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Stress hyperglycemia ratio as an independent predictor of acute kidney injury in critically ill patients with acute myocardial infarction: a retrospective U.S. cohort study

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ABSTRACT

Background: Acute kidney injury (AKI) is a frequent and severe complication in critically ill patients with acute myocardial infarction (AMI), significantly worsening prognosis. Identifying early risk markers for AKI in AMI patients is critical for timely intervention. The stress hyperglycemia ratio (SHR), a marker of acute glycemic response to physiological stress, has been proposed as a predictor of AKI, but its role remains unclear.

Objective: This study investigates the association between SHR and AKI development in critically ill patients with AMI, using data from the MIMIC-III and MIMIC-IV databases.

Methods: A total of 4,663 critically ill AMI patients were analyzed. SHR was evaluated for its association with AKI incidence using logistic regression, restricted cubic splines, and mediation analysis. Subgroup and sensitivity analyses were performed to confirm robustness. Additionally, Cox regression and Kaplan-Meier survival analysis were used to explore SHR's association with in-hospital mortality in the overall cohort and AKI subgroup.

Results: Higher SHR levels were independently associated with an increased risk of AKI, demonstrating a J-shaped relationship. Mediation analysis revealed that neutrophil count and albumin partially mediated this effect. Kaplan-Meier survival curves showed significant differences in in-hospital mortality among SHR quartiles (log-rank $p < 0.001$). However, Cox regression analysis indicated that SHR was not an independent predictor of in-hospital mortality in either the full cohort or the AKI subgroup.

Conclusions: SHR serves as an early and independent marker for AKI risk in critically ill AMI patients, offering potential utility in clinical risk stratification. However, its role in predicting in-hospital mortality appears limited. These findings underscore the importance of glycemic monitoring and management in AMI patients at risk of AKI.

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Stress hyperglycemia ratio; acute myocardial infarction; acute kidney injury; critical care; glycemic stress response; prognostic biomarker

Introduction

Ischemic heart disease (IHD) remains the leading cause of death globally [1], with acute myocardial infarction (AMI) representing one of the most common and fatal events associated with IHD. Despite continuous advancements in medical technology leading to a gradual reduction in in-hospital mortality for AMI patients, associated complications—particularly acute kidney injury (AKI)—continue to significantly impact patients' quality of life and long-term prognosis. AKI not only increases mortality and morbidity during hospitalization, but is also strongly linked to dialysis dependence and the recurrence of cardiovascular events [2–5]. As such, the early prediction of AKI development and the risk of in-hospital mortality is critically important for the clinical management of patients with cardiovascular diseases.

In 2023, the concept of Cardiovascular-Kidney-Metabolic Syndrome (CKM) was proposed by the American Heart Association (AHA), which formally connects metabolic risk factors with cardiac and renal diseases through shared pathophysiological mechanisms [6]. Among these, hyperglycemia and diabetes are prominent metabolic risk factors that may enhance renal cell sensitivity to apoptosis induced by hypoxia or oxidative stress, thereby increasing the susceptibility of AMI patients to AKI [7].

Stress hyperglycemia (SH) is a common physiological response in critically ill patients, and it has been shown to serve as an important prognostic marker. However, the

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typical assessment of SH is often based on admission blood glucose (ABG) levels, which may not accurately reflect the degree of glucose elevation during acute stress, as it can be influenced by preexisting chronic hyperglycemia. Consequently, in recent years, the stress hyperglycemia ratio (SHR)—defined as the ratio of ABG to estimated average glucose (eAG)—has gained significant attention [8]. SHR is thought to control for background glucose levels, thereby providing a more accurate reflection of the acute stress impact on glucose metabolism in critically ill patients. A systematic review encompassing 26 cohort studies with 87,974 patients demonstrated a significant correlation between elevated SHR levels and adverse short-term and long-term outcomes in patients with AMI [9]. Additionally, a Chinese cohort study involving 1,215 patients with diabetes and AMI found that SHR was significantly associated with an increased risk of developing AKI and adverse cardiovascular events [10].

Currently, the diagnosis of AKI primarily relies on changes in serum creatinine (Scr), which is not a highly sensitive marker for kidney injury. This limitation may result in delayed AKI diagnosis, thereby hindering timely clinical intervention. Despite growing interest in SHR as a potential biomarker for AKI, there is a lack of systematic research on its correlation with AKI occurrence in critically ill patients with AMI, particularly within large clinical cohorts. Therefore, this study aims to explore the potential relationship between SHR and AKI in critically ill AMI patients using data from the MIMIC-III and MIMIC-IV databases. We will employ both univariable and multivariable logistic regression models to investigate this association. The goal of this research is to provide scientific evidence that can aid in the early identification of high-risk groups for AKI in critically ill AMI patients and inform timely intervention strategies.

Methods

Study design and population

This retrospective cohort study analyzed data from the MIMIC-III (version 1.4) and MIMIC-IV (version 3.0) datasets, large datasets developed and maintained by the Laboratory of Computational Physiology at the Massachusetts Institute of Technology. The study included adult patients (aged 18 years or older) diagnosed with AMI who were admitted to the intensive care units (ICUs) of Beth Israel Deaconess Medical Center between 2001 and 2022. If a patient had multiple admissions, only the first hospitalization was considered. The exclusion criteria included: (1) Missing essential data (ABG or HbA1c), (2) Missing information regarding the diagnosis of AKI, (3) Lack of discharge information from the first hospitalization. Ultimately, a cohort of 4663 patients was established (Figure 1).

Access to the datasets was granted upon completion of required training by one of the study authors (Liang Ruan), who received certification (Certification number: 60092717). Given that both datasets are anonymized and have received approval from the Institutional Review Board (IRB), this study waived the requirement for informed consent.

The diagnoses of AMI, acute heart failure (AHF), hypertension (HP), atrial fibrillation (AF), diabetes, and chronic kidney disease (CKD) were based on the International Classification of Diseases (ICD-9 and ICD-10) codes.

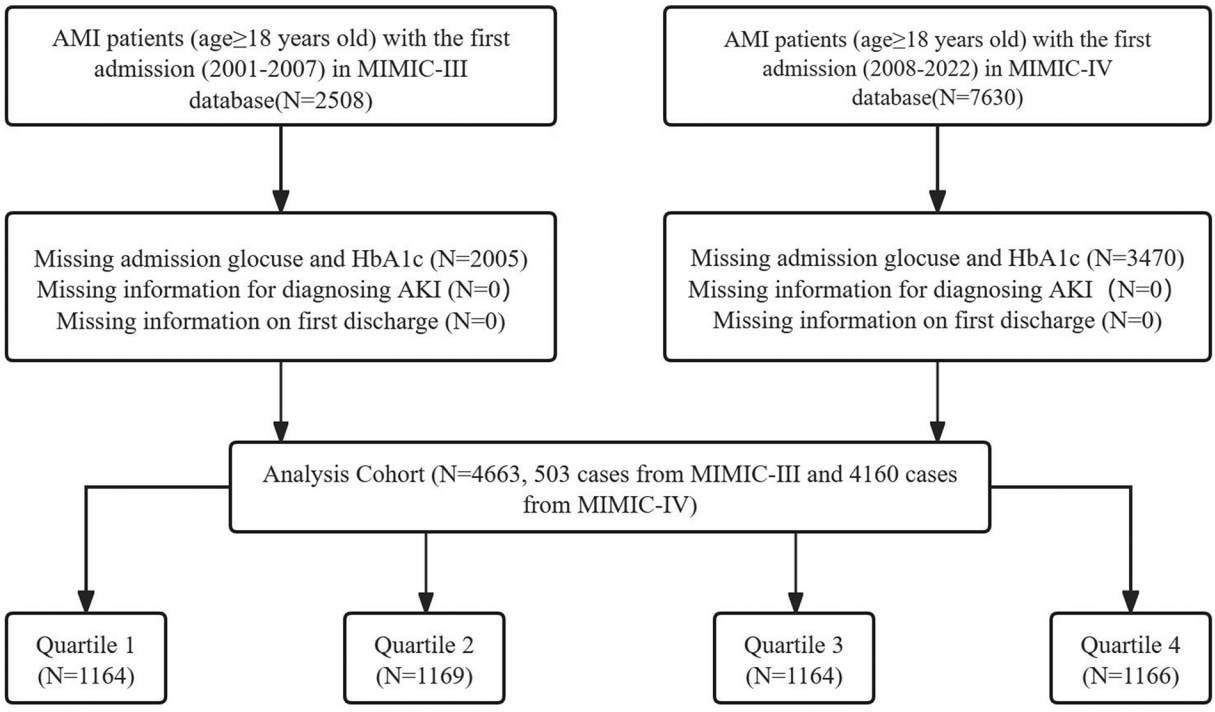

Figure 1. Flow chart of patient selection.

