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Association between stress hyperglycemia ratio and all-cause mortality in critically ill patients with sepsis: results from the MIMIC-IV database

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Abstract

Background This study aimed to explore the association between the stress hyperglycemia ratio (SHR) and short- and long-term outcomes in critically ill patients with sepsis.

Methods This retrospective observational cohort study was conducted using the Medical Information Mart for Intensive Care-IV (MIMIC-IV v2.2) database. Patients were categorized into 4 SHR quartiles. The main focus was on in-hospital mortality and 1-year all-cause mortality as primary endpoints, while intensive care unit and hospital stays were considered as secondary outcomes. Regression and subgroup analyses were used to assess the correlation between SHR and the primary and secondary outcomes. Restricted cubic spline analysis was utilized to explore the nonlinear relationships between SHR and in-hospital and 1-year all-cause mortality.

Results This study included two groups of patients, comprising 7456 and 6564 individuals. The in-hospital and 1-year mortality was 11.96% and 17.96% in Cohort 1 and 2, respectively. SHR was associated with an elevated risk of in-hospital mortality (OR: 2.08, 95%CI 1.66–2.61) and 1-year mortality (HR: 1.70, 95% CI 1.42–2.04). Patients in SHR quartile 4 had a higher risk of in-hospital (OR: 1.86, 95% CI 1.51–2.30) and 1-year (HR: 1.44, 95% CI 1.23–1.69) mortality than those in quartile 2. Restricted cubic spline analysis showed a "J-shaped" relationship between SHR and all-cause mortality in both cohorts. The relationship between high SHR and mortality remained consistent across almost all predefined subgroups.

Conclusions Our study suggests that high SHR is associated with increased in-hospital and 1-year mortality in critically ill sepsis patients. Further investigations are needed to validate these results.

Keywords Stress hyperglycemia ratio, Mortality, Sepsis, MIMIC-IV database, Diabetes

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Introduction

Sepsis manifests as a dysregulated host response to infection, leading to life-threatening organ dysfunction [1]. Given the poor prognosis associated with sepsis, timely outcome prediction is of paramount importance to guide clinical decision-making [2]. The identification of biomarkers to accurately predict and improve sepsis outcomes is therefore an urgent priority.

Glycometabolic disorders are common in patients with sepsis. Hormones involved in glycogenolysis and gluconeogenesis, including catecholamines, glucagon, and cortisol, are often elevated in these patients [3]. Magee et al. found that early glucose fluctuations increase 30-day and overall hospital mortality in individuals with sepsis [4]. Recent research has also indicated that stringent glycemic control is associated with poor outcomes in sepsis [5–7].

Stress hyperglycemia (SH) manifests as a physiological response occurring in non-diabetic critically ill patients. SH significantly impacts sepsis prognosis, as patients often present with acute hyperglycemia upon admission [8, 9]. In patients with diabetes mellitus (DM) admitted to the intensive care unit (ICU), elevated blood glucose levels may result from severe illness, suboptimal chronic glycemic control, or a combination thereof, posing a challenge for differentiation [10]. Glycated hemoglobin (HbA1c) provides a retrospective measure of blood glucose status over 3 months and is less influenced by acute illness. By combining absolute blood glucose levels with HbA1c, the stress hyperglycemia ratio (SHR) has been proposed as an innovative measure of SH [11]. SHR shows significant potential for accurately assessing relative hyperglycemia during acute conditions such as sepsis.

Our previous study demonstrated a significant correlation between high SHR and ventricular arrhythmias [12]. However, data on the impact of SHR on sepsis outcomes remain limited. Therefore, the primary objective of this study is to investigate the relationship between SHR and sepsis outcomes.

Methods

Study design and population

This retrospective cohort investigation utilized the Medical Information Mart for Intensive Care IV v2.2 (MIMIC-IV v2.2) database for primary analysis. The MIMIC-IV database contains anonymized data on 73,181 ICU stays for 50,920 adult patients at Beth Israel Deaconess Medical Center (Boston, Massachusetts, USA) from 2008 to 2019 [13]. Access to this database was granted to one of the authors (H Shen) after obtaining the necessary certification, who then extracted pertinent variables for this study (Record ID 49784899). Since the patient data were anonymized, individual informed consent was not required. Critically ill patients diagnosed with sepsis were included based on the sepsis 3.0 diagnostic criteria [14]: characterized by infection and a Sequential Organ Failure Assessment (SOFA) score ≥ 2. The method for identifying patients with sepsis from the MIMIC database was consistent with a previously published study (details in Additional file 1-A) [15]. Exclusion criteria were as follows: (1) ICU stays less than 48 h; (2) multiple admissions for sepsis with data extraction limited to the first admission; (3) insufficient critical data (e.g., glucose and/or HbA1c). As shown in Fig. 1, Cohort 1 included a total of 7456 patients. Additionally, 6564 patients (Cohort 2) from Cohort 1 discharged from the hospital were followed up for 1 year.

