

Stress hyperglycemia ratio as a predictor of acute kidney injury in intensive care patients with acute ischemic stroke: a retrospective cohort study using the MIMIC-IV database analysis

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Research Article

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Abstract

Background

The stress hyperglycemia ratio (SHR) is a recognized predictor of acute kidney injury (AKI) in critically ill populations, yet its specific association and dose-response relationship with AKI in patients with acute ischemic stroke (AIS) remain unclear. Our study aimed to investigate the relationship between SHR and the risk of AKI in ICU-admitted patients with AIS.

Methods

In a cohort of 2,073 AIS patients from MIMIC-IV database, SHR was evaluated as both continuous and categorical (quartile) variables. Logistic regression, restricted cubic splines, and mediation analyses were used to assess AKI risk. Cox regression and Kaplan-Meier survival analyses were used to evaluate the association between SHR and 28-day ICU mortality.

Results

Elevated SHR levels were independently associated with an increased risk of AKI, exhibiting a non-linear, J-shaped correlation. Mediation analysis revealed that red blood cell count, hemoglobin and serum total calcium partially mediated this association. Kaplan-Meier survival analysis demonstrated statistically significant differences in 28-day ICU mortality across SHR quartiles (log-rank $P < 0.001$). Nevertheless, Cox regression analysis revealed that SHR did not independently predict 28-day ICU mortality in either the overall population or the AKI subgroup.

Conclusions

SHR is a non-linear predictor of AKI in ICU patients with AIS, with a possible protective range (0.75–0.91) and lowest risk at SHR 0.82. It may serve as an early indicator for AKI risk in this population, but its prognostic value for mortality warrants further study.

Introduction

Acute ischemic stroke (AIS) is a common acute cerebrovascular disease characterized by high incidence, high disability rate, and high mortality rate [1, 2]. In recent years, with the aging of the population and lifestyle changes, especially among middle-aged and elderly people, stroke is expected to place a huge burden on the global public health system by 2040 [3]. Although advances in revascularization therapy and neurological monitoring have significantly improved clinical outcomes for some patients, related systemic complications—particularly acute kidney injury (AKI)—still severely impact neurological recovery and long-term quality of life in patients. In AIS patients, AKI is not only closely associated with increased in-hospital mortality and prolonged hospitalization but may also further exacerbate systemic inflammatory responses, affect fluid management and drug metabolism, and subsequently aggravate cerebral edema progression, hemorrhagic transformation, or long-term chronic kidney disease, creating a vicious cycle [4, 5]. Therefore, accurate prognostication of AKI risk in AIS patients and precise prediction of their adverse outcomes are of critical clinical importance for improving overall patient outcomes.

Acute ischemic stroke (AIS) not only causes direct damage to the nervous system but also leads to systemic injuries, including acute kidney injury (AKI). The occurrence of AKI in acute ischemic stroke is driven by multiple mechanisms, such as autonomic dysfunction [6], systemic immune dysregulation [7], triggering of the hypothalamic-pituitary-adrenal (HPA) axis [8], and cardiovascular effects [9]. Stress hyperglycemia (SH), as a frequently observed pathophysiological process in critical conditions, has been clearly established as a key prognostic indicator. However, traditional methods of assessing SHR using admission blood glucose (ABG) have limitations, as this metric is easily influenced by the patient's pre-existing diabetes, making it difficult to accurately reflect the extent of acute stress-induced glucose metabolism abnormalities. Recently, the stress hyperglycemia ratio (SHR)—calculated as the ratio of admission blood glucose to estimated average glucose (eAG)—has been increasingly recognized [10]. By adjusting for individual baseline blood glucose levels, this indicator is considered to more accurately reflect the impact of acute physiological stress on glycemic control in ICU-admitted individuals. A meta-analysis of patients with acute ischemic stroke (AIS) revealed that elevated SHR is significantly associated with neurological deterioration, poor functional outcomes, and mortality [11]. Furthermore, in ICU-admitted individuals, SHR serves as a significant predictor for the incidence of AKI [12].

Currently, the clinical diagnosis of acute kidney injury (AKI) remains largely dependent on fluctuations in serum creatinine (Scr) levels. However, the sensitivity of this indicator for early renal injury is limited, which can lead to delayed diagnosis and subsequently affect timely intervention. Over the past decade, SHR has gained attention due to its potential role as a biomarker for AKI prediction. Yet, the association between SHR and the occurrence of AKI in critically ill AIS patients remains insufficiently explored through systematic large-scale clinical cohort studies. Therefore, this study aims to utilize clinical data from the MIMIC-IV database to examine the correlation between SHR and AKI in critically ill AIS patients, providing scientific evidence for early identification of high-risk AKI patients and facilitating timely clinical interventions.

Methods

Data resource

Our study utilized data derived from the Medical Information Mart for Intensive Care IV (MIMIC-IV, version 3.1), a publicly available, U.S.-based clinical database. MIMIC-IV contains extensive health-related information from 65366 ICU admissions of patients who received critical care at Beth Israel Deaconess Medical Center between 2008 and 2022 [13]. The author (Huang Zhencan) obtained access to the database (Record ID: 68219793). To safeguard patient privacy, all personally identifiable information was removed from the dataset. This retrospective analysis of a de-identified public database was exempt from local institutional review board review.

Study design and population

We conducted a retrospective cohort study employing data from a large-scale critical care database. The study included adult patients diagnosed with AIS in the MIMIC-IV database, identified using ICD-9 codes (433, 434, 436, 437.0, 437.1) or ICD-10 codes (I63, I65, I66) [14]. For patients with multiple hospitalizations, only the first admission was investigated. The exclusion criteria were as follows: (1) age below 18 or above 89 years; (2) ICU length of stay less than 24 hours; (3) missing essential data (ABG or HbA1c); (4) more than 20% of individual data missing. We enrolled a total of 2,073 patients in the final cohort, who were then divided into quartiles based on their SHR levels (Fig. 1).

Data collection

In this study, we collected patient demographic data (including age, gender, and weight), common comorbidities (such as diabetes mellitus [DM], hypertension [HTN], atrial fibrillation [AF], hyperlipidemia, heart failure, coronary artery disease, chronic obstructive pulmonary disease [COPD], chronic kidney disease [CKD], liver disease, and malignancy), scale scores (SOFA score, GCS score), laboratory parameters (e.g., glucose, glycated hemoglobin [HbA1c], serum creatinine [SCr], blood urea nitrogen [BUN], electrolytes, transaminases, and complete blood count), interventions (including intravenous thrombolysis), and data on various related variables. The SHR was calculated using the formula: $SHR = ABG \text{ (mg/dL)} / (28.7 \times HbA1c \text{ (\%)} - 46.7)$ [15]. To handle missing data, variables with more than 20% missing values were excluded. For other variables, missing values were imputed using the random forest method. Clinical and laboratory data, including initial post-admission glucose and HbA1c levels, along with comorbidities identified via ICD-9/10 codes, were extracted from the MIMIC-IV database. Key information pertaining to the first 24 hours of ICU hospitalization was specifically retrieved using PostgreSQL (version 14.0). Our study was conducted in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [16].

Clinical outcomes

The primary endpoint assessed whether patients developed AKI. AKI was defined according to the KDIGO guidelines, requiring at least one of the following criteria to be met: (1) Serum creatinine ≥ 1.5 times baseline within 7 days; (2) Increase in serum creatinine by ≥ 0.3 mg/dL (≥ 26.5 $\mu\text{mol/L}$) within 48 hours; or (3) Urine output < 0.5 mL/kg/hour for 6 consecutive hours [17]. Secondary outcomes were defined as 28-day in-ICU mortality. This was assessed for the overall cohort and also specifically evaluated in the subgroup of patients with AKI.

