parameters in various conditions, including COVID-19 [22] and idiopathic pulmonary fibrosis [23]. Emerging research has further investigated the potential clinical utility of the AISI in CVD. For instance, AISI exhibited a non-linear association with CVD prevalence in the general population, with an inflection point at 467 [9]. In patients with acute myocarditis, higher AISI levels were associated with greater myocarditis severity [24]. Similarly, in hypertension patients, AISI independently predicted cardiovascular mortality even after full adjustment for confounders [25]. Consistent with prior findings, our study identified AISI as an independent risk factor for both 30-day, 90-day, 365-day and 180-day mortality in CAD patients without sepsis across all multivariable models. However, unlike the nonlinear relationships observed in broader adult cohorts [9], the linear pattern observed in our non-septic CAD cohort suggested a dose-dependent inflammatory burden on mortality risk without a clear inflection point. This pattern may reflect unique pathophysiological mechanisms in this specific subgroup. Additionally, the superior predictive performance of AISI over the SOFA score further underscored its value as a comprehensive inflammatory biomarker. These results emphasized the critical role of inflammatory markers in refining risk stratification and improving prognostic assessment in non-sepsis CAD populations.

The underlying pathophysiological mechanisms linking AISI to adverse outcomes in CAD remain incompletely elucidated. Inflammation is a well-established driver of CAD pathogenesis [26]. A meta-analysis reported that elevated NLR

Table 3: Baseline characteristics of training and testing cohorts.

	Test (n=716)	Train (n=1,670)	p-Value
Age, years	68.54 ± 11.65	67.97 ± 11.87	0.279
Male sex, %	531 (74.16)	1,216 (72.81)	0.496
Race			0.902
White	506 (70.67)	1,156 (69.22)	
Asian	43 (6.01)	103 (6.17)	
Black	13 (1.82)	40 (2.40)	
Hispanic/Latino	13 (1.82)	32 (1.92)	
Other	141 (19.69)	339 (20.30)	
SBP, mmHg	117.66 ± 22.37	119.05 ± 21.48	0.153
DBP, mmHg	63.49 ± 14.89	64.50 ± 15.66	0.144
HR, beats/min	82.44 ± 15.92	81.42 ± 15.89	0.153
RR, insp/min	17.93 ± 5.83	17.70 ± 5.02	0.332
Temperature, °C	36.58 ± 0.54	36.54 ± 0.57	0.174
SOFA	4.00 (2.00–6.00)	4.00 (2.00–6.00)	0.599
Hypertension, %	329 (49.95)	800 (47.90)	0.381
Diabetes mellitus, %	292 (40.78)	716 (42.87)	0.343
Cerebrovascular disease, %	88 (12.29)	240 (14.37)	0.176
Congestive heart failure, %	255 (35.62)	609 (36.47)	0.691
Atrial fibrillation, %	306 (42.74)	708 (42.40)	0.877
Respiratory failure, %	94 (13.13)	212 (12.70)	0.771
WBC (10^9/L)	9.60 (7.48–12.70)	9.70 (7.50–13.20)	0.637
Neutrophil (10^9/L)	8.89 (6.60–11.90)	9.21 (6.61–12.14)	0.277
Lymphocyte (10^9/L)	1.66 (1.08–2.30)	1.64 (1.10–2.36)	0.448
Monocyte (10^9/L)	0.61 (0.44–0.88)	0.63 (0.44–0.88)	0.766
Hemoglobin, g/dL	11.12 ± 2.28	11.17 ± 2.33	0.608
Platelet (10^9/L)	187.00 (148.00–239.25)	191.00 (150.00–234.00)	0.982
FPG, mmol/L	6.67 (5.78–8.13)	6.72 (5.67–8.39)	0.378
Creatinine, μmol/L	88.40 (70.72–114.92)	88.40 (70.72–106.08)	0.485
AISI	617.88 (318.00–1,212.00)	561.11 (315.00–1,150.77)	0.599
Outcomes			
30-day mortality	38 (5.31)	82 (4.91)	0.684
90-day mortality	59 (8.24)	132 (7.90)	0.782
180-day mortality	71 (9.92)	157 (9.40)	0.695
365-day mortality	85 (11.87)	201 (12.04)	0.910