Data collection

In this study, data were extracted using PostgreSQL software (version 13.7.2) and Navicat Premium software (version 16) through Structured Query Language (SQL). The extracted data included demographic characteristics (age, sex, race, body mass index [BMI]), comorbidities (diabetes, atrial fibrillation [AF], acute heart failure [AHF], ST-segment elevation myocardial infarction [STEMI], hypertension [HP], chronic kidney disease [CKD], stage 5 chronic kidney disease [CKD5]), history of coronary artery surgery (coronary artery bypass grafting [CABG], percutaneous coronary intervention [PCI]), sequential organ failure assessment (SOFA) scores, laboratory test results (neutrophils, hemoglobin, troponin T [TNT], creatine kinase MB [CKMB], glycated hemoglobin [HbA1c], creatinine, blood urea nitrogen [BUN], admission blood glucose [ABG], albumin, alanine aminotransferase [ALT], aspartate aminotransferase [AST], triglycerides [TG], total cholesterol [TC], high-density lipoprotein [HDL], low-density lipoprotein [LDL], lactate[Lac], ejection fraction [EF], urine output[UO]), as well as treatment medications and discharge information. All laboratory test results were based on the initial measurements taken upon patient admission.

The SHR was defined as the ratio of ABG to estimated average glucose (eAG), calculated using the following formula: SHR = ABG (mmol/L)/(1.59 × HbA1c [%]-2.59) [8]. To handle missing data, variables with more than 50% missing values were excluded (only N-terminal forebrain natriuretic peptide [NT-pro BNP] had more than 50% missing data) (Figure 2). For other variables, missing values were imputed using the random forest method. The imputation process was performed using the "missForest" package in R, which iteratively builds random forest models to predict missing values based on the observed data [11].

Clinical outcomes

The primary outcome was the occurrence of AKI. The diagnostic criteria for AKI were based on the Kidney Disease: Improving Global Outcomes (KDIGO) guidelines, which require fulfillment of at least one of the following conditions: (1) an increase in Scr to ≥1.5 times baseline within the previous 7 days; (2) an increase in Scr by ≥0.3 mg/dL (≥26.5 μmol/L) within 48 h; or (3) a UO of less than 0.5 mL/kg/hour for 6 consecutive hours [12]. The secondary outcome

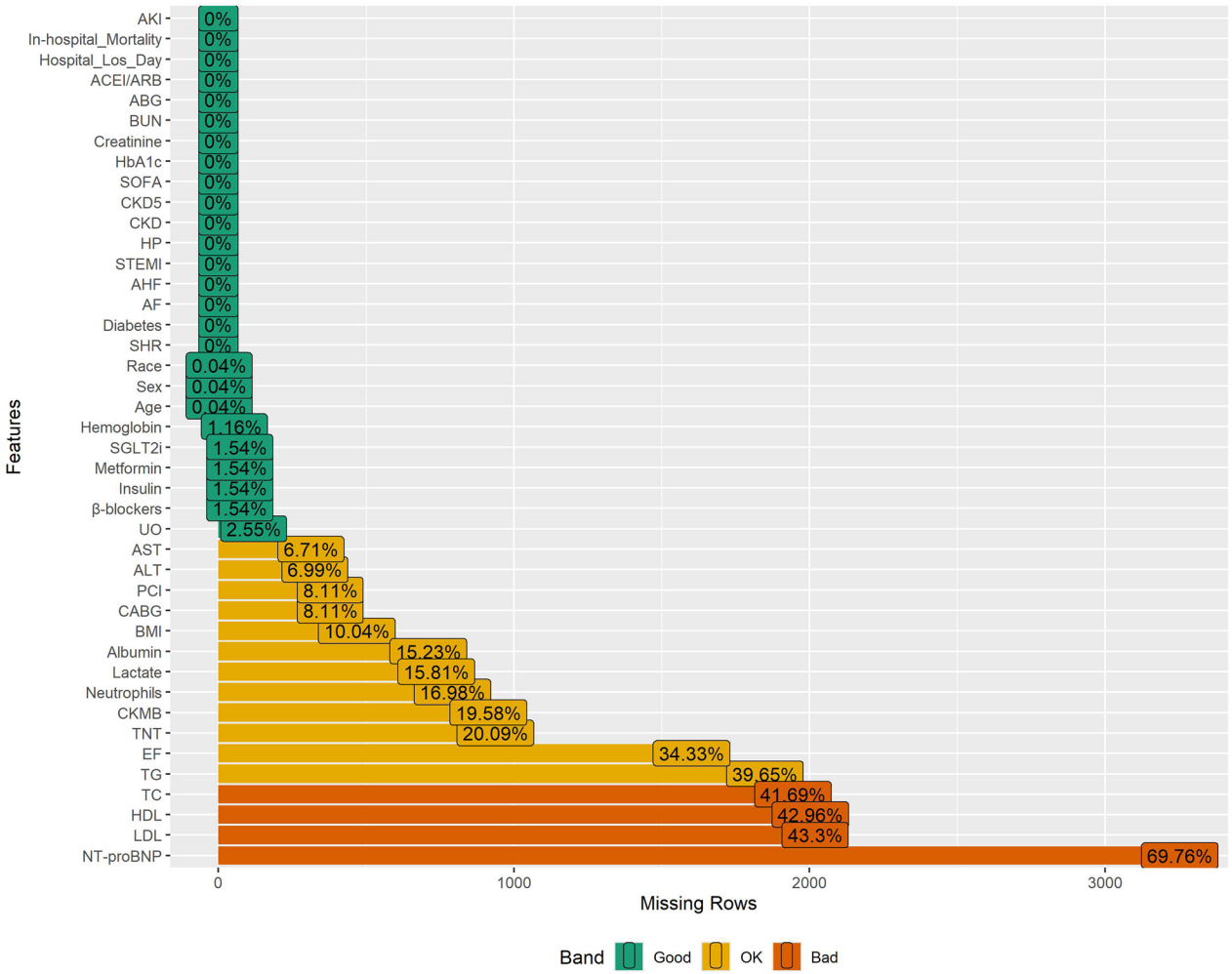

Figure 2. Missing data analysis. Good (green): 0% missing values, OK (yellow): missing values not exceeding 40%; bad (orange): missing values exceeding 40%.

was the overall in-hospital mortality, both for the entire cohort and for those who developed AKI.

Statistical analysis

Patients were categorized into four groups based on the quartiles of the SHR from the MIMIC-III and MIMIC-IV databases. Normally distributed continuous variables are reported as mean ± standard deviation (SD), whereas non-normally distributed variables are reported as median (interquartile range [IQR]). Group comparisons were performed using the Kruskal-Wallis H test, Student's t-test, or one-way analysis of variance (ANOVA), depending on the data distribution and study design. Categorical variables are expressed as frequency and percentage (%), with between-group comparisons assessed using either the chi-square test or Fisher's exact test.

To assess the association between SHR and the risk of AKI in critically ill patients with AMI, both univariable and multivariable logistic regression analyses were performed. Model 1 was unadjusted, and Model 2 was adjusted for age, race, and BMI. In Model 3, variables with statistical or clinical significance from the univariable analysis were included, after excluding multicollinearity using variance inflation factor (VIF) and eigenvalue diagnostics. The variables adjusted for in Model 3 included age, BMI, race, diabetes, AF, AHF, STEMI, hypertension, CKD, CKD5, CABG, PCI, SOFA, neutrophils, CKMB, creatinine, BUN, albumin, ALT, AST, TC, HDL, Lac, EF, UO, angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (ACEI/ARB), and insulin. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to quantify the impact of SHR on AKI.

