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The association between stress hyperglycemia ratio and clinical outcomes in patients with sepsis-associated acute kidney injury: a secondary analysis of the MIMIC-IV database

Yuanjun Zhou[1*], Liping Zhong[1], Yuting Zhong[1] and Yilin Liao[1]

Abstract

Background The stress hyperglycemia ratio (SHR) is associated with poor outcomes in critically ill patients. However, the relationship between SHR and mortality in patients with sepsis-associated acute kidney injury (SA-AKI) remains unclear.

Methods The data of patients with SA-AKI, identified based on the KDIGO criteria, were retrospectively collected from the Beth Israel Deaconess Medical Center between 2008 and 2019. SHR was calculated as follows: (glycemia [mmol/L]) / (1.59 × HbA1c [%] – 2.59). Primary outcomes were 30-day and 1-year mortality. The cumulative incidence of all-cause mortality was assessed using Kaplan–Meier survival analysis. Multivariable-adjusted logistic and Cox models and restricted cubic spline curves were used to analyze the correlation between SHR and all-cause mortality. Post-hoc subgroup analysis was performed to compare the effects of SHR across different subgroups.

Results 1161 patients with SA-AKI were identified and categorized into four SHR quartiles as follows: Q1 (0.26, 0.90), Q2 (0.91, 1.08), Q3 (1.09, 1.30), and Q4 (1.31, 5.42). The median age of patients was 69 years, with 42.7% of the patients being women and 20.2% of the patients having chronic kidney disease. The 30-day and 1-year mortality were 22.1% and 35.0% respectively. Kaplan–Meier survival analysis indicated a gradual decrease in survival probability with increasing SHR quartiles. An increased SHR exhibited a strong correlation with 30-day mortality (hazard ratio [HR], 1.50; 95% confidence interval [CI], 1.18–1.90; $P < 0.001$) and 1-year mortality (HR, 1.32; 95% CI, 1.06–1.65; $P = 0.014$). SHR has a nonlinear relationship with 1-year mortality but not with 30-day mortality (P-nonlinear = 0.048 and 0.114, respectively). The results of subgroup analysis were mostly consistent with these findings.

Conclusion An increased SHR is independently associated with 30-day and 1-year mortality in patients with SA-AKI. Therefore, SHR may serve as an effective tool for risk stratification in patients with SA-AKI.

Keywords Glycemia, Glycated hemoglobin A1c, Mortality, Sepsis, Acute kidney injury

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Introduction

Sepsis leads to approximately 45–70% of acute kidney injury (AKI) cases, and more than 60% of patients with sepsis have AKI [1–5]. Consequently, sepsis-associated acute kidney injury (SA-AKI) represents a crucial pathological condition in patients with sepsis. Compared with individuals without SA-AKI, those with SA-AKI have a lower survival rate [6–8]. The occurrence of SA-AKI is closely related to inflammatory responses induced by infection, renal tubular injury, and microcirculatory disturbances. The primary clinical manifestations of SA-AKI include an increase in serum creatinine levels and a persistent reduction in urine output. The risk factors of mortality in patients with SA-AKI include the severity of AKI; the severity of sepsis; and comorbidities, such as cardiovascular diseases and diabetes.

In patients with SA-AKI, various hormones are released in response to an infection, leading to stress-induced hyperglycemia. Stress-induced hyperglycemia is a transient increase in blood glucose levels that occurs during illness and is usually limited to patients without prior evidence of diabetes [9]. Diabetes is associated with AKI, subsequently contributing to higher mortality from AKI [10–12]. AKI in patients with diabetes is a major cause of renal replacement therapy (RRT), deterioration of chronic kidney disease (CKD), and death [13, 14]. In critically ill patients without diabetes, stress-induced hyperglycemia occurs frequently [15] and is associated with poor outcomes [16]. Hyperglycemia at the onset of sepsis is independently associated with a poor prognosis [17]. However, a study showed that hyperglycemia failed to serve as an indicator of short-term prognosis in patients with diabetes with sepsis [18]. Absolute hyperglycemia is unrelated to critical illness [19].

Therefore, to better understand the glucose metabolism status of critically ill patients, researchers have proposed the use of relative hyperglycemia, or the stress hyperglycemia ratio (SHR), to assess background glycemia [19]. Compared with absolute hyperglycemia, SHR exhibited a stronger correlation with critical illness outcomes [19]. The SHR index is calculated as follows: (glycemia [mmol/L]) / (1.59 × glycated hemoglobin A1c [%] – 2.59). SHR has been associated with all-cause mortality in patients with heart failure or myocardial infarction [20, 21]. Additionally, SHR has been positively associated with the 28-day mortality rate in patients with sepsis [22].

Despite the notable increase in the number of studies investigating the relationship between SHR and clinical outcomes in critically ill patients, the precise influence of an increased SHR on the risk of mortality in patients with SA-AKI remains unclear. Stress-induced hyperglycemia is closely related to infection and kidney injury. Understanding the relationship between SHR and clinical outcomes in patients with SA-AKI may help identify patients with a high risk of death earlier, which may in turn facilitate early intervention and monitoring for the management of hyperglycemia. In this study, considering the clinical practicality, we divided patients with SA-AKI into four groups based on SHR quartiles (25%, 50%, 75%, and 100%). We hypothesized that SHR might be positively associated with all-cause mortality in patients with SA-AKI.

Materials and methods

Data source and ethical approval

In this retrospective cohort study, the clinicopathological data of patients with SA-AKI were extracted from the Medical Information Mart for Intensive Care IV v2.2 (MIMIC-IV v2.2) database [23]. This database contains the clinical information of thousands of critically ill patients who received intensive care at the Beth Israel Deaconess Medical Center (BIDMC) between 2008 and 2019 [24, 25]. The Institutional Review Boards (IRBs) of the Massachusetts Institute of Technology (MIT) and BIDMC approved this study. A researcher (YJ Zhou) from our team completed the CITI course (Certificate Code: 39149215) as required by the official administration. After signing the Data Use Agreement, the researcher was granted permission to access the database and share the results of the search. Because this study was retrospective and was based on anonymous information, the IRB of our institution waived ethical approval and the requirement for informed consent.