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SOFA, sequential organ failure assessment; WBC, white blood cell; FPG, fasting plasma glucose; AISI, aggregate index of systemic inflammation.

values were associated with more extensive coronary artery involvement in patients with acute coronary syndrome undergoing revascularization [27]. Additionally, NLR has been linked to raised risks of myocardial damage and cardiac dysfunction following acute myocardial infarction [28]. In patients with unstable angina pectoris, NLR was positively correlated with the SYNTAX score and long-term cardiovascular mortality [29]. However, in non-ST-elevation acute coronary syndrome (NSTE-ACS), the predictive value of NLR for the SYNTAX score was diminished after adjustment for the TIMI score [30]. Neutrophilia and lymphopenia may exacerbate carotid plaque vulnerability through the release of bioactive substances, oxidative stress and apoptosis [31]. The SII, calculated from platelet, neutrophil, and lymphocyte counts, independently predicted post-procedural no-reflow in patients with ST-segment-elevation myocardial infarction (STEMI) [32]. Activated platelets may contribute to ischemia/reperfusion injury by promoting microthrombi formation, enhancing platelet-leucocyte aggregation, and releasing proinflammatory molecules [33]. By incorporating monocyte counts in addition to the components of NLR and SII, AISI offers a more comprehensive and robust assessment of systemic inflammatory status. Notably, monocytes played a pivotal role in CAD [34], as circulating monocytes and vascular macrophages drive atherosclerotic plaque formation and progression [35].

Using LASSO followed by multivariate logistic regression model, we identified seven independent predictors and developed a risk prediction model for 30-day mortality in CAD patients without sepsis, including age, lymphocyte, creatinine, SOFA, log (AISI), cerebrovascular disease and

Table 4: Baseline characteristics of the training cohort by 30-day survival status.

	Survival (n=1,588)	Non-survival (n=82)	p-Value
Age, years	67.45 ± 11.72	78.09 ± 10.15	<0.001
Male sex, %	1,166 (73.43)	50 (60.98)	0.013
Race			0.169
White	1,093 (68.83)	63 (76.83)	
Asian	102 (6.42)	1 (1.22)	
Black	40 (2.52)	0 (0.00)	
Hispanic/Latino	31 (1.95)	1 (1.22)	
Other	322 (20.28)	17 (20.73)	
SBP, mmHg	118.86 ± 15.55	122.74 ± 25.17	0.174
DBP, mmHg	64.42 ± 15.55	66.04 ± 17.73	0.363
HR, beats/min	81.08 ± 15.51	87.90 ± 21.08	0.005
RR, insp/min	17.54 ± 4.87	20.93 ± 6.69	<0.001
Temperature, °C	36.54 ± 0.58	36.67 ± 0.38	0.004
SOFA	4.00 (2.00–6.00)	4.00 (3.00–8.00)	<0.001
Hypertension, %	775 (48.80)	25 (30.49)	0.001
Diabetes mellitus, %	686 (43.20)	30 (36.59)	0.238
Cerebrovascular disease, %	216 (13.60)	24 (29.27)	<0.001
Congestive heart failure, %	560 (35.26)	49 (59.76)	<0.001
Atrial fibrillation, %	662 (41.69)	46 (56.10)	0.010
Respiratory failure, %	176 (11.08)	36 (43.90)	<0.001
WBC (10^9/L)	9.70 (7.40–13.2)	10.80 (8.20–14.48)	0.024
Neutrophil (10^9/L)	9.21 (6.64–12.16)	9.23 (6.38–11.53)	0.946
Lymphocyte (10^9/L)	1.68 (1.13–2.40)	1.06 (0.70–1.41)	<0.001
Monocyte (10^9/L)	0.60 (0.43–0.87)	0.81 (0.54–1.04)	<0.001
Hemoglobin, g/dL	11.21 ± 2.34	10.42 ± 2.07	0.003
Platelet (10^9/L)	192.00 (151.00–234.00)	178.50 (134.25–229.5)	0.158
FPG, mmol/L	6.72 (5.67–8.33)	7.36 (5.79–9.25)	0.105
Creatinine, μmol/L	88.40 (70.72–106.08)	114.92 (81.77, 201.11)	<0.001
AISI	544.66 (306.77–1,067.64)	1,251.12 (659.86–2,393.77)	<0.001