The dose-response relationship between SHR and the risk of AKI was further explored using restricted cubic splines (RCS), with adjustments for the same variables as in Models 2 and 3. Mediation analysis, performed using the "mediation" package in R, was conducted to examine whether SHR influences the occurrence of AKI *via* neutrophil count, albumin levels, and HbA1c. Additionally, subgroup analyses were performed by age, sex, AHF, CKD, HP, and diabetes status. Sensitivity analyses were conducted by excluding patients with CKD5 to assess the robustness of the association between SHR and AKI.

For the secondary endpoint, survival curves were plotted according to the SHR quartiles, and log-rank tests were used to compare differences between groups. Univariate and multivariable Cox proportional hazards regression models were applied to assess the relationship of SHR with in-hospital mortality, both in the entire cohort and in the AKI subgroup. The fully adjusted model included the following covariates: age, race, diabetes, STEMI, PCI, CABG, SOFA, neutrophils, TNT, CKMB, BUN, albumin, ALT, AST, HDL, lactate, EF, UO, ACEI/ARB, metformin, and β-blockers.

All statistical analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing, Vienna, Austria). Statistical significance was defined as a two-tailed P-value below 0.05.

Results

Baseline characteristics

A total of 4,663 patients were included, with 4,160 patients from the MIMIC-IV dataset and the remaining 503 patients from the MIMIC-III dataset. Among these patients, 1,508 were female (median age [IQR]: 74.22 [17.04] years, 32.34%), and 3,155 were male (median age [IQR]: 69.22 [16.84] years, 68.66%). A total of 3,567 patients (76.60%) developed AKI, and 320 patients (6.86%) died during hospitalization.

The baseline characteristics are summarized in Table 1, stratified by quartiles of the SHR: Q1 ($n = 1,164$, SHR < 0.89), Q2 ($n = 1,169$, $0.89 \leq$ SHR < 1.07), Q3 ($n = 1,164$, $1.07 \leq$ SHR < 1.34), and Q4 ($n = 1,166$, SHR ≥ 1.34). Compared to the lower SHR groups, the Q4 group was older and had higher incidences of diabetes, AF, AHF, and CKD, while the incidences of HP and CABG were lower. Patients in the Q4 group also exhibited higher levels of neutrophils, TNT, CKMB, creatinine, BUN, ALT, AST, and Lac, but lower levels of hemoglobin, albumin, and TC. Among the four SHR groups, the Q2 group had the lowest incidence of AKI (71.00%), whereas the Q4 group had the highest incidence (84.13%) and the highest in-hospital mortality rate (12.18%), which was significantly higher than the other three groups ($p < 0.001$).

In Table 2, we observed that patients in the AKI group were older, had a higher BMI, and a higher proportion of diabetes, AF, AHF, CKD, and CKD5, but a lower proportion of HP and STEMI. Laboratory findings in the AKI group indicated higher levels of neutrophils, creatinine, and BUN, while hemoglobin, CKMB, albumin, and TC levels were lower. Additionally, patients in the AKI group had lower UO (1700.00 [IQR, 1379.00] mL vs. 2385.50 [IQR, 1599.25] mL, $p < 0.001$), lower EF (50.00 [IQR, 26.45] vs. 54.82 [IQR, 28.46], $p < 0.001$), and higher SOFA scores (5.00 [IQR, 5.00] vs. 2.00 [IQR, 3.00], $p < 0.001$).

Correlation of SHR with primary outcome

As shown in Table 3, when treating the SHR as a continuous variable, in the unadjusted Model 1, each one-unit increase in SHR was associated with a 65% higher risk of developing AKI. In Model 2, which adjusted for age, race, and BMI, the risk of AKI increased by 68%. In the fully adjusted Model 3, the risk of AKI increased by 39% for each one-unit increase in SHR.

When dividing SHR into four groups based on quartiles, with the Q2 group (the reference group) having the lowest incidence of AKI (Table 1), statistical analysis was performed. In both Model 1 and Model 2, the risk of AKI was significantly higher in all SHR groups compared to the Q2 group. In Model 3, the highest SHR quartile (Q4) still showed a statistically significant association with an increased risk of AKI (Q4 vs. Q2: OR = 1.57 [95% CI 1.24, 2.00], $p < 0.001$).

To further investigate the potential dose-response association between SHR levels and AKI risk, we plotted RCS. As shown in Figure 3, in the unadjusted Model 1, SHR exhibited a J-shaped association with the occurrence of AKI (P for nonlinear < 0.001). This J-shaped relationship persisted after

Table 1. Baseline characteristics according to SHR quartiles.

Characteristics	Total($n=4663$)	Q1 ($n=1164$)	Q2 ($n=1169$)	Q3 ($n=1164$)	Q4 ($n=1166$)	P
		<0.89	0.89-1.07	1.07-1.34	≥1.34	
Age (years)	70.61 (17.55)	70.60 (17.99)	69.99 (17.15)	70.25 (18.96)	71.73 (16.33)	0.016
Female (n, %)	1,508 (32.34)	368 (31.62)	339 (29.00)	364 (31.27)	437 (37.48)	<.001
Race (n, %)						<.001
White	3,013 (64.62)	734 (63.06)	775 (66.30)	765 (65.72)	739 (63.38)	
Black	372 (7.98)	129 (11.08)	75 (6.42)	66 (5.67)	102 (8.75)	
Asian	110 (2.36)	24 (2.06)	29 (2.48)	32 (2.75)	25 (2.14)	
Others	1,168 (25.05)	277 (23.80)	290 (24.81)	301 (25.86)	300 (25.73)	
BMI (kg/m^2)	28.16 (7.40)	28.36 (7.59)	28.24 (7.01)	28.35 (7.19)	27.77 (8.09)	0.112
Diabetes (n, %)	2,206 (47.31)	595 (51.12)	524 (37.13)	524 (45.02)	653 (56.00)	<.001
AF (n, %)	1,580 (33.88)	406 (34.88)	348 (29.77)	397 (34.11)	429 (36.79)	0.003
AHF (n, %)	1,362 (29.21)	274 (23.54)	301 (25.75)	333 (28.61)	454 (38.94)	<.001
STEMI (n, %)	2,572 (55.16)	605 (51.98)	665 (56.89)	646 (55.50)	656 (56.26)	0.078
HP (n, %)	1,998 (42.85)	537 (46.13)	539 (46.11)	504 (43.30)	418 (35.85)	<.001
CKD (n, %)	1,226 (26.29)	323 (27.75)	272 (23.27)	272 (23.37)	359 (30.79)	<.001
CKD5 (n, %)	288 (6.18)	68 (5.84)	67 (5.73)	67 (5.76)	86 (7.38)	0.276
CABG (n, %)	1,880 (40.32)	600 (51.55)	537 (45.94)	445 (38.23)	298 (25.56)	<.001
PCI (n, %)	1,241 (26.61)	249 (21.39)	349 (29.85)	338 (29.04)	305 (26.16)	<.001
SOFA	4.00 (4.00)	4.00 (4.00)	3.00 (4.00)	4.00 (4.00)	5.00 (5.00)	<.001
Neutrophils (10^9/L)	7.52 (5.15)	6.41 (3.76)	7.13 (4.25)	7.74 (5.42)	9.51 (6.56)	<.001
Hemoglobin (g/L)	12.00 (3.30)	12.00 (3.22)	12.30 (3.10)	12.10 (3.20)	11.50 (3.60)	<.001
TNT (μg/L)	0.47 (1.75)	0.32 (1.28)	0.52 (1.99)	0.49 (1.86)	0.54 (1.96)	<.001
CKMB (IU/L)	13.00 (55.00)	8.00 (31.66)	15.00 (71.00)	13.00 (60.00)	17.00 (65.57)	<.001
HbA1c (%)	6.00 (1.50)	6.30 (2.00)	5.90 (1.10)	5.90 (1.40)	6.10 (1.80)	<.001
Creatinine (mg/dL)	1.10 (0.80)	1.00 (0.70)	1.00 (0.60)	1.00 (0.60)	1.20 (1.00)	<.001
BUN (mg/dL)	20.00 (18.00)	20.00 (17.00)	18.00 (14.00)	20.00 (17.00)	25.00 (25.00)	<.001
ABG (mg/dL)	139.00 (83.00)	101.00 (29.25)	118.00 (34.00)	147.50 (53.00)	229.00 (136.00)	<.001
Albumin (g/dL)	3.60 (0.80)	3.68 (0.73)	3.70 (0.69)	3.60 (0.80)	3.47 (0.80)	<.001
ALT (U/L)	27.00 (33.00)	24.00 (24.00)	27.00 (30.00)	28.00 (34.00)	30.00 (46.00)	<.001
AST (U/L)	37.00 (68.00)	29.00 (35.00)	37.00 (71.00)	39.50 (69.25)	47.50 (109.75)	<.001
TG (mg/dL)	123.54 (113.00)	125.98 (115.06)	122.69 (110.87)	123.21 (113.06)	121.28 (113.04)	0.872
TC (mg/dL)	151.29 (60.00)	151.30 (60.24)	154.00 (58.11)	154.83 (60.00)	146.86 (59.03)	<.001
HDL (mg/dL)	43.00 (20.00)	42.82 (19.04)	42.00 (19.85)	44.00 (20.00)	44.00 (21.96)	0.103
LDL (mg/dL)	80.00 (50.00)	81.82 (50.12)	82.00 (49.00)	82.08 (49.33)	73.00 (46.47)	<.001
Lactate (mmol/L)	1.50 (1.20)	1.40 (0.70)	1.40 (0.90)	1.58 (1.19)	1.90 (1.70)	<.001
EF (%)	50.70 (26.99)	53.38 (25.31)	50.65 (28.07)	50.00 (27.60)	50.00 (27.00)	0.495
Urine output (ml)	1,850.00 (1,519.5)	1,955.00 (1,516.25)	1,928.00 (1,470.00)	1,850.00 (1,466.25)	1,672.50 (1,568.25)	<.001
Insulin (n, %)	3,656 (78.40)	971 (83.42)	855 (73.14)	865 (74.31)	965 (82.76)	<.001
In-hospital Mortality (n, %)	320 (6.86)	53 (4.55)	63 (5.39)	62 (5.33)	142 (12.18)	<.001
AKI (n, %)	3,567 (76.50)	880 (75.60)	830 (71.00)	876 (75.26)	981 (84.13)	<.001
Hospital Los Day (day)	8.66 (8.27)	8.89 (7.21)	7.88 (7.31)	8.10 (8.56)	9.61 (9.48)	<.001

