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Stress hyperglycemia ratio linked to all-cause mortality in critically ill patients with ischemic heart disease

Tao Liu[1†], Lili wang[2†], Hao Zhang[1] and Qiming Dai[1*]

Abstract

Background The stress hyperglycaemia ratio (SHR), a quantitative indicator of hyperglycaemia in stress, has been shown to correlate with poor disease prognosis. However, the relationship between SHR and short-term prognosis in critically ill patients with ischemic heart disease (IHD) remains unclear.

Methods This retrospective study analyzed data of 2559 critically ill patients with IHD from the Medical Information Mart for Intensive Care III database. Endpoints were in-hospital mortality and intensive care unit (ICU) mortality. Kaplan-Meier survival curves, Cox proportional hazards models, restricted cubic spline, subgroup analysis, and receiver operating characteristic curves were used to explore the association between SHR and mortality in critically ill patients with IHD.

Results A total of 99 (3.87%) in-hospital deaths and 62 (2.42%) ICU deaths were recorded. In multivariate Cox proportional hazards models, higher SHR was independently associated with in-hospital mortality (hazard ratio (HR): 1.93 [95% confidence interval (CI): 1.42–2.61], *P*-value < 0.0001) and ICU mortality (HR, 1.70; 95% CI, 1.17–2.47; *P*-value = 0.01). Restricted cubic splines showed that SHR was linearly positive correlated with both in-hospital mortality and ICU mortality. Subgroup analysis revealed the robustness of the results. The area under the curve of SHR for predicting in-hospital mortality and ICU mortality was 0.715 and 0.711, respectively.

Conclusion SHR was significantly positively correlated with in-hospital mortality and ICU mortality in patients with critical IHD. It might enhance the predictive accuracy of existing clinical disease scores and guide personalized blood glucose control.

Keywords Stress hyperglycemia ratio, Ischemic heart disease, Mortality, MIMIC-III database

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Introduction

Ischemic heart disease (IHD) is a group of heart diseases caused by insufficient blood supply to the coronary arteries, resulting in myocardial ischemia and hypoxia [1]. The American College of Cardiology states that IHD causes about 380,000 heart attacks in the United States each year [2]. The latest Global Burden of Disease report shows that the global burden of IHD is continuing to increase [2, 3]. Critically ill patients with IHD are a particularly vulnerable group, as they usually suffer from multiple severe complications (myocardial ischemia, heart failure, cardiogenic shock, etc.) with critical and fast-changing conditions, and they are at a higher risk than the average IHD patient [4–6]. Therefore, precise intervention and close monitoring of potential risk factors in such patients are key to reducing mortality.

Patients with IHD admitted to intensive care units (ICUs) often experience significant metabolic disturbances, among which stress hyperglycemia is a common and clinically significant phenomenon [7, 8]. Stress hyperglycemia, driven by acute neuroendocrine responses to physiological stress, is a common and potentially modifiable risk factor associated with adverse outcomes [9]. The stress hyperglycemia ratio (SHR) is currently recognized as a quantitative measure to assess the severity of stress hyperglycemia, which is distinguished from stress hyperglycemia, diabetes, or basal hyperglycemia by comparing acute blood sugar with the patient's basal blood sugar level [10]. Previous studies on SHR and acute coronary syndrome, atrial fibrillation, diabetes, and other diverse populations have discovered that SHR is associated with a variety of adverse outcomes, including new infections, prolonged hospital stays, and increased rates of re-hospitalization, among others [11–15]. However, the association between SHR and short-term prognosis in critically ill patients with IHD has not been clarified.

This study was designed to investigate the association between SHR and all-cause mortality in critically ill patients with IHD. The findings are expected to inform clinical decision-making and optimize blood glucose management in patients with critical heart disease.

Method

Study population

The data for this retrospective study were from the Medical Information Mart for Intensive Care III (MIMIC III) database, which is a large, freely available, publicly available database containing information on patients who stayed in critical care units of the Beth Israel Deaconess Medical Center between 2001 and 2012 [16]. One of the authors of this study (LT) passed the National Institutes of Health online course and obtained permission to access the dataset for free (certificate number: 9008147). The establishment of the MIMIC III database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and informed consent was obtained for all patients. Therefore, no additional ethical approval statement and informed consent requirements were required for this study.

Firstly, we included 13,680 patients with IHD admitted to the intensive care unit (ICU) in the MIMIC-III database, of whom 864 patients were excluded because they were younger than 18 years or older than 89 years. Subsequently, we further excluded 10,257 patients with missing admission blood glucose and hemoglobin A1c (HbA1c) data on the first day of hospitalization. Finally, 2559 patients with IHD were included in this study (Fig. 1). In this study, the diagnosis of IHD was based on the International Classification of Diseases ICD-9 codes 410–414 (Table S1).

Data extraction

Structured query language (SQL) was used to retrieve information recorded on the first day of ICU admission of IHD patients. The demographic data of patients included age, sex, and body mass index (BMI) [weight(kg)/height^2(m^2)]; Severity of illness score on admission included Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score II (SAPS II), Acute Physiology Score III (APS III), Systemic Inflammatory Response Syndrome (SIRS) score; Comorbidities included acute myocardial infarction (AMI), diabetes mellitus (DM), hypertension, atrial fibrillation/flutter (AF), chronic obstructive pulmonary disease (COPD), acute kidney injury (AKI), chronic kidney disease (CKD), and history of percutaneous coronary intervention (PCI); Laboratory tests included white blood cells (WBC), serum sodium, serum potassium, serum creatinine (Scr), admission blood glucose (ABG), HbA1c, low-density lipoprotein (LDL), high-density lipoprotein (HDL), triglyceride (TG), total cholesterol (TC), activated partial thromboplastin time (APTT), prothrombin time (PT), international normalized ratio (INR), and lactate. Additionally, we also extracted length of stay (LOS) hospital, LOS ICU, hospital mortality, and ICU mortality. All the extracted data could be found in Table 1. All laboratory variables were the results of the first examination in the first 24 h after admission. For variables with missing values less than 20%, multiple imputation was performed to solve missing values using the "mi estimate" command in STATA software version 15.0. In addition, to avoid biased results caused by too many missing values, variables with missing values exceeding 20% were removed (Table S2) [17, 18].

In the present study, our primary outcome was all-cause mortality, including hospital all-cause mortality and ICU all-cause mortality. The exposure variable