Population criteria

Patients with sepsis (≥18 years old) with AKI who had stayed ≥1 day in an intensive care unit (ICU) on initial hospitalization were the target population of this study. Patients with sepsis were identified based on the Third International Consensus Definitions for Sepsis and Septic Shock (Sepsis-3) [26]. The diagnostic criteria for AKI followed the Kidney Disease: Improving Global Outcomes (KDIGO) standards [27], including (1) a reduction in urine output to <0.5 mL/kg/h for ≥6 h and (2) an increase in serum creatinine levels by ≥0.3 mg/dL within 48 h or an increase of ≥1.5 times from the level within the previous 7 days. On the contrary, patients meeting the following criteria were excluded from this study: (1) missing data on HbA1c or admission glycemia and (2) discharge or death within 24 h of ICU admission.

Data processing

We used the Structured Query Language and Microsoft Excel to extract predefined variables and outcomes from the MIMIC-IV database. Data on all variables were collected within 24 h of ICU admission. When continuous variables were measured multiple times, the average value was considered. In addition, comorbidities

were identified based on ICD-9/10 codes. The variables included the following: (1) demographic characteristics: age, sex, race, and body mass index (BMI); (2) vital signs and pathological results: admission glycemia; heart rate; mean blood pressure (MBP); red blood cell distribution width (RDW); platelet counts; HbA1c, hemoglobin, bicarbonate, blood urea nitrogen (BUN), creatinine, chloride, sodium, potassium, alanine transaminase (ALT), and aspartate transaminase (AST) levels; anion gap; prothrombin time (PT); and partial thromboplastin time (PTT); (3) comorbidities: chronic obstructive pulmonary disease (COPD), a history of myocardial infarction, cerebrovascular diseases, congestive heart failure (CHF), CKD, diabetes, chronic liver disease, and cancer; (4) disease status: Simplified Acute Physiology Score II (SAPS II), Sequential Organ Failure Assessment (SOFA) score, and AKI stage; and (5) initial therapies: RRT, insulin, glucocorticoids, β-blockers, inotropes (dopamine, dobutamine, and epinephrine), vasopressors (norepinephrine and vasopressin), and mechanical ventilation (MV).

Exposure

The exposure was baseline SHR, which was calculated as (glycemia [mmol/L]) / (1.59 × HbA1c [%] – 2.59) [19, 28]. The estimated average glucose is 1.59 × HbA1c [%] – 2.59.

Outcomes

The primary outcomes included 30-day mortality and 1-year mortality. The secondary outcomes included in-hospital mortality, length of stay (LOS) in the ICU, and LOS in the hospital. All-cause mortality was determined based on the recorded dates of death, whereas LOS was calculated based on the respective dates of admission and discharge.

Statistical analysis

Eligible individuals in the database determined the sample size; therefore, no statistical power was calculated. Variables with >25% of missing data were excluded to avoid potential biases (Supplementary Table S1), whereas the random forest algorithm was used to perform multiple imputations for variables with <25% of missing data [29, 30]. Patients with SA-AKI were divided into four groups according to the SHR quartiles, denoted as Q1, Q2, Q3, and Q4. Continuous variables were expressed as the median (25th–75th percentile) and analyzed using the Kruskal–Wallis or Mann–Whitney U test. Categorical variables were expressed as the total count (percentage) and analyzed using the chi-square test or Fisher's exact test. Receiver operating characteristic (ROC) curves were plotted to compare the performance of SHR, admission glycemia, and HbA1C in predicting all-cause mortality. Kaplan–Meier survival curves were plotted to analyze the cumulative incidence of outcomes. A logistic regression model was established to determine the odds ratios (ORs) and 95% confidence intervals (CIs) for in-hospital mortality, whereas a Cox proportional hazards model was established to determine the hazard ratios (HRs) and 95% CIs for 30-day and 1-year mortality. Patients were stratified into subgroups based on the median age and SOFA scores. Post-hoc subgroup analysis was performed to evaluate the HRs of continuous SHR for 30-day and 1-year mortality in different subgroups stratified by age (<68 years or ≥68 years), sex, diabetes, CKD, and SOFA scores (<4 or ≥4). All statistical analyses were performed using the R software (version 4.2.3; Vienna, Austria). A two-tailed *P*-value of <0.05 was considered statistically significant.

Reporting guideline

We reported the findings of this study following the Reporting of Studies Conducted using Observational Routinely-collected Health Data (RECORD) guidelines [31].

Results

Baseline characteristics

A total of 1161 patients with SA-AKI were included in this study (Fig. 1). Details regarding the missing data of variables and collinearity detection are provided in Supplementary Tables S1 and S2, respectively. Table 1 summarizes the baseline characteristics of all included patients. The patients were divided into the following four groups based on the quartile ranges of SHR: Q1 (0.26, 0.90), Q2 (0.91, 1.08), Q3 (1.09, 1.30), and Q4 (1.31, 5.42). The overall population had a median age of 69 (59, 80) years, with 42.7% of the patients being women and 56.0% of the patients being white. The median glycemia at ICU admission was 7.7 (6.2, 10.2) mmol/L, and the median HbA1c was 6.0% (5.5%, 7.1%). A total of 132 (11.4%) and 235 (20.2%) patients had diabetes and CKD, respectively. A total of 223 (19.2%), 611 (52.6%), and 327 (28.2%) patients had stage-I, stage-II, and stage-III AKI, respectively. The overall 30-day mortality, 1-year mortality, and in-hospital mortality rates were 22.1% (256 patients), 35.0% (406 patients), and 18.5% (215 patients).