SBP, systolic blood pressure; DBP, diastolic blood pressure; HR, heart rate; RR, respiratory rate; SOFA, sequential organ failure assessment; WBC, white blood cell; FPG, fasting plasma glucose; AISI, aggregate index of systemic inflammation.

respiratory failure. By integrating the AISI with clinical variables (e.g., SOFA score, respiratory failure), the nomogram achieved high discriminatory power (AUC 0.870 in training cohort), and provided a practical, user-friendly tool for multidimensional risk assessment. Advanced age is a well-established risk factor for adverse prognosis in CAD [36], contributing to increased risks of multivessel coronary disease, recurrent interventions, and cerebrovascular disease [37]. Renal dysfunction, a frequent and serious complication in CAD, substantially increased healthcare costs and disease burden [38]. Elevated creatinine levels may exacerbate inflammatory and oxidative stress responses, particularly through the activation of NF-κB signaling axis [39]. Consequently, clinicians should prioritize early risk assessment and tailored treatment strategies for elderly CAD patients with concomitant cerebrovascular disease and renal dysfunction. Patients with pre-existing cerebrovascular conditions were particularly susceptible to worsening intermittent hypoxemia [40]. Impaired oxygenation can amplify systemic inflammation, oxidative stress, and sympathetic nervous system activation, thereby increasing the risks of stroke, hypertension and heart disease [41]. Our findings confirmed respiratory failure as a significant predictor of 30-day mortality in CAD patients without sepsis, highlighting the critical need for vigilant monitoring of oxygen saturation in this population. The SOFA score is widely used to evaluate organ dysfunction in patients admitted to ICU [42], and has well-established prognostic value in septic populations [43, 44]. However, its association with 28-day mortality was non-significant in patients with concomitant sepsis and CAD [15]. In contrast, our study-focused exclusively on CAD patients without sepsis-demonstrated that the SOFA score was a significant predictor of 30-day mortality, consistent with observations in acute myocardial infarction patients [45]. Differences in underlying infection status or inflammatory triggers may modulate the predictive performance of the SOFA score [42], which could account for its variable utility across CAD subpopulations. Collectively, our

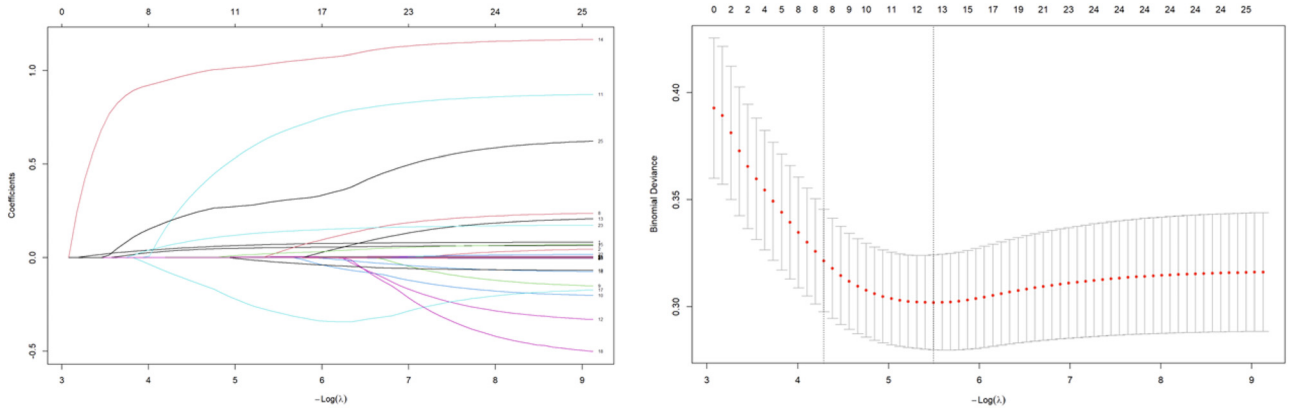

Figure 4: LASSO regression for feature selection.