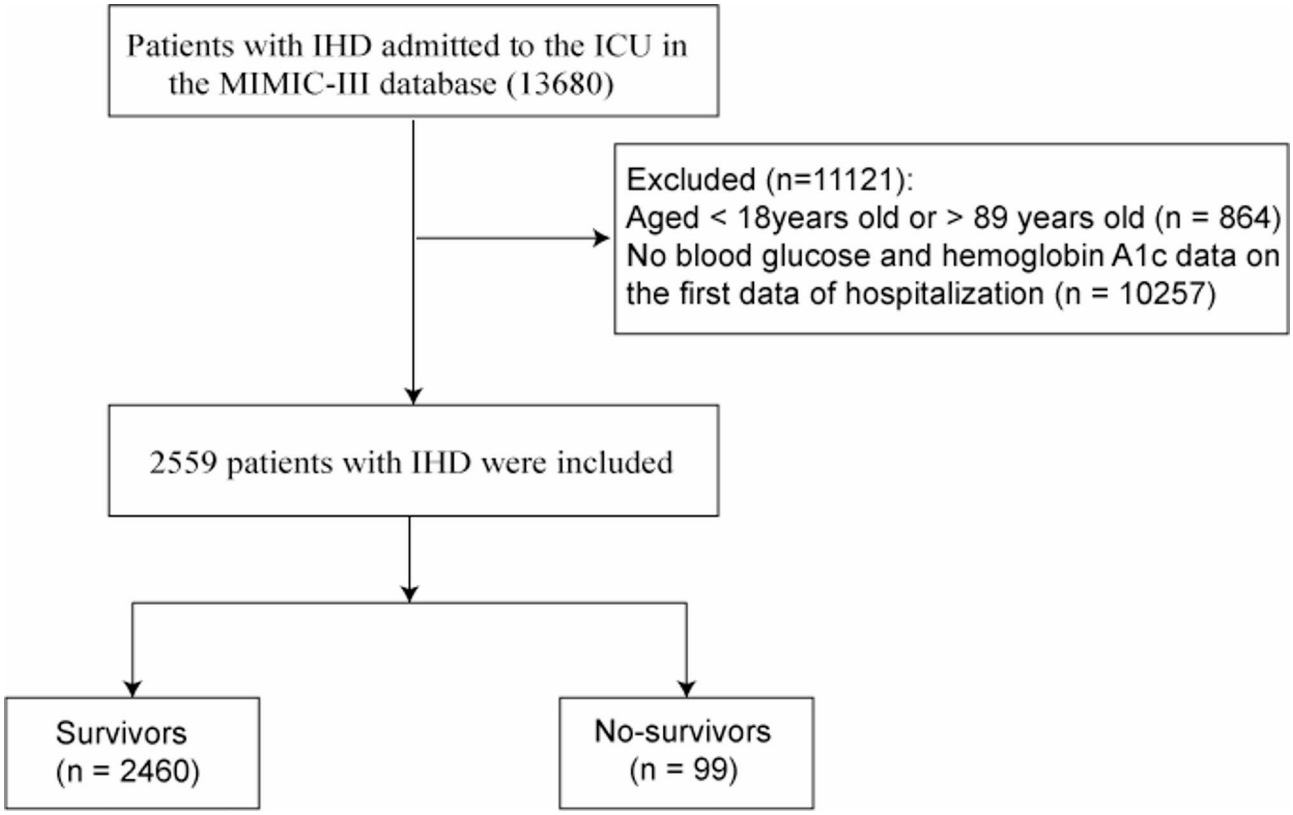

Fig. 1 Flowchart of the inclusion and exclusion of study participants

was stress hyperglycemia ratio (SHR), which was calculated by the following formula: SHR = (ABG (mg/dl)) / (28.7×HbA1c (%)-46.7) [10, 19]. The patients were divided into three groups according to the tertiles of SHR on the first day of ICU hospitalization (Table 1). In addition, the baseline characteristics according to whether the baseline HbA1c/ABG was missing were listed in Table S3.

Statistical analysis

Continuous variables conforming to normal distribution were expressed as mean and standard deviation (SD) and were analyzed using the student t-tests. Continuous variables conforming to non-normal distribution were expressed as median and interquartile range (IQR) and were analyzed using the Wilcoxon rank sum test. Categorical variables were expressed as counts and percentages and were analyzed using the chi-square or Fisher's exact probability method.

Kaplan-Meier survival analysis was used to evaluate the incidence of primary outcome events among groups with different SHR levels, and the log-rank test was used to evaluate the differences between groups. Cox proportional hazards models were used to estimate the hazard ratio (HR) and 95% confidence interval (CI) between SHR and the primary outcome. The variance inflation factor (VIF) was calculated to evaluate multicollinearity between variables. Variables with a VIF of more than 5 were removed due to concerns about multicollinearity. Finally, clinically relevant and prognostic variables were included in the multivariate model (Table S4): Model 1: No variable was unadjusted; Model 2: Age, BMI, SOFA score, SIRS score, APS III, SAPS II, AMI, DM, AF, AKI, WBC, LDL, HDL, TC, APTT, lactate, and LOS ICU were adjusted (based on the univariate analysis in Table 2). SHR was entered into the model as a categorical variable (with the first tertile of SHR as the reference group) and as a continuous variable. *P* for trend was obtained by using tertiles as ordinal variables. We implemented restricted cubic spline function (RCS) to analyze the dose-effect relationship between SHR and outcomes. Next, a receiver operating characteristic (ROC) curve analysis was conducted to assess the additional impact of SHR on the four disease scores' predictive value for all-cause mortality. We further performed stratified analyses according to age (≤ 65 years and > 65 years), sex, BMI (≤ 30 and > 30 kg/m 2), AMI, CKD, hypertension, and CKD. *P* values for interaction between SHR and stratification variables were evaluated using the likelihood ratio test. Finally, we conducted two sensitivity analyses, as follows: (1) Model 3 was analyzed again using stepwise backward Cox proportional hazards models. (2) Model 3

Table 1 Baseline characteristics of critical patients with ischemic heart disease according to SHR[a] tertiles

Variables	Overall (*n* = 2559)	T1 (*n* = 854)	T2 (*n* = 846)	T3 (*n* = 859)	*P*-value
Age, years	67.09 ± 12.22	66.84 ± 12.38	67.09 ± 12.37	67.33 ± 11.92	0.71
Male, *n* (%)	1654(64.63)	546(63.93)	585(69.15)	523(60.88)	< 0.01
BMI, kg/m2	29.65 ± 6.93	29.65 ± 7.06	29.73 ± 7.13	29.58 ± 6.61	0.90
SOFA score	3.00(2.00,5.00)	3.00(2.00,5.00)	3.00(1.25,5.00)	4.00(2.00,6.00)	< 0.0001
SAPS II	32.00(25.00,40.00)	31.00(25.00,39.00)	30.00(24.00,38.00)	35.00(27.00,44.00)	< 0.0001
APS III	37.00(28.00,48.00)	35.00(27.00,46.00)	34.00(27.00,44.00)	41.00(31.00,55.00)	< 0.0001
SIRS score	3.00(2.00,3.00)	2.00(1.00,3.00)	2.50(2.00,3.00)	3.00(2.00,4.00)	< 0.0001
Comorbidities, *n* (%)					
AMI	1281(50.06)	372(43.56)	448(52.96)	461(53.67)	< 0.0001
DM	1279(49.98)	481(56.32)	345(40.78)	453(52.74)	< 0.0001
Hypertension	1390(54.32)	461(53.98)	494(58.39)	435(50.64)	< 0.01
AF	841(32.86)	274(32.08)	255(30.14)	312(36.32)	0.02
COPD	439(17.16)	158(18.50)	122(14.42)	159(18.51)	0.04
AKI[b]	455(17.78)	141(16.51)	133(15.72)	181(21.07)	< 0.01
CKD	687(26.85)	262(30.68)	185(21.87)	240(27.94)	< 0.001
PCI	588(22.98)	164(19.20)	231(27.30)	193(22.47)	< 0.001
Laboratory tests					
WBC, K/uL	10.80(8.10,13.90)	9.50(7.50,12.50)	10.60(8.00,13.40)	11.90(9.20,15.50)	< 0.0001
Serum sodium, mEq/L	137.99 ± 3.94	138.57 ± 3.69	137.83 ± 3.53	137.56 ± 4.45	< 0.0001
Serum potassium, mEq/L	4.24 ± 0.74	4.17 ± 0.72	4.20 ± 0.68	4.33 ± 0.81	< 0.0001
Scr, mg/dL	1.00(0.80,1.50)	1.00(0.80,1.50)	1.00(0.80,1.30)	1.10(0.90,1.60)	< 0.0001
Glucose, mg/dL	142.00(113.00,188.00)	106.00(94.00,125.00)	135.00(121.00,156.75)	203.00(169.00,258.00)	< 0.0001
HbA1c, %	6.20(5.70,7.10)	6.50(5.90,7.60)	6.00(5.60,6.70)	6.10(5.60,6.90)	< 0.0001
LDL, mg/dL	80.00(58.49,105.00)	80.00(59.00,104.00)	82.00(60.00,107.14)	79.50(57.00,103.00)	0.48
HDL, mg/dL	43.00(35.00,54.00)	43.00(36.00,53.96)	43.91(35.00,53.01)	43.00(34.58,54.47)	0.98
TG, mg/dL	125.00(81.00,188.00)	127.00(85.00,194.65)	121.00(78.00,178.88)	128.00(81.00,188.50)	0.17
TC, mg/dL	154.00(124.00,183.00)	154.00(124.00,182.00)	154.78(125.00,185.00)	153.00(123.50,183.41)	0.93
APTT, s	31.70(26.80,42.50)	31.50(26.90,40.07)	31.80(26.70,43.38)	32.00(26.90,44.40)	0.18
PT, s	13.80(12.90,15.40)	13.75(12.83,15.30)	13.70(12.80,15.40)	13.90(13.00,15.40)	0.28
INR	1.20(1.10,1.50)	1.20(1.10,1.40)	1.20(1.10,1.50)	1.20(1.10,1.50)	0.03
lactate, mmol/L	1.70(1.10,2.66)	1.50(1.00,2.40)	1.70(1.10,2.65)	1.80(1.20,2.90)	< 0.0001
SHR	1.06(0.87,1.34)	0.78(0.67,0.87)	1.06(1.00,1.14)	1.51(1.34,1.81)	< 0.0001
Events					
LOS Hospital, days	6.79(4.14,11.05)	6.79(4.17,10.81)	6.03(3.71,9.88)	7.73(4.74,12.56)	< 0.0001
LOS ICU, days	2.20(1.25,4.15)	2.05(1.14,3.89)	2.06(1.20,3.51)	2.82(1.56,5.59)	< 0.0001
Hospital mortality, *n* (%)	99(3.87)	12(1.41)	26(3.07)	61(7.10)	< 0.0001
ICU mortality, *n* (%)	62(2.42)	7(0.82)	15(1.77)	40(4.66)	< 0.0001