Statistical analysis

Patients were stratified into quartiles based on their SHR. Continuous data are presented as mean $\pm$ SD or median (IQR), as appropriate. Between-group comparisons were conducted using the Student's t-test, one-way ANOVA, or the Kruskal-Wallis H test, selected according to the data distribution and the number of groups compared. Categorical variables are presented as n (%), with group comparisons made using the chi-square or Fisher's exact test, as appropriate. To assess the association between SHR and AKI risk in critically ill AIS patients, we performed both univariate and multivariate logistic regression analyses. Model 1 was unadjusted. Model 2 was adjusted for age, weight, SOFA score, GCS score, atrial fibrillation (AF), hypertension (HTN), chronic kidney disease (CKD), heart failure, coronary artery disease, and COPD. In Model 3, LASSO regression was employed for feature selection using variables identified as statistically significant in the univariate analysis presented in Table 2 (Supplementary Material 1). This process identified 17 predictors with non-zero coefficients for inclusion in Model 3 ($\lambda_{1se} = 0.0227$). The adjusted variables in Model 3 included age, weight, SOFA score, GCS score, AF, HTN, CKD, heart failure, coronary artery disease, COPD, total serum calcium, high-density lipoprotein (HDL), triglycerides, white blood cell count, Red Blood Cell Distribution Width (RDW), aspartate aminotransferase (AST), and creatinine. Odds ratios (OR) with 95% confidence intervals (CI) were calculated to quantify the effect of SHR on AKI. Restricted cubic splines (RCS) were applied to explore the dose-response relationship between SHR and AKI risk, with full covariate adjustment as specified in Models 2 and 3. Mediation analyses were conducted in R to test for potential mediation of the SHR-AKI association by total serum calcium, red blood cell count, and hemoglobin levels. Further subgroup analyses were conducted, stratified by age, sex, and key comorbidities (hypertension, diabetes, CKD, atrial fibrillation, and heart failure). For 28-day ICU mortality, survival curves were generated by SHR quartiles and compared using the log-rank test. Subsequently, univariate and multivariate Cox regression models were applied to quantify the association between SHR and 28-day ICU mortality risk in the overall cohort and the AKI subgroup. All analyses were conducted in R (v4.4.1). A two-tailed p -value < 0.05 was considered statistically significant.

Results

Baseline characteristics

A total of 2,073 patients were included, among whom 1,110 were male (53.55%) and 963 were female (46.45%). Acute kidney injury (AKI) occurred in 1,184 patients (57.12%), and 245 patients (11.82%) died within 28 days of ICU admission. The baseline characteristics are summarized in Table 1, stratified by quartiles of the SHR: Q1 (n = 518, SHR < 0.86), Q2 (n = 518, 0.86 ≤ SHR < 1.00), Q3 (n = 518, 1.00 ≤ SHR < 1.21), and Q4 (n = 519, SHR ≥ 1.21). Relative to the reference SHR groups, patients in Q4 had higher admission respiratory rate and heart rate, as well as a higher incidence of diabetes, heart failure, coronary artery disease, chronic kidney disease (CKD), and liver disease, while the incidence of hyperlipidemia was lower. Additionally, patients in Q4 exhibited higher SOFA scores, admission glucose, sodium, potassium, white blood cell count, creatinine, blood urea nitrogen (BUN), aspartate aminotransferase (AST), and total cholesterol (TC) levels, but lower Glasgow Coma Scale (GCS) scores, glycated hemoglobin, total serum calcium, chloride, low-density lipoprotein (LDL), triglycerides (TG), hemoglobin, and red blood cell count. The lowest AKI incidence (44.79%) was observed in Q2, whereas Q4 exhibited both the highest AKI incidence (73.22%) and the highest 28-day in-ICU mortality (18.50%).

In Table 2, patients who developed AKI were significantly older, had greater body weight, and presented with higher admission respiratory and heart rates compared to those without AKI. They also showed a higher prevalence of comorbidities, including diabetes mellitus, hypertension, heart failure (HF), atrial fibrillation, coronary artery disease, chronic kidney disease (CKD), and liver disease. Furthermore, laboratory parameters in the AKI group demonstrated higher levels of white blood cell count, triglycerides (TG), admission blood glucose, glycated hemoglobin, aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine, and blood urea nitrogen (BUN), while levels of hemoglobin, red blood cell count, low-density lipoprotein (LDL), high-density lipoprotein (HDL), and total cholesterol (TC) were lower. Moreover, patients in the AKI group had lower Glasgow Coma Scale (GCS) scores and higher Sequential Organ Failure Assessment (SOFA) scores.

Table 1
Patient Baseline Characteristics by SHR Quartile

Characteristics	Overall (N = 2,073)	Q1 (N = 518)	Q2 (N = 518)	Q3 (N = 518)	Q4 (N = 519)	P
		< 0.86	0.86-1.00	1.00-1.21	≥ 1.21	
age, year	68.01 ± 14.11	68.13 ± 13.54	67.66 ± 14.79	67.28 ± 14.48	68.96 ± 13.56	0.359
Male, %	1,110.00 (53.55%)	276.00 (53.28%)	296.00 (57.14%)	268.00 (51.74%)	270.00 (52.02%)	0.275
Weight, kg	81.84 ± 31.81	82.05 ± 51.07	81.44 ± 21.43	81.68 ± 21.98	82.19 ± 22.41	0.179
Vital Signs						
Heart rate, bpm	83.04 ± 18.94	80.25 ± 17.38	80.09 ± 18.57	83.54 ± 19.30	88.28 ± 19.33	< 0.001
Respiratory Rate, bpm	18.96 ± 5.24	18.50 ± 5.10	18.45 ± 4.98	18.99 ± 5.16	19.88 ± 5.58	< 0.001
Spo2, %	97.24 ± 2.97	97.18 ± 2.76	97.28 ± 2.74	97.37 ± 2.85	97.13 ± 3.45	0.410
Temperature, °C	36.78 ± 1.42	36.81 ± 0.48	36.82 ± 0.60	36.63 ± 2.63	36.84 ± 0.74	0.070
Comorbidities						
Hypertension, %	1,147.00 (55.33%)	294.00 (56.76%)	296.00 (57.14%)	288.00 (55.60%)	269.00 (51.83%)	0.295
DM, %	732.00 (35.31%)	213.00 (41.12%)	150.00 (28.96%)	151.00 (29.15%)	218.00 (42.00%)	< 0.001
Hyperlipemia, %	1,025.00 (49.45%)	270.00 (52.12%)	282.00 (54.44%)	243.00 (46.91%)	230.00 (44.32%)	0.004
Heart failure, %	441.00 (21.27%)	108.00 (20.85%)	81.00 (15.64%)	96.00 (18.53%)	156.00 (30.06%)	< 0.001
CAD, %	638.00 (30.78%)	171.00 (33.01%)	129.00 (24.90%)	136.00 (26.25%)	202.00 (38.92%)	< 0.001
COPD, %	212.00 (10.23%)	62.00 (11.97%)	50.00 (9.65%)	48.00 (9.27%)	52.00 (10.02%)	0.486
AF, %	719.00 (34.68%)	158.00 (30.50%)	189.00 (36.49%)	180.00 (34.75%)	192.00 (36.99%)	0.113
Liver diseases, %	62.00 (2.99%)	9.00 (1.74%)	12.00 (2.32%)	16.00 (3.09%)	25.00 (4.82%)	0.022
CKD, %	304.00 (14.66%)	73.00 (14.09%)	66.00 (12.74%)	71.00 (13.71%)	94.00 (18.11%)	0.073
Scales						
SOFA	3.40 ± 2.82	2.72 ± 2.41	2.97 ± 2.58	3.34 ± 2.63	4.56 ± 3.24	< 0.001
Data are mean ± standard deviation, or n (%)						