Supplementary Table S3 provides information on the baseline characteristics of survivors and non-survivors. Non-survivors had a higher RDW, anion gap, bicarbonate level, and BUN level, whereas survivors had fewer comorbidities; lower disease scores; and lower frequencies of RRT, MV, and vasopressor use. However, no significant differences in the frequency of insulin, glucocorticoid, or β-blocker use were observed between survivors and non-survivors. The 1-year mortality rates were higher among non-survivors with CKD and diabetes ($P<0.001$, $P=0.022$, respectively). However, no

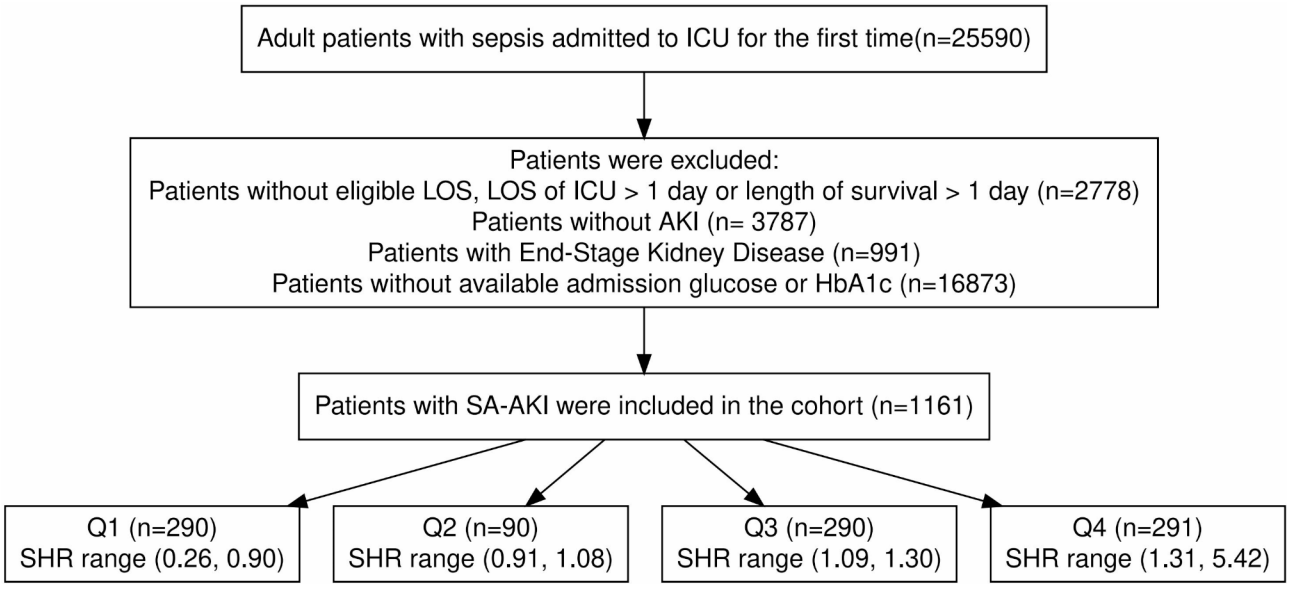

Fig. 1 Flowchart of the inclusion of patients. ICU, intensive care unit; AKI, acute kidney injury; HbA1c, glycated hemoglobin A1c; SA-AKI, sepsis-associated acute kidney injury; SHR, stress hyperglycemia ratio. According to the KDIGO criteria, a total of 19,025 patients with sepsis developed AKI

significant differences in 30-day mortality rates were observed between non-survivors with and without CKD or between non-survivors with and without diabetes ($P=0.149$ and 0.673, respectively).

ROC curve analysis

With regard to the prediction of 30-day, 1-year, and in-hospital mortality, the area under the curve (AUC) of SHR was higher than that of admission glycemia and HbA1c (AUC=0.613, 0.562, and 0.619, respectively) (Supplementary Figure S4). The DeLong test revealed significant differences among the AUC values of SHR, admission glycemia, and HbA1c regarding the prediction of in-hospital and 30-day mortality. However, no significant differences were observed between the AUC values of SHR and HbA1c regarding the prediction of 1-year mortality. The optimal cutoff AUC values of SHR for predicting 30-day, 1-year, and in-hospital mortality were 1.18, 1.18, and 1.13, respectively.

Relationship between SHR and outcomes

Patients with SA-AKI with higher SHRs had higher 30-day and 1-year mortality rates (log-rank test $P<0.001$ for both, Fig. 2). The cumulative incidence of events was higher in the Q3 and Q4 groups than in the Q1 group. However, no significant differences in the cumulative incidence of events were observed between the Q1 and Q2 groups (30-day mortality, $P=0.615$; 1-year mortality, $P=0.463$). Notably, the SHR in the Q2 group ranged from 0.91 to 1.08, which was close to the optimal cutoff value of 1.18. Continuous SHR was independently associated with 1-year mortality (HR, 1.50; 95% CI, 1.18–1.90; $P<0.001$) and 30-day mortality (HR, 1.32; 95% CI, 1.06–1.65; $P=0.014$) (Table 2) in patients with SA-AKI. All trend tests (quartiles) showed significant differences. Furthermore, the RCS curve (Fig. 3) showed that as the SHR increased, the 30-day and 1-year mortality rates exhibited different and complex increasing trends (P-nonlinear=0.114 and 0.048, respectively). However, SHR was not found to be an independent indicator of in-hospital mortality (OR, 1.33; 95% CI, 0.90–1.99; $P=0.157$; Supplementary Table S5).

Subgroup analysis

After potential confounding factors were controlled for, the results of subgroup analysis were mostly consistent with those of the primary analysis (Fig. 4). However, the relationship between SHR and 1-year mortality was not found to be significant in the <68-year group (HR, 1.27; 95% CI, 0.87–1.86) and the <4-SOFA score group (HR, 1.08; 95% CI, 0.69–1.71). Similarly, no significant relationship between SHR and 30-day mortality was observed in the <4-SOFA score group (HR, 1.28; 95% CI, 0.78–2.11). The interaction effects between subgroups were insignificant for both 30-day mortality and 1-year mortality.