Abbreviations: SHR, stress hyperglycemia ratio; BMI, body mass index; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APSIII, acute physiology score III; SAPSII, simplified acute physiological score II; AMI, acute myocardial infarction; DM, diabetes mellitus; AF, atrial fibrillation/flutter; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; WBC, white blood cell; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; Scr, serum creatinine; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; LOS, length of stay, ICU, intensive care unit

[a]SHR tertiles: T1 (0.103,0.933), T2 (0.933–1.223), T3 (1.223–4.311)

[b]AKI was defined according to KDIGO guidelines as an increase in serum creatinine (Scr) by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) from baseline within 48 h

was analyzed again using the dataset (2229 patients with IHD) that excluded patients with a LOS hospital < 3 days.

We used R statistical software version 4.3.3 and STATA software version 15.0 for data analysis. Two-sided $P < 0.05$ was considered as statistically significant. All methods were performed in accordance with the relevant guidelines and regulations.

Results

The analysis in this study comprised 2559 critically ill patients with IHD, with a mean age (SD) of 67.09 (12.22), 1654 (64.63%) of whom were male, and a median SHR of 1.06 (IQR: 0.87–1.34) for all patients. The in-hospital mortality was 3.87%, while the ICU mortality was 2.42% (Table 1).

Table 2 Baseline characteristics of the survivors and Non-survivors groups

Variables	Overall (*n* = 2559)	Survivors (*N* = 2460)	Non-survivors (*N* = 99)	*P*-value
Age, years	67.09 ± 12.22	66.83 ± 12.19	73.38 ± 11.40	< 0.001
Male, *n* (%)	1654(64.63)	1596(64.88)	58(58.59)	0.24
BMI, kg/m2	29.65 ± 6.93	29.74 ± 6.98	27.38 ± 5.27	< 0.001
SOFA score	3.00(2.00,5.00)	3.00(2.00,5.00)	5.00(3.00,7.00)	< 0.001
SAPS II	32.00(25.00,40.00)	32.00(25.00,40.00)	46.00(35.50,55.00)	< 0.001
APS III	37.00(28.00,48.00)	36.00(27.00,47.00)	54.00(40.00,69.00)	< 0.001
SIRS score	3.00(2.00,3.00)	3.00(2.00,3.00)	3.00(2.00,4.00)	< 0.001
Comorbidities, *n* (%)				
AMI	1281(50.06)	1213(49.31)	68(68.69)	< 0.001
DM	1279(49.98)	1242(50.49)	37(37.37)	0.01
Hypertension	1390(54.32)	1341(54.51)	49(49.49)	0.38
AF	841(32.86)	781(31.75)	60(60.61)	< 0.001
COPD	439(17.16)	421(17.11)	18(18.18)	0.89
AKI[a]	455(17.78)	426(17.32)	29(29.29)	< 0.01
CKD	687(26.85)	668(27.15)	19(19.19)	0.10
PCI	588(22.98)	559(22.72)	29(29.29)	0.16
Length of stay				
Hospital	6.79(4.14,11.05)	6.78(4.14,10.99)	7.35(3.96,12.22)	0.37
ICU	2.20(1.25,4.15)	2.16(1.24,4.03)	4.96(2.33,8.62)	< 0.0001
Laboratory tests				
WBC, K/uL	10.80(8.10,13.90)	10.60(8.00,13.70)	14.30(10.50,18.15)	< 0.001
Serum sodium, mEq/L	137.99 ± 3.94	138.01 ± 3.90	137.36 ± 4.72	0.18
Serum potassium, mEq/L	4.24 ± 0.74	4.23 ± 0.74	4.28 ± 0.81	0.54
Scr, mg/dL	1.00(0.80,1.50)	1.00(0.80,1.50)	1.40(1.00,1.85)	0.20
Glucose, mg/dL	142.00(113.00,188.00)	141.00(112.00,185.00)	201.00(128.50,295.50)	< 0.001
HbA1c, %	6.20(5.70,7.10)	6.20(5.70,7.10)	6.00(5.75,6.65)	0.02
LDL, mg/dL	80.00(58.49,105.00)	80.77(59.00,105.78)	76.00(51.35,93.22)	0.01
HDL, mg/dL	43.00(35.00,54.00)	43.22(35.00,54.00)	38.64(32.76,52.73)	0.03
TG, mg/dL	125.00(81.00,188.00)	125.00(81.00,187.25)	118.57(77.50,195.28)	0.46
TC, mg/dL	154.00(124.00,183.00)	154.00(124.44,184.00)	145.81(116.28,169.92)	< 0.01
APTT s	31.70(26.80,42.50)	31.70(26.80,41.80)	36.20(27.90,68.05)	< 0.001
PT, s	13.80(12.90,15.40)	13.80(12.90,15.30)	14.20(13.20,16.20)	0.25
INR	1.20(1.10,1.50)	1.20(1.10,1.50)	1.30(1.10,1.60)	0.46
lactate, mmol/L	1.70(1.10,2.66)	1.69(1.10,2.60)	2.53(1.50,3.55)	< 0.001
SHR	1.06(0.87,1.34)	1.05(0.86,1.33)	1.45(1.06,2.25)	< 0.001