Variable extraction

Patient information from the MIMIC-IV database was retrieved using PostgreSQL software (version 13.7.2) and Navicat Premium software (version 16) through the execution of Structured Query Language (SQL) queries. Extracted data included demographics (age, gender, race, height, and weight), comorbidities [e.g., myocardial infarction (MI), coronary artery disease (CAD), congestive heart failure (CHF)], vital signs, laboratory tests, and blood gas analyses. Relevant scores and indices were also extracted. SHR was calculated as admission blood glucose divided by estimated average glucose, based on the formula provided in previous literature by Roberts et al. [11]. To estimate average glucose levels, we used the formula: $[(28.7 \times \text{HbA1c}\ (\%) - 46.7]$. SHR was then calculated as follows: SHR = admission glucose (mg/dl)/$(28.7 \times \text{HbA1c}\ (\%) - 46.7)$. Table S1 summarizes the missing rates for variables extracted from the database. A 30% threshold was set for excluding variables with high missing values, while multiple imputation was applied to those with missing rates below this threshold.

Outcomes

The primary endpoints were in-hospital and 1-year all-cause mortality, representing short- and long-term mortality, respectively. Secondary endpoints included the length of stay (LOS) in both the hospital and ICU. Mortality data for discharged patients were obtained from the US Social Security Death Index, and survival time was calculated based on the death date recorded in the MIMIC-IV-v2.2 database.

Statistical analysis

The study population was divided into four groups according to SHR quartiles, with quartile 4 representing the highest SHR, consistent with previously published studies [16, 17]. Baseline characteristics were presented