Discussion

This study revealed the effects of admission SHR on mortality in patients with SA-AKI. To date, no studies have evaluated the efficacy of SHR in predicting survival outcomes in patients with SA-AKI. This study showed that an increased SHR was independently and nonlinearly associated with increased 30-day and 1-year mortality

Table 1 Baseline characteristics of patients with SA-AKI grouped by SHR quartiles

Characteristics	Overall, *N* = 1161	Q1, *N* = 290	Q2, *N* = 290	Q3, *N* = 290	Q4, *N* = 291	*P*
SHR range		(0.26, 0.90)	(0.91, 1.08)	(1.09, 1.30)	(1.31, 5.42)	
SHR quartile	1.09 [0.91, 1.31]	0.79 [0.71, 0.85]	1.00 [0.96, 1.04]	1.19 [1.14, 1.23]	1.52 [1.40, 1.76]	< 0.001
HbA1c (%)	5.9 [5.5, 6.8]	6.2 [5.8, 8.2]	5.9 [5.5, 6.6]	5.8 [5.4, 6.5]	5.8 [5.4, 6.6]	< 0.001
Admission glucose (mmol/L)	7.7 [6.2, 10.2]	5.8 [5.1, 7.5]	6.7 [6.1, 7.8]	7.9 [7.2, 9.5]	10.6 [9.1, 14.0]	< 0.001
Age (years)	69 [59, 80]	68 [58, 80]	69 [60, 78]	71 [60, 81]	67 [59, 78]	0.141
Sex (Woman)	496 (42.7)	132 (45.5)	105 (36.2)	132 (45.5)	127 (43.6)	0.072
Race						0.227
White	650 (56.0)	157 (54.1)	166 (57.2)	175 (60.3)	152 (52.2)	
Black	111 (9.6)	36 (12.4)	22 (7.6)	25 (8.6)	28 (9.6)	
Others	400 (34.5)	97 (33.4)	102 (35.2)	90 (31.0)	111 (38.1)	
Vital signs						
Heart rate (beats/minute)	83 [73, 95]	81 [73, 92]	81 [71, 92]	85 [73, 97]	86 [74, 96]	0.005
MBP (mmHg)	80 [74, 89]	80 [74, 89]	80 [74, 90]	81 [74, 89]	79 [73, 87]	0.270
Lab results						
RDW (%)	14.1 [13.3, 15.3]	14.2 [13.3, 15.3]	14.0 [13.3, 14.9]	14.1 [13.3, 15.1]	14.3 [13.3, 15.8]	0.096
Platelets (10^9/L)	196 [149, 256]	196 [152, 258]	191 [147, 252]	207 [151, 260]	195 [145, 252]	0.565
Hemoglobin (g/dL)	11.4 [9.9, 12.9]	11.20[9.7, 12.8]	11.7 [10.2, 12.9]	11.5 [10.3, 12.9]	11.2 [9.7, 13.0]	0.057
Anion gap (mmol/L)	14.7 [12.8, 17.0]	14.0 [12.3, 16.0]	14.0 [12.5, 15.5]	14.6 [13.0, 16.7]	16.0 [13.7, 18.0]	< 0.001
Bicarbonate (mmol/L)	22.7 [20.3, 25.0]	23.0 [21.0, 25.5]	23.0 [21.0, 25.0]	22.5 [20.5, 24.7]	21.5 [18.7, 24.0]	< 0.001
BUN (mg/dL)	20 [14, 31]	20 [14, 30]	17 [13, 26]	20 [14, 30]	24 [17, 37]	< 0.001
Chloride (mmol/L)	104.3 [101.0, 107.9]	104.9 [101.3, 108.0]	105.0 [102.0, 108.0]	104.0 [101.0, 107.0]	104.0 [100.6, 107.3]	0.076
Sodium (mmol/L)	139.0 [136.8, 141.8]	139.5 [136.4, 142.0]	139.0 [137.5, 141.3]	139.0 [137.0, 141.7]	139.0 [136.0, 141.6]	0.293
Potassium (mmol/L)	4.07 [3.80, 4.41]	4.08 [3.80, 4.40]	4.05 [3.76, 4.37]	4.05 [3.79, 4.49]	4.10 [3.80, 4.54]	0.214
PT (s)	13.6 [12.3, 15.4]	13.7 [12.3, 15.4]	13.3 [12.1, 14.9]	13.7 [12.2, 15.4]	13.8 [12.4, 16.3]	0.029
PTT (s)	32 [27, 47]	33 [28, 43]	31 [27, 48]	32 [28, 42]	34 [27, 52]	0.183
ALT (U/L)	34 [19, 64]	29 [17, 54]	31 [18, 51]	34 [19, 62]	46 [21, 121]	< 0.001
AST (U/L)	51 [25, 109]	40 [22, 76]	43 [23, 90]	55 [26, 102]	78 [30, 210]	< 0.001
Culture positive	305 (26.3)	77 (26.6)	76 (26.2)	80 (27.6)	72 (24.7)	0.891
Medical histories						
Myocardial infarction	374 (32.2)	91 (31.4)	83 (28.6)	91 (31.4)	109 (37.5)	0.135
Congestive heart failure	457 (39.4)	110 (37.9)	105 (36.2)	113 (39.0)	129 (44.3)	0.214
Chronic renal disease	235 (20.2)	75 (25.9)	45 (15.5)	55 (19.0)	60 (20.6)	0.019
Cerebrovascular disease	498 (42.9)	117 (40.3)	132 (45.5)	149 (51.4)	100 (34.4)	< 0.001
Chronic pulmonary disease	267 (23.0)	78 (26.9)	57 (19.7)	58 (20.0)	74 (25.4)	0.080
Diabetes	132 (11.4)	40 (13.8)	19 (6.6)	33 (11.4)	40 (13.7)	0.019
Chronic liver disease	112 (9.6)	18 (6.2)	23 (7.9)	29 (10.0)	42 (14.4)	0.006
Malignant cancer	79 (6.8)	18 (6.2)	16 (5.5)	22 (7.6)	23 (7.9)	0.625
Therapies						
RRT	62 (5.3)	8 (2.8)	7 (2.4)	19 (6.6)	28 (9.6)	< 0.001
MV	1,026 (88.4)	242 (83.4)	264 (91.0)	262 (90.3)	258 (88.7)	0.019
Insulin	549 (47.3)	130 (44.8)	113 (39.0)	129 (44.5)	177 (60.8)	< 0.001
Inotropes	152 (13.1)	28 (9.7)	24 (8.3)	37 (12.8)	63 (21.6)	< 0.001
Vasopressors	245 (21.1)	38 (13.1)	40 (13.8)	57 (19.7)	110 (37.8)	< 0.001
Glucocorticoids	52 (4.5)	15 (5.2)	6 (2.1)	7 (2.4)	24 (8.2)	< 0.001
β-adrenergic blocking agents	280 (24.1)	68 (23.4)	74 (25.5)	82 (28.3)	56 (19.2)	0.075
AKI stage						0.205
I	223 (19.2)	67 (23.1)	59 (20.3)	51 (17.6)	46 (15.8)	
II	611 (52.6)	151 (52.1)	156 (53.8)	147 (50.7)	157 (54.0)	
III	327 (28.2)	72 (24.8)	75 (25.9)	92 (31.7)	88 (30.2)	
Creatinine (mg/dL)	1.1 [0.80, 1.5]	1.0 [0.8, 1.4]	1.0 [0.8, 1.3]	1.1 [0.8, 1.5]	1.2 [0.9, 1.8]	< 0.001
Disease scores						
SOFA	4.0 [3.0, 7.0]	4.0 [2.0, 6.0]	4.0 [2.0, 6.0]	5.0 [3.0, 7.0]	6.0 [4.0, 9.0]	< 0.001
SAPSII	37 [30, 44]	35 [27, 43]	35 [29, 41]	37 [31, 45]	39 [32, 48]	< 0.001

