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Risk analysis and mediation analysis of stress hyperglycemia ratio and all-cause mortality in patients with acute kidney injury

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Abstract

Background Stress hyperglycemia ratio (SHR) has been associated with increased mortality from various cerebrovascular events and a higher incidence of acute kidney injury (AKI) in certain patient populations. However, the relationship between SHR and the mortality risk in patients with AKI has not been fully elucidated. Our study sought to comprehensively investigate the association and potential mediating effects between SHR and 28-day and 90-day mortality in patients with AKI.

Methods 3703 patients with AKI were included in this study. Feature importance variables were screened by a random forest algorithm, and the independent association of SHR with mortality risk was determined by Kaplan – Meier survival analysis with Cox regression analysis. Restricted cubic spline (RCS) was conducted to assess the non-linear relationship between SHR and mortality risk. Mediation analysis was deployed to investigate the indirect effect of SHR on respiratory failure (RF) -mediated mortality risk.

Results Among the patients with AKI included in this study, the 28-day mortality was 13.6% and the 90-day mortality was 18.7%. Fully adjusted Cox regression demonstrated that SHR was an independent risk factor for 28-day mortality (HR, 1.77 [95% CI 1.38–2.27], $P < 0.001$) and 90-day mortality (HR, 1.69 [95% CI 1.36–2.11], $P < 0.001$) in patients with AKI. RCS analysis revealed a linear relationship between SHR and outcome events. Additionally, the effect of SHR on 28-day and 90-day mortality risk were mediated by an increased RF risk in 6.62% and 6.54%, respectively.

Conclusion High SHR is an independent risk factor for 28-day and 90-day mortality in patients with AKI, and its effect is partly mediated by an increased risk of RF.

Keywords Stress hyperglycemia ratio, Acute kidney injury, Mortality, MIMIC-IV, Cohort study, Mediation analysis

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Introduction

Acute kidney injury (AKI) represents a major global public health challenge, affecting millions of patients worldwide and characterized by a rapid deterioration of renal function over a short period of time [1]. Approximately 10–15% of hospitalized patients experience AKI, with the incidence reaching 30–70% in critically ill populations [2, 3]. The incidence of AKI is gradually increasing, influenced by a multitude of factors, including population aging, increased use of nephrotoxic medications, and invasive surgical procedures. Globally, AKI is associated with poor outcomes, including cardiovascular disease, chronic kidney disease (CKD), and significantly elevated mortality risk. It is estimated that around 1.7 million deaths occur annually due to AKI worldwide [4]. Therefore, the identification of AKI patients at high risk of mortality is paramount for improving their prognosis. In recent years, while novel biomarkers such as neutrophil gelatinase-associated lipocalin and kidney injury molecule-1 have emerged, there remains a paucity of effective prognostic assessment tools for AKI patients. There is a pressing need to establish a convenient and reliable prognostic parameter to identify and adequately manage AKI patients at heightened risk of mortality.

Stress hyperglycemia refers to a transient increase in blood glucose levels triggered by physiological or psychological stress, commonly observed in critically ill ICU patients. Stress hyperglycemia is closely associated with inflammation, oxidative stress, and endothelial dysfunction, and is a significant risk factor for adverse outcomes [5, 6]. The stress hyperglycemia ratio (SHR), calculated from admission blood glucose and glycated hemoglobin A1c (HbA1c), is a representative indicator for evaluating stress hyperglycemia. By considering both current blood glucose and baseline glycemic status, SHR more effectively assesses a patient's true blood glucose profile and is thus regarded as a marker of disease severity in critically ill patients. Extensive research has consistently demonstrated that SHR is closely linked to the mortality risk of major adverse cardiovascular and cerebrovascular events, such as acute myocardial infarction, coronary artery disease, and stroke [7–9]. Furthermore, SHR has been shown to be significantly associated with the risk of AKI in patients with acute heart failure (HF) and in non-diabetic critically ill patients [10, 11]. However, the relationship between SHR and the 28-day and 90-day mortality risks in AKI patients has not been fully elucidated. Therefore, the present study aims to evaluate the association and potential mediating effects between SHR upon ICU admission and the 28-day and 90-day mortality in AKI patients.

Methods

Study population

This was a retrospective cohort study based on a large-scale critical care database. The data source was the medical information mart for intensive care IV (MIMIC-IV) database, a publicly available, free, and open-access database that records health-related data for ICU inpatients at Beth Israel Deaconess Medical Center from 2008 to 2019. The author, Yue Shi, obtained the necessary certification to use the MIMIC-IV database. Due to the de-identified nature of patient information in the database, the study was exempt from the requirement of ethical approval and informed consent.

The study included adult ICU patients diagnosed with AKI according to ICD-9 or ICD-10 codes. For patients with multiple ICU admissions, only data from the first admission was extracted. Patients lacking blood glucose and HbA1c measurements within 24 h of ICU admission were excluded (Fig. 1).

Data acquisition and definition

The data was extracted using Structured Query Language (SQL) running on PostgreSQL (version 13.7.2) from the MIMIC-IV database. The following information was retrieved: (1) Demographic information: sex, age, body mass index (BMI); (2) Illness severity scores: Sequential Organ Failure Assessment (SOFA) score, Simplified Acute Physiology Score (SAPS II); (3) Comorbidities: CKD, HF, RF, hypertension, diabetes, chronic obstructive pulmonary disease (COPD), malignancy, and acute coronary syndrome (ACS); RF was defined as arterial oxygen partial pressure (PaO_2) < 60 mmHg or PaO_2/fractions of inspired oxygen ≤ 300 mmHg, with or without carbon dioxide retention. (4) Interventions: renal replacement therapy (RRT), diuretics, and vasoactive drugs; (5) Laboratory parameters: white blood cell (WBC) count, hemoglobin, red cell distribution width (RDW), platelet count, creatinine, blood urea nitrogen (BUN), albumin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC), triglycerides (TG), potassium, sodium, chloride, glucose, and HbA1c. These laboratory parameters were obtained from the initial records after ICU admission. Except for a portion of ALT, AST, TC, and TG, all the variables were complete. For the missing ALT, AST, TC, and TG values, multiple imputation using a random forest algorithm was performed.

Exposure variables and outcome endpoints

SHR is calculated as follows [12]: [Plasma glucose (mg/dL) / (28.7 × HbA1c (%) – 46.7)]. The primary outcome endpoints were 28-day mortality and 90-day mortality.