Abbreviations: SHR, stress hyperglycemia ratio; BMI, body mass index; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APSIII, acute physiology score III; SAPSII, simplified acute physiological score II; AMI, acute myocardial infarction; DM, diabetes mellitus; AF, atrial fibrillation/flutter; COPD, chronic obstructive pulmonary disease; AKI, acute kidney injury; CKD, chronic kidney disease; PCI, percutaneous coronary intervention; WBC, white blood cell; TC, total cholesterol; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein; HbA1c, hemoglobin A1c; Scr, serum creatinine; PT, prothrombin time; INR, international normalized ratio; APTT, activated partial thromboplastin time; ICU, intensive care unit

[a]AKI was defined according to KDIGO guidelines as an increase in serum creatinine (Scr) by ≥ 0.3 mg/dl (≥ 26.5 μmol/l) from baseline within 48 h

Baseline characteristics

As shown in Table 1, the baseline characteristics of critical IHD patients were divided according to the SHR tertiles at admission [tertiles (T) 1: 0.103–0.933; T2: 0.933–1.223; T3: 1.223–4.311]. Patients in the highest SHR tertile (T3) generally had higher severity of illness scores on admission, a higher prevalence of AMI, AF, COPD, and AKI, and higher rates of PCI history, a lower prevalence of DM, hypertension, and CKD, higher levels of WBC, serum potassium, Scr, blood glucose, INR, lactate, and lower levels of serum sodium, HbA1c compared with the lower SHR group (T1). Meanwhile, compared to critically ill patients with IHD in the lower tertiles (T1) of SHR, high tertiles (T3) in the higher tertiles had longer LOS ICU (median, 2.05 days vs. 2.82 days, *P*-value < 0.0001) and LOS hospital (median, 6.79 days vs. 7.73 days, *P*-value < 0.0001), higher ICU mortality (percentage, 0.82% vs. 4.66%, *P*-value < 0.0001) and hospital mortality (percentage, 1.41% vs. 7.10%, *P*-value < 0.0001).

The baseline characteristics of survivors and non-survivors grouped were shown in Table 2. Critically ill patients with IHD in the non-survivors group were older, had lower BMI, a higher prevalence of AMI, AF, and AKI, and a lower prevalence of DM (*P*-value < 0.05). In terms

of disease severity scores on admission, the SOFA score, SIRS score, APS III, and SAPS II of critically ill patients with IHD in the non-survivors group were higher than those in the survival group (*P*-value < 0.05). In terms of laboratory tests, critically ill patients with IHD in the non-survivors group had higher levels of WBC, ABG, APTT, and lactate and lower levels of HbA1c, LDL, HDL, and TC (*P*-value < 0.05). There were no statistically significant differences in sex, hypertension, CODP, CKD, PCI history, serum sodium, serum potassium, Scr, TG, PT, and INR between the two groups (*P*-value < 0.05). The SHR of critically ill patients with IHD in the non-survivors group was significantly higher than that in the survivors group (median, 1.05 vs. 1.45, *P*-value < 0.001).

SHR and all-cause mortality in critically ill patients with IHD

Based on SHR tertiles, Kaplan-Meier survival analysis curves were displayed for all-cause mortality between groups (Fig. 2). The all-cause mortality in the groups differed statistically significantly at the 1-month follow-up (log-rank *P*-value < 0.0001, Fig. 2A). At the 3-month follow-up, significant outcomes were also noted (log-rank *P*-value < 0.0001, Fig. 2B).

Cox proportional hazards analysis showed that, when SHR was a continuous variable, there was a significant correlation between SHR and hospital mortality in both the unadjusted model (HR: 2.87 [95%CI: 2.23–3.69], *P*-value < 0.0001) and the fully adjusted model (HR: 1.93 [95%CI: 1.42–2.61], *P*-value < 0.0001). In addition, when SHR is a categorical variable, it is related to hospital mortality in both the unadjusted model (T1 vs. T2: HR: 2.50 [95%CI: 1.26–4.96]; T3: HR: 4.06 [95%CI: 2.17–7.60]; *P* for trend < 0.0001) and the fully adjusted model (T1 vs. T2: HR: 2.06 [95%CI: 1.02–4.14]; T3: HR: 2.16 [95%CI: 1.11–4.19]; *P* for trend = 0.04) and shows an increasing trend as SHR increases. The fully adjusted Cox proportional hazards analysis of SHR and ICU mortality also obtained similar results (Table 3; Fig. 3). The RCS regression model showed that elevated SHR levels were associated with an increased risk of hospital death and ICU death (nonlinear *P* = 0.946 and nonlinear *P* = 0.599, Fig. 4).

Subgroup analysis and sensitivity analysis

We performed stratified analysis of the relationship between SHR and in-hospital all-cause mortality according to age (≤ 65 years and > 65 years), sex, BMI (≤ 30 and > 30 kg/m 2), AMI, CKD, hypertension, and CKD subgroups. The results showed that the primary results remained robust in all subgroups, and no significant interactions were observed (Fig. 5). Interestingly, in the stratified analysis of the relationship between SHR and ICU mortality, the association between SHR and ICU mortality seemed to be more prominent in both male patients [HR (95%CI): male 2.394 (1.367–4.192) vs. female 1.873 (0.996–3.519), *P* for interaction = 0.018] and patients with hypertension [HR (95%CI): hypertension 3.404 (1.95–4.12) vs. no-hypertension 0.917 (0.507–1.656), interaction *P* for interaction = 0.008] (Figure S1).

To clarify the robustness of the association between SHR and all-cause mortality in critically ill patients with IHD, we performed a sensitivity analysis. Stepwise backward regression analysis of cox regression revealed that SHR levels were still positively correlated with all-cause risk. In addition, by excluding patients with a LOS hospital < 3 days, the results consistently showed a positive correlation between SHR and all-cause mortality in critically ill patients with IHD (Table S5 and Table S6).

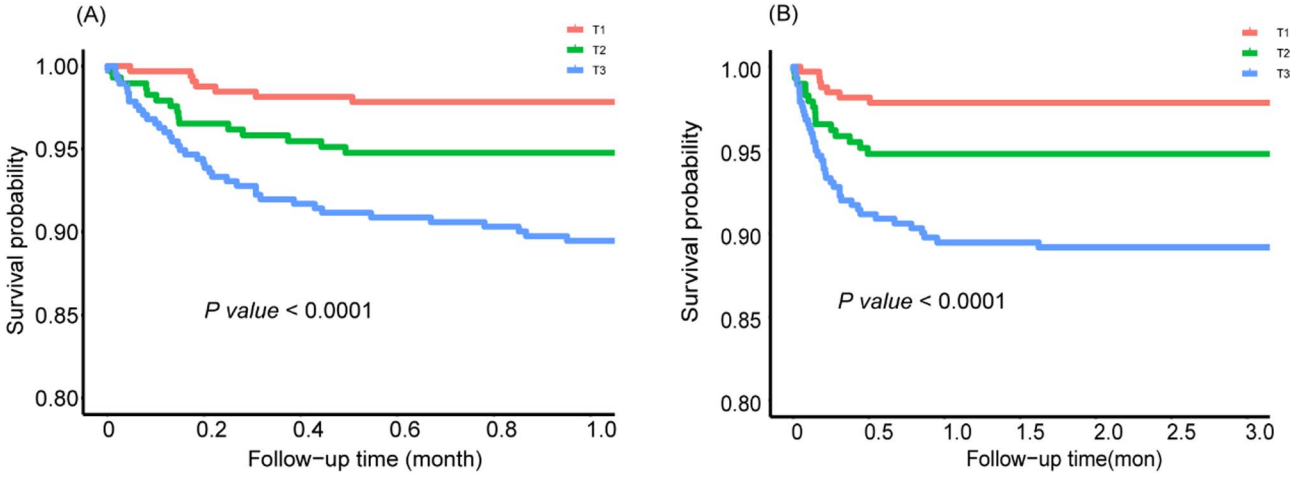

Fig. 2 Kaplan-Meier survival analysis curves for all-cause mortality
SHR tertiles: T1 (0.103,0.933), T2 (0.933–1.223), T3 (1.223–4.311)
Kaplan-Meier curves showing survival probability of all-cause mortality ac-cording to groups at 1 month (**A**), and 3 months (**B**)