Characteristics	Overall (N = 2,073)	Q1 (N = 518)	Q2 (N = 518)	Q3 (N = 518)	Q4 (N = 519)	P
		< 0.86	0.86-1.00	1.00-1.21	≥ 1.21	
GCS	12.95 ± 2.75	13.31 ± 2.55	13.05 ± 2.57	12.67 ± 2.89	12.78 ± 2.93	0.003
Laboratory tests						
HbA1c, %	6.32 ± 1.54	6.90 ± 1.94	6.14 ± 1.25	6.03 ± 1.33	6.19 ± 1.38	< 0.001
Glucose, mg/dL	143.02 ± 67.58	108.74 ± 35.42	120.03 ± 33.30	139.17 ± 42.95	204.04 ± 92.84	< 0.001
Potassium, mmol/L	4.10 ± 0.67	4.01 ± 0.58	4.05 ± 0.60	4.10 ± 0.70	4.23 ± 0.76	< 0.001
Sodium, mmol/L	138.97 ± 4.39	139.66 ± 3.66	139.13 ± 4.14	138.78 ± 4.32	138.32 ± 5.20	< 0.001
Calcium total, mg/dL	8.68 ± 0.76	8.69 ± 0.78	8.74 ± 0.66	8.71 ± 0.74	8.56 ± 0.83	< 0.001
Chloride, mmol/L	103.77 ± 5.24	104.69 ± 4.98	103.76 ± 4.97	103.65 ± 4.82	102.97 ± 5.98	< 0.001
HDL, mg/dL	45.86 ± 17.03	45.67 ± 16.53	47.18 ± 16.79	46.43 ± 16.82	44.14 ± 17.87	0.015
LDL, mg/dL	89.21 ± 41.86	93.00 ± 43.44	91.22 ± 40.56	90.15 ± 42.84	82.49 ± 39.84	< 0.001
TC, mg/dL	159.79 ± 49.03	163.16 ± 49.49	161.83 ± 49.16	161.18 ± 48.73	153.01 ± 48.21	0.001
TG, mg/dL	146.80 ± 220.58	143.34 ± 196.85	132.16 ± 163.81	155.12 ± 311.64	156.57 ± 178.45	0.019
RBC,10 ¹² /L	4.05 ± 0.74	4.16 ± 0.73	4.13 ± 0.66	4.06 ± 0.72	3.88 ± 0.81	< 0.001
WBC,10 ⁹ /L	11.03 ± 7.84	9.49 ± 7.48	9.77 ± 4.32	11.02 ± 4.55	13.86 ± 11.77	< 0.001
Hemoglobin, g/dL	12.07 ± 2.23	12.16 ± 2.12	12.35 ± 2.00	12.17 ± 2.20	11.60 ± 2.49	< 0.001
Platelet count,10 ⁹ /L	222.07 ± 89.42	229.97 ± 82.90	216.91 ± 90.41	218.72 ± 90.19	222.68 ± 93.54	0.027
RDW, %	14.20 ± 1.89	14.22 ± 1.92	14.10 ± 1.85	14.09 ± 1.86	14.39 ± 1.92	0.005
ALT, IU/L	51.30 ± 202.13	36.47 ± 97.10	43.71 ± 147.63	52.52 ± 256.18	72.45 ± 256.96	0.066
AST, IU/L	71.73 ± 306.65	55.66 ± 215.37	51.00 ± 182.73	69.47 ± 350.68	110.70 ± 414.18	< 0.001
SCr, mg/dL	1.19 ± 1.21	1.11 ± 1.23	1.10 ± 0.98	1.07 ± 0.89	1.47 ± 1.59	< 0.001
Data are mean ± standard deviation, or n (%)						

Characteristics	Overall (N = 2,073)	Q1 (N = 518)	Q2 (N = 518)	Q3 (N = 518)	Q4 (N = 519)	P
		< 0.86	0.86-1.00	1.00-1.21	≥ 1.21	
BUN, mg/dL	20.85 ± 15.82	19.22 ± 14.49	18.61 ± 13.04	19.42 ± 13.59	26.16 ± 19.97	< 0.001
Medical History						
IVT, %	221.00 (10.66%)	60.00 (11.58%)	72.00 (13.90%)	53.00 (10.23%)	36.00 (6.94%)	0.003
Clinical outcomes						
AKI, %	1,184.00 (57.12%)	261.00 (50.39%)	232.00 (44.79%)	311.00 (60.04%)	380.00 (73.22%)	< 0.001
AKI stage, %						< 0.001
0	889.00 (42.88%)	257.00 (49.61%)	286.00 (55.21%)	207.00 (39.96%)	139.00 (26.78%)	
1	227.00 (10.95%)	53.00 (10.23%)	53.00 (10.23%)	57.00 (11.00%)	64.00 (12.33%)	
2	618.00 (29.81%)	136.00 (26.25%)	129.00 (24.90%)	154.00 (29.73%)	199.00 (38.34%)	
3	339.00 (16.35%)	72.00 (13.90%)	50.00 (9.65%)	100.00 (19.31%)	117.00 (22.54%)	
Los icu, day	5.75 ± 6.34	5.02 ± 5.40	4.75 ± 5.16	6.00 ± 6.29	7.23 ± 7.86	< 0.001
28-Day Mortality, %	245.00 (11.82%)	41.00 (7.92%)	49.00 (9.46%)	59.00 (11.39%)	96.00 (18.50%)	< 0.001
Data are mean ± standard deviation, or n (%)						

DM: diabetes mellitus, CAD: coronary artery disease, COPD: Chronic Obstructive Pulmonary Disease, AF: atrial fibrillation, CKD: chronic kidney disease, SOFA: sequential organ failure assessment, GCS: Glasgow Coma Scale, HbA1c: glycosylated hemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TC: total cholesterol, TG: total triglyceride, RBC: red blood cell, WBC: white blood cell, RDW: Red Cell Distribution Width, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SCr: Serum Creatinine, BUN: blood urea nitrogen, IVT: intravenous thrombolysis, los icu: length of stay in icu.

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

Characteristics	Overall (N = 2,073)	Without AKI (N = 889)	AKI (N = 1,184)	P
SHR	1.08 ± 0.45	1.01 ± 0.48	1.14 ± 0.42	< 0.001
age, year	68.01 ± 14.11	66.88 ± 14.89	68.85 ± 13.44	0.002
Male, %	1,110.00 (53.55%)	478.00 (53.77%)	632.00 (53.38%)	0.860
Weight, kg	81.84 ± 31.81	77.62 ± 20.54	85.01 ± 37.84	< 0.001
Vital Signs				
Heart rate, bpm	83.04 ± 18.94	79.99 ± 17.89	85.33 ± 19.39	< 0.001
Respiratory Rate, bpm	18.96 ± 5.24	18.14 ± 4.94	19.57 ± 5.37	< 0.001
Spo2, %	97.24 ± 2.97	97.22 ± 2.74	97.25 ± 3.12	0.828
Temperature, °C	36.78 ± 1.42	36.77 ± 1.24	36.78 ± 1.54	0.930
Comorbidities				
Hypertension, %	1,147.00 (55.33%)	522.00 (58.72%)	625.00 (52.79%)	0.007
DM, %	732.00 (35.31%)	266.00 (29.92%)	466.00 (39.36%)	< 0.001
Hyperlipemia, %	1,025.00 (49.45%)	449.00 (50.51%)	576.00 (48.65%)	0.402
Heart failure, %	441.00 (21.27%)	111.00 (12.49%)	330.00 (27.87%)	< 0.001
CAD, %	638.00 (30.78%)	202.00 (22.72%)	436.00 (36.82%)	< 0.001
COPD, %	212.00 (10.23%)	73.00 (8.21%)	139.00 (11.74%)	0.009
AF, %	719.00 (34.68%)	244.00 (27.45%)	475.00 (40.12%)	< 0.001
Liver diseases, %	62.00 (2.99%)	16.00 (1.80%)	46.00 (3.89%)	0.006
CKD, %	304.00 (14.66%)	78.00 (8.77%)	226.00 (19.09%)	< 0.001
Scales				
SOFA	3.40 ± 2.82	2.24 ± 1.90	4.27 ± 3.08	< 0.001
GCS	12.95 ± 2.75	13.23 ± 2.40	12.74 ± 2.97	< 0.001
Laboratory tests				
HbA1c, %	6.32 ± 1.54	6.20 ± 1.45	6.40 ± 1.60	0.003
Glucose, mg/dL	143.02 ± 67.58	130.13 ± 65.08	152.70 ± 67.83	< 0.001
Potassium, mmol/L	4.10 ± 0.67	4.03 ± 0.54	4.15 ± 0.75	< 0.001
Sodium, mmol/L	138.97 ± 4.39	139.09 ± 3.96	138.88 ± 4.69	0.260
Calcium total, mg/dL	8.68 ± 0.76	8.83 ± 0.60	8.56 ± 0.84	< 0.001
Chloride, mmol/L	103.77 ± 5.24	103.78 ± 4.39	103.76 ± 5.80	0.926
Data are mean ± standard deviation, or n (%)				