Data are median (interquartile range), or n (%) BMI: body mass index, AF: atrial fibrillation, AHF: acute heart failure, STEMI: ST-segment elevation myocardial infarction, HP: Hypertension, CKD: chronic kidney disease, CKD5: chronic kidney disease stage 5, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, SOFA: sequential organ failure assessment, TNT: Troponin T, CKMB: creatine kinase MB, HbA1c: glycosylated hemoglobin, BUN: blood urea nitrogen, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TG: total triglyceride, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, EF: ejection fraction, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, SGLT2i: sodium-glucose cotransporter 2 inhibitor, Hospital Los Day: hospital length of stay.

adjusting for age, race, and BMI. However, in Model 3, the risk of AKI increased linearly with increasing SHR (P for non-linear = 0.213), with a critical threshold of SHR at 0.86, below which the risk of AKI was the lowest.

Mediation analysis

Mediation analysis revealed that both neutrophils and albumin partially mediate the effect of the SHR on AKI ($p<0.001$ and $p=0.008$, respectively), while HbA1c did not mediate this effect ($p=0.096$) (Figure 4). Neutrophils mediated approximately 11.08% of the total effect of SHR on the risk of AKI ($p<0.001$), and the mediating effect of albumin was 10.74% ($p=0.008$).

Subgroup and sensitivity analyses

We further performed subgroup analyses based on age, sex, diabetes, AHF, HP, and CKD status. As shown in Figure 5, the highest quartile group (Q4) continued to demonstrate a significant association with the incidence of AKI in the following subgroups: age < 70 years (OR = 1.63 [95% CI 1.14, 2.32]), age ≥ 70 years (OR = 1.45 [95% CI 1.03, 2.05]), male (OR = 1.64 [95% CI 1.21, 2.23]), non-diabetes (OR = 1.45 [95% CI 1.05, 2.02]), HP (OR = 1.53 [95% CI 1.09, 2.13]), non-HP (OR = 1.52 [95% CI 1.06, 2.20]), and non-CKD (OR = 1.48 [95% CI 1.12, 1.95]) subgroups (all P for interaction > 0.05). An interaction effect between SHR and AHF on the incidence of AKI was observed (P for interaction = 0.04), with the association between SHR and AKI present only in the non-AHF group (OR = 1.85 [95% CI 1.38, 2.46]). Additionally, a subgroup analysis was performed for type 1 and type 2 diabetes in the diabetic group. As shown in Table 4, there were no statistically significant relationship between SHR and the occurrence of AKI (all $p>0.05$). To evaluate the consistency and reliability of the findings regarding the

Table 2. Baseline characteristics of the AKI and non-AKI groups.

Characteristics	Total ($n=4663$)	Without AKI ($n=1096$)	AKI ($n=3567$)	P
SHR	1.07 (0.45)	1.02 (0.36)	1.08 (0.49)	<.001
Age (years)	70.61 (17.55)	67.18 (17.25)	71.83 (17.09)	<.001
Female (n, %)	1,508 (32.34)	340 (31.02)	1,168 (32.74)	0.286
Race (n, %)				0.003
White	3,013 (64.62)	703 (64.14)	2,310 (64.76)	
Black	372 (7.98)	87 (7.94)	285 (7.99)	
Asian	110 (2.36)	42 (3.83)	68 (1.91)	
Others	1,168 (25.05)	264 (24.09)	904 (25.34)	
BMI, kg/m2	28.17 (7.40)	27.37 (6.83)	28.50 (7.67)	<.001
Diabetes (n, %)	2206 (47.31)	416(37.96)	1790(50.18)	<.001
AF (n, %)	1580 (33.88)	223 (20.35)	1,357 (38.04)	<.001
AHF (n, %)	1,362 (29.21)	180 (16.42)	1,182 (33.14)	<.001
STEMI (n, %)	2,572 (55.16)	678 (61.86)	1,894 (53.10)	<.001
HP (n, %)	1,998 (42.85)	524 (47.81)	1,474 (41.32)	<.001
CKD (n, %)	1,226 (26.29)	179 (16.33)	1,047 (29.35)	<.001
CKD5 (n, %)	288 (6.18)	15 (1.37)	273 (7.65)	<.001
CABG (n, %)	1,880 (40.32)	321 (29.29)	1,559 (43.71)	<.001
PCI (n, %)	1,241 (26.61)	493 (44.98)	748 (20.97)	<.001
SOFA	4.00 (4.00)	2.00 (3.00)	5.00 (5.00)	<.001
Neutrophils (10^9/L)	7.52 (5.15)	6.98 (4.85)	7.68 (5.30)	<.001
Hemoglobin (g/L)	12.00 (3.30)	12.60 (2.90)	11.80 (3.30)	<.001
TNT (μg/L)	0.47 (1.75)	0.49 (2.06)	0.46 (1.66)	0.443
CKMB (IU/L)	13.00 (55.00)	17.00 (81.21)	12.00 (48.00)	<.001
HbA1c (%)	6.00 (1.50)	5.90 (1.33)	6.10 (1.6)	0.038
Creatinine (mg/dL)	1.10 (0.80)	0.90 (0.40)	1.10 (0.80)	<.001
BUN (mg/dL)	20.00 (18.00)	17.00 (12.00)	22.00 (19.00)	<.001
ABG (mg/dL)	139.00 (83.00)	127.00 (65.00)	142.00 (89.00)	<.001
Albumin (g/dL)	3.60 (0.80)	3.80 (0.70)	3.50 (0.80)	<.001
ALT (U/L)	27.00 (33.00)	27.00 (34.00)	27.00 (32.00)	0.634
AST (U/L)	37.00 (68.00)	37.00 (70.00)	37.00 (67.00)	0.120
TG (mg/dL)	123.54 (113.00)	120.93 (115.25)	124.25 (111.95)	0.305
TC (mg/dL)	151.29 (60.00)	158.66 (58.34)	149.71 (58.35)	<.001
HDL (mg/dL)	43.00 (20.00)	45.45 (20.00)	42.66 (20.55)	<.001
LDL (mg/dL)	80.00 (50.00)	82.94 (51.00)	79.00 (49.93)	<.001
Lactate (mmol/L)	1.50 (1.20)	1.60 (1.32)	1.50 (1.10)	0.593
EF (%)	50.70 (26.99)	54.82 (28.46)	50.00 (26.45)	<.001
Urine output (ml)	1,850.00 (1,519.5)	2,382.50 (1,599.25)	1,700.00 (1,379.00)	<.001
ACEI/ ARB (n, %)	2,646 (56.74)	671 (61.22)	1,975 (55.37)	<.001
B-blockers (n, %)	4,128 (88.53)	974 (88.87)	3,154 (88.42)	0.685
Insulin (n, %)	3,656 (78.40)	692 (63.14)	2,964 (83.10)	<.001
Metformin (n, %)	430 (9.22)	102 (9.31)	328 (9.20)	0.911
SGLT2i (n, %)	31 (0.66)	8 (0.73)	23 (0.64)	0.762
In-hospital Mortality (n, %)	320 (6.86)	18 (1.64)	302 (8.47)	<.001
Hospital Los Day (day)	8.66 (8.27)	4.94 (5.04)	9.83 (8.27)	<.001

Data are median (interquartile range), or n (%).