Table 3 Cox proportional hazard ratios (HR) for all-cause mortality

Categories	Model 1		Model 2	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Hospital mortality				
Continuous variable per 1 unit	2.87(2.23,3.69)	< 0.0001	1.93(1.42,2.61)	< 0.0001
Tertiles of SHR [a]				
T1	Ref.		Ref.	
T2	2.5(1.26,4.96)	0.01	2.06(1.02,4.14)	0.04
T3	4.06(2.17,7.60)	< 0.0001	2.16(1.11,4.19)	0.02
P for trend		< 0.0001		0.04
ICU mortality				
Continuous variable per 1 unit	2.75(2.02,3.74)	< 0.0001	1.7(1.17,2.47)	0.01
Tertiles of SHR [a]				
T1	Ref.		Ref.	
T2	2.47(1.01, 6.06)	0.05	1.97(0.79,4.93)	0.15
T3	5.2(2.33,11.62)	< 0.0001	2.43(1.04,5.67)	0.04
P for trend		< 0.0001		0.04

Model 1: No variables were adjusted

Model 2: Age, BMI, SOFA score, SIRS, APS III, SAPS II, AMI, DM, AF, AKI, WBC, LDL, HDL, TC, APTT, lactate, and LOS ICU were adjusted

[a]SHR tertiles: T1 (0.103–0.933), T2 (0.933–1.223), T3 (1.223–4.311)

Abbreviations: SHR, stress hyperglycemia ratio; BMI, body mass index; SOFA, sequential organ failure assessment; SIRS, systemic inflammatory response syndrome; APS III, acute physiology score III; SAPS II, simplified acute physiological score II; AMI, acute myocardial infarction; DM, diabetes mellitus; AF, atrial fibrillation/flutter; AKI, acute kidney injury; WBC, white blood cell; TC, total cholesterol; LDL, low-density lipoprotein; HDL, high-density lipoprotein; APTT, activated partial thromboplastin time; LOS, length of stay, ICU, intensive care unit

The predictive ability and incremental effect of SHR

We calculated the area under the ROC curve (AUC) to examine the ability of SHR to predict all-cause mortality. The results showed that among critically ill patients with IHD, SHR had a high predictive value for in-hospital all-cause mortality (AUC: 0.715, 95%CI: 0.697–0.732) and ICU all-cause mortality (AUC: 0.711, 95%CI: 0.693–0.729) (Table S7, Fig. 6 and Figure S2). Additionally, we also performed ROC according to DM subgroups and found that the AUC values of the predictive value of SHR for in-hospital all-cause mortality (0.723 vs. 0.711, *P*-value = 0.846) and ICU all-cause mortality (0.679 vs. 0.732, *P*-value = 0.479) did not change due to DM status (Table S8 and Figure S3). We also analyzed the impact of SHR on the predictive ability of scoring tools (SOFA score, APS III, SAPS II, and SIRS score) and found that SHR significantly increased the predictive value of the SIRS score (AUC (95% CI): SIRS score 0.621 (0.602–0.640) vs. SIRS score + SHR 0.737 (0.719–0.754), *P*-value < 0.001), APS III (AUC (95%CI): APS III 0.759 (0.742–0.776) vs. APS III + SHR 0.802 (0.786–0.817), *P*-value = 0.012), SAPS II (AUC (95%CI) SAPS II 0.771 (0.754–0.787) vs. SAPS II + SHR 0.822 (0.806–0.836), *P*-value = 0.004), and SOFA score (AUC (95%CI) SOFA score 0.667 (0.648–0.685) vs. SOFA score + SHR 0.763 (0.746–0.780), *P*-value < 0.001) for all-cause mortality that occurred in hospitals. Likewise, consistent results were observed for ICU deaths (Table S7 and Figure S2).

Discussion

This study investigated the correlation between SHR and mortality in critically ill patients with IHD, revealing that elevated SHR levels were significantly associated with both higher in-hospital mortality and ICU mortality. After fully adjusting for potential confounders, SHR levels remained linearly and positively associated with in-hospital mortality and ICU mortality. Subgroup analyses demonstrated the robustness of the results. In addition, SHR not only has a strong predictive power for mortality but also significantly enhances the predictive power of existing scoring systems for mortality. These findings highlight the potential of the SHR as a prognostic marker, providing an evidence-based approach to identifying critically ill patients at high risk of IHD.

The formula for SHR (SHR = ABG (mg/dl) / (28.7×HbA1c (%)-46.7)) was adopted from Roberts et al. [10]. This calculation accounts for baseline glycemia (reflected by HbA1c) while isolating the acute glycemic surge during stress, thereby providing a more specific measure of metabolic dysregulation than absolute glucose levels alone. Prior studies have validated SHR's utility in diverse critical care settings, including sepsis and acute coronary syndromes, where it independently predicted mortality and organ dysfunction [13, 20]. In our cohort, this formula ensured that hyperglycemic effects were contextualized within individual glycemic baselines, mitigating confounding by pre-existing diabetes. The association observed between SHR and mortality aligns with earlier findings, reinforcing its role as a robust