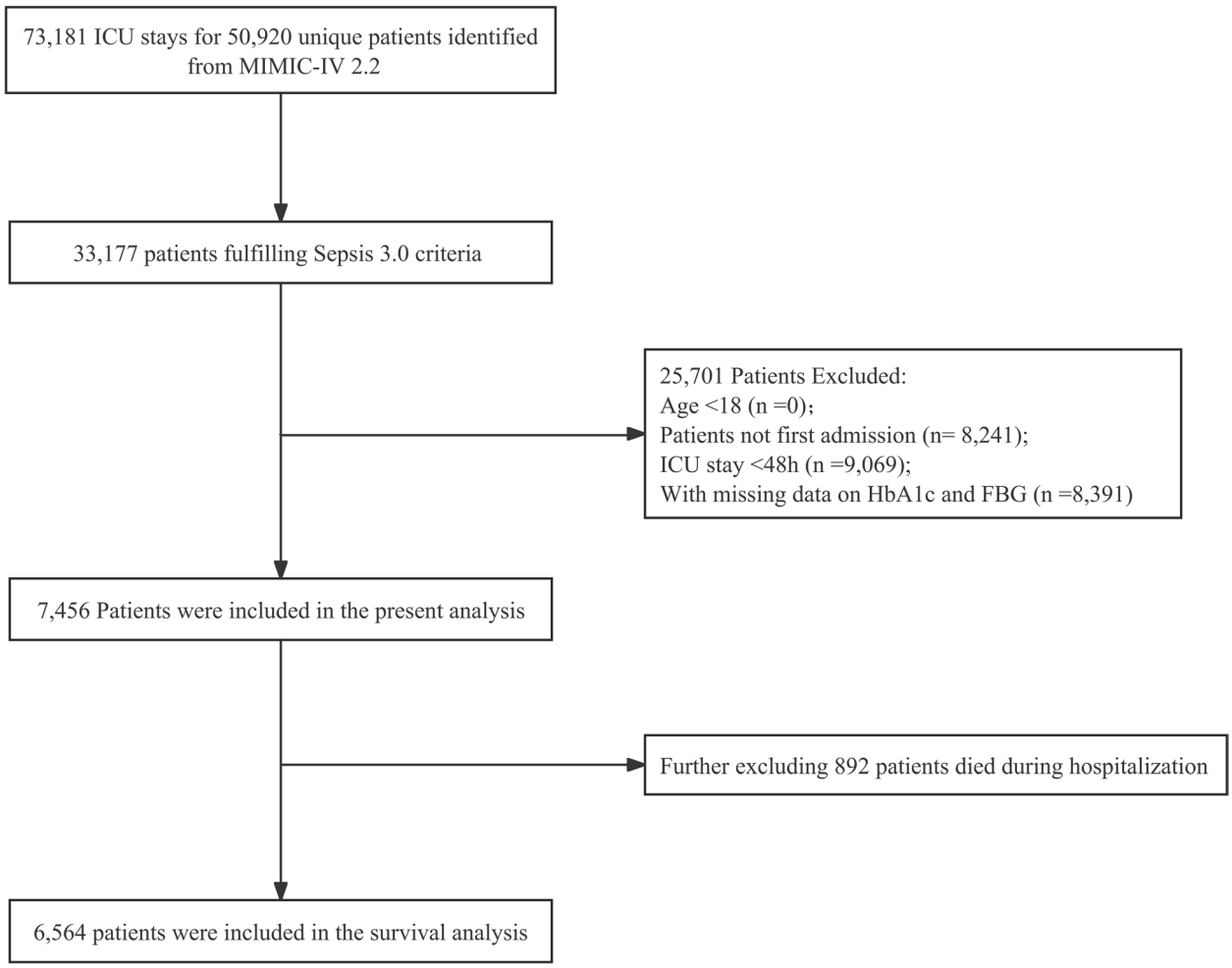

Fig. 1 Flowchart of the screening of patient selection. *ICU* intensive care unit, *MIMIC* Medical Information Mart for Intensive Care, *FBG* fasting blood glucose

as raw values or percentages for categorical variables, and mean ± standard deviation (SD) or median/interquartile range (IQR) for continuous variables. Statistical analyses, including ANOVA, Kruskal–Wallis, and Chi-square tests, were employed to examine differences between groups. Multivariate logistic regression analysis was utilized to evaluate the association between SHR and in-hospital mortality in Cohort 1. Linear regression analyses were conducted to determine the relationships between SHR and LOS in the hospital and ICU. Odds ratios (ORs), standardized regression coefficients, and corresponding 95% confidence intervals (CIs) were calculated to quantify the effect of the SHR on patient outcomes. Kaplan–Meier analysis and multivariate Cox regression were used to evaluate the relationship between SHR and 1-year mortality in Cohort 2, with hazard ratios (HR) and 95% CI used to present the results. Model 1 included only SHR and was unadjusted. Model 2 was adjusted for age, gender, and body mass index (BMI), as these are known to be important demographic factors. Model 3 was further adjusted for variables with significant baseline differences or clinical relevance, commonly observed in both cohorts, including SOFA score, race, MI, CAD, CHF, hypertension, cerebrovascular disease, DM, chronic pulmonary disease, and renal disease. Restricted cubic splines (RCS) were applied to explore the potential nonlinear relationships between SHR and in-hospital and 1-year outcome. Four knots were placed at the 5th, 35th, 65th, and 95th percentiles as recommended by Harrell et al. [18]. Subgroup analyses were conducted to evaluate the impact of SHR on in-hospital and 1-year mortality within specific patient subgroups. All statistical analyses were performed using R version 4.1.2 (R Foundation) and Stata version 17.0, with statistical significance set at a two-sided *P*-value of less than 0.05.

Results

Baseline characteristics

In Cohort 1, 7456 critically ill sepsis patients were included, while Cohort 2 consisted of 6564 patients followed up for 1 year after hospital discharge. The mean age in Cohort 1 was 65.37 ± 14.50 years, and 4379 (58.73%) were male. Diabetes, hypertension, CHF, renal disease, and CAD affected 32.26% of the patients (n = 2405), (36.68% (n = 2735), 37.42% (n = 2790), 26.53% (n = 1978), and 52.84% (n = 3940), respectively). The median SOFA score was 6.00 (IQR: 4.00–9.00). In Cohort 2, the mean age was 65.04 ± 14.43 years, and 3868 (58.93%) patients were male. Diabetes, hypertension, CHF, renal disease, and CAD were observed in 32.19% (n = 2113), 35.76% (n = 2347), 36.26% (n = 2380), 25.62% (n = 1682), and 51.60% (n = 3387) of the patients, respectively. The median SOFA score was 6.00 (IQR: 4.00–9.00). The baseline characteristics of both cohorts are summarized in Table 1 and Supplementary Table S2, respectively.