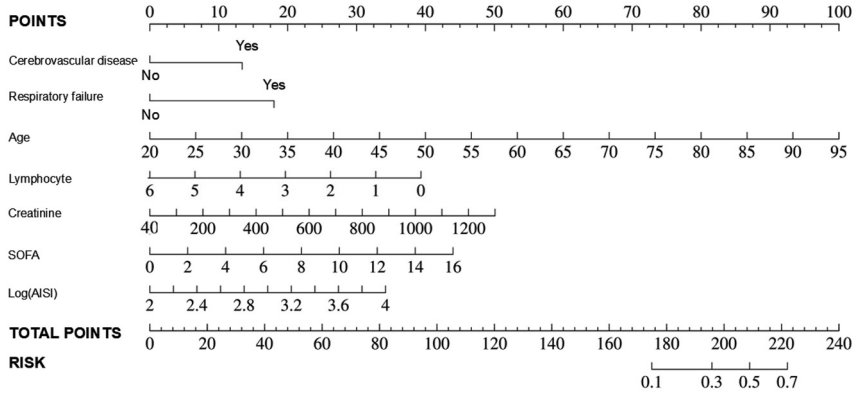

Figure 5: Nomogram for predicting 30-day mortality in CAD patients without sepsis.

Table 5: Multivariable logistic regression analysis for 30-day mortality predictors.

Variable	β	S.E.	Z	p-Value	OR (95 % CI)
Age	0.085	0.013	6.393	<0.001	1.09 (1.06–1.12)
Lymphocyte	−0.387	0.190	−2.036	0.042	0.68 (0.47–0.99)
Creatinine	0.002	0.001	2.993	0.003	1.00 (1.00–1.00)
SOFA	0.179	0.044	4.094	<0.001	1.20 (1.10–1.30)
Respiratory failure	1.110	0.268	4.136	<0.001	3.03 (1.79–5.13)
Cerebrovascular disease	0.886	0.286	3.095	0.002	2.43 (1.38–4.25)
Log (AISI)	0.983	0.343	2.866	0.004	2.67 (1.36–5.23)

novel predictive model, integrating immune status, comorbidities, and clinically relevant variables, offered multidimensional insights for the early identification of non-septic CAD patients at high mortality risk. In particular, elderly patients with cerebrovascular disease and respiratory failure warrant frequent monitoring of inflammation markers and SOFA scores-even in the absence of sepsis-with prompt initiation of targeted interventions to reduce mortality risk.

Our findings represented several novel contributions to the field. To our knowledge, this is the first study to demonstrate a clear linear association between AISI and all-cause mortality in critically ill CAD patients without sepsis, thereby addressing a critical gap in prior research that has largely focused on septic or general CAD populations. Clinically, these findings have substantial implications for the management of non-septic CAD patients in critical care settings. An elevated AISI may serve as an early warning signal of heightened mortality risk, enabling more accurate risk stratification at ICU admission and guiding timely, targeted interventions-such as intensified anti-inflammatory therapies, enhanced hemodynamic monitoring, or preventive measures against respiratory failure or kidney function impairment.