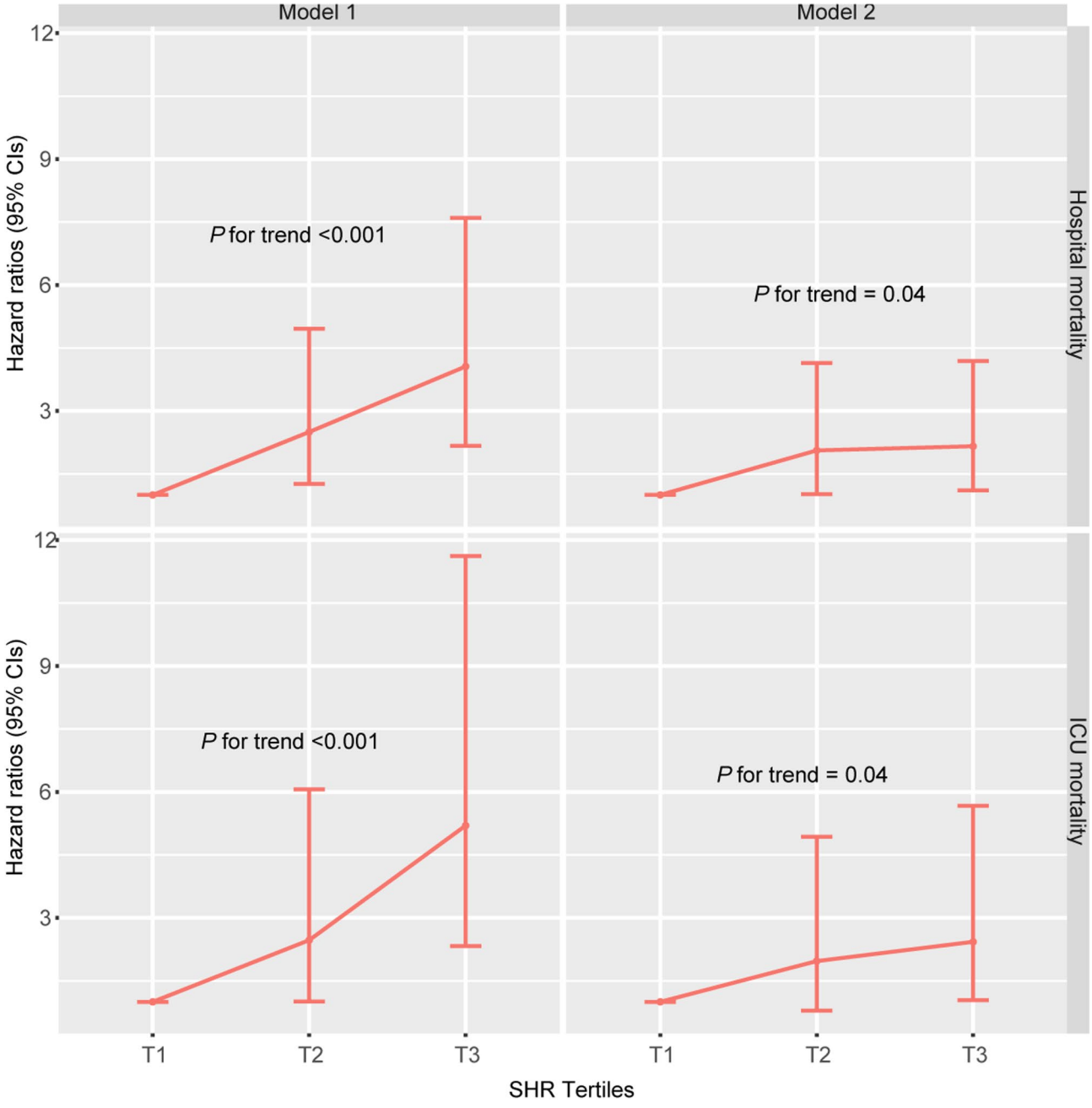

Fig. 3 Adjusted hazard ratios (95% CIs) for hospital mortality and ICU mortality according to SHR tertiles

biomarker of stress-induced metabolic derangements in critically ill IHD patients.

Previous studies have validated SHR's prognostic utility across diverse critical care populations, though with notable variations in risk patterns [19, 21–24]. In sepsis patients ($n = 2312$), Yan et al. [19] reported a U-shaped association between SHR and mortality, where both excessively low and high SHR predicted poor outcomes-a phenomenon attributed to the dual risks of immunosuppression (hypoglycemia) and hyperinflammation (severe hyperglycemia). In contrast, our study found a linear association between elevated SHR and mortality in IHD patients, suggesting that the cardiovascular-specific effects of stress hyperglycemia (e.g., endothelial dysfunction, platelet activation) may dominate in this population. Similarly, Li et al. [22] observed a U-shaped SHR-mortality relationship in a mixed cardiac ICU cohort, but their study did not account for disease-specific severity scores (e.g., SOFA score/SAPS II), which were rigorously adjusted in our analysis. These comparisons highlight that SHR's predictive profile may be context-dependent, with linear risks in IHD potentially reflecting its unique

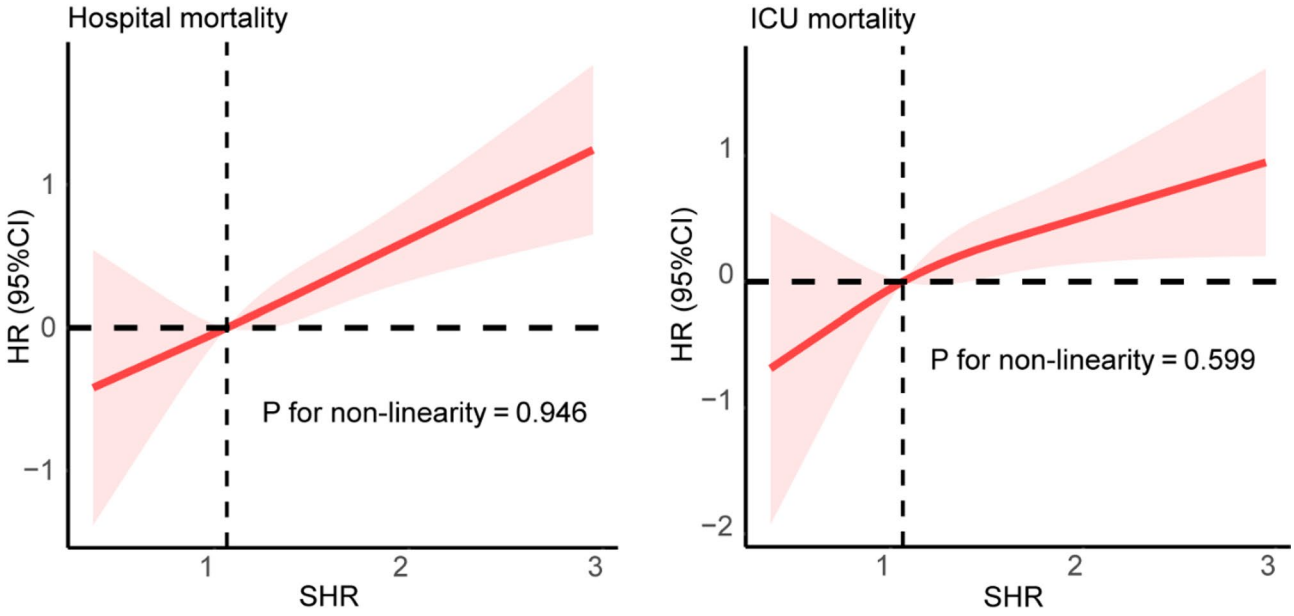

Fig. 4 Restricted cubic spline curve of SHR hazard ratio for hospital mortality and ICU mortality. Models adjusted for the same covariables as in Model 2

susceptibility to acute metabolic disturbances in the present study. In addition, in the study by Yan and Li et al., the inflection points of SHR were 0.85 and 0.95, respectively, while in this study, the number of deaths in the population with SHR less than 0.85 and 0.95 accounted for only 0.31% and 0.59% of the total population. Therefore, the failure to observe a nonlinear relationship may also be due to the small sample size. In addition, although no obvious threshold was found in this study, our results showed that patients with SHR > 1.223 (the highest tertile) had a 2.16-fold increased risk of death (adjusted HR: 2.16). Therefore, in this study, SHR > 1.223 can be used as a high-risk threshold for death in critically ill ischemic heart disease (IHD) patients, and it is recommended to be combined with ICU scores to improve risk stratification. Furthermore, we suggest personalized glucose monitoring in patients with high SHR, with priority given to nondiabetic patients because they are more susceptible to metabolic stress. However, these conclusions need to be validated by large-scale prospective trials.

SHR are more widely applied in cardiovascular disease patients, especially in patients with coronary heart disease and heart failure, etc [24–26]. In an analysis of a large study involving US and Chinese populations, Gao et al. found that elevated SHR was an independent risk factor for 1-year and long-term all-cause mortality in patients with critical acute infarction [23]. A study published by Wang Dong et al. on acute ischemic stroke patients reported that high SHR was significantly associated with early neurological deterioration and long-term dysfunction in patients. This association was particularly evident in nondiabetic patients, suggesting that metabolic abnormalities during stress may cause further damage to brain function [27]. Such studies further confirm the value of SHR in different types of acute diseases. However, research specifically linking SHR with mortality in critically ill patients with IHD has been limited. The present study builds on these findings by adjusting not only for traditional risk factors but also further adjusting for other scoring tools (e.g., SOFA score, APS III) and finds that SHR remains an independent predictor of mortality. In addition, excluding a large proportion of patients might affect the generalizability of our results, particularly if these patients differed systematically from the included cohort. To assess potential bias, we compared baseline characteristics between included and excluded patients (Table S2). Reassuringly, no significant differences were observed in severity scores (e.g., SOFA score, SAPS II, and APS III), suggesting that the exclusion might not disproportionately favor high- or low-risk groups. Therefore, the retained cohort ($n = 2559$) represents well-characterized critically ill IHD patients with complete glucose metabolism data, which strengthens the internal validity of our SHR-mortality association analysis. The consistency of our findings across sensitivity analyses (e.g., excluding short-stay patients and stepwise *COX* proportional hazards models) further supports the robustness of the results.