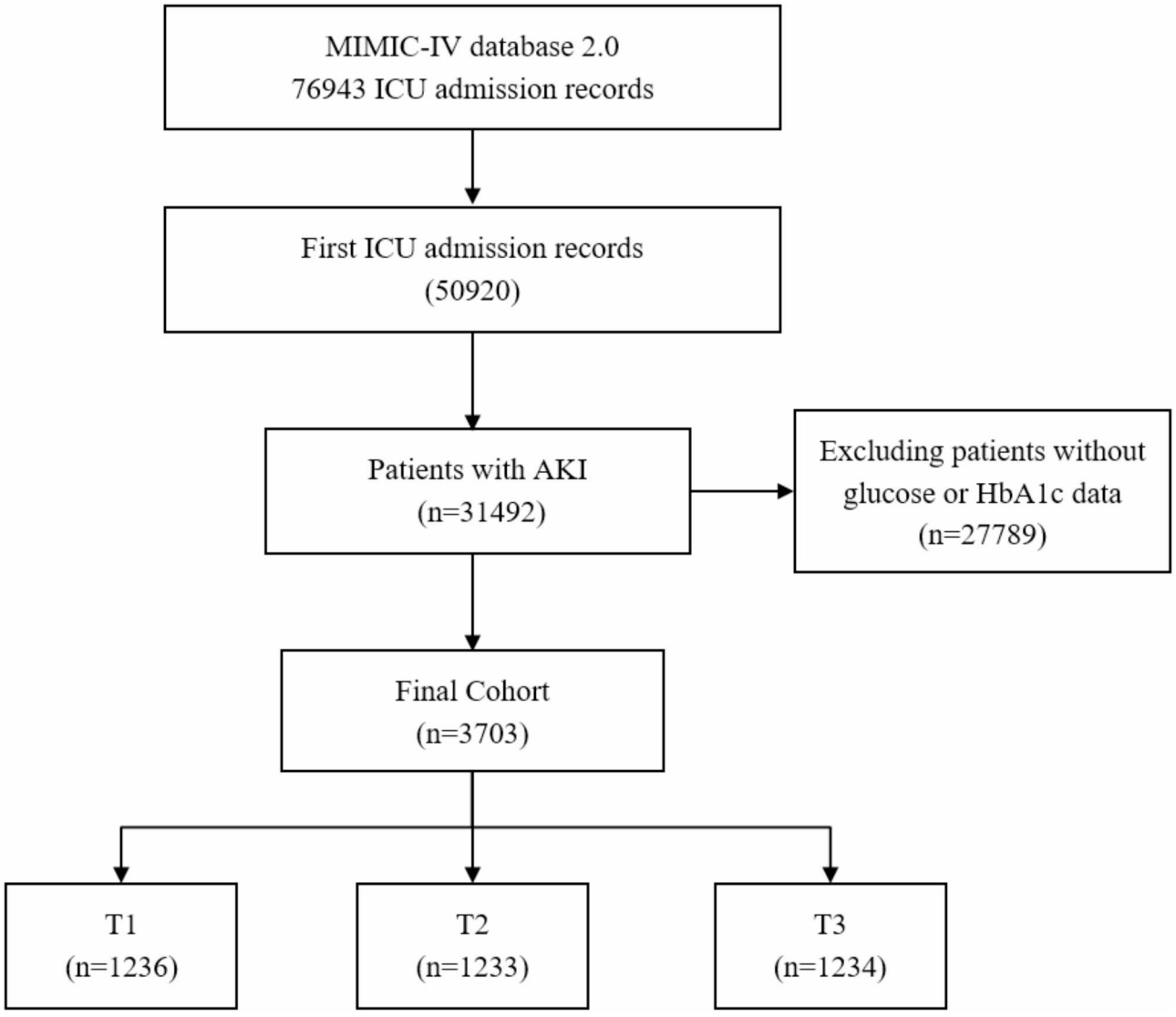

Fig. 1 Flow chart of patient selection

Feature selection

Prior to investigating the association between SHR and clinical outcomes in AKI patients, we employed machine learning algorithms to perform feature selection and confirm the importance of the variables in the prognostic model. We primarily utilized the random forest model for variable feature selection, and the SHapley Additive extension package was used to visualize the variable importance [13].

Statistical analysis

The continuous variables were expressed as medians (quartiles) due to their non-normal distribution, while categorical variables were presented as percentages. Comparisons between groups for continuous variables were performed using the Kruskal-Wallis H or Mann-Whitney U test, while categorical variables were compared using the chi-square or Fisher's exact test.

Cox regression models were employed to determine the association between SHR and 28-day and 90-day mortality in AKI patients, with adjustment for multiple confounding variables. Model 1 was unadjusted, and Model 2 was adjusted for sex, age, and BMI. Model 3 was comprehensively adjusted based on the feature importance selected by the random forest algorithm (Fig. 2), as well as clinical and previous literature experience, including variables such as sex, age, BMI, SOFA, SAPS II, CKD, hypertension, HF, RF, COPD, diabetes, malignancy, diuretics, vasoactive drugs, RRT, WBC, hemoglobin, RDW, platelet, creatinine, BUN, albumin, ALT, AST, TC, TG, potassium, sodium, chlorine, and glucose. Kaplan-Meier survival analysis was used to evaluate the mortality among groups based on the tertiles of SHR, and the