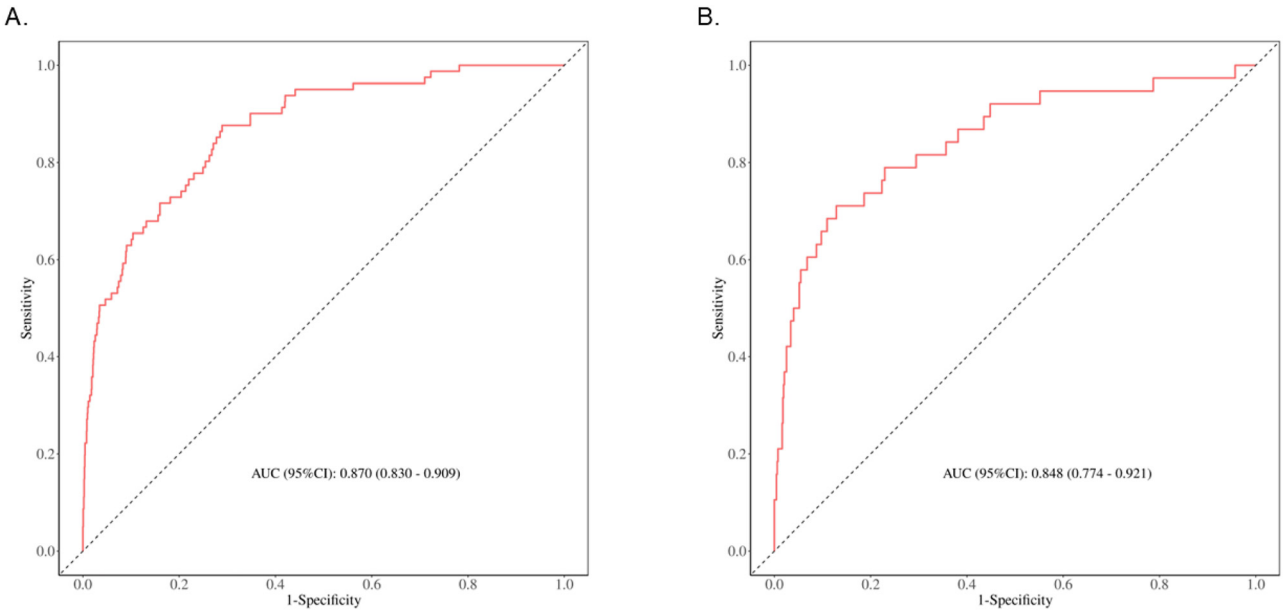

Figure 6: Receiver operating characteristic curves for nomogram.

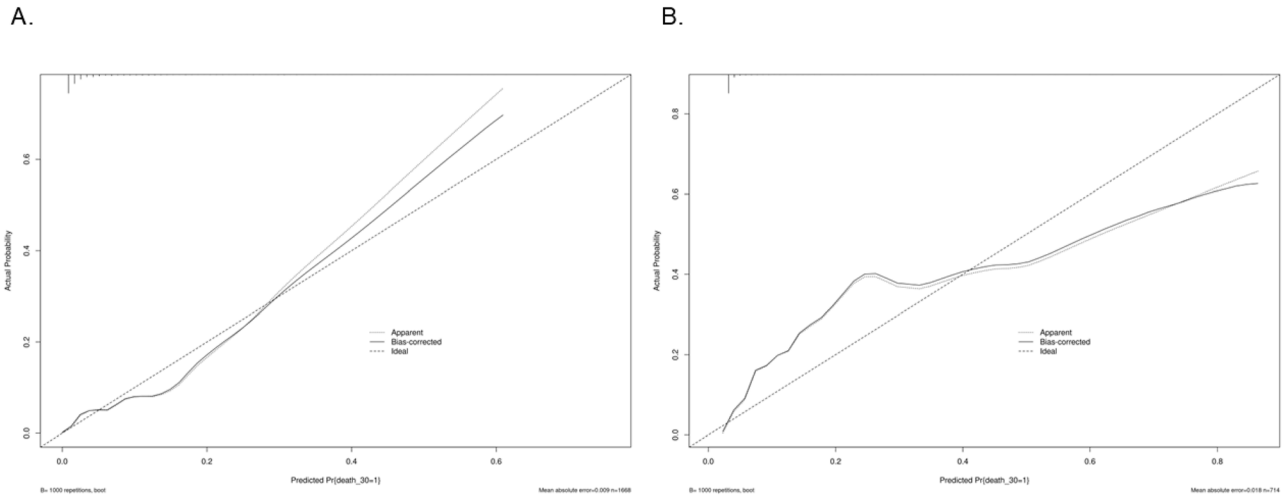

Figure 7: Calibration curves for nomogram performance.