BMI: body mass index, AF: atrial fibrillation, AHF: acute heart failure, STEMI: ST-segment elevation myocardial infarction, HP: Hypertension, CKD: chronic kidney disease, CKD5: chronic kidney disease stage 5, CABG: coronary artery bypass grafting, PCI: percutaneous coronary intervention, SOFA: sequential organ failure assessment, TNT: Troponin T, CKMB: creatine kinase MB, HbA1c: glycosylated hemoglobin, BUN: blood urea nitrogen, ALT: alanine aminotransferase, AST: aspartate aminotransferase, TG: total triglyceride, TC: total cholesterol, HDL: high-density lipoprotein, LDL: low-density lipoprotein, EF: ejection fraction, ACEI: angiotensin-converting enzyme inhibitor, ARB: angiotensin receptor blocker, SGLT2i: sodium-glucose cotransporter 2 inhibitor, Hospital Los Day: hospital length of stay.

Table 3. Logistic regression analyses for primary outcome.

	Model 1		Model 2		Model 3	
SHR group	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
SHR (continuous)	1.65 (1.40,1.93)	<.001	1.68 (1.43,1.97)	<.001	1.39 (1.15,1.69)	<.001
Q1	1.27 (1.05,1.52)	0.012	1.24 (1.03,1.50)	0.023	1.09 (0.89,1.35)	0.402
Q2	Ref		Ref		Ref	
Q3	1.24 (1.03,1.49)	0.020	1.24 (1.03,1.50)	0.021	1.13 (0.91,1.39)	0.269
Q4	2.17 (1.77,2.65)	<.001	2.17 (1.77,2.66)	<.001	1.57 (1.24,2.00)	<.001

Model 1 was unadjusted.

Model 2 was adjusted for race, age, and BMI.

Model 3 was adjusted for age, BMI, race, diabetes, AF, AHF, STEMI, HP, CKD, CKD5, CABG, PCI, SOFA, hemoglobin, neutrophils, CKMB, creatinine, BUN, albumin, ALT, AST, TC, HDL, Lac, EF, UO, ACEI/ARB, insulin.

association of SHR with AKI, we excluded patients with CKD5 and repeated logistic regression analyses (Table 5). The results remained consistent with those obtained from the original cohort.

Correlation of SHR with secondary outcome

Kaplan-Meier survival curves revealed notable differences in in-hospital mortality rates across SHR quartiles, both in the overall cohort and in the AKI group (Figure 6). To further

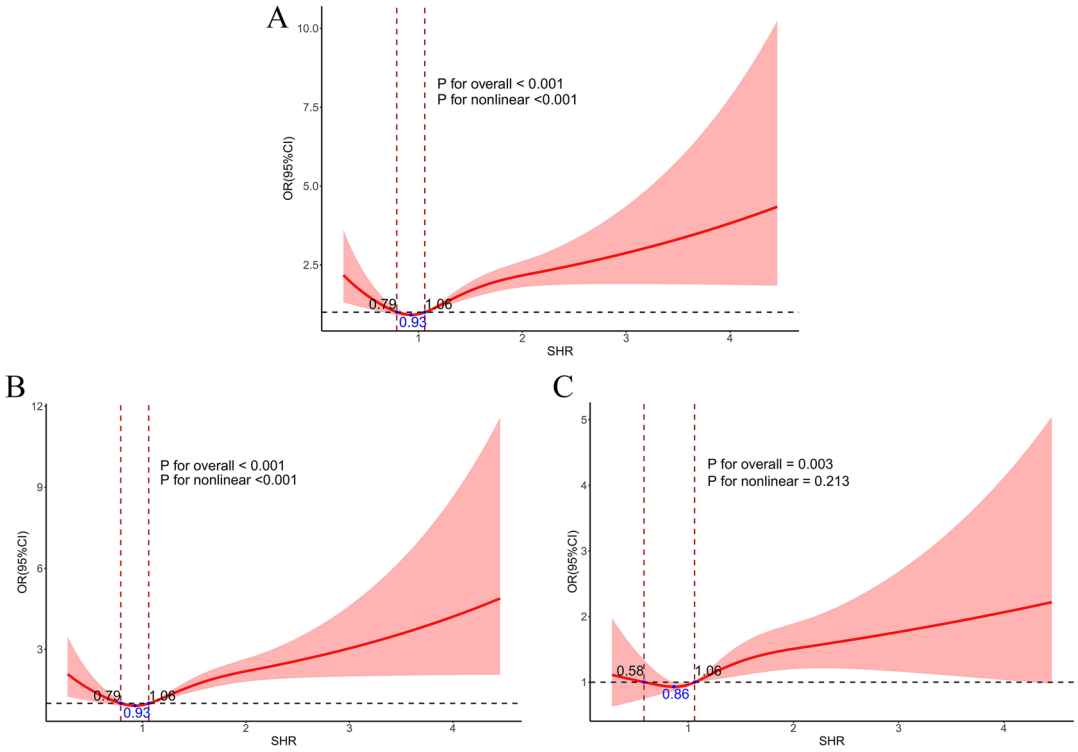

Figure 3. Restricted cubic spline for association of SHR and AKI in critical AMI patients (A) Model 1 was unadjusted. (B) Model 2 was adjusted for race, age, and BMI. (C) Model 3 was adjusted for age, BMI, race, diabetes, AF, AHF, STEMI, HP, CKD, CKD5, CABG, PCI, SOFA, hemoglobin, neutrophils, CKMB, creatinine, BUN, albumin, ALT, AST, TC, HDL, Lac, EF, UO, ACEI/ARB, insulin.