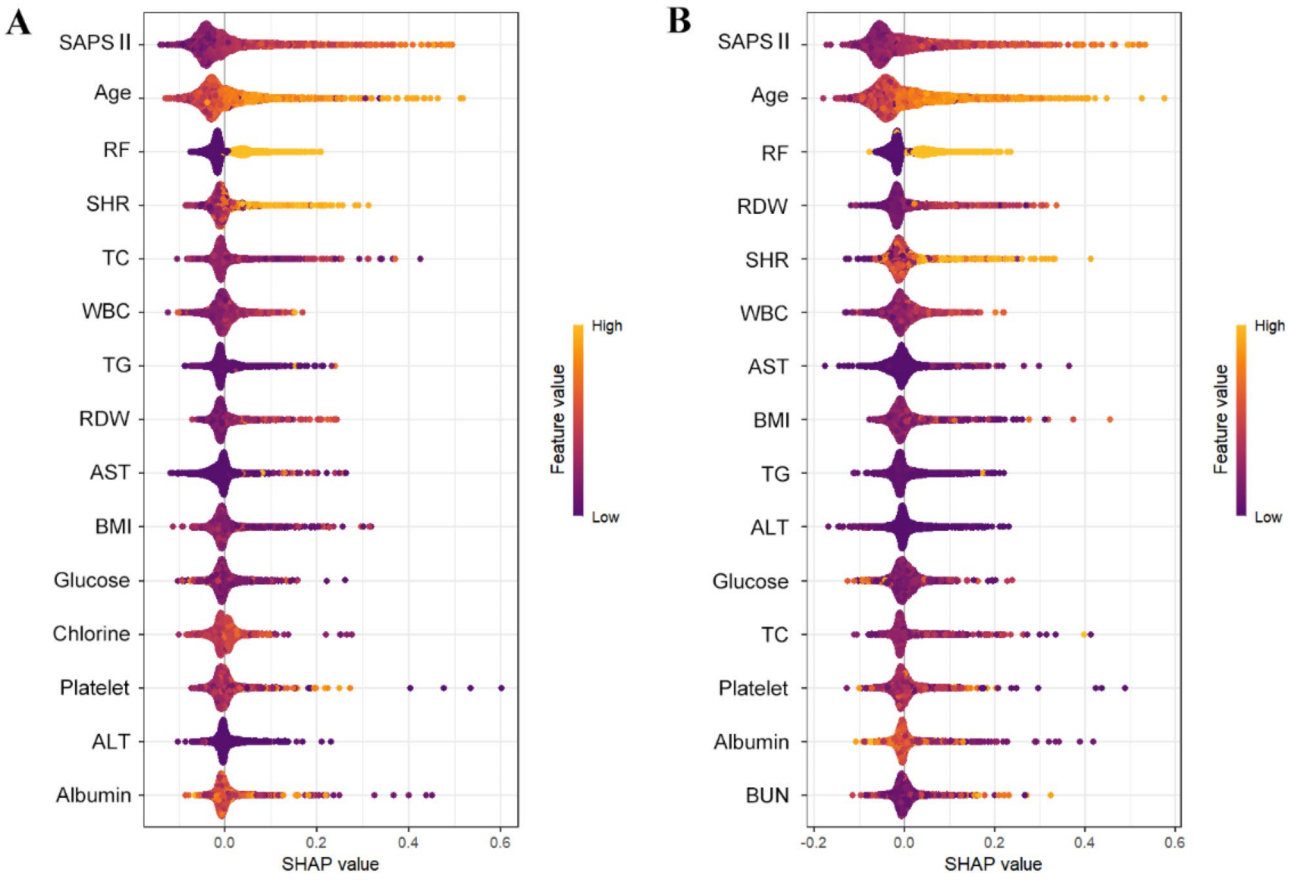

Fig. 2 Feature selection based on random forest algorithm for 28-day mortality (**A**) and 90-day mortality (**B**)

Log-Rank test was employed to assess the between-group differences.

RCS was utilized to evaluate the potential non-linear relationship between SHR and 28-day and 90-day mortality. Furthermore, we performed subgroup analyses to further investigate the effects of SHR on clinical outcomes in different subgroups (age, sex, BMI, diabetes, hypertension, CKD, HF, and RF). Finally, we conducted mediation analysis to assess the direct effect of SHR on mortality and the indirect effect mediated through RF.

Data analysis was performed using R software (Version 4.2.0) and STATA software (Version 16.0). A two-sided *P*-value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 3703 patients with AKI were enrolled in this study, with an overall median age of 68.4 years, and 2,163 (58.4%) were male. Patients were divided into three groups based on the tertiles of SHR in the cohort (T1: SHR ≤ 0.95, T2: SHR 0.95–1.25, T3: SHR > 1.25), and their baseline characteristics are presented in Table 1. Patients with higher SHR were generally younger, had higher BMI, SOFA, and SAPS II scores, and had a higher prevalence of CKD, HF, RF, DM, and ACS as well as a higher likelihood of receiving RRT, diuretics, and vasoactive drug treatment. In terms of laboratory indicators, WBC, creatinine, BUN, TG, ALT, AST, potassium and blood glucose levels were higher for those with higher SHR, while the opposite was true for albumin, sodium and chlorine.

The baseline characteristics of 28-day survivors and non-survivors are presented in Table 2. Compared to survivors, non-survivors tended to be older, more likely to be female, and had higher SOFA and SAPS II scores. Non-survivors had a higher proportion of concomitant RF and malignancy, and were more likely to receive vasoactive drugs and RRT. Additionally, non-survivors exhibited higher levels of WBC, RDW, creatinine, BUN, AST, potassium, sodium, chlorine, blood glucose, and SHR, while they had lower levels of hemoglobin, albumin, TC, TG, and HbA1c.

SHR is associated with all-cause mortality in patients with AKI

During follow-up, 505 patients (13.6%) died within 28 days, and 692 patients (18.7%) died during the 90 days. The 28-day and 90-day mortality rates were 9.9% and 15.1% for patients with low SHR, 13.0% and 17.6% for