Our study has several limitations. First, this study was based on a retrospective critical care cohort, which may limit the generalizability of the findings to other clinical settings and populations. Patients with an ICU length of stay shorter than 24 h were excluded to ensure the availability of complete first-day laboratory parameters for AISI calculation. These short-stay patients likely included both those who improved rapidly and were transferred to general wards and those who died early. Although this exclusion criterion helped maintain a standardized assessment of admission inflammatory status prior to major therapeutic interventions, it may have introduced selection bias by omitting the most critically ill patients who experienced very early mortality. Future studies could consider including short-stay patients to explore very early prognostic markers. Additionally, the data were derived from the MIMIC-IV database spanning 2008 to 2022, during which therapeutic protocols for CAD (such as antiplatelet therapy, revascularization strategies, and secondary prevention measures) may have evolved. Although we focused on readily available clinical variables upon ICU admission, changes in treatment practices over time could partially influence the observed associations. Future studies using more recent cohorts are warranted to validate our findings in contemporary clinical settings. Second, CAD was identified in any diagnostic

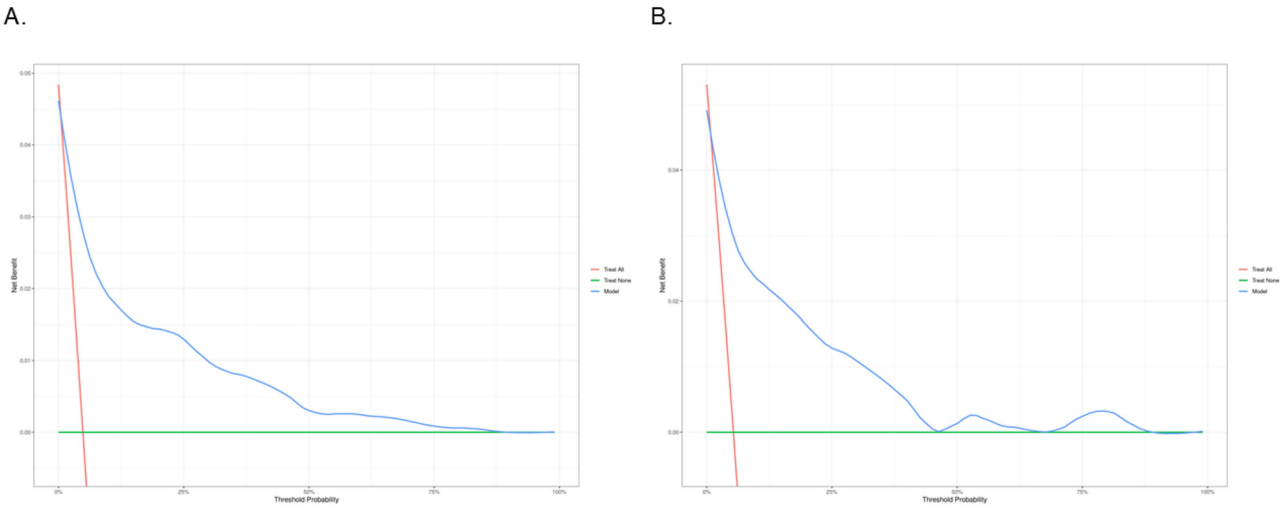

Figure 8: Decision curve analysis for nomogram clinical utility.