Table 1 (continued)

Characteristics	Overall, *N* = 1161	Q1, *N* = 290	Q2, *N* = 290	Q3, *N* = 290	Q4, *N* = 291	*P*
Endpoints						
30-day mortality	256 (22.1)	45 (15.5)	49 (16.9)	68 (23.5)	94 (32.3)	< 0.001
1-year mortality	406 (35.0)	91 (31.4)	82 (28.3)	106 (36.6)	127 (43.6)	< 0.001
In-hospital mortality	215 (18.5)	37 (12.8)	36 (12.4)	56 (19.3)	86 (29.6)	< 0.001
LOS of hospital (days)	11 (6, 18)	10 (6, 17)	11 (7, 18)	12 (7, 18)	11 (6, 19)	0.202
LOS of ICU (days)	5 (3, 10)	4 (2, 8)	5 (3, 9)	5 (3, 10)	6 (3, 11)	< 0.001

Continuous variables were presented as median [quartile]; Categorical variables were presented as n (%). SA-AKI: sepsis-associated acute kidney injury; SHR: stress hyperglycemia ratio; HbA1c: hemoglobin A1c; MBP: mean blood pressure; RDW: red blood cell distribution width; BUN: blood urea nitrogen; PT: prothrombin time; PTT: Partial thromboplastin time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RRT: Renal Replacement Therapy; MV: Mechanical Ventilation; AKI stage: acute kidney injury stage; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score II; LOS: length of stay. Inotropes included dobutamine, dopamine, epinephrine, milrinon; vasopressors included norepinephrine and vasopressin; LOS: length of stay

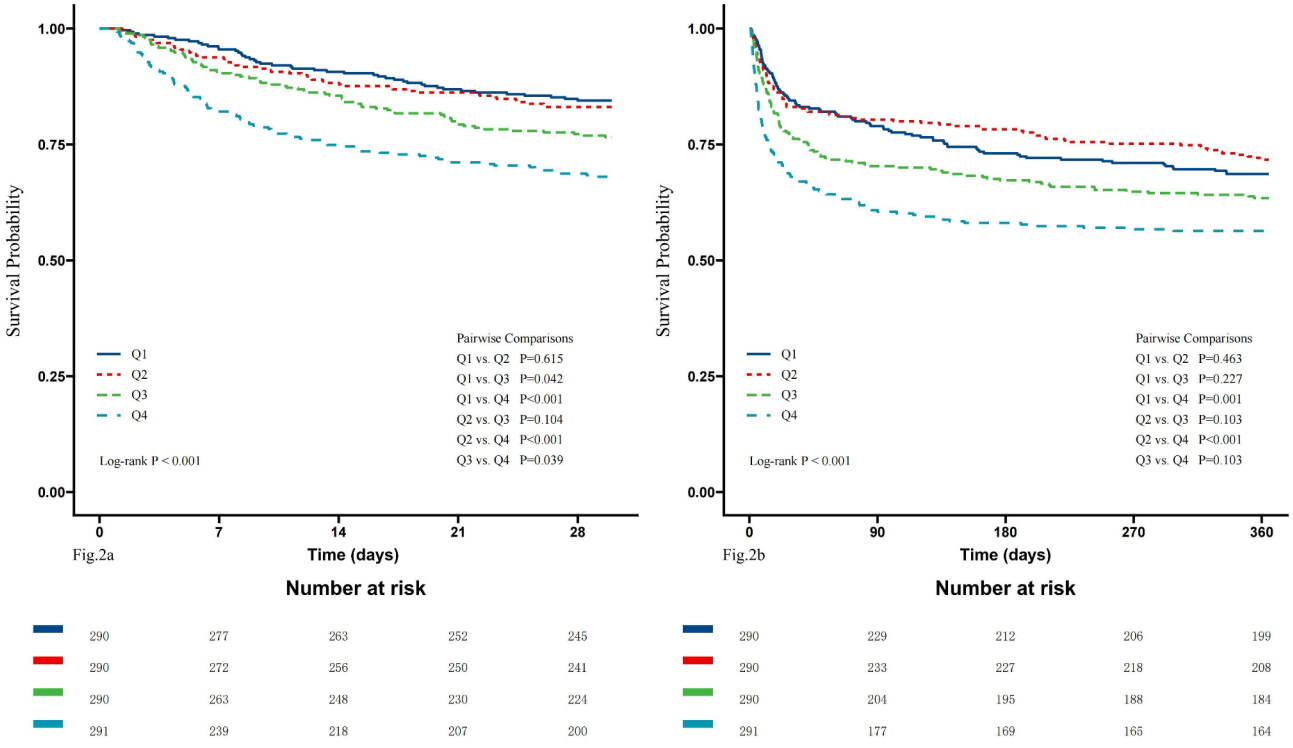

Fig. 2 Kaplan–Meier survival curves. **a** Kaplan–Meier curve demonstrating the relationship between SHR and 30-day mortality. Figure 2**b** Kaplan–Meier curve demonstrating the relationship between SHR and 1-year mortality. Q1 (0.26, 0.90), Q2 (0.91, 1.08), Q3 (1.09, 1.30), Q4 (1.31, 5.42). SHR, stress hyperglycemia ratio

rates in patients with SA-AKI. Compared with admission glycemia and HbA1c, SHR demonstrated a stronger ability to predict all-cause mortality. These findings suggest that SHR is a valuable index for risk stratification in patients with SA-AKI.