Table 1 Baseline characteristics of participants categorized by SHR

Variables	Overall *n* = 3703	T1 (≤ 0.95) *n* = 1236	T2 (0.95–1.25) *n* = 1233	T3 (> 1.25) *n* = 1234	*P*-value
Age (years)	68.4 (56.8, 79.1)	69.6 (57.9, 79.9)	68.9 (56.8, 79.8)	67.1 (56.0, 77.5)	0.003
Male, n (%)	2163 (58.4)	715 (57.9)	733 (59.5)	715 (57.9)	0.664
BMI (kg/m^2)	28.6 (24.5, 33.8)	28.7 (24.3, 33.5)	28.2 (24.5, 33.5)	29.1 (24.7, 34.3)	0.025
SOFA	4.0 (2.0, 6.0)	3.0 (1.0, 5.0)	3.0 (2.0, 5.0)	5.0 (2.0, 8.0)	<0.001
SAPS II	33.0 (26.0, 42.0)	32.0 (25.0, 40.0)	33.0 (26.0, 40.0)	36.0 (28.0, 45.0)	<0.001
Comorbidities, n (%)					
CKD	756 (20.4)	255 (20.6)	211 (17.1)	290 (23.5)	<0.001
HF	1179 (31.8)	365 (29.5)	364 (29.5)	450 (36.5)	<0.001
RF	1075 (29.0)	269 (21.8)	322 (26.1)	484 (39.2)	<0.001
Hypertension	1833 (49.5)	618 (50.0)	643 (52.2)	572 (46.4)	0.014
Diabetes	898 (24.3)	298 (24.1)	247 (20.0)	353 (28.6)	<0.001
COPD	238 (6.4)	73 (5.9)	74 (6.0)	91 (7.4)	0.250
Malignancy	562 (15.2)	174 (14.1)	216 (17.5)	172 (13.9)	0.019
ACS	405 (10.9)	97 (7.9)	127 (10.3)	181 (14.7)	<0.001
Interventions, n (%)					
RRT	258 (7.0)	63 (5.1)	70 (5.7)	125 (7.0)	<0.001
Diuretics	1195 (32.3)	371 (30.0)	364 (29.5)	460 (37.3)	<0.001
Vasoactive drugs	738 (19.9)	180 (14.6)	192 (15.6)	366 (29.7)	<0.001
Laboratory tests					
WBC (K/uL)	10.7 (8.0, 14.3)	9.2 (7.1, 11.9)	10.8 (9.2, 13.7)	12.6 (9.2, 16.8)	<0.001
Hemoglobin (g/dL)	11.9 (10.2, 13.4)	11.8 (10.3, 13.4)	12.1 (10.5, 13.5)	11.6 (9.9, 13.4)	<0.001
RDW (%)	14.0 (13.2, 15.1)	14.0 (13.2, 15.1)	13.8 (13.1, 14.9)	14.1 (13.2, 15.3)	<0.001
Platelet (K/uL)	204.0 (159.0, 259.0)	208.0 (162.0, 259.0)	206.0 (163.0, 256.0)	200.5 (152.0, 262.0)	0.124
Creatinine (mg/dL)	1.0 (0.8, 1.4)	1.0 (0.7, 1.4)	1.0 (0.8, 1.3)	1.1 (0.8, 1.6)	<0.001
Albumin (g/dL)	3.3 (2.9, 3.7)	3.4 (2.9, 3.8)	3.4 (2.9, 3.8)	3.3 (2.8, 3.7)	<0.001
BUN (mg/dL)	19.0 (14.0, 29.0)	18.0 (13.0, 28.0)	18.0 (13.0, 26.0)	21.0 (15.0, 34.0)	<0.001
TC (mg/dL)	156.0 (124.1, 193.0)	155.0 (125.0, 191.0)	158.0 (125.0, 195.0)	156.0 (121.6, 192.2)	0.118
TG (mg/dL)	119.0 (87.0, 202.6)	119.0 (87.0, 191.6)	119.0 (85.0, 197.0)	127.0 (91.3, 219.5)	0.014
ALT (U/L)	25.0 (17.0, 38.0)	25.0 (16.0, 31.0)	25.0 (18.0, 36.0)	25.0 (20.0, 53.0)	<0.001
AST (U/L)	33.0 (23.0, 53.0)	33.0 (21.0, 42.0)	33.0 (24.0, 47.0)	33.0 (27.0, 80.0)	<0.001
Sodium (mmol/L)	138.0 (137.0, 140.0)	138.0 (138.0, 141.0)	138.0 (137.0, 140.0)	138.0 (136.0, 140.0)	<0.001
Potassium (mmol/L)	4.1 (3.7, 4.5)	4.0 (3.7, 4.4)	4.0 (3.7, 4.4)	4.2 (3.7, 4.6)	<0.001
Chlorine (mmol/L)	103.0 (100.0, 107.0)	104.0 (101.0, 107.0)	103.0 (100.0, 106.0)	102.0 (98.0, 106.0)	<0.001
Glucose (mg/dL)	137.0 (109.0, 191.0)	104.0 (92.0, 126.0)	131.0 (116.0, 153.0)	204.0 (164.0, 277.0)	<0.001
HbA1c (%)	5.9 (5.5, 6.8)	6.0 (5.6, 7.2)	5.8 (5.4, 6.4)	6.0 (5.4, 6.9)	<0.001

SHR: stress hyperglycemia ratio; BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; CKD, chronic kidney disease; HF, heart failure; RF, respiratory failure; COPD, chronic obstructive pulmonary diseases; ACS, acute coronary syndrome; RRT, renal replacement therapy; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c: glycosylated hemoglobin A1c.

those with medium SHR, and 18.1% and 23.3% for patients with high SHR, respectively (Fig. 3). Similarly, the Kaplan-Meier curves (Fig. 4) showed that the 28-day and 90-day mortality of AKI patients gradually increased with higher SHR (Log-rank $P < 0.0001$).

Multivariable Cox regression analysis (Table 3) showed that SHR was an independent risk factor for both 28-day mortality (HR, 1.77 [95% CI 1.38–2.27], $P < 0.001$) and 90-day mortality (HR, 1.69 [95% CI 1.36–2.11], $P < 0.001$) in patients with AKI. After full adjustment, each one-unit increase in SHR was associated with a 77% and 69% increased risk of 28-day and 90-day mortality, respectively. Additionally, patients in the highest tertile of SHR had a significantly increased risk of adjusted 28-day mortality (HR, 1.56 [95% CI 1.18–2.05], $P = 0.002$) and 90-day mortality (HR, 1.42 [95% CI 1.12–1.79], $P = 0.003$).

The RCS curve (Fig. 5) demonstrated a linear association between SHR and the outcomes (P for non-linearity > 0.05), indicating that the risk of 28-day and 90-day mortality increased linearly with increasing SHR.

Subgroup analysis

To further assess the impact of SHR on AKI mortality, stratified and interaction analyses were conducted based on subgroups of age, sex, BMI, CKD, diabetes, hypertension, HF, RF, and ACS (Fig. 6). The results showed

Table 2 Baseline characteristics of participants categorized by 28-day mortality

Variables	Overall (*n* = 3703)	Survivors (*n* = 3198)	Non-survivors (*n* = 505)	*P*-value
Age (years)	68.4 (56.8, 79.1)	67.5 (56.1, 77.8)	76.2 (64.0, 85.0)	<0.001
Male, n (%)	2163 (58.4)	1913 (59.8)	250 (49.5)	<0.001
BMI (kg/m^2)	28.6 (24.5, 33.8)	28.9 (24.7, 34.1)	26.7 (23.2, 32.0)	<0.001
SOFA	4.0 (2.0, 6.0)	3.0 (2.0, 6.0)	5.0 (3.0, 8.0)	<0.001
SAPS II	33.0 (26.0, 42.0)	32.0 (25.0, 40.0)	42.0 (35.0, 51.0)	<0.001
Comorbidities, n (%)				
CKD	756 (20.4)	642 (20.1)	114 (22.6)	0.195
HF	1179 (31.8)	1010 (31.6)	169 (33.5)	0.399
RF	1075 (29.0)	813 (25.4)	262 (51.9)	<0.001
Hypertension	1833 (49.5)	1585 (49.6)	248 (49.1)	0.850
Diabetes	898 (24.3)	793 (24.8)	105 (20.8)	0.051
COPD	238 (6.4)	201 (6.3)	37 (7.3)	0.375
Malignancy	562 (15.2)	461 (14.4)	101 (20.0)	<0.001
ACS	405 (10.9)	347 (10.9)	58 (11.5)	0.671
Interventions, n (%)				
RRT	258 (7.0)	192 (6.0)	66 (13.1)	<0.001
Diuretics	1195 (32.3)	1018 (31.8)	177 (35.1)	0.151
Vasoactive drugs	738 (19.9)	582 (18.2)	156 (30.9)	<0.001
Laboratory tests				
WBC (K/uL)	10.7 (8.0, 14.3)	10.5 (7.9, 13.9)	12.3 (9.2, 16.8)	<0.001
Hemoglobin (g/dL)	11.9 (10.2, 13.4)	12.0 (10.3, 13.4)	11.4 (9.9, 13.0)	<0.001
RDW (%)	14.0 (13.2, 15.1)	13.9 (13.2, 15.0)	14.4 (13.4, 15.9)	<0.001
Platelet (K/uL)	204.0 (159.0, 259.0)	204.0 (161.0, 259.0)	203.0 (10.0, 262.0)	0.339
Creatinine (mg/dL)	1.0 (0.8, 1.4)	1 (0.8, 1.4)	1.1 (0.8, 1.6)	<0.001
Albumin (g/dL)	3.3 (2.9, 3.7)	3.4 (2.9, 3.8)	3.2 (2.7, 3.6)	<0.001
BUN (mg/dL)	19.0 (14.0, 29.0)	19.0 (13.0, 28.0)	22.0 (15.0, 36.0)	<0.001
TC (mg/dL)	156.0 (124.1, 193.0)	157.2 (125.0, 194.0)	150.0 (118.0, 185.6)	<0.001
TG (mg/dL)	119.0 (87.0, 202.6)	121.0 (88.0, 205.0)	119.0 (81.0, 185.0)	0.010
ALT (U/L)	25.0 (17.0, 38.0)	25.0 (18.0, 38.0)	25.0 (15.0, 44.0)	0.726
AST (U/L)	33.0 (23.0, 53.0)	33.0 (23.0, 51.0)	33.0 (25.0, 76.0)	<0.001
Sodium (mmol/L)	138.0 (137.0, 140.0)	138.0 (137.0, 140.0)	138.0 (137.0, 141.0)	0.007
Potassium (mmol/L)	4.1 (3.7, 4.5)	4.1 (3.7, 4.5)	4.1 (3.7, 4.6)	0.366
Chlorine (mmol/L)	103.0 (100.0, 107.0)	103.0 (100.0, 106.0)	104.0 (100.0, 107.0)	<0.001
Glucose (mg/dL)	137.0 (109.0, 191.0)	136.0 (108.0, 188.0)	145.0 (118.0, 214.0)	<0.001
HbA1c (%)	5.9 (5.5, 6.8)	5.9 (5.5, 6.9)	5.8 (5.4, 6.5)	<0.001
SHR	1.1 (0.9, 1.4)	1.1 (0.9, 1.3)	1.2 (1.0, 1.6)	<0.001