Characteristics	Overall (N = 2,073)	Without AKI (N = 889)	AKI (N = 1,184)	P
HDL, mg/dL	45.86 ± 17.03	48.90 ± 17.18	43.57 ± 16.57	< 0.001
LDL, mg/dL	89.21 ± 41.86	95.03 ± 41.56	84.84 ± 41.57	< 0.001
TC, mg/dL	159.79 ± 49.03	167.80 ± 47.89	153.78 ± 49.03	< 0.001
TG, mg/dL	146.80 ± 220.58	128.26 ± 138.57	160.73 ± 265.24	< 0.001
RBC,10 ¹² /L	4.05 ± 0.74	4.16 ± 0.68	3.97 ± 0.77	< 0.001
WBC,10 ⁹ /L	11.03 ± 7.84	9.93 ± 8.42	11.86 ± 7.26	< 0.001
Hemoglobin, g/dL	12.07 ± 2.23	12.40 ± 2.01	11.82 ± 2.35	< 0.001
Platelet count,10 ⁹ /L	222.07 ± 89.42	221.27 ± 77.31	222.67 ± 97.56	0.715
RDW, %	14.20 ± 1.89	13.88 ± 1.73	14.44 ± 1.97	< 0.001
ALT, IU/L	51.30 ± 202.13	29.79 ± 68.08	67.44 ± 259.75	< 0.001
AST, IU/L	71.73 ± 306.65	33.06 ± 72.03	100.76 ± 398.54	< 0.001
SCr, mg/dL	1.19 ± 1.21	0.94 ± 0.59	1.38 ± 1.50	< 0.001
BUN, mg/dL	20.85 ± 15.82	17.25 ± 11.64	23.56 ± 17.87	< 0.001
Medical History				
IVT, %	221.00 (10.66%)	102.00 (11.47%)	119.00 (10.05%)	0.299
Clinical outcomes				
los icu, day	5.75 ± 6.34	3.30 ± 2.87	7.59 ± 7.50	< 0.001
28-Day Mortality, %	245.00 (11.82%)	59.00 (6.64%)	186.00 (15.71%)	< 0.001
Data are mean ± standard deviation, or n (%)				

DM: diabetes mellitus, CAD: coronary artery disease, COPD: Chronic Obstructive Pulmonary Disease, AF: atrial fibrillation, CKD: chronic kidney disease, SOFA: sequential organ failure assessment, GCS: Glasgow Coma Scale, HbA1c: glycosylated hemoglobin, HDL: high-density lipoprotein, LDL: low-density lipoprotein, TC: total cholesterol, TG: total triglyceride, RBC: red blood cell, WBC: white blood cell, RDW: Red Cell Distribution Width, ALT: alanine aminotransferase, AST: aspartate aminotransferase, SCr: Serum Creatinine, BUN: blood urea nitrogen, IVT: intravenous thrombolysis, los icu: length of stay in icu.

Correlation of SHR with primary outcome

In Table 3, when analyzed as a continuous variable, each one-unit increase in SHR was associated with a nearly threefold increase in AKI risk in Model 1 (OR = 2.98 [95% CI 2.24, 4.00]). In Model 2, after adjusting for age, weight, SOFA score, GCS score, AF, hypertension, CKD, heart failure, coronary artery disease, and COPD, the risk of AKI increased by 69%. After adjusting for all covariates in Model 3, every one-unit rise in SHR conferred a 48% greater likelihood of developing AKI. When SHR was categorized into quartile groups, with Q2 as the reference group due to its lowest incidence of AKI (Table 1), statistical analyses were conducted. Across all models, compared to Q2, all SHR groups showed a significantly increased risk of AKI, except for Q1 in Model 1, which did not reach statistical significance. Furthermore, having established that both Q3 and Q4 remained significantly associated with elevated AKI risk in the fully adjusted Model 3 (P < 0.001), we further investigated the potential dose–response relationship

using restricted cubic splines (RCS). As shown in Fig. 2, across all three models, SHR demonstrated a J-shaped relationship with the incidence of AKI within a certain range (P for nonlinearity < 0.001). AKI risk initially decreased, reached a minimum, and then increased with rising SHR levels. Beyond that range, although the risk of AKI showed a slight decline with further increases in SHR, it remained significantly higher than the baseline level. Moreover, in Model 3, this J-shaped relationship persisted when SHR was below 1.54. Specifically, an SHR within the range of 0.72–0.91 may be associated with a reduced risk of AKI in critically ill AIS patients. Restricted cubic spline analysis revealed that AKI risk was minimized at an SHR threshold of 0.82.

Table 3
Logistic regression analyses for primary outcome

SHR group	Model 1		Model 2		Model 1	
	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>	OR (95%CI)	<i>P</i>
SHR (continuous)	2.98 (2.24,4.00)	< 0.001	1.69 (1.23,2.35)	0.002	1.48 (1.07,2.08)	0.024
Q1	1.25 (0.98,1.60)	0.071	1.36 (1.04,1.79)	0.025	1.32 (1.01,1.74)	0.046
Q2	Ref		Ref		Ref	
Q3	1.85 (1.45,2.37)	< 0.001	1.86 (1.42,2.44)	< 0.001	1.82 (1.38,2.39)	< 0.001
Q4	3.37 (2.60,4.38)	< 0.001	2.40 (1.80,3.21)	< 0.001	2.18 (1.62,2.95)	< 0.001

Model 1 was unadjusted.

Model 2 was adjusted for age, weight, SOFA score, GCS score, AF, HTN, CKD, heart failure, coronary artery disease, and COPD.

Model 3 was adjusted for age, weight, SOFA score, GCS score, AF, HTN, CKD, heart failure, coronary artery disease, COPD, total serum calcium, HDL, triglycerides, white blood cell count, RDW, AST, and creatinine.

Mediation analysis and Subgroup analysis

Mediation analysis revealed that serum total calcium, red blood cell counts, and hemoglobin each partially mediated the effect of SHR on AKI (all $p < 0.001$). Serum total calcium accounted for approximately 8.06% of the total effect of SHR on AKI risk ($p = 0.006$), red blood cell counts mediated 6.69% of the effect ($p = 0.002$), and hemoglobin mediated 6.37% ($p < 0.001$) (Fig. 3). Furthermore, in subgroup analyses stratified by age, sex, hypertension, diabetes, atrial fibrillation, heart failure, and CKD status, SHR remained a robust predictor of AKI. The significant association between the highest SHR quartile (Q4) and AKI incidence persisted across key patient subgroups (Table 4): age ≥ 70 years (OR = 2.88 [95% CI 2.01, 4.14]), age < 70 years (OR = 3.98 [95% CI 2.73, 5.80]), male (OR = 3.87 [95% CI 2.70, 5.54]), female (OR = 2.89 [95% CI 1.98, 4.23]), diabetes mellitus (OR = 3.20 [95% CI 2.05, 4.99]), non-diabetes mellitus (OR = 3.32 [95% CI 2.40, 4.60]), Hypertension (OR = 3.59 [95% CI 2.53, 5.10]), non- Hypertension (OR = 3.04 [95% CI 2.06, 4.50]), CKD (OR = 3.66 [95% CI 1.66, 8.05]), non-CKD (OR = 3.27 [95% CI 2.47, 4.32]), AF (OR = 2.61 [95% CI 1.66, 4.11]), non-AF (OR = 4.01 [95% CI 2.90, 5.56]), HF (OR = 1.99 [95% CI 1.08, 3.67]) and non- HF (OR = 3.42 [95% CI 2.55, 4.60]) subgroups (all P for interaction > 0.05).