Additionally, our finding that non-survivors exhibited lower HbA1c levels (6.00% vs. 6.20%, P-value < 0.05) compared to survivors suggests that the adverse effects of stress hyperglycemia may be more pronounced in patients without pre-existing chronic hyperglycemia. In these patients, the abrupt rise in blood glucose during

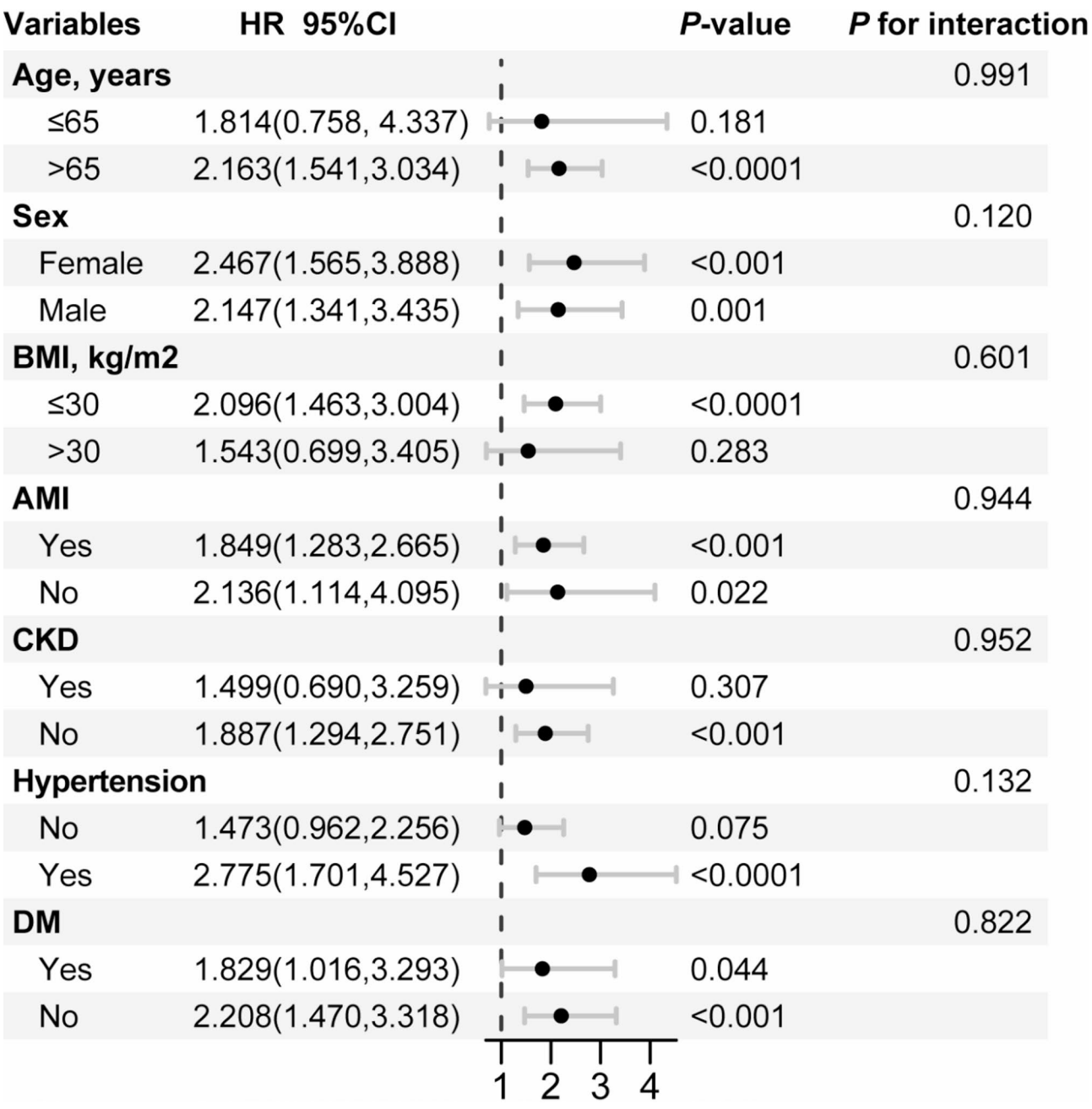

Fig. 5 Forest plots of hazard ratios for the primary endpoint in different subgroups. HR, hazard ratio; CI, confidence interval; BMI, body mass index; AMI, acute myocardial infarction; CKD, chronic kidney disease; DM, diabetes mellitus

acute illness-unbuffered by pre-existing diabetic adaptation-may lead to exacerbated oxidative stress and endothelial dysfunction [28]. Similarly, the lower LDL levels observed in non-survivors (76.00 mg/dL vs. 80.77 mg/dL, *P*-value < 0.05) may reflect a systemic inflammatory state where lipid metabolism is drastically altered. During critical illness, pro-inflammatory cytokines (e.g., IL-6, TNF-α) suppress hepatic LDL production while promoting lipid peroxidation, further contributing to vascular injury [29]. This phenomenon, often termed the 'acute-phase lipid response,' correlates with worse outcomes in IHD and aligns with the mortality risk identified in our cohort. Unlike chronic hyperglycemia or dyslipidemia, SHR captures the dynamic imbalance between acute glucose surge and baseline metabolic reserve, making it particularly prognostic in critical IHD. These observations support the need for tailored glucose management in ICU settings, where strategies to mitigate stress hyperglycemia (e.g., cautious insulin therapy) may improve outcomes. In addition, our diabetes-stratified