position during the hospital admission, rather than being restricted to the primary admission diagnosis. As a result, CAD may have been the primary reason for ICU admission in some patients but merely a comorbidity in others, which could introduce heterogeneity into the study population. Nevertheless, we attempted to mitigate potential confounding by rigorously excluding patients with sepsis, comprehensively adjusting for disease severity and other relevant comorbidities in the multivariable models. Importantly, the independent association between AISI and mortality remained consistent across different time points, supporting the robustness of our findings in this CAD cohort. Future prospective studies with clearer stratification according to the primary reason for ICU admission are warranted to further validate and refine our results in more homogeneous populations. Third, the predictor variables included in this model were limited, potentially resulting in residual confounding. For example, although we excluded patients with sepsis to reduce major sources of confounding on blood cell counts, detailed information on specific medications (such as high-dose systemic corticosteroids, chemotherapy, or other myelosuppressive/immunomodulatory agents) that could transiently influence the components of AISI was not incorporated into the exclusion criteria. Although we rigorously adjusted for disease severity, organ dysfunction, and other key comorbidities in the multivariable regression models, future prospective studies should systematically collect and adjust for these medication exposures to further minimize potential residual confounding and enhance the precision of AISI as a prognostic biomarker. Fourth, AISI was calculated using blood cell counts obtained only on the first day of ICU admission. Given the highly dynamic nature of inflammatory parameters in critically ill patients, a single early measurement may not fully capture temporal changes or trends that could provide additional prognostic information. To address potential limitations, we evaluated the association with mortality at multiple time points, and the independent predictive value of AISI remained consistent. Future prospective studies with serial AISI measurements would help determine whether incorporating dynamic changes further improves risk stratification beyond the baseline value. Additionally, interventional trials targeting AISI-modifiable components (e.g., antiplatelet or immunomodulatory therapies) could assess whether reducing AISI lowers mortality in non-septic CAD patients, paving the way for inflammation-guided precision medicine in cardiology. Fifth, although Cox proportional hazards models were appropriately used to evaluate the time-to-event association between AISI and mortality across multiple time points, the nomogram was constructed using multivariate logistic regression for the binary 30-day mortality outcome. This approach was selected because logistic regression directly estimates event probabilities at a fixed time point, which is the conventional and most practical method for developing user-friendly, bedside-applicable nomograms in clinical research. However, logistic regression does not fully incorporate time-to-event information or censoring, which may result in a minor loss of temporal dynamics compared with a time-dependent Cox-based model. Future studies could address this by developing dynamic or time-dependent nomograms to further enhance long-term risk prediction. Finally, external validation using larger, independent datasets is needed to confirm the clinical applicability and accuracy of our nomogram. Future research should involve larger, multicenter, multi-ethnic cohorts to identify novel biomarkers and further enhance the model's predictive performance.

Conclusions

In this study, we demonstrated that the AISI was independently and significantly associated with both short-term and long-term mortality in CAD patients without sepsis. Furthermore, we developed and validated a novel nomogram that integrates AISI with readily available clinical variables. This model exhibited excellent discriminatory ability and provided a practical tool for early risk stratification and prognostic assessment in this population. By facilitating more precise identification of high-risk patients, the nomogram may contribute to improved outcomes in non-septic critically ill CAD patients.

Patient and public involvement statement

Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research. This study was a retrospective observational analysis based on de-identified routinely collected clinical data. No patients were directly contacted, and there was no active patient or public participation in setting the research question, selecting outcome measures, or interpreting the results.

Research ethics: The study was conducted in accordance with the Declaration of Helsinki and approved by the institutional review boards of Beth Israel Deaconess Medical Center and the Massachusetts Institute of Technology.
Informed consent: The MIMIC-IV database contains fully de-identified patient information; therefore, the requirement for informed consent was waived. Access to the database was granted after completion of the required training and certification by the study investigators.
Author contributions: All authors have accepted responsibility for the entire content of this manuscript and approved its submission. Yumei Wen and Lu Yang contributed to study design, data analysis, and manuscript drafting. Libin Zhang and Yiqing Shen were responsible for data extraction, statistical analysis, and interpretation of results. Guangyao Zhai conceived the study, supervised the research process, critically revised the manuscript, and approved the final version.
Use of Large Language Models, AI and Machine Learning Tools: None declared.
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Data availability: The data that support the findings of this study are available from the MIMIC-IV database. Access to these data requires completion of the relevant training and approval procedures. The datasets analyzed during the current study are available from the corresponding author upon reasonable request.

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