Table 4

Subgroup analysis evaluating the association between SHR and AKI by means of odds ratios

Variable	Groups (group 1–4) divided by SHR				P for interaction
	< 0.86	0.86–1.00	1.00–1.21	≥ 1.21	
Age					0.225
≥ 70	1.05(0.75–1.48)	Ref	1.44(1.02–2.04)	2.88(2.01–4.14)	
< 70	1.51(1.06–2.14)	Ref	2.41(1.69–3.42)	3.98(2.73–5.80)	
Gender					0.724
male	1.30(0.93–1.80)	Ref	1.89(1.35–2.64)	3.87(2.70–5.54)	
female	1.20(0.83–1.72)	Ref	1.79(1.24–2.59)	2.89(1.98–4.23)	
DM					0.529
yes	1.38(0.90–2.09)	Ref	2.34(1.46–3.76)	3.20(2.05–4.99)	
no	1.11(0.82–1.51)	Ref	1.70(1.27–2.28)	3.32(2.40–4.60)	
Hypertension					0.594
yes	1.39(1.00–1.92)	Ref	2.14(1.54–2.98)	3.59(2.53–5.10)	
no	1.09(0.75–1.59)	Ref	1.53(1.05–2.22)	3.04(2.06–4.50)	
CKD					0.837
yes	1.03(0.51–2.07)	Ref	1.57(0.75–3.29)	3.66(1.66–8.05)	
no	1.28(0.98–1.66)	Ref	1.90(1.46–2.48)	3.27(2.47–4.32)	
AF					0.136
yes	1.01(0.66–1.55)	Ref	1.28(0.84–1.95)	2.61(1.66–4.11)	
no	1.51(1.11–2.05)	Ref	2.35(1.72–3.20)	4.01(2.90–5.56)	
Heart failure					0.325
yes	1.17(0.63–2.20)	Ref	1.42(0.74–2.73)	1.99(1.08–3.67)	
no	1.20(0.91–1.57)	Ref	1.92(1.46–2.52)	3.42(2.55–4.60)	

DM: diabetes mellitus, CKD: chronic kidney disease, AF: atrial fibrillation.

Correlation of SHR with secondary outcome

Significant differences in 28-day ICU survival were observed when stratified by SHR quartiles, both overall and within the AKI subgroup (Fig. 4). Given that Q1 had the lowest 28-day in-ICU mortality, it was designated as the reference group. Cox regression analysis was then conducted to assess the independent association of SHR quartiles with this mortality outcome. When analyzed continuously, SHR was significantly associated with 28-day in-ICU mortality in Model A for both the overall cohort ($p < 0.001$) and the AKI subgroup ($p = 0.007$). However, after full adjustment in Model B, these associations lost statistical significance (overall cohort: $p = 0.769$; AKI subgroup: $p = 0.504$). When analyzed categorically (by quartile), the contrast between the Q4 and Q1 groups did not reach statistical significance

in the fully adjusted Model B, whether in the entire study population or in the AKI subgroup alone ($p = 0.107$ and $p = 0.176$, respectively) (Table 5).

Table 5
Cox regression for secondary outcome

	Whole Population				AKI Population			
	Model A		Model B		Model A		Model B	
SHR group	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>	HR (95%CI)	<i>P</i>
SHR(continuous)	1.27 (1.15,1.41)	< 0.001	0.95 (0.68,1.33)	0.769	1.44 (1.11,1.87)	0.007	1.18 (0.73,1.90)	0.504
Q1	Ref		Ref		Ref		Ref	
Q2	1.21 (0.80,1.84)	0.356	1.21 (0.80,1.84)	0.372	1.21 (0.75,1.99)	0.434	1.29 (0.78,2.14)	0.326
Q3	1.47 (0.99,2.19)	0.058	1.26 (0.84,1.90)	0.268	1.30 (0.83,2.05)	0.252	1.38 (0.86,2.21)	0.189
Q4	2.48 (1.72,3.58)	< 0.001	1.42 (0.93,2.18)	0.107	1.75 (1.15,2.65)	0.009	1.42 (0.86,2.34)	0.176

Model A was unadjusted.

Model B was adjusted for age, weight, respiratory rate, heart failure, CAD, AF, CKD, SOFA, GCS, glucose, potassium, calcium total, HDL, TC, TG, RBC, WBC, RDW, and BUN.

Discussion

This pioneering large-scale U.S. cohort study demonstrates that elevated SHR is an independent risk factor for AKI in critically ill AIS patients, may exhibiting a J-shaped dose-response relationship. This association was partially mediated by serum total calcium, red blood cell count, and hemoglobin. Although survival curves differed significantly by SHR quartile, SHR was not an independent predictor of 28-day in-ICU mortality upon multivariate adjustment. Crucially, SHR serves as an early, effective, and easily obtainable marker to identify AIS patients at high risk for AKI in the ICU.

Given that admission blood glucose alone cannot differentiate chronic from acute hyperglycemia, researchers have suggested adjusting ABG levels using HbA1c as a marker of chronic glycemic control. Consequently, the Stress Hyperglycemia Ratio (SHR) was developed and has subsequently been validated as a superior and more reliable biomarker for critically ill patients. [18]. In our study, after comprehensive adjustment for confounders, SHR maintained a statistically significant relationship with the occurrence of AKI both as a continuous and categorical measure. Furthermore, subgroup analyses indicated that sex, age, hypertension, diabetes, atrial fibrillation, heart failure, and CKD status did not affect the predictive ability of SHR for AKI development.

The findings of this study are consistent with previous research exploring the association between SHR and AKI. For example, a study by Gao et al. demonstrated that in patients with acute myocardial infarction and a history of diabetes, SHR remained an independent predictor of AKI after adjusting for multiple confounders (OR = 3.18 [95% CI 1.99, 5.09]) [19]. Li et al. revealed that SHR is an independent predictor of AKI in critically ill AMI patients, reporting a

J-shaped relationship where both elevated and decreased SHR values beyond the inflection point of 0.86 were associated with a higher incidence of in-hospital AKI [20]. Our study found that SHR may exhibit a J-shaped correlation with the occurrence of AKI within a certain range. Beyond this range, although the risk of AKI slightly decreases with further increases in SHR, it remains significantly higher than the baseline level. Notably, when SHR falls within the range of 0.72 to 0.91, it appears to have a protective effect against AKI. The observed decrease in AKI risk after SHR reaches a certain threshold may be attributed to the higher HbA1c levels in the Q4 group compared to the Q2 and Q3 groups, which could attenuate the relationship between SHR and AKI occurrence. A congestive heart failure cohort study found that patients in the highest SHR group ($\text{SHR} \geq 1.75$) faced substantially elevated AKI risks, with increases of 81% for those with diabetes and 3.49-fold for those without, compared to controls [21]. One proposed mechanism is that chronic hyperglycemia induces downregulation of cellular glucose transporters, thereby conferring a relative tolerance that mitigates injury during subsequent acute hyperglycemic episodes [22].