BMI, body mass index; SOFA, sequential organ failure assessment; SAPS II, simplified acute physiology score II; CKD, chronic kidney disease; HF, heart failure; RF, respiratory failure; COPD, chronic obstructive pulmonary diseases; ACS, acute coronary syndrome; RRT, renal replacement therapy; WBC, white blood cell; RDW, red blood cell distribution width; BUN, blood urea nitrogen; TC, total cholesterol; TG, triglyceride; ALT, alanine aminotransferase; AST, aspartate aminotransferase; HbA1c: glycosylated hemoglobin A1c; SHR: stress hyperglycemia ratio.

that SHR was significantly associated with the 28-day mortality risk in various subgroups of patient with AKI, including those aged ≤ 65 years or > 65 years, females, BMI ≤ 30 kg/m^2 or > 30 kg/m^2, non-diabetic, non-ACS, non-CKD, and non-HF patients, as well as those with or without hypertension and RF. Similar findings were observed in the subgroup analyses using 90-day mortality as the outcome. Notably, the association between SHR and AKI mortality was more pronounced in patients aged < 65 years, with BMI > 30 kg/m^2, and without diabetes (*P* for interaction < 0.05).

Mediation analysis of the effect of SHR on mortality in patients with AKI

We performed mediation analysis to explore the mediating effect of RF. Figure 7 depicted the mediating effect of RF on the relationship between SHR and 28-day and 90-day mortality. With regard to 28-day mortality, the mediation analysis revealed that RF mediated 6.62% of the detrimental effect of SHR. Likewise, for 90-day mortality, RF accounted for 6.54% of the association between SHR and the outcome.

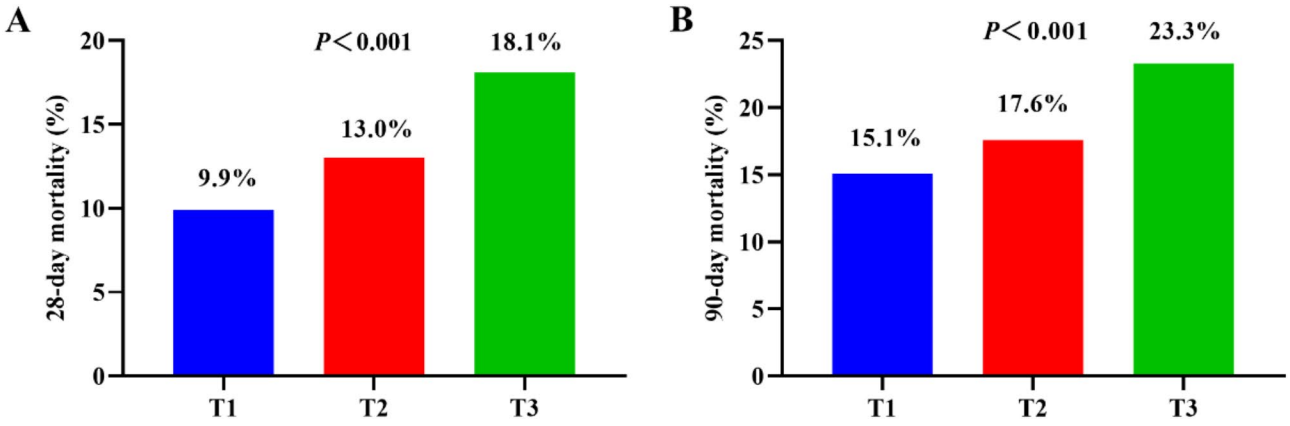

Fig. 3 Mortality based on SHR tripartite groups (**A**) 28-day mortality; (**B**) 90-day mortality

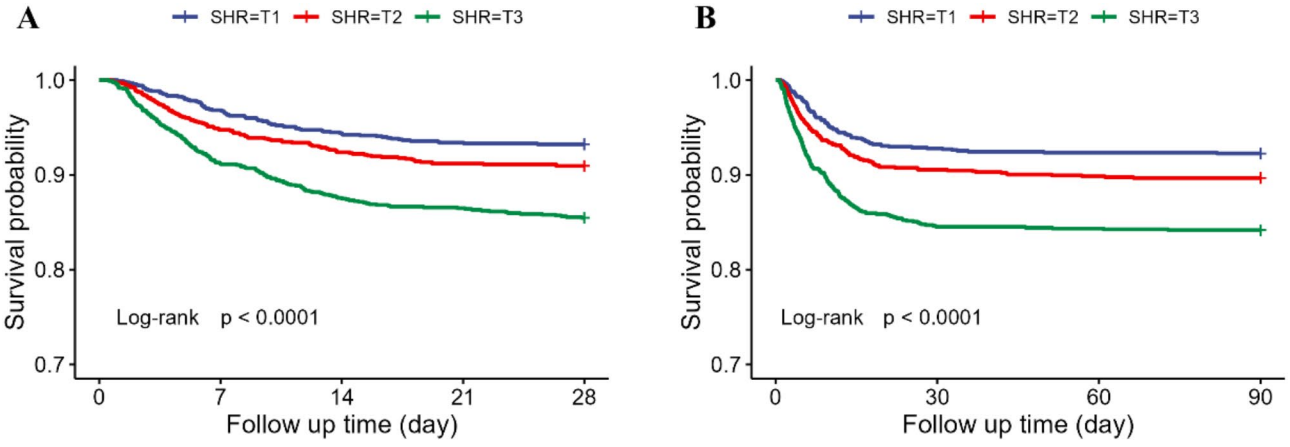

Fig. 4 Kaplan–Meier analysis for 28-day mortality (**A**) and 90-day mortality (**B**)