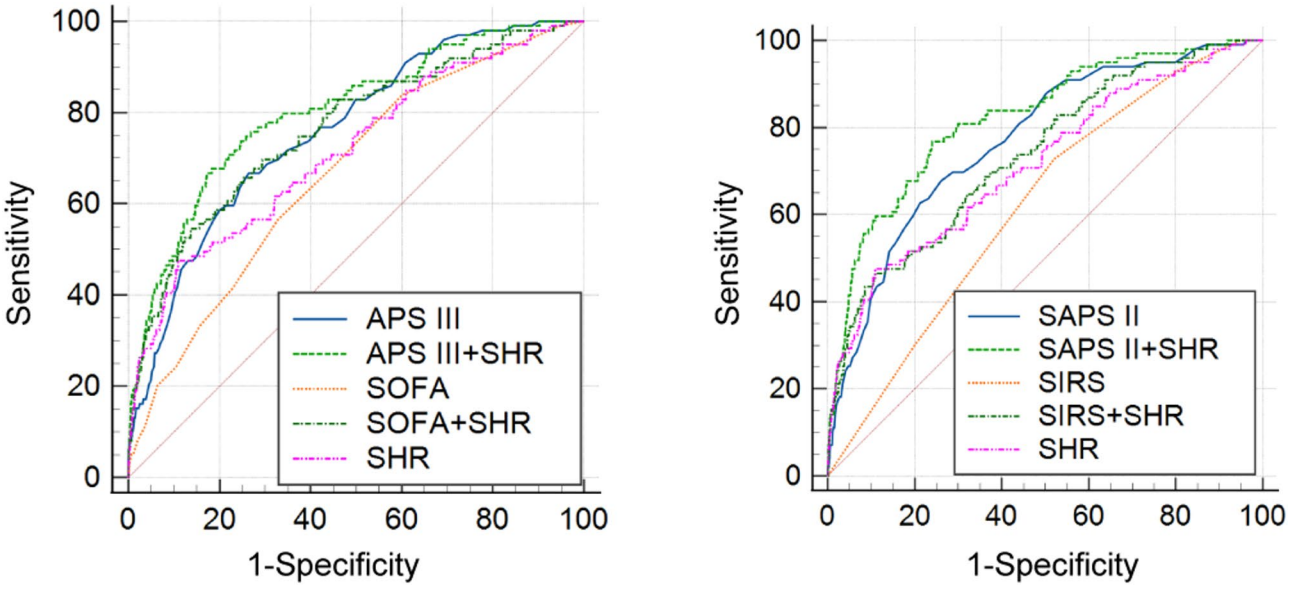

Fig. 6 The ROC curves of SHR as a marker to predict hospital all-cause mortality
Abbreviations: SHR, stress hyperglycemia ratio; ICU, intensive care unit

analysis showed that SHR was a risk factor for mortality in both diabetic patients (in-hospital all-cause mortality: HR = 1.829 and ICU all-cause mortality: HR = 1.170) and non-diabetic patients (in-hospital all-cause mortality: HR = 2.208 and ICU all-cause mortality: HR = 2.142), with the association being stronger in the latter, but this difference might not be differential. Despite this, non-diabetic patients lack the compensatory mechanisms acquired in chronic hyperglycemia, which might make them more vulnerable to acute glycemic surges. This metabolic sensitivity is further supported by the lower HbA1c levels observed in non-diabetic mortality patients. These findings emphasize that non-diabetic patients with high SHR may require earlier intervention to reduce oxidative stress, while diabetic patients may require more stringent monitoring to avoid glycemic excursions.

In addition, in-hospital mortality was significantly higher in critically ill patients with IHD who had elevated SHR levels, both when SHR was studied as a continuous [HR: 1.93 [95%CI: 1.42–2.61]] and categorical variable [HR: 2.16 [95%CI: 1.11–4.19]]. Similar results were obtained when ICU mortality was studied as an endpoint event. In addition, we found that when combined with an existing critical patient scoring system, SHR significantly improved its predictive accuracy, particularly for SOFA score, SIRS score, and APS III scores. This finding emphasizes the role of SHR in complementing existing clinical tools for more accurate mortality risk stratification [30]. Interestingly, we observed that the association between SHR and mortality was more pronounced in male patients and hypertensive patients. Therefore, the relationship between SHR and all-cause mortality might vary significantly in different specific populations. The interaction between SHR and hypertension may reflect the additional cardiovascular stress imposed by both conditions, which together exacerbate endothelial dysfunction and increase the risk of thrombosis [29, 31]. The pathophysiology of elevated SHR and increased mortality is complex and multifactorial, involving the interplay between the stress response, inflammation, and insulin resistance [32]. First, acute hyperglycemia exacerbates oxidative stress and systemic inflammation, with excess glucose promoting the production of reactive oxygen species and activating pro-inflammatory pathways, which can lead to endothelial dysfunction, exacerbate myocardial damage, and impair the recovery process [33, 34]. Second, the hyperglycemia state during stress leads to increased release of counter-regulatory hormones such as cortisol and catecholamines, thereby increasing insulin resistance. This increased insulin resistance worsens hyperglycaemia, creating a vicious cycle that disrupts myocardial recovery and increases the risk of death [28, 35]. Third, the hyperglycemia state also stimulates the release of pro-inflammatory cytokines, such as TNF-α and IL-6 [36]. These cytokines are known to play a role in cardiovascular inflammation and plaque instability, which can lead to adverse cardiac events. For IHD patients in intensive care, cytokine storms triggered by severe hyperglycemia can lead to multiple organ failure [37]. In addition, stress hyperglycaemia leads to increased platelet activity, triggering a hypercoagulable state in the body and increasing the risk of thrombosis [38]. Further increasing the risk of arterio-venous thrombosis in patients with IHD.

Although this study provides important insights, there are some limitations to consider. Firstly, the retrospective nature of this study utilized data from the MIMIC database, which may have been subject to residual confusion despite adjustments. Secondly, SHR is calculated based on glycated hemoglobin, which may not fully capture individual glycaemic variability. Thirdly, the exclusion of 10,257 patients (80% of the original cohort) due to missing glucose or HbA1c data may limit the generalizability of our findings. While there were no systematic differences in disease severity between included and excluded patients, the large proportion of missing data could still introduce selection bias, particularly if the excluded patients had distinct clinical profiles (e.g., milder IHD cases not requiring intensive glucose monitoring). In addition, this study focused on short-term mortality; therefore, further studies are needed to examine the impact of SHR on the long-term prognosis of critically ill IHD patients. This study's results suggested that SHR has potential as both a prognostic marker and a target for tailored glucose management in ICU settings. Future prospective trials should investigate interventions like insulin therapy and anti-inflammatory agents in high-SHR subgroups to validate clinical utility.

Conclusion

SHR levels were linearly and positively correlated with both in-hospital mortality and ICU mortality in critically ill patients with IHD. In addition, the SHR significantly improved the accuracy of the traditional critical patient scores in predicting poor prognosis.

Abbreviations

SHR	Stress hyperglycemia ratio
BMI	Body mass index
SOFA score	Sequential organ failure assessment
SIRS	Systemic inflammatory response syndrome
APSIII	Acute physiology score III
SAPSII	Simplified acute physiological score II
AMI	Acute myocardial infarction
DM	Diabetes mellitus
AF	Atrial fibrillation/flutter
COPD	Chronic obstructive pulmonary disease
AKI	Acute kidney injury
CKD	Chronic kidney disease
PCI	Percutaneous coronary intervention
WBC	White blood cell
TC	Total cholesterol
TG	Triglyceride
LDL	Low-density lipoprotein
HDL	High-density lipoprotein
HbA1c	Hemoglobin A1c
Scr	Serum creatinine
PT	Prothrombin time
INR	International normalized ratio
APTT	Activated partial thromboplastin time
ICU	Intensive care unit
IHD	Ischemic heart disease
HR	Hazard ratio
CI	Confidence interval
ROC	receiver operating characteristic

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12872-025-04831-4.

Supplementary Material 1

Author contributions

Tao Liu contributed to the conceptualization and design of the study, data collection and analysis, and drafting of the manuscript. Lili Wang and Hao Zhang contributed to the literature review, data interpretation and critical revision of the manuscript. Qiming Dai contributed to data analysis, interpretation of results, and provided intellectual input throughout the study. All authors have read and approved the final version of the manuscript.

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Data availability

Online repositories contain the datasets used in this investigation. The names of the repository/ repositories and accession number(s) can be found at: https://mimic.mit.edu/.

Declarations

Consent for publication

Not applicable, this study did not contain any details, images, or videos relating to an individual person.

Ethics and consent to participate declarations

The establishment of the MIMIC III database was approved by the review boards of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center, and informed consent was obtained for all patients. Therefore, no additional ethical approval statement and informed consent requirements were required for this study.

Conflict of interest

All authors have no competing interests.

Clinical trial number

Not applicable.

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