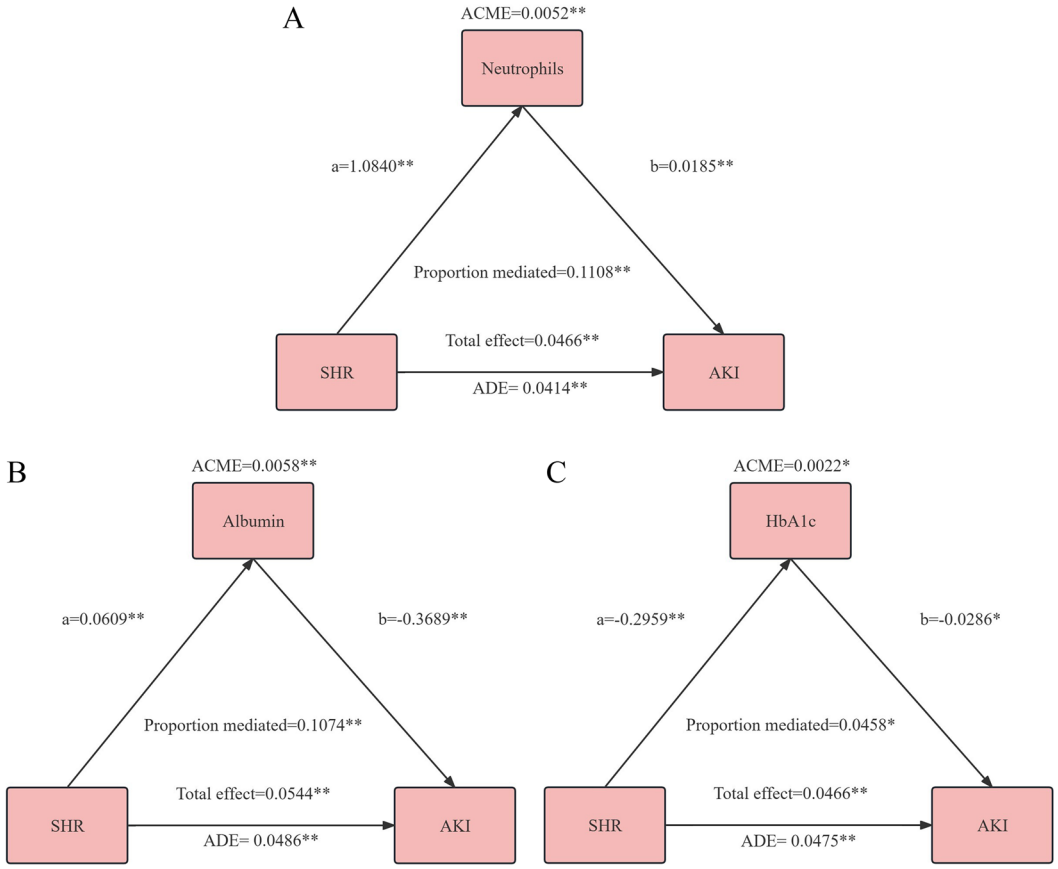

Figure 4. Mediation analysis for the impact of SHR on AKI: the mediating effects of (A) neutrophils, (B) albumin, and (C) HbA1c. Adjusted for age, BMI, race, diabetes, AF, AHF, STEMI, HP, CKD, CKD5, CABG, PCI, SOFA, hemoglobin, CKMB, creatinine, BUN, ALT, AST, TC, HDL, Lac, EF, UO, ACEI/ARB, insulin, (A)+ albumin, (B)+ neutrophils, (C)+ neutrophils and albumin. ACMI: average causal mediated effect, ADE: average direct effect. $^{**}p < 0.05$. *P> =0.05.

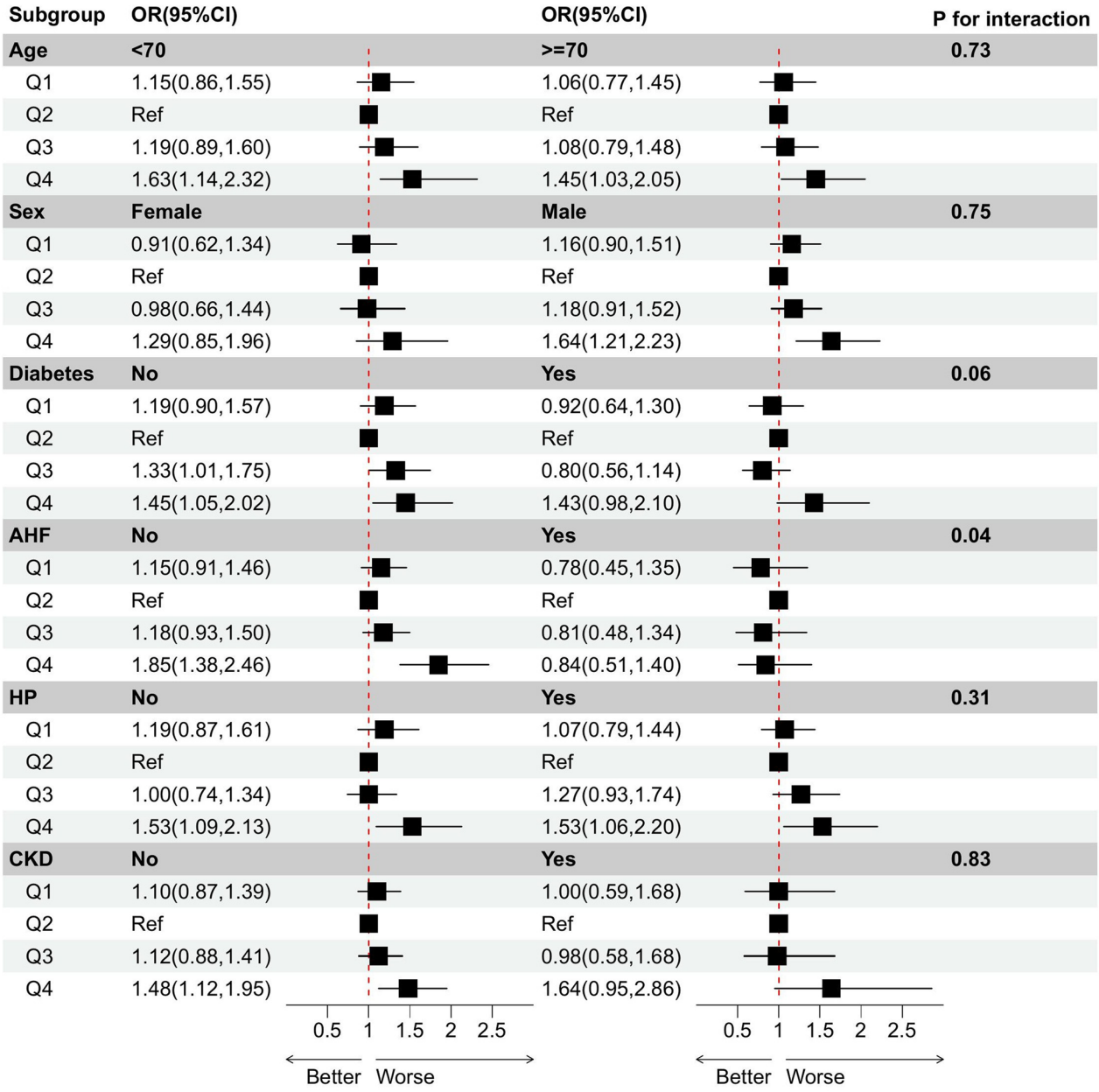

Figure 5. Forest Plot for the associations of SHR and AKI occurrence in different subgroups. AHF: acute heart failure, HP: hypertension, CKD: chronic kidney disease.

Table 4. Logistic regression for primary outcome in T1DM and T2DM.

	T1DM				T2DM			
	Model 1		Model 3		Model 1		Model 3	
SHR group	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
Q1	0.85 (0.19,3.73)	0.828	0.32 (0.03,2.88)	0.307	1.05 (0.77,1.44)	0.752	0.93 (0.65,1.34)	0.700
Q2	Ref		Ref		Ref			
Q3	0.61 (0.14,2.60)	0.508	0.29 (0.03,2.56)	0.264	0.95 (0.69,1.30)	0.731	0.82 (0.57,1.18)	0.285
Q4	1.53 (0.38,6.25)	0.553	1.08 (0.13,9.10)	0.946	1.69 (1.20,3.37)	0.002	1.41 (0.95,2.10)	0.086

Model 1 was unadjusted.
Model 3 was adjusted for age, BMI, race, diabetes, AF, AHF, STEMI, HP, CKD, CKD5, CABG, PCI, SOFA, hemoglobin, neutrophils, CKMB, creatinine, BUN, albumin, ALT, AST, TC, HDL, Lac, EF, UO, ACEI/ARB, insulin.
T1DM: type 1 diabetes mellitus; T2DM: type 2 diabetes mellitus.

evaluate the independent association of SHR with in-hospital mortality, we performed Cox regression analyses, with the Q1 group (which had the lowest in-hospital mortality rate) serving as the reference group (Table 6). When SHR was treated as a continuous variable, in model A, SHR was independently associated with an increased risk of in-hospital

Table 5. Logistic regression for primary outcome (without CKD5 population).