SHR has been associated with in-hospital and 1-year mortality in critically ill patients [32]. Similarly, irrespective of the glucose metabolism status, SHR during fasting is associated with an increased in-hospital mortality rate in patients with acute myocardial infarction [33]. Additionally, a previous study demonstrated a nonlinear relationship between SHR and survival in patients with sepsis [22]. Although these findings indicate that SHR is a promising prognostic biomarker in patients with critical illnesses, the relationship between SHR and prognosis in patients with SA-AKI remains unclear. This study demonstrated that patients with SA-AKI with increased SHRs had a higher risk of 30-day and 1-year mortality. The independent relationship between SHR and both 1-year and 30-day mortality reveals the long-term impact of SHR on critically ill patients, whereas the severity of acute events and clinical management may more directly influence in-hospital mortality. Although SHR is a valuable predictor of mortality, its AUC value did not meet our expectations; however, this does not necessarily imply a weak correlation between SHR and mortality. Various factors, including metabolic abnormalities, comorbidities, complications, and treatment responses,

Table 2 Results of Cox regression and logistic regression between SHR and all-cause mortality

	Model 1		Model 2		Model 3	
Endpoints	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
30-day mortality						
Continuous SHR per unit	1.93 (1.58–2.36)	< 0.001	1.75 (1.39–2.20)	< 0.001	1.50 (1.18–1.90)	< 0.001
SHR quartile range						
Q1 (0.26, 0.90)	Reference		Reference		Reference	
Q2 (0.91, 1.08)	1.11 (0.74–1.66)	0.618	1.15 (0.76–1.73)	0.507	1.19 (0.78–1.79)	0.420
Q3 (1.09, 1.30)	1.59 (1.09–2.32)	0.016	1.35 (0.92–1.97)	0.128	1.30 (0.88–1.91)	0.188
Q4 (1.31, 5.42)	2.40 (1.68–3.42)	< 0.001	2.04 (1.41–2.95)	< 0.001	1.82 (1.24–2.65)	0.002
P_{trend}	< 0.001		< 0.001		0.002	
1-year mortality						
Continuous SHR per unit	1.61 (1.32–1.96)	< 0.001	1.43 (1.15–1.79)	0.002	1.32 (1.06–1.65)	0.014
SHR quartile range						
Q1 (0.26, 0.90)	Reference		Reference		Reference	
Q2 (0.91, 1.08)	0.90 (0.67–1.21)	0.490	0.89 (0.66–1.20)	0.448	0.90 (0.66–1.22)	0.499
Q3 (1.09, 1.30)	1.25 (0.94–1.65)	0.124	1.02 (0.76–1.35)	0.915	0.99 (0.74–1.32)	0.928
Q4 (1.31, 5.42)	1.66 (1.27–2.17)	< 0.001	1.42 (1.07–1.88)	0.015	1.34 (1.00-1.79)	0.049
P_{trend}	< 0.001		0.010		0.037	

The range for Q1 was 0.26–0.90, for Q2 was 0.91–1.08, for Q3 was 1.09–1.30, and for Q4 was 1.31–5.42. SHR, the stress hyperglycemia ratio; HR: hazard ratio; OR: odds ratio; 95%CI: 95% confidence interval; Model 1: crude model; Model 2: adjusted for age, gender, race, congestive heart failure, chronic renal disease, cerebrovascular disease, diabetes, cancer, chronic liver disease; Model 3: based on Model 2, adjusted for heart rate, MBP, RDW, platelets, hemoglobin, anion gap, bicarbonate, BUN, sodium, potassium, PT, ALT, AST, culture results, RRT, insulin, inotropes, vasopressors, glucocorticoids, AKI stage, SOFA score, SAPSII score. MBP: mean blood pressure; RDW: red blood cell distribution width; BUN: blood urea nitrogen; PT: prothrombin time; ALT: alanine aminotransferase; AST: aspartate aminotransferase; RRT: Renal Replacement Therapy; AKI stage: acute kidney injury stage; SOFA: Sequential Organ Failure Assessment; SAPSII: Simplified Acute Physiology Score II. Inotropes included dobutamine, dopamine, epinephrine, milrinon; vasopressors included norepinephrine and vasopressin

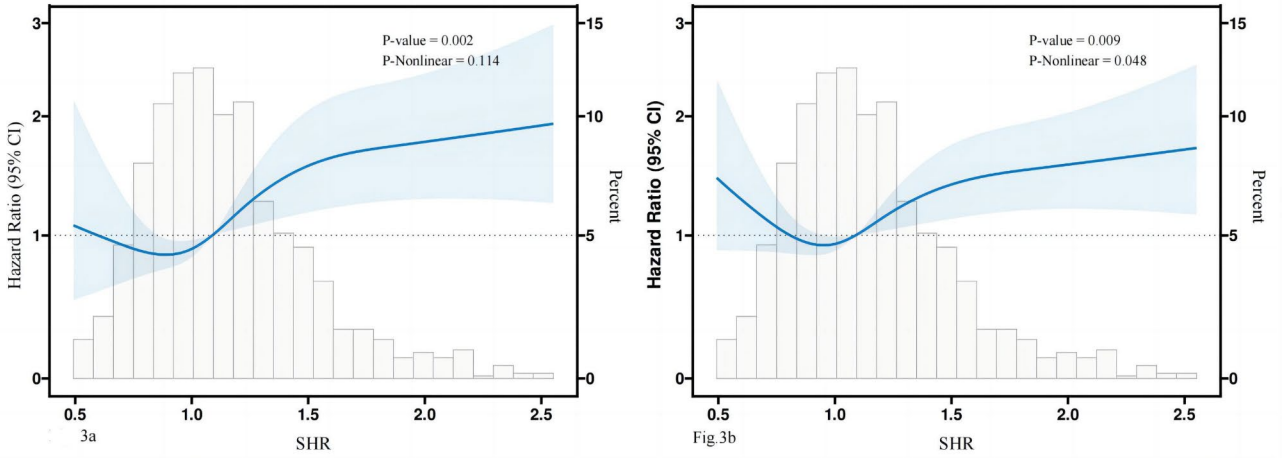

Fig. 3 Restricted cubic spline curves. **a** Restricted cubic spline (RCS) curve demonstrating the relationship between SHR and 30-day mortality. Figure 3**b** RCS curve demonstrating the relationship between SHR and 1-year mortality. The blue solid line represents the hazard ratio, whereas the light blue background represents the 95% confidence interval. SHR, stress hyperglycemia ratio

can influence the risk of death. SHR is one of these complex factors. Therefore, the impact of other risk factors should be considered when interpreting the relationship between SHR and adverse outcomes.