The brain and kidneys are engaged in a complex, bidirectional interplay via multiple integrated physiological pathways. During acute ischemic stroke (AIS), mechanisms such as hemodynamic changes, neuroendocrine overactivation, the release of inflammatory mediators, along with immune response activation, collectively contribute to the development of AKI. This interrelated pathophysiological relationship is often referred to as the brain-kidney axis [23]. Stress hyperglycemia (SH) is an acute physiological response mediated by the interaction of the HPA axis, the sympathetic-adrenal system, and inflammatory factors, a process in which catecholamines, cortisol, and cytokines play critical roles [24]. Cortisol can influence glomerular function, leading to short-term increases in glomerular filtration rate and proteinuria [25]. Furthermore, the release of catecholamines leads to renal vasoconstriction, pre-renal hypoperfusion, and may contribute to acute kidney injury due to prolonged renal ischemia and hypoxia [26, 27]. The primary function of red blood cells is to bind and transport oxygen via hemoglobin. The kidneys are highly perfusion-dependent organs with substantial oxygen consumption, and renal tubular epithelial cells are particularly sensitive to hypoxia. In this study, patients in the highest SHR quartile showed significantly lower red blood cell counts and hemoglobin concentrations compared to those in the lowest quartile. Mediation analysis further revealed that red blood cell counts and hemoglobin concentration partially mediated the relationship between SHR and AKI, supporting the notion that renal hypoperfusion and subsequent ischemia-hypoxia contribute to AKI development in AIS patients.

Furthermore, due to hypoxia and nutrient deficiency from sustained hypoperfusion in AIS, the blood-brain barrier—a crucial biochemical barrier for central nervous system homeostasis that regulates solute passage via specific transporters and channels—can become damaged. Dysfunction of this barrier disrupts its essential regulatory role [28, 29]. Damage to the blood-brain barrier leads to the early transfer of pro-inflammatory factors, immune-related substances, and upstream regulatory signals from the site of brain injury into the circulatory system. This process promotes the upregulation of hormones such as antidiuretic hormone and aldosterone, contributing to systemic electrolyte disturbances, which may subsequently exacerbate renal dysfunction [30, 31]. In our study, Serum total calcium was found to be a partial mediator of the SHR-AKI association, suggesting a potential pathway through which stress hyperglycemia may influence renal outcomes.

Earlier meta-analyses have revealed that elevated SHR is significantly associated with 90-day mortality, early neurological deterioration, and symptomatic intracranial hemorrhage in AIS patients treated with mechanical thrombectomy [32]. Furthermore, SHR has been consistently linked to adverse clinical outcomes across a spectrum of critical conditions, such as acute myocardial infarction, congestive heart failure, and ischemic stroke [21, 33, 34]. In our study, although significant differences in 28-day ICU mortality were observed across SHR quartiles in unadjusted analysis ($p < 0.001$), SHR lost its independent prognostic value for this outcome in both the overall cohort and the AKI subgroup after multivariable adjustment. This divergence likely stems from many factors: (1) population differences:

our cohort comprised exclusively ICU-admitted AIS patients; (2) methodological variations in SHR calculation: specifically, the use of admission versus fasting blood glucose as the baseline measure. Large-scale, multicenter prospective cohorts are required to definitively determine the association between SHR and 28-day ICU mortality in critically ill AIS; (3) glycemic management in the ICU: multiple studies associate strict control with an increased risk of hypoglycemia and fail to show clear clinical benefit[35–38]; and (4) the impact of comorbidities: critically ill AIS patients suffer from concurrent infections and multiple system failure, which may dilute the effect of SHR on acute kidney injury.

Current diagnosis of AKI still primarily relies on observed changes in serum creatinine (Scr) levels and/or reductions in urine output (UO). However, they are unable to promptly predict the occurrence of AKI, leading to delays in clinical intervention. Notably, this study found that after full adjustment for confounding factors, baseline serum creatinine level was not an independent risk factor for AKI (OR = 1.11 [95% CI 0.98, 1.31], $p = 0.14$). This suggests that admission serum creatinine cannot serve as a reliable early diagnostic indicator for AKI. Moreover, despite the promising performance of urinary biomarkers like urinary liver-type fatty acid-binding protein (L-FABP) and neutrophil gelatinase-associated lipocalin (NGAL) for early AKI detection, their clinical application is constrained by several limitations, including cost, standardization issues, and uncertain diagnostic thresholds [39, 40]. While urinary biomarkers are limited by their dependence on baseline renal function (leading to inaccuracies in low-filtration states) and lack of routine clinical integration, SHR offers a distinct advantage. Derived from commonly measured parameters (ABG and HbA1c), SHR serves as a simple, practical composite index for the early identification of high AKI risk. This capability empowers clinicians to initiate timely interventions, which may prevent the onset of AKI and thereby improve clinical outcomes.

Limitations

This study also has some shortcomings. First, as the cohort primarily represents the U.S. patient population with limited ethnic diversity, the findings may not be fully generalizable to other ethnic populations or healthcare settings. Second, although major clinically relevant variables were adjusted for in the multivariable models and subgroup analyses were performed, potential residual confounding factors—such as the effects of nephrotoxic medications—were not analyzed, which may influence the study outcomes. Third, the retrospective design limits causal inference between SHR and AKI. To translate these findings into clinical practice, future multicenter randomized trials should assess whether glycemic management strategies specifically targeting SHR (versus ABG) offer renal protective benefits in AIS, while also seeking to refine predictive biomarkers.

Conclusion

In critically ill AIS patients, SHR is an independent predictor of AKI, exhibiting a J-shaped dose-response relationship with a protective range of 0.72–0.91. It offers a simple, early-warning biomarker for AKI risk stratification, although its value in predicting short-term mortality requires further investigation. Nevertheless, in this cohort, SHR did not appear to be an independent risk factor for 28-day in-ICU mortality.

Abbreviations

SHR: Stress Hyperglycemia Ratio

AKI: Acute Kidney Injury

AIS: Acute Ischemic Stroke

ICU: Intensive Care Unit

MIMIC-IV: Medical Information Mart for Intensive Care IV

SH: Stress hyperglycemia

ABG: Admission Blood Glucose

eAG: Estimated Average Glucose

Scr: Serum Creatinine

HbA1c: Glycated Hemoglobin

HTN: hypertension

CKD: Chronic Kidney Disease

HPA: Hypothalamic-Pituitary-Adrenal

WBC: White Blood Cell

RBC: Red Blood Cell

HF: Heart Failure

IRB: Institutional Review Board

RCS: Restricted Cubic Splines

OR: Odds Ratio

HR: Hazard Ratio

CI: Confidence Interval

ANOVA: Analysis of Variance

RCT: Randomized Controlled Trial

AUC: Area Under the Curve

STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

KDIGO: Kidney Disease: Improving Global Outcomes

CONSORT: Consolidated Standards of Reporting Trials

LASSO regression: Least Absolute Shrinkage and Selection Operator regression

DM: diabetes mellitus

CAD: coronary artery disease

COPD: Chronic Obstructive Pulmonary Disease

AF: atrial fibrillation

CKD: chronic kidney disease

SOFA: sequential organ failure assessment

GCS: Glasgow Coma Scale

HDL: high-density lipoprotein

LDL: low-density lipoprotein

TC: total cholesterol

TG: total triglyceride

RDW: Red Cell Distribution Width

ALT: alanine aminotransferase

AST: aspartate aminotransferase

BUN: blood urea nitrogen

IVT: intravenous thrombolysis

los icu: length of stay in icu

L-FABP: Liver-type Fatty Acid-Binding Protein

NGAL: Neutrophil Gelatinase-Associated Lipocalin

UO: Urine Output

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

Online repositories(<https://physionet.org/>) contain the datasets used in this investigation. Registration as a user on the website would be needed to obtain the data. After registration is reviewed and approved, the data set could be downloaded following the provided instructions.

Competing interests

The authors declare no competing interests.