Table 3 The associations of SHR with all-cause mortality in patients with AKI

Categories	Model 1 HR (95% CI)	*P*-value	Model 2 HR (95% CI)	*P*-value	Model 3 HR (95% CI)	*P*-value
28-day mortality						
SHR, Per 1-point increment	1.70 (1.49, 1.94)	<0.001	1.78 (1.56, 2.02)	<0.001	1.77 (1.38, 2.27)	<0.001
SHR (category)						
T1 (≤ 0.95)	Ref.		Ref.		Ref.	
T2 (0.95–1.25)	1.35 (1.06, 1.70)	0.013	1.37 (1.08, 1.73)	0.009	1.29 (1.02, 1.66)	0.036
T3 (> 1.25)	1.94 (1.55, 2.41)	<0.001	2.05 (1.65, 2.56)	<0.001	1.56 (1.18, 2.05)	0.002
P for trend		<0.001		<0.001		0.002
90-day mortality						
SHR, Per 1-point increment	1.60 (1.39, 1.77)	<0.001	1.66 (1.47, 1.87)	<0.001	1.69 (1.36, 2.11)	<0.001
SHR (category)						
T1 (≤ 0.95)	Ref.		Ref.		Ref.	
T2 (0.95–1.25)	1.19 (0.98, 1.45)	0.077	1.22 (1.00, 1.48)	0.050	1.18 (0.96, 1.45)	0.106
T3 (> 1.25)	1.64 (1.37, 1.98)	<0.001	1.76 (1.46, 2.12)	<0.001	1.42 (1.12, 1.79)	0.003
P for trend		<0.001		<0.001		0.003

Model 1 was unadjusted.

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

Model 3 was adjusted for sex, age, BMI, SOFA, SAPS II, CKD, hypertension, HF, RF, COPD, diabetes, malignancy, diuretics, vasoactive drugs, RRT, WBC, hemoglobin, RDW, platelet, creatinine, BUN, albumin, ALT, AST, TC, TG, potassium, sodium, chlorine, and glucose.

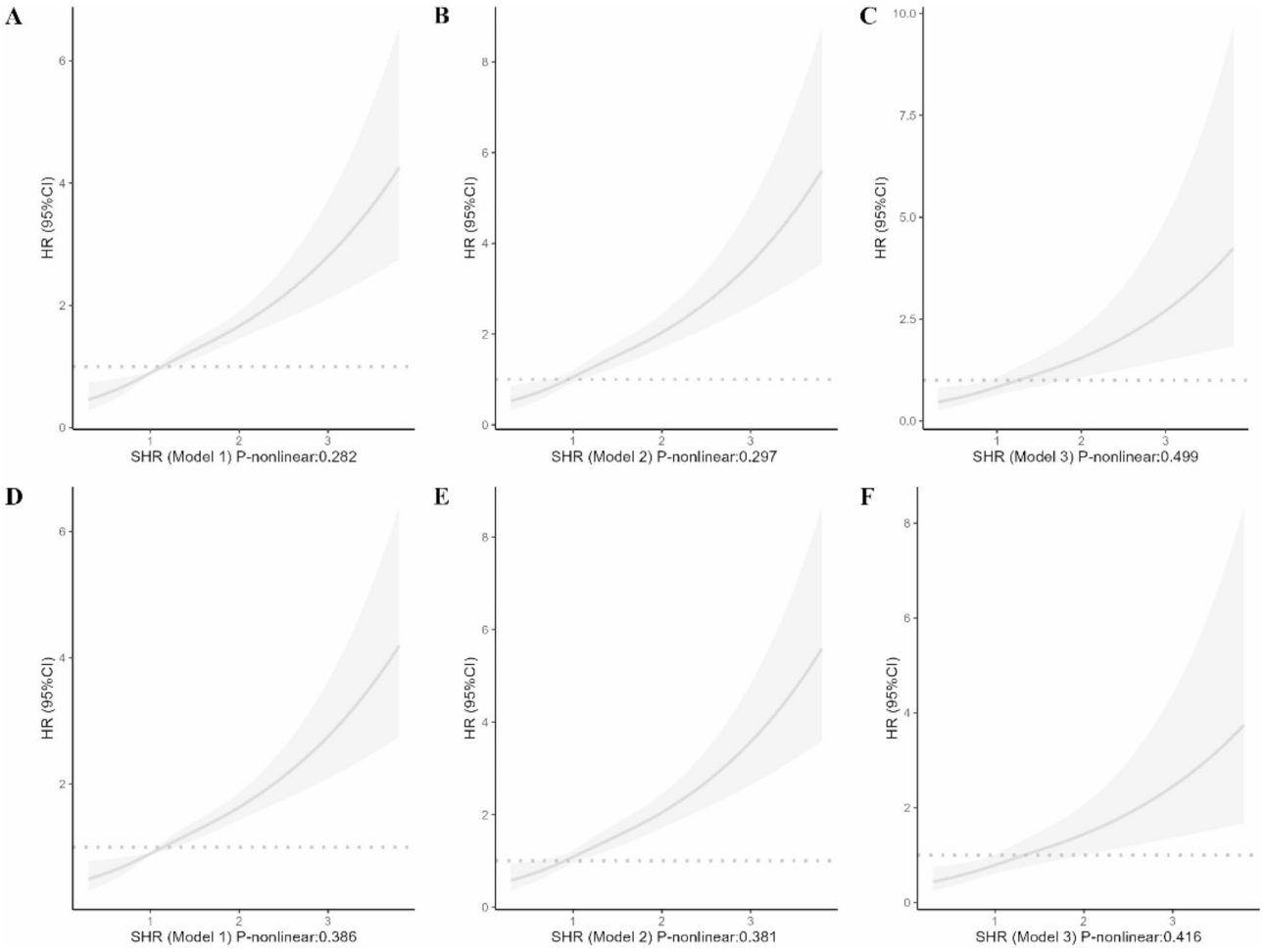

Fig. 5 RCS curve of SHR with mortality. SHR was linearly associated with 28-day mortality (**A**, **B**, **C**) and 365-day mortality (**D**, **E**, **F**). Model 1 was unadjusted. Model 2 was adjusted for sex, age, and BMI. Model 3 was adjusted for sex, age, BMI, SOFA, SAPS II, CKD, hypertension, HF, RF, COPD, diabetes, malignancy, diuretics, vasoactive drugs, RRT, WBC, hemoglobin, RDW, platelet, creatinine, BUN, albumin, ALT, AST, TC, TG, potassium, sodium, chlorine, and glucose