The relationship between SHR and all-cause mortality may follow a complex injury accumulation model. In the lower SHR range, each unit increase in SHR may be associated with the cumulative presence of inflammation, oxidative stress, and microvascular damage, all of which contribute to a rapid increase in the risk of mortality. In the higher SHR range, these pathological conditions might reach a plateau, resulting in a slower increase in the risk of mortality. In this state, other complications or comorbidities may serve as primary factors affecting the prognosis, thereby diminishing the relative impact of SHR. In this study, irrespective of whether patients with SA-AKI had concurrent diabetes or CKD, a higher SHR was closely associated with higher 30-day and 1-year mortality rates. Diabetes is the leading cause of CKD. When patients with diabetes or CKD have stress-induced hyperglycemia, it may exert a synergistic negative effect on outcomes. The relationship between baseline SHR and

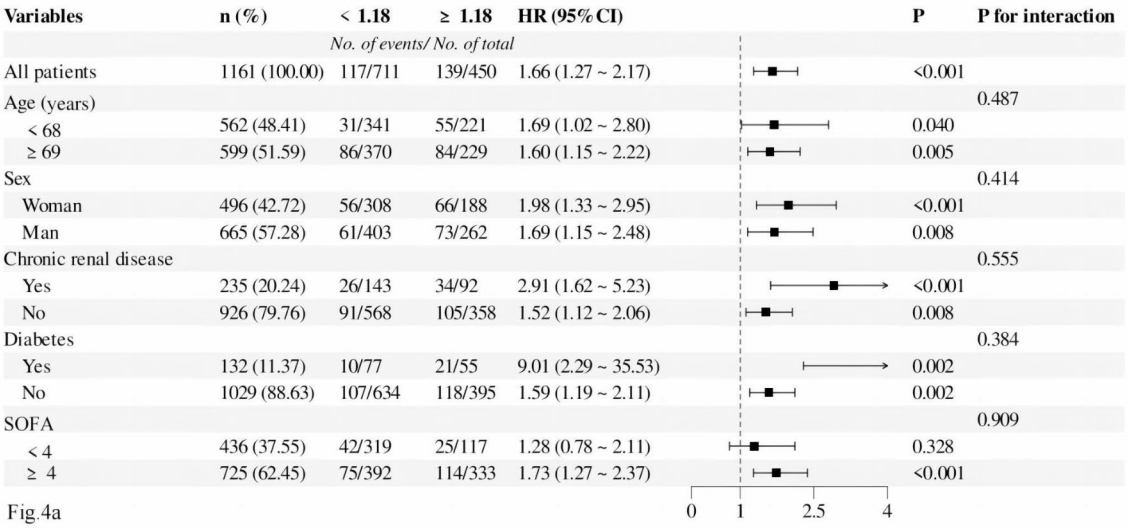

Fig.4a

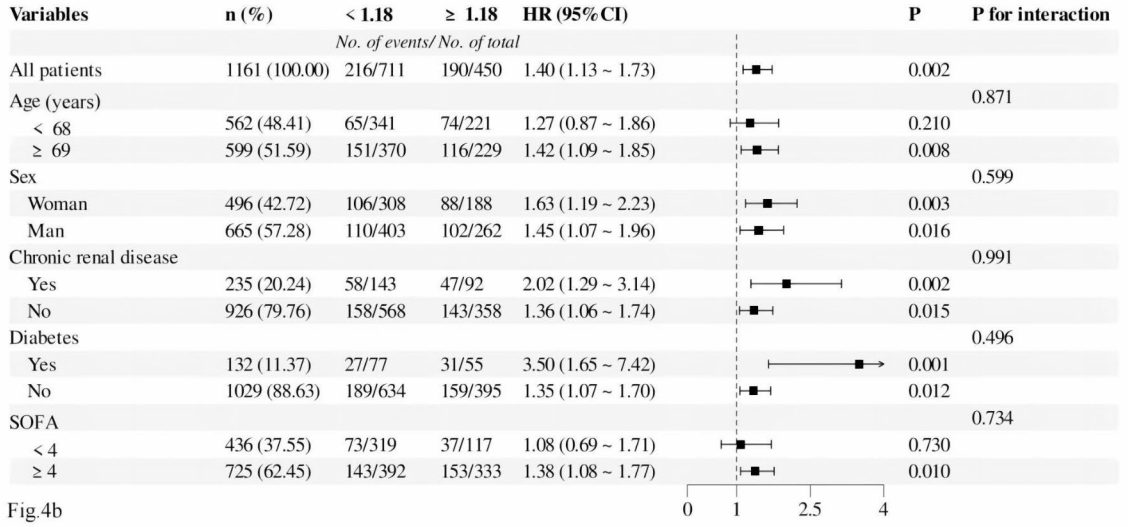

Fig.4b

Fig. 4 Subgroup analysis. **a** Subgroup analysis of 30-day mortality. Figure 4**b** Subgroup analysis of 1-year mortality. The cohort was divided into two groups based on the cut-off value of SHR (1.18). Variables with a *P*-value of < 0.2 and other clinically important variables were adjusted for in the Cox regression model. HR, hazard ratio; 95% CI, 95% confidence interval; SOFA, Sequential Organ Failure Assessment

mortality varied among patients with sepsis of varying severity. In patients with SOFA scores of < 4, the baseline SHR was not correlated with mortality, possibly owing to milder organ dysfunction. However, in patients with SOFA scores of ≥ 4, the baseline SHR was independently associated with mortality, indicating that the impact of SHR on prognosis became more significant as the severity of organ dysfunction increased.