SHR and short- and long-term outcomes

In Cohort 1, 892 patients (11.96%) experienced all-cause mortality, with the highest rate (n = 316, 16.95%) observed in SHR quartile 4 (SHR ≥ 1.253). The effect values (OR) and 95% CIs for the three models are shown in Table 2. After adjusting for confounders, a high SHR value was significantly associated with in-hospital all-cause mortality (OR: 2.08, 95% CI 1.66–2.61). When SHR was treated as a categorical variable (quartiles), similar trends were observed. The OR for in-hospital mortality in SHR quartile 4 (SHR ≥ 1.253) was 1.86 (95% CI 1.51–2.30) compared to patients in quartile 2 (0.889 ≤ SHR < 1.063). As shown in Fig. 2A, the RCS analysis revealed a "J-shaped" association between SHR and in-hospital mortality (P-value for nonlinearity = 0.003). Additionally, high SHR was identified as a significant predictor of hospital and ICU LOS (Table S3).

In Cohort 2, 1179 patients (17.96%) experienced all-cause mortality, with the highest rate (n = 366, 22.30%) in quartile 4 (SHR ≥ 1.237). Kaplan–Meier analysis revealed significant differences in 1-year mortality across SHR groups (Fig. 3A and B). Quartile 4 (SHR ≥ 1.237) exhibited the highest incidence of 1-year all-cause mortality. According to Cox regression analysis, SHR was associated with an increased risk of 1-year all-cause mortality in Model 1 (HR: 1.61, 95% CI 1.34–1.93), Model 2 (HR: 1.75, 95% CI 1.45–2.11), and Model 3 (HR: 1.70, 95% CI 1.42–2.04). SHR Quartile 4 (SHR ≥ 1.237) emerged as a significant risk factor for 1-year mortality when compared to quartile 2 (0.886 ≤ SHR < 1.057) (HR: 1.44, 95% CI 1.23–1.69) after adjusting for multiple variables (Table 3). Furthermore, the RCS analysis also revealed a "J-shaped" relationship between SHR and 1-year mortality (P-value for nonlinearity = 0.002) (Fig. 2B).

Subgroup analysis

To validate the association between SHR and in-hospital as well as 1-year mortality, stratified analyses were performed based on age, gender, BMI, CAD, hypertension, DM, and SOFA score. The relationship between SHR and both in-hospital and 1-year outcome remained consistent across all predefined subgroups, although notable heterogeneity was observed between patients with and without hypertension (Fig. 4). High SHR was significantly associated with an elevated risk of 1-year all-cause mortality specifically within the hypertensive subgroup (HR: 1.99, 95% CI 1.57–2.52) (P-value for interaction = 0.036). Sepsis patients without DM appeared to exhibit higher rates of in-hospital (OR: 2.55, 95% CI 1.84–3.53) and 1-year mortality (HR: 2.07, 95% CI 1.55–2.75) compared to those with DM (OR: 1.70, 95% CI 1.23–2.34; HR: 1.52, 95% CI 1.20–1.93).

Discussion

In this study, we investigated the relationship between the stress hyperglycemia ratio (SHR) and both short- and long-term outcomes in critically ill sepsis patients. Our findings demonstrated a significant association between elevated SHR and increased in-hospital mortality, as well as prolonged hospital and ICU stays. Furthermore, a higher SHR was strongly linked to an increased risk of 1-year all-cause mortality. We observed a "J-shaped" pattern in the relationship between SHR and in-hospital and 1-year mortality, consistent with findings from a prior study examining 90-day outcomes [19]. Notably, our results underscore the potential utility of SHR as a simple and effective biomarker for risk stratification in sepsis patients.

SH refers to elevated blood glucose levels during acute stress events, such as infection. Unlike diabetes-induced hyperglycemia, mild-to-moderate SH might exert protective effects during the acute phase of severe illness. However, this transient hyperglycemia can lead to detrimental pathophysiological effects and poor outcomes, particularly in critically ill patients [20–24].