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Clinical trial number

Not applicable

Patient and Public Involvement

Patients or the public WERE NOT involved in the design, or conduct, or reporting, or dissemination plans of our research

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Figures

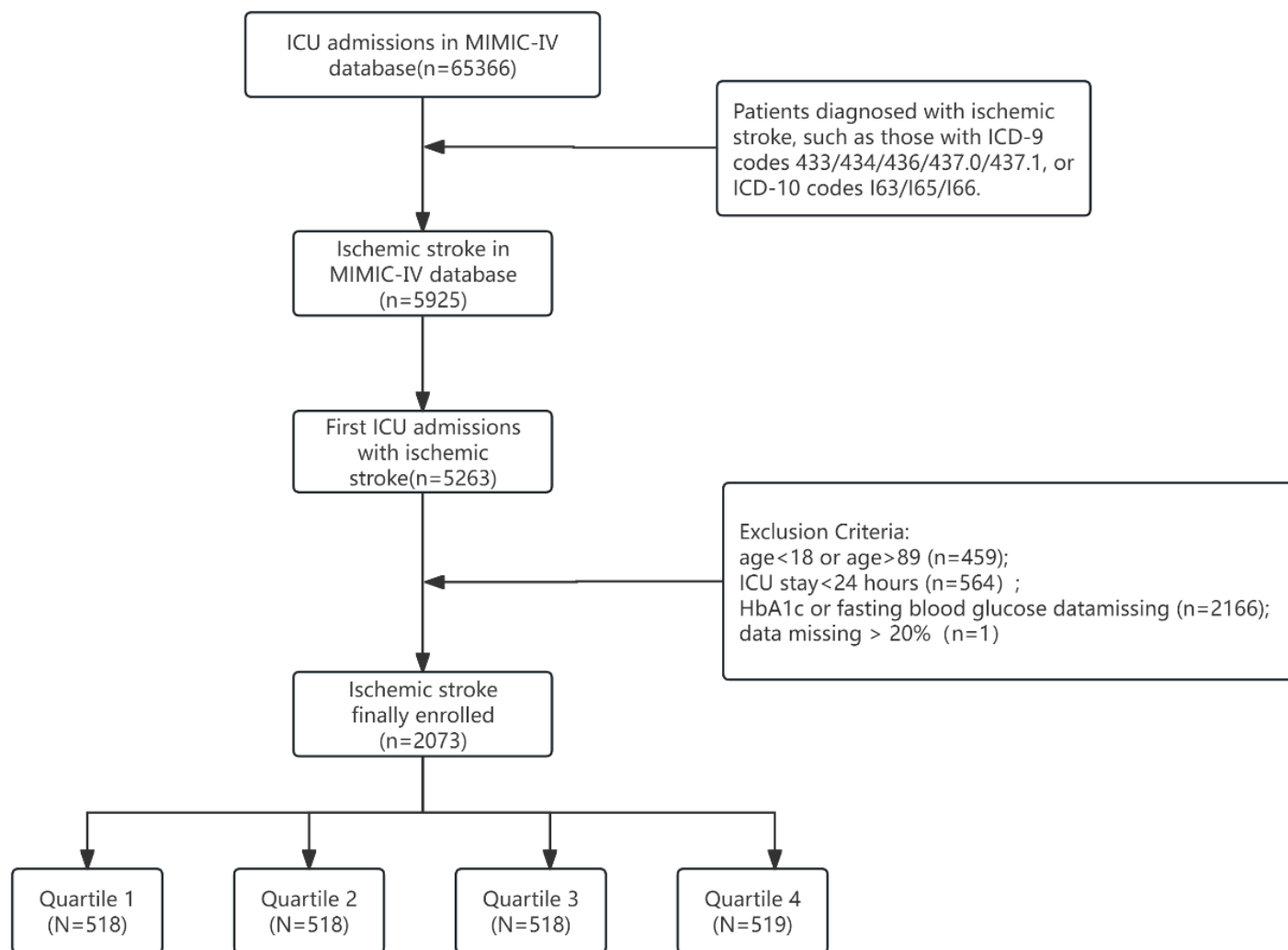


Figure 1

Flow Diagram of Patient Selection and Study Cohort Formation.

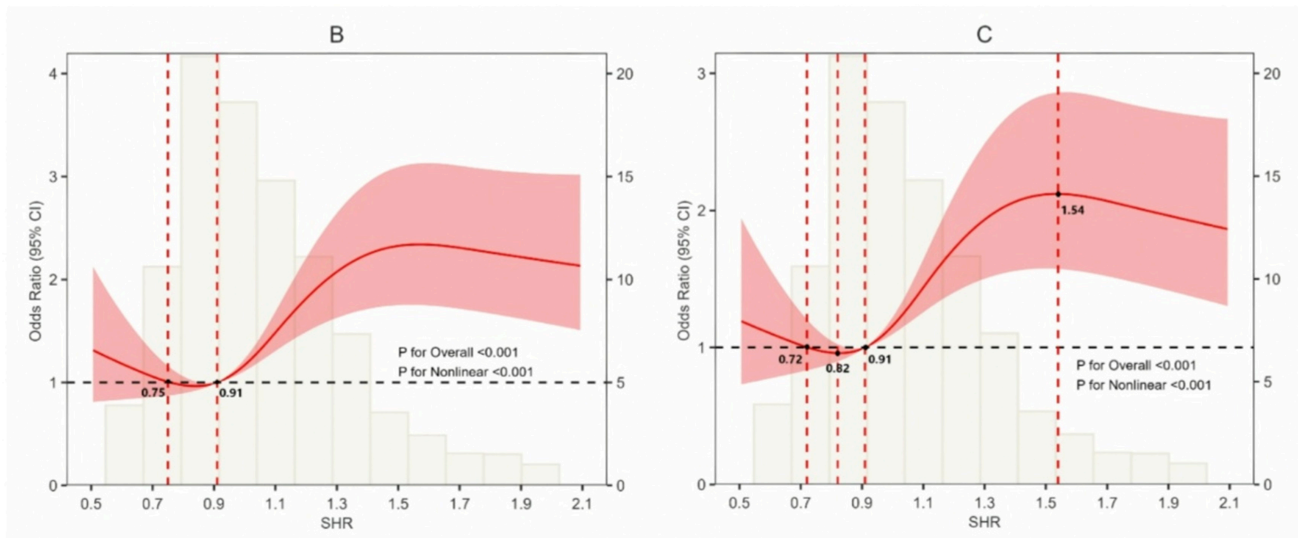
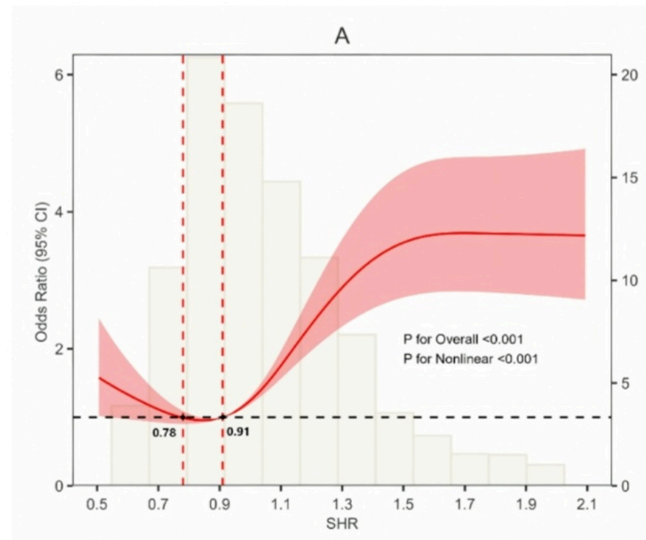


Figure 2

Restricted cubic spline for correlation of SHR and AKI in critical AIS patients

(A) Model 1 was unadjusted.

(B) Model 2 was adjusted for age, weight, SOFA score, GCS score, AF, HTN, CKD, heart failure, coronary artery disease, and COPD.

(C) Model 3 was adjusted for age, weight, SOFA score, GCS score, AF, HTN, CKD, heart failure, coronary artery disease, COPD, total serum calcium, HDL, triglycerides, white blood cell count, RDW, AST, and creatinine.