Most patients with SA-AKI have concurrent stress-induced hyperglycemia, irrespective of whether they have diabetes mellitus [15]. Acute hyperglycemia can directly exacerbate inflammation and oxidative stress, which may reduce renal reperfusion [34]. Moreover, stress-induced hyperglycemia can lead to osmotic diuresis, fluid depletion, and dehydration, further impairing renal function [35]. These pathophysiological changes may lead to the development of renal complications, eventually resulting in a poor prognosis. Therefore, timely and accurate assessment of glycemia in patients with SA-AKI is beneficial for improving the prognosis. Absolute hyperglycemia is associated with ICU mortality [36], which is consistent with the results of this study. However, absolute hyperglycemia is influenced by acute stress and potentially chronic hyperglycemia [37]. The failure to consider the background glycemia of a patient limits the ability to accurately identify actual acute hyperglycemia. HbA1c can reflect background glycemia over the past 8–12 weeks [28, 38]. SHR, which reflects relative

hyperglycemia, is a better index than absolute hyperglycemia, as it can control for background glycemia [39]. It can provide novel insights into the relationship between abnormal glycemic regulation and patient prognosis [40]. In addition, it can distinguish between glycemic changes and critical illness or metabolic status. The ability of SHR to predict prognosis is stronger than that of absolute hyperglycemia, especially in patients with acute diseases such as acute myocardial infarction, sepsis, and stroke [39, 41, 42], which is consistent with the findings of this study. SHR is associated with in-hospital mortality irrespective of whether patients with myocardial infarction have diabetes [33], which is consistent with the results of subgroup analysis in this study. In this study, SHR was strongly correlated with patient outcomes, irrespective of the pre-disease glucose metabolism status. Moreover, when SHR is used in combination with SPASII scores, it has a more robust ability to predict poor outcomes in patients with critical illness and AKI [36]. Altogether, SHR is an independent and more widely applicable predictor of prognosis.

An increased SHR indicates a state of stress associated with hyperglycemia, irrespective of the previous glycemic levels [22]. Compared with patients with absolute hyperglycemia, those with relative hyperglycemia are at an increased risk of developing severe pathological conditions [19]. Assessment of SHR may facilitate the early identification of patients with SA-AKI who have a high risk of mortality. As glycemia and HbA1c tests are widely available, SHR is highly generalizable. In addition, SHR can more comprehensively reflect the glucose metabolism status of patients. Therefore, further investigation into SHR and its clinical utility, such as guiding the management of glycemia, is warranted. Compared with admission glycemia and HbA1c levels, the SHR index more effectively predicts adverse outcomes. Owing to the impact of CKD on the lifespan of red blood cells and glycation, HbA1c levels may not accurately reflect the glycemic status [43]. In patients with diabetes and CKD, assessing hyperglycemia and its impact on prognosis remains challenging. Therefore, other more effective indicators, such as continuous glucose monitoring or sustained SHR data, should be used to accurately assess the glycemic status as well as predict and improve patient outcomes.

Limitations

This retrospective cohort study has some limitations that should be acknowledged. First, we did not determine the specific causes of death in this study due to the database limitation. Second, some potential confounding factors, such as BMI, might have introduced bias in the results. Given that the relationship between BMI and metabolism is essential, we conducted multivariate regression analysis for all patients with available BMI data. The results were consistent with those of the primary analysis (Supplementary Table S6), validating the robustness of the findings. Third, we did not evaluate the potential relationship between SHR trajectory and adverse events. Fourth and last, poor blood glucose control may exacerbate the condition of patients with underlying diseases, leading to death. Continuous SOFA scoring facilitates a more accurate assessment of disease progression. However, owing to limitations in the structure of the MIMIC-IV database, we could not include these data, which restricted our ability to assess the dynamic interplay between blood glucose levels and disease progression. We believe this is an important focus area for future research, and prospective studies will be best suited to address these issues.

Conclusion

An increased SHR is closely associated with all-cause mortality in patients with SA-AKI. As an easily generalizable indicator, SHR is an effective tool for risk stratification in patients with SA-AKI. Further investigation is warranted to assess the clinical significance of SHR in regulating glycemic levels in patients with SA-AKI.

Abbreviations

SA-AKI	Septic-associated acute kidney injury
AKI	Acute Kidney Injury
RRT	Renal Replacement Therapy
CKD	Chronic Kidney Disease
SHR	Stress Hyperglycemia Ratio
HbA1c	Hemoglobin A1c
MIMIC-IV v2.2	Medical Information Mart for Intensive Care IV v2.2
BIDMC	Beth Israel Deaconess Medical Center
IRBs	Institutional Review Boards
MIT	Massachusetts Institute of Technology
ICU	Intensive care unit
BMI	Body Mass Index
MBP	Mean Blood Pressure
RDW	Red Cell Distribution Width
BUN	Blood Urea Nitrogen
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
ALT	Alanine Transaminase
AST	Aspartate Transaminase
COPD	Chronic Obstructive Pulmonary Disease
CHF	Congestive Heart Failure
SAPS II	Simplified Acute Physiology Score II
SOFA	Sequential Organ Failure Assessment
MV	Mechanical Ventilation
LOS	Length of stay
ROC	Receiver operating characteristic
AUCs	Areas under the curves
OR	Odds ratio
CI	95% confidence interval
HR	Hazard ratio

Supplementary Information

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Supplementary Material 1

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Author contributions
Zh. YJ: study design, data collection and examination, data analysis, and manuscript drafting, manuscript revision, the supervision of the study process, response to reviewers; ZH. LP: study design, data collection, and examination, data analysis, manuscript drafting, manuscript revision and supervision of the study process; Zh. YT: data examination and analysis, manuscript drafting, and supervision of the study process, manuscript revision; L. YL: data examination and analysis and the supervision of the study process, manuscript revision.

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Data availability
The MIMIC-IV database is open-access (https://physionet.org/content/mimiciv/2.2/), and the corresponding author can grant data access to this study upon request.

Declarations

Ethics approval and consent to participate
The Institutional Review Boards of both the Massachusetts Institute of Technology (MIT) and Beth Israel Deaconess Medical Center (BIDMC) have approved this study and the sharing of the research resource (the NO. of official certification 39149215) and waived the requirement of informed consent due to retrospective design.

Consent for publication
Not applicable.

Patient consent for publication
Informed consent was not required as the study design was retrospective and data was anonymized.

Competing interests
The authors declare no competing interests.

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