SH involves a complex interplay of factors, including increased secretion of insulin-antagonistic hormones (e.g., corticosteroid, glucagon, growth hormone, and catecholamines), the release of cytokines [interleukin (IL)−1 and tumor necrosis factor-alpha (TNF-α)], and insulin resistance [25]. Elevated blood glucose levels facilitate the aggregation of monocytes and macrophages [26], which in turn trigger the production and secretion of biologically active molecules, including cytokines like IL-6 and IL-8. TNF-α, a critical

Table 1 Baseline characteristics and outcomes of patients of cohort 1

Variables	Q1 ($n=1864$) (SHR < 0.889)	Q2($n=1865$) (0.889 ≤ SHR < 1.063)	Q3 ($n=1863$) (1.063 ≤ SHR < 1.253)	Q4 ($n=1864$) (SHR ≥ 1.253)	*P*
Demographic					
Age (years)	65.20 ± 13.90	67.25 ± 14.01	65.15 ± 14.96	63.87 ± 14.92	< 0.001
BMI (kg/m^2)	29.58 ± 6.97	29.41 ± 7.55	29.68 ± 7.34	29.55 ± 7.18	0.720
Male	1097 (58.85)	1105 (59.25)	1120 (60.12)	1057 (56.71)	0.183
Race					< 0.001
White	1167 (62.61)	1273 (68.26)	1255 (67.36)	1221 (65.50)	
African American	273 (14.65)	205 (10.99)	198 (10.63)	199 (10.68)	
Asian	56 (3.00)	56 (3.00)	39 (2.09)	66 (3.54)	
Hispanic	91 (4.88)	67 (3.59)	65 (3.49)	78 (4.18)	
Other[a]	277 (14.86)	264 (14.16)	306 (16.43)	300 (16.09)	
ICU type					< 0.001
CVICU	808 (43.35)	807 (43.27)	496 (26.62)	188 (10.09)	
CCU	188 (10.09)	166 (8.90)	226 (12.13)	252 (13.52)	
MICU	327 (17.54)	281 (15.07)	317 (17.02)	451 (24.20)	
SICU	158 (8.48)	174 (9.33)	282 (15.14)	310 (16.63)	
Other	383 (20.55)	437 (23.43)	542 (29.09)	663 (35.57)	
Vital signs					
Heart rate (beats/min)	83.85 (76.29–94.05)	82.03 (74.72–91.30)	83.90 (74.28–96.39)	88.10 (75.92–100.26)	< 0.001
SBP (mmHg)	113.18 (106.31–122.20)	111.96 (104.82–122.11)	113.83 (104.88–125.92)	114.67 (104.85–127.71)	< 0.001
DBP (mmHg)	57.80 (52.57–64.16)	58.98 (53.44–65.14)	60.82 (54.55–68.33)	61.58 (55.38–69.40)	< 0.001
MBP (mmHg)	74.18 (69.16–80.00)	74.67 (70.10–81.28)	76.17 (70.44–83.28)	76.78 (70.41–84.92)	< 0.001
Respiratory rate (breaths/min)	18.46 (16.43–20.88)	18.25 (16.22–20.76)	19.16 (17.03–21.77)	19.87 (17.25–23.25)	< 0.001
Temperature (℃)	36.82 (36.53–37.15)	36.82 (36.54–37.14)	36.89 (36.60–37.27)	36.93 (36.66–37.32)	< 0.001
SpO_2 (%)	97.83 (96.46–98.88)	97.72 (96.23–98.83)	97.33 (95.90–98.63)	97.14 (95.56–98.52)	< 0.001
Laboratory tests					
HbA1c (%)	7.20 (6.10–8.80)	5.90 (5.60–6.40)	5.70 (5.40–6.20)	5.60 (5.20–6.20)	< 0.001
Hematocrit	33.40 (30.20–37.60)	34.10 (30.60–38.50)	34.80 (30.90–39.30)	34.30 (29.70–39.40)	< 0.001
Hemoglobin (g/dL)	11.00 (9.90–12.40)	11.30 (10.10–12.70)	11.50 (10.00–13.00)	11.30 (9.60–13.00)	< 0.001
(K/uL)	200.50 (153.00–270.00)	192.00 (145.00–254.00)	204.00 (152.00–270.00)	206.00 (148.00–280.00)	< 0.001
WBC (K/uL)	14.80 (10.70–19.40)	14.00 (10.10–18.50)	13.70 (9.80–18.40)	14.60 (10.50–19.30)	< 0.001
Anion gap (mEq/L)	16.00 (13.00–19.00)	15.00 (12.00–18.00)	16.00 (13.00–19.00)	17.00 (14.50–20.00)	< 0.001
Bicarbonate (mEq/L)	24.00 (22.00–26.00)	24.00 (22.00–27.00)	24.00 (22.00–27.00)	24.00 (21.00–26.00)	< 0.001
BUN (mg/dL)	25.00 (17.00–43.00)	21.00 (15.00–32.00)	21.00 (15.00–35.00)	26.00 (17.00–42.00)	< 0.001
Calcium (mg/dL)	8.50 (8.05–9.10)	8.50 (8.10–9.08)	8.50 (8.10–9.00)	8.60 (8.10–9.10)	0.736
Chloride (mEq/L) Platelets	108.00 (104.00–111.00)	108.00 (104.00–111.00)	106.00 (102.00–110.00)	105.00 (101.00–109.00)	< 0.001
Creatinine (mg/dL)	1.30 (0.90–2.10)	1.10 (0.80–1.60)	1.10 (0.80–1.80)	1.30 (0.90–2.00)	< 0.001
Sodium (mEq/L)	140.00 (137.00–142.00)	140.00 (138.00–142.00)	140.00 (137.00–142.00)	140.00 (137.00–143.00)	0.913
Potassium (mEq/L)	4.70 (4.30–5.20)	4.50 (4.20–5.00)	4.50 (4.10–4.90)	4.50 (4.10–5.00)	< 0.001
Lactate (mmol/L)	2.67 (1.80–4.00)	2.50 (1.60–3.80)	2.29 (1.40–3.70)	2.40 (1.49–3.97)	< 0.001
pH	7.43 (7.39–7.48)	7.44 (7.40–7.48)	7.43 (7.38–7.47)	7.42 (7.37–7.46)	< 0.001
pO_2 (mmHg)	301.50 (131.00–420.00)	316.47 (135.52–421.00)	198.00 (104.00–353.00)	160.00 (87.00–270.00)	< 0.001
pCO_2 (mmHg)	48.00 (42.00–54.00)	48.00 (42.00–54.47)	46.00 (39.34–54.00)	45.00 (38.00–54.00)	< 0.001
Comorbidities					
Myocardial infarct	520 (27.90)	413 (22.14)	360 (19.32)	434 (23.28)	< 0.001
Congestive heart failure	759 (40.72)	698 (37.43)	636 (34.14)	697 (37.39)	< 0.001
Peripheral vascular disease	323 (17.33)	299 (16.03)	307 (16.48)	228 (12.23)	< 0.001
Cerebrovascular disease	333 (17.86)	387 (20.75)	448 (24.05)	435 (23.34)	< 0.001
Dementia	51 (2.74)	58 (3.11)	70 (3.76)	82 (4.40)	0.031