	Model 1		Model 2		Model 3	
SHR group	OR (95%CI)	P	OR (95%CI)	P	OR (95%CI)	P
SHR (continuous)	1.66 (1.41, 1.94)	<.001	1.69 (1.44, 1.99)	<.001	1.35 (1.11, 1.65)	0.003
Q1	1.26 (1.05, 1.52)	0.014	1.24 (1.03, 1.49)	0.026	1.08 (0.87, 1.33)	0.441
Q2	Ref		Ref		Ref	
Q3	1.25 (1.04, 1.51)	0.017	1.25 (1.04, 1.51)	0.017	1.11 (0.90, 1.38)	0.324
Q4	2.16 (1.76, 2.64)	<.001	2.17 (1.77, 2.66)	<.001	1.51 (1.18, 1.92)	<.001

Model 1 was unadjusted.
Model 2 was adjusted for race, age, and BMI.
Model 3 was adjusted for age, BMI, race, diabetes, AF, AHF, STEMI, HP, CKD, CKD5, CABG, PCI, SOFA, hemoglobin, neutrophils, CKMB, creatinine, BUN, albumin, ALT, AST, TC, HDL, Lac, EF, UO, ACEI/ARB, insulin.

mortality among critically ill patients with AMI and the AKI subgroup (both $p < 0.001$). However, in the fully adjusted model B, SHR was no longer statistically significant ($p = 0.409$ for the entire cohort, $p = 0.281$ for the AKI subgroup). When SHR was analyzed as a categorical variable, there was no statistical significance in the comparison between the Q4 and Q1 groups in the fully adjusted model B, regardless of whether the entire study population or only the AKI patients were considered ($p = 0.072$ and $p = 0.206$, respectively).

Discussion

This study represents the first large-scale cohort analysis exploring the potential association between the SHR and the incidence of AKI in American patients with AMI admitted to the ICU. The key findings of this investigation can be summarized as follows: (1) SHR is an independent risk factor for increased AKI occurrence in critically ill patients with AMI, exhibiting a J-shaped correlation; (2) after controlling for potential confounding factors, no statistically significant association was found between SHR and in-hospital mortality in the cohort. Importantly, this study suggests that SHR can effectively and easily identify high-risk individuals for AKI at an early stage in ICU patients with AMI.

Much of the prior research on SH has relied on ABG measurements, which fail to distinguish between chronic and acute hyperglycemia. As a result, some researchers have proposed using the HbA1c as an indicator of long-term glycemic control to adjust ABG levels, leading to the concept of SHR. SHR has since been demonstrated to serve as a more reliable biomarker for critical illness [8]. Our findings indicate that whether SHR is treated as a categorical or continuous variable, there is a statistically significant association with AKI occurrence after full adjustment for confounding factors. However, subgroup analyses reveal that this association is present only in non-diabetes patients (OR = 1.45 [95% CI 1.05, 2.02]), while it is not statistically significant in diabetes patients (OR = 1.43 [95% CI 0.98, 2.10]). This contrasts with findings from Gao et al. who studied 1,215 AMI patients with diabetes and found SHR to be an independent predictor of AKI following adjustment for confounding variables. (OR = 3.18 [95% CI 1.99, 5.09]) [12]. The discrepancy between these studies may arise from the fact that new-onset hyperglycemia is often associated with worse prognosis compared to chronic diabetes with hyperglycemia [13–16]. Liu et al. explored the impact of SHR on mortality in AMI patients in both American and Chinese cohorts and found significant associations with one-year and long-term mortality in non-diabetes patients, while no such association was found in diabetes patients [17]. Similarly, a study on patients with congestive heart failure (CHF) reported that individuals with diabetes in the highest SHR group (SHR ≥ 1.75) had an 81% increased risk of developing AKI, compared to controls, but was 3.49 times higher in non-diabetes patients [18]. This implies that the presence of diabetes may attenuate the relationship between SHR and AKI in critically ill patients with AMI. A potential underlying mechanism is that chronic hyperglycemia leads to a cell regulatory pattern that downregulates glucose transporters, which may protect against the damage caused by acute hyperglycemia [19]. Additionally, animal studies have shown that after myocardial infarction, diabetic animals may reduce cardiac fibrosis and improve contractile function through compensatory mechanisms, such as the positive balance of regulatory genes related to programmed cell survival, this may impact the occurrence of AKI[20]. Previous studies have suggested that the threshold for increased mortality in diabetic individuals is higher than in non-diabetic individuals, leading to the hypothesis that, in critically ill AMI patients, the SHR threshold for the occurrence of AKI may also be elevated [21]. Li et al. categorized patients based on SHR into seven groups and observed a statistical correlation between SHR and AKI only in the highest and lowest SHR groups among diabetic patients, possibly suggesting a degree of rationale in our inference [18].

The heart and kidneys are interconnected through several physiological pathways, and it is well-established that hemodynamic changes, neurohormonal regulation, and inflammatory activation during AMI contribute significantly to the development of AKI, often referred to as Type 1 Cardiorenal Syndrome (CRS) [22]. SH is an acute response mediated by interactions among the hypothalamic-pituitary-adrenal (HPA) axis, the sympathetic-adrenal system, and inflammatory factors, with catecholamines, cortisol, and cytokines playing key roles [23]. Acute hyperglycemia and insulin resistance (IR) are core components of SHR, and both may increase the risk of myocardial ischemia-reperfusion injury. This occurs through activation of stress kinases including c-Jun N-terminal kinase (JNK) and inhibition of insulin-dependent survival pathways regulated by insulin receptor substrate-1 (IRS-1) [24]. These mechanisms contribute to a larger myocardial infarction area, which in turn can lead to AHF, causing elevated central venous pressure, renal congestion, and consequently, an

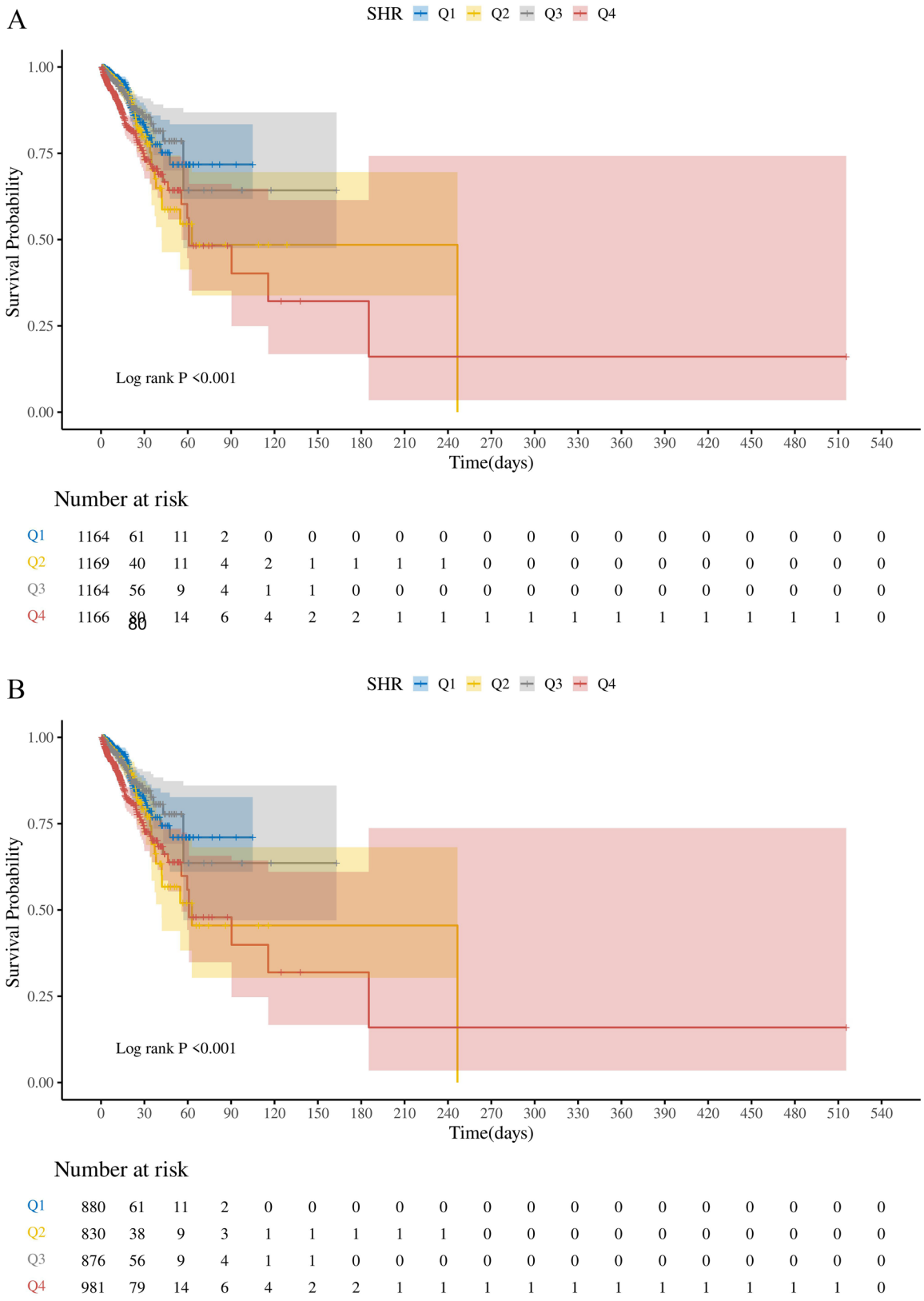

Figure 6. Kaplan–meier analysis for in-hospital mortality of SHR groups in (A) whole population and (B) AKI population.

increased risk of AKI [25–27]. This might explain the observed interaction effect of SHR with AHF on AKI risk in our study (P for interaction = 0.04), with SHR serving as an independent predictor for AKI only in non-AHF patients, not in those with AHF. Such interactions have been recorded in other retrospective studies as well (P for interaction = 0.017) [18].