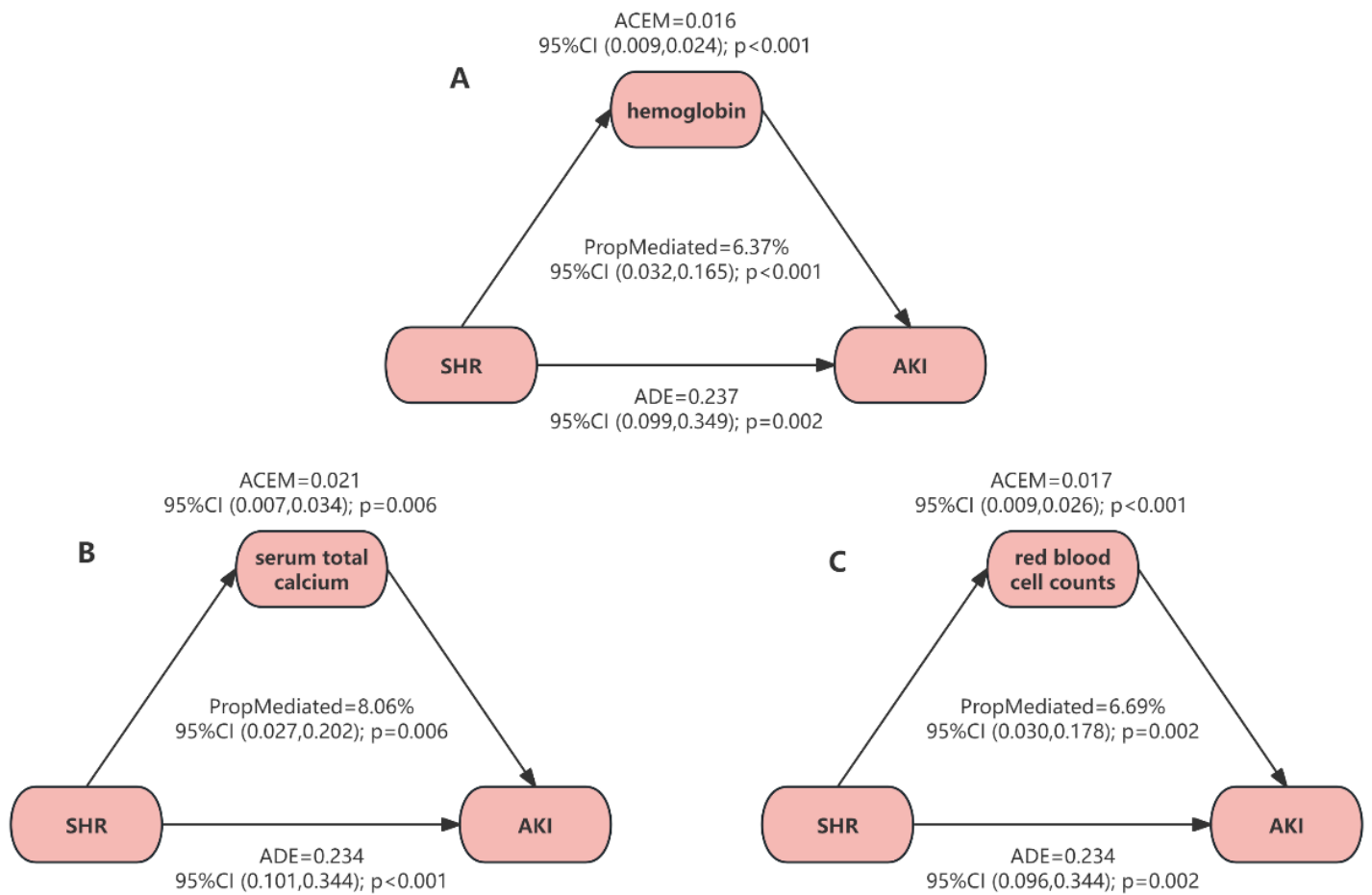


Figure 3

The figure illustrates the potential mediation pathways through (A) hemoglobin, (B) serum total calcium, and (C) red blood cell count. ACME: average causal mediated effect, ADE: average direct effect.

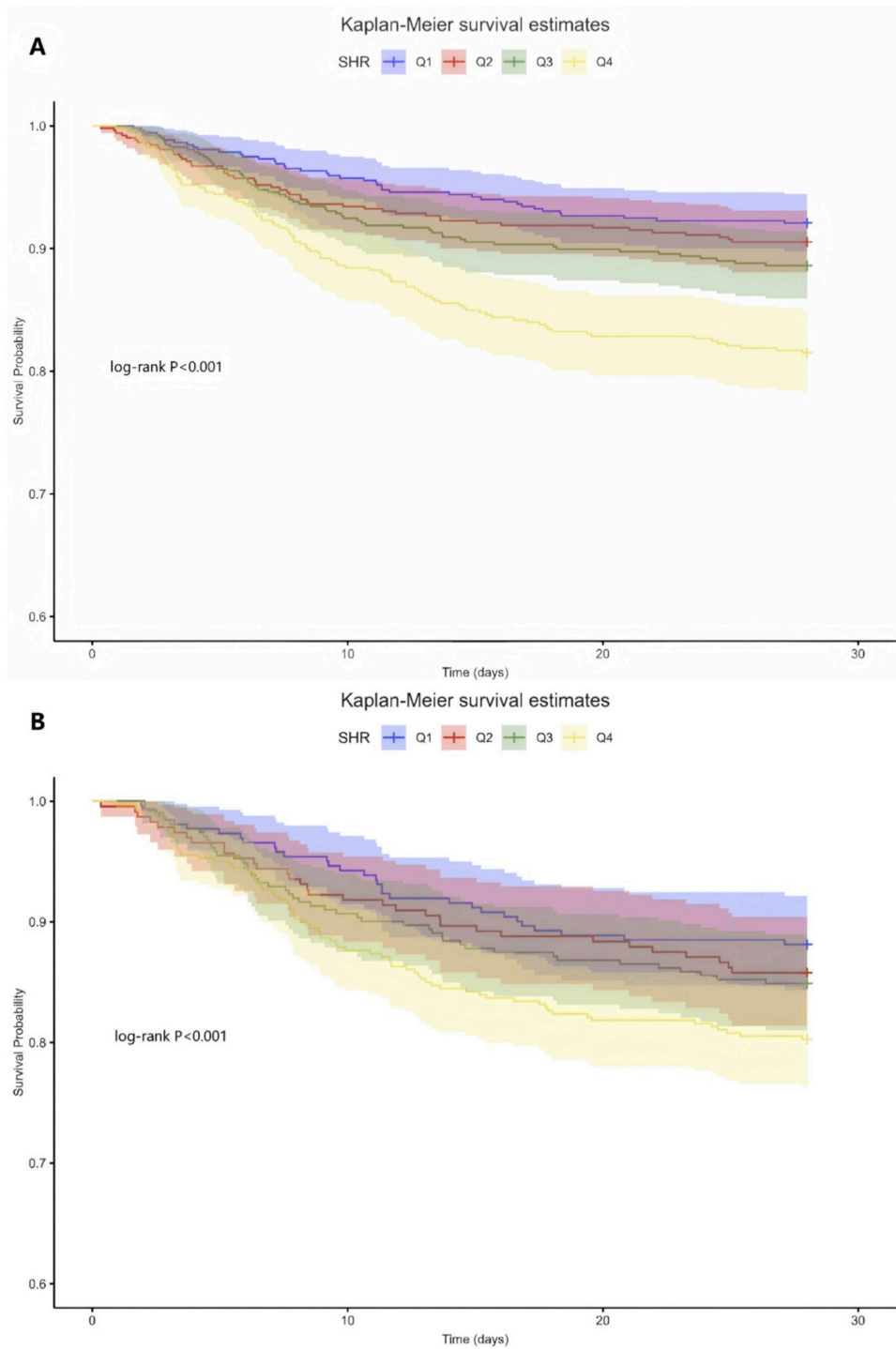


Figure 4

Kaplan–Meier analysis for 28-day in-ICU mortality of SHR groups in (A) whole population and (B) AKI population.