Discussion

This study comprehensively investigated the association of SHR with 28-day and 90-day mortality in AKI population employing multiple analytical approaches. To our knowledge, this is the first study to reveal that higher SHR levels are independent risk factors for 28-day and 90-day mortality in patients with AKI. After adjusting for potential confounding factors based on random forest algorithm-derived feature importance and clinical/literature-based experience, this association remained robust. Specifically, the study demonstrated a significant linear relationship between SHR and 28-day and 90-day mortality in patients with AKI. Notably, the SHR-mortality relationship was more pronounced in the non-diabetic subgroup. Furthermore, the mediation analysis revealed that the adverse impact of SHR on 28-day and 90-day mortality is achieved in part by increasing RF risk.

Critically ill patients often experience excessive activation of the sympathetic nervous system, leading to stress-induced insulin resistance and the development of stress hyperglycemia. Recently, SHR has been highlighted as a marker of acute glycemic changes under stressful conditions or critical illness [14]. Existing studies have found a close relationship between SHR and AKI. Xia et al. found that SHR is one of the risk factors for adverse outcomes in patients with AKI [15]. Similarly, Shan et al. reported a J-shaped nonlinear relationship between SHR and the risk of AKI in patients with coronary angiography [16], which is consistent with the findings of Li [17]. Furthermore, another study has demonstrated a U-shaped relationship between SHR and AKI in patients with congestive HF [10].

Our study is the first to reveal a significant and independent positive linear relationship between SHR and 28-day and 90-day mortality in patients with AKI. The underlying mechanisms for this association have not been fully elucidated, but several potential pathways have been proposed: Firstly, stress hyperglycemia is mediated by the hypothalamic-pituitary-adrenal axis and the sympathetic adrenal system to re-establish homeostasis

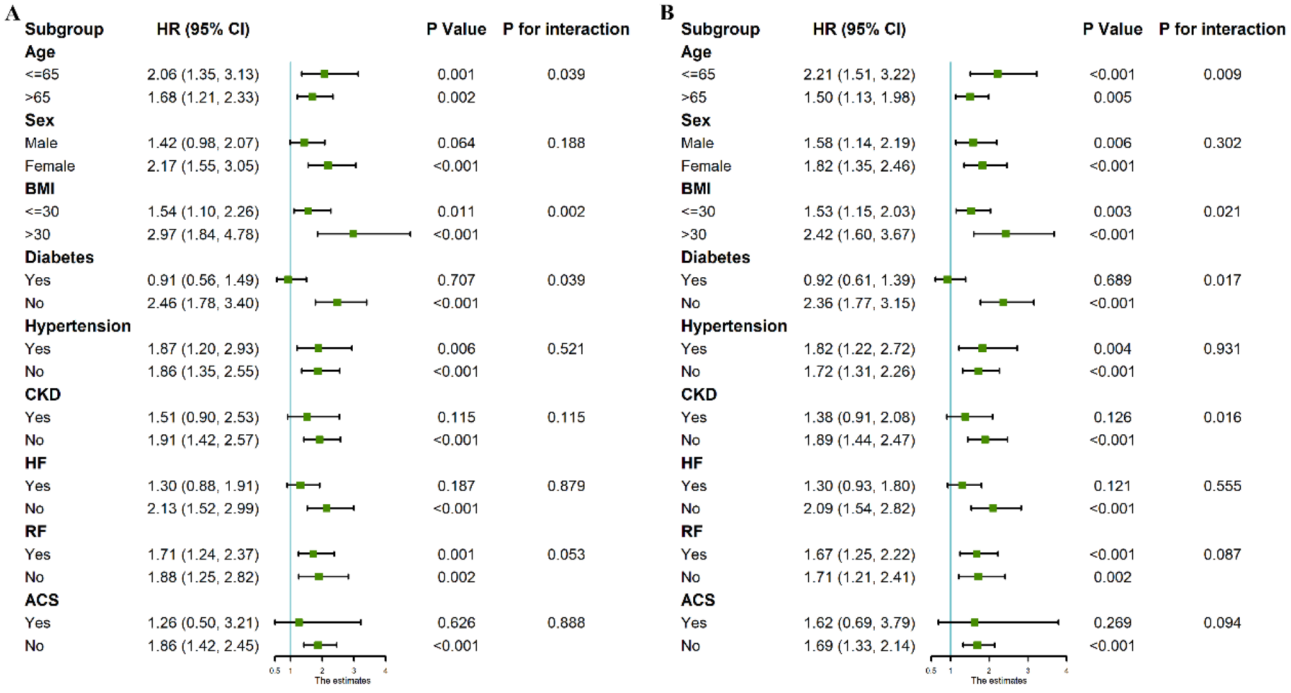

Fig. 6 Forest plots for the 28-day mortality (**A**) and 90-day mortality (**B**)

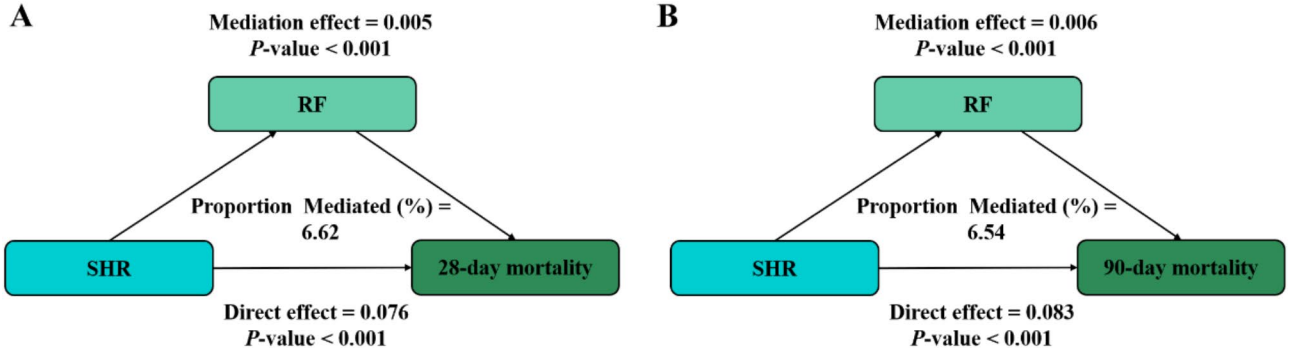

Fig. 7 The mediating effect of RF on the relation between SHR and 28-day mortality (**A**) and 90-day mortality (**B**)