Table 6. Cox regression for secondary outcome.

	Whole Population				AKI Population			
	Model A		Model B		Model A		Model B	
SHR group	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
SHR (continuous)	1.31 (1.21,1.41)	<.001	1.05 (0.94,1.17)	0.409	1.28 (1.18,1.39)	<.001	0.88 (0.70,1.11)	0.281
Q1	Ref		Ref		Ref			
Q2	1.35 (0.93,1.94)	0.110	1.16 (0.80,1.69)	0.437	1.38 (0.95,2.00)	0.095	1.22 (0.83,1.79)	0.307
Q3	1.24 (0.86,1.79)	0.253	0.97 (0.66,1.41)	0.862	1.20 (0.82,1.74)	0.349	0.98 (0.66,1.45)	0.911
Q4	2.42 (1.76,3.32)	<.001	1.36 (0.97,1.89)	0.072	2.21 (1.60,3.05)	<.001	1.25 (0.88,1.77)	0.206

Model A was unadjusted.
Model B was adjusted for age, race, diabetes, STEMI, PCI, CABG, SOFA, neutrophils, CKMB, TNT, BUN, ALB, ALT, AST, HDL, Lac, EF, UO, ACEI/ARB, Metformin, β-blockers.

Moreover, SHR exacerbates oxidative stress during AMI, and renal tubular epithelial cells, which are rich in mitochondria, are particularly susceptible to oxidative damage. This process triggers the production of reactive oxygen species (ROS), ultimately inducing cellular apoptosis and contributing to kidney injury [24,28]. Oxidative stress has been shown to drive inflammatory responses by upregulating TNF-α through the NF-κB pathway, and inflammation is often correlated with renal function impairment [29]. In our study, neutrophils—an inflammatory marker—were identified as partially mediating the relationship between SHR and AKI.

Previous research has found that SHR is closely correlated with adverse clinical outcomes in conditions like acute ischemic stroke (AIS) and sepsis [30,31]. For instance, Yang et al. found that SHR was significantly linked to in-hospital cardiovascular mortality as well as long-term unfavorable outcomes in patients with acute coronary syndrome (ACS) and drug-eluting stents (DES) [32]. Similarly, Xu et al. reported that SHR serves as a robust predictor of in-hospital mortality in coronary artery disease (CAD) patients, particularly among those with prediabetes and diabetes [33]. In our study, significant differences in in-hospital mortality rates were observed across SHR quartiles ($p < 0.001$), but after adjusting for potential confounders in multivariable Cox regression, no statistically significant association was observed between SHR and in-hospital mortality, either in the overall cohort or in the AKI subgroup. This finding contrasts with a 2023 systematic review on SHR and in-hospital mortality in AMI patients, which found a higher in-hospital mortality rate in the high SHR group compared to the low SHR group. The discrepancy may be due to differences in study cohorts (we focused on ICU AMI patients) and the methods used to calculate SHR (some studies used fasting blood glucose (FBG) levels, while we used the first glucose measurement upon admission) [9]. To further elucidate the relationship between SHR and in-hospital mortality in critically ill AMI patients, more prospective studies are needed.

Blood glucose management is a critical aspect of ICU treatment, with strict glycemic control linked to an increased risk of hypoglycemia without clear evidence of clinical benefit [34–37]. Although the debate about strict vs. conventional blood glucose control continues, it is widely accepted that the prevention of severe hypoglycemia and hyperglycemia is crucial. The spectrum of diseases in ICU patients is complex, and the occurrence of AKI is not only related to AMI but also to conditions such as sepsis and the exacerbation of preexisting kidney diseases [38]. This study focused exclusively on AMI patients, and we found that SHR is J-shaped in relation to the risk of AKI, with a threshold point at 0.86. While severe elevations in SHR were significantly correlated with a higher risk of AKI, mild to moderate SH was not a risk factor for AKI, on the contrary, it may exert a protective effect by establishing a new glucose balance, thereby enhancing glucose utilization as an energy source [39]. Interestingly, the lowest SHR group had the highest rate of insulin use (83.42%), lower ABG levels, and a prevalence of diabetes (51.12%) and AKI occurrence rate (75.60%) second only to the highest SHR group. In Model 3, insulin use was associated with AKI (OR = 1.50 [95% CI 1.18, 1.90]). Thus, we hypothesize that the development of AKI may be linked to low blood glucose levels resulting from insulin use, a correlation that has been observed in previous studies [40]. This suggests that SHR could serve as a valuable reference for developing glycemic control protocols in ICU settings, enabling better management of SH and potentially reducing AKI risk and improving patient outcomes.

Currently, changes in Scr or UO are the primary clinical indicators for diagnosing AKI, which results in a delay of 24 to 48 h in clinical intervention [27]. Notably, this study found that, after fully adjusting for confounding factors, baseline Scr levels were not an independent risk factor for AKI (OR = 1.03 [95% CI 0.92, 1.15], $p = 0.588$), suggesting that Scr levels at admission cannot serve as a reference for the early diagnosis of AKI. Additionally, although urinary biomarkers, such as neutrophil gelatinase-associated lipocalin (NGAL), the combination of tissue inhibitor of metalloproteinase-2 (TIMP-2) and insulin-like growth factor–binding protein 7 (IGFBP7), have demonstrated promising performance in the early diagnosis of AKI, they still have limitations [27,41]. On one hand, the baseline functional status of renal tissue influences the levels of these biomarkers, potentially leading to inaccuracies in low filtration states. On the other hand, these markers are not yet part of routine clinical testing. SHR, as a composite index derived from ABG and HbA1c which are routinely measured in clinical practice, can be used to simply and effectively identify high-risk populations for AKI at an early stage. This facilitates early intervention by clinicians, potentially reducing the incidence of AKI and improving patient outcomes. To date, there have been no clinical studies investigating the relationship between SHR and AKI in American patients with AMI admitted to the ICU, and our study fills this gap.

Strengths and limitations

This study represents the first investigation to explore the relationship between SHR and the risk of AKI in AMI patients admitted to ICU. By analyzing a large cohort comprising 4,663 individuals, we were able to draw significant conclusions regarding the role of SHR in predicting AKI in this high-risk population. However, like any study, this one has certain limitations. First, as a retrospective cohort study, this research is inherently limited in its ability to establish causal relationships between SHR and AKI. To mitigate this limitation, we included a large sample size, which increases the statistical power and robustness of our findings. Moreover, the study relies on data from the MIMIC-III and MIMIC-IV datasets, which, while extensive, lack detailed information on several key factors, including the duration of diabetes, prior glycemic control, the severity of AMI, and social determinants of health (SODH). These missing variables may impact the accuracy and external validity of the findings. Finally, the study population predominantly consisted of American patients, with a majority being of Caucasian ethnicity, potentially restricting the generalizability of the results to other ethnic groups or healthcare systems. Future prospective studies that address these gaps are necessary to confirm the findings and further elucidate the association between SHR and AKI risk in critically ill AMI patients.

Conclusion

This study demonstrates a J-shaped relationship between SHR and the incidence of AKI in critically ill patients with AMI, with elevated SHR levels independently predicting AKI, particularly in individuals without diabetes or AHF. Despite this association, SHR does not appear to be an independent risk factor for in-hospital mortality in this cohort. The findings indicate SHR could be a valuable early indicator of AKI risk, though its role in predicting mortality requires further investigation in prospective studies.

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Disclosure statement

No potential conflict of interest was reported by the author(s).

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Data availability statement

The datasets used during the current study are available from the second author on reasonable request

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