during stress [18]. However, excessive hyperglycemia may lead to disorders in the neuroendocrine hormones, aggravate the inflammation load and oxidative stress, endoplasmic reticulum stress, and mitochondrial dysfunction, which together result in a decline in renal hemodynamics, ischemia and hypoxia of renal tissue, accelerating renal function impairment [19, 20]. Indirectly, hyperglycemia may also facilitate renal underperfusion by affecting the cardiovascular system such as reduced cardiac output and venous congestion. Secondly, the rapid rise in blood glucose can induce a hypertonic state, resulting in osmotic diuresis, which further contributes to dehydration and impaired renal perfusion [21]. Thirdly, the balance between mitochondrial ATP, nitric oxide (NO), and reactive oxygen species is crucial for maintaining renal homeostasis [22]. However, this balance may be disrupted by stress hyperglycemia, leading to increased reactive oxygen species, reduced NO synthesis, and endothelial cell injury [23]. Damaged endothelial cells increase vascular permeability and rarefaction, further exacerbating renal hypoxia and worsening kidney function. Fourthly, stress hyperglycemia stimulates the production of advanced glycation end-products and trigger their interaction with receptors, leading to microvascular damage, extracellular matrix degeneration, and subsequent glomerulosclerosis, affecting kidney structure and function [24]. Fifthly, stress hyperglycemia is often accompanied by insulin resistance, which causes the kidney to lose sensitivity to the biological effects of insulin, thus affecting kidney metabolism and repair [25]. In summary, a series of pathological changes caused by stress hyperglycemia jointly promote the development of renal complications, ultimately leading to poor prognosis. Our research findings underscore the significance of assessing

the SHR in patients with AKI, which is beneficial for optimizing the stratification of mortality risk and guiding early clinical interventions. This highlights the necessity of considering long-term chronic glucose levels in high-glucose patients upon admission to determine the optimal target for glucose reduction. Furthermore, for patients whose initial blood glucose levels do not reach the conventional therapeutic threshold of 11 mmol/L, the assessment of SHR serves as a valuable tool to discern genuine hyperglycemia, thereby determining the appropriate time to initiate glucose-lowering treatment.

Furthermore, we observed that the relationship between SHR and AKI mortality was more pronounced in non-diabetic patients. Compared to AKI patients with diabetes, higher SHR was more likely to lead to poorer outcomes in non-diabetic AKI patients, which is consistent with the findings of Guvercin [26]. This may be related to the fact that patients with diabetes generally have higher baseline blood glucose levels and a greater tolerance for glucose fluctuations [27]. As a result, the threshold blood glucose level associated with poor prognosis in this specific population may be elevated.

Notably, through mediation analysis, we found that SHR increased the risk of 28-day and 90-day mortality in part by increasing the risk of RF, suggesting that RF may partially explain the mechanism by which SHR leads to poor outcomes in patients with AKI. Studies have shown that SHR is closely related to the degree of systemic inflammation in pneumonia patients with diabetes, and is non-linearly related to their adverse clinical outcomes [28]. In addition, elevated blood glucose levels may induce acute lung injury by promoting the formation of AGEs and directly impairing endothelial function and microcirculatory perfusion, leading to multi-organ failure, including the lungs [29, 30]. Over the past two decades, extensive research has demonstrated the existence of a lung-kidney crosstalk in critically ill patients [31]. AKI combined with RF is associated with high mortality [32, 33]. One study even put the mortality rate as high as 80% [34]. RF significantly increases the mortality risk of AKI patients, with an odds ratio of 2.62 [35]. In recent years, several studies have attempted to elucidate the communication networks between the kidney-lung and lung-kidney organs, involving immune responses, inflammatory mediators, acid-base balance, gas exchange, and neuroendocrine mechanisms [32, 36]. RF is often accompanied by hypoxemia and hypercapnia, with the former leading to decreased renal perfusion due to hypoxia, and the latter directly activating renal vasoconstriction, resulting in impaired renal hemodynamics [37]. Additionally, RF may lead to a comprehensive decompensation of acid-base homeostasis and the release of various inflammatory mediators, such as interleukin-6, soluble tumor necrosis factor receptors I and II, and plasminogen activator inhibitor-1, contributing to AKI progression [38]. Severe RF requires mechanical ventilation to improve lung function; however, mechanical ventilation may result in a 3-fold increased risk of AKI [39]. This is because mechanical ventilation may lead to barotrauma, biological trauma, the release of circulating inflammatory mediators, and hemodynamic disturbances, all of which adversely impact the prognosis of AKI [40, 41]. These potential mechanisms may explain the effect of SHR on the mortality risk of AKI patients in part mediated through RF risk.

The key strengths of this study include, first and foremost, the fact that our analysis was based on the large, publicly available MIMIC-IV database, with relatively comprehensive follow-up data. Furthermore, the diverse analytical approaches and the feature importance selection using the random forest algorithm, along with the comprehensive adjustment for confounding factors based on clinical experience and previous literature, have contributed to the robustness of the study findings. Most importantly, our study is the first to uncover the potential role of RF in mediating the relationship between SHR and mortality risk in patients with AKI.

However, there are some limitations to this study. First of all, given the retrospective and single-center nature of this investigation, further multi-center, large-scale prospective studies are needed to corroborate these findings. Second, as with all observational studies, we cannot establish a definitive causal relationship between this factor and the outcome. Third, SHR may be affected by a multitude of factors, including enteral or parenteral nutrition, insulin administration, and others. Due to the relative limitations of the MIMIC-IV dataset, these confounding variables were not accounted for, potentially introducing biases into the study results. Finally, this study only included AKI patients in the United States, further investigation is warranted to determine the generalizability of these findings to AKI populations in other countries.

Conclusion

In conclusion, our study revealed a linear relationship between SHR and 28-day and 90-day mortality in patients with AKI. Furthermore, the adverse impact of SHR on the mortality risk is partially achieved through an increased risk of RF. Evaluating SHR can help identify risk stratification for mortality and guide early interventions, thereby improving outcomes in patients with AKI.

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Author contributions

Yue Shi: Conceptualization, Data Curation, Writing-Original Draft, Visualization. Hangyu Duan: Data Curation, Investigation, Writing-Original Draft. Jing

Liu: Formal analysis, Software, Writing-Original Draft. Xiujie Shi: Writing-Review & Editing. Mingming Zhao: Writing-Review & Editing. Yu Zhang: Conceptualization, Writing-Review & Editing, Supervision, Funding acquisition.

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Data availability
Data will be made available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

Conflict of interest
The authors declare no conflict of interest.

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