Table 1 (continued)

Variables	Q1 ($n=1864$) (SHR < 0.889)	Q2($n=1865$) (0.889 ≤ SHR < 1.063)	Q3 ($n=1863$) (1.063 ≤ SHR < 1.253)	Q4 ($n=1864$) (SHR ≥ 1.253)	*P*
Chronic pulmonary disease	492 (26.39)	570 (30.56)	483 (25.93)	512 (27.47)	0.007
Rheumatic disease	73 (3.92)	66 (3.54)	59 (3.17)	55 (2.95)	0.379
Peptic ulcer disease	35 (1.88)	49 (2.63)	48 (2.58)	63 (3.38)	0.041
Mild Liver disease	193 (10.35)	212 (11.37)	221 (11.86)	370 (19.85)	< 0.001
Diabetes	1043 (55.95)	476 (25.52)	402 (21.58)	484 (25.97)	< 0.001
Paraplegia	79 (4.24)	136 (7.29)	202 (10.84)	157 (8.42)	< 0.001
Renal disease	619 (33.21)	461 (24.72)	428 (22.97)	470 (25.21)	< 0.001
Malignant cancer	155 (8.32)	191 (10.24)	196 (10.52)	258 (13.84)	< 0.001
Severe liver disease	65 (3.49)	80 (4.29)	88 (4.72)	192 (10.30)	< 0.001
Metastatic solid tumor	54 (2.90)	70 (3.75)	73 (3.92)	88 (4.72)	0.037
AIDS	11 (0.59)	9 (0.48)	13 (0.70)	18 (0.97)	0.316
CAD	727 (39.00)	919 (49.28)	1112 (59.69)	1182 (63.41)	< 0.001
Hypertension	644 (34.55)	693 (37.16)	677 (36.34)	721 (38.68)	0.068
Severity of illness score					
SOFA	7.00 (4.00–9.00)	6.00 (4.00–9.00)	6.00 (4.00–9.00)	6.00 (4.00–9.00)	< 0.001
CCI	6.00 (5.00–8.00)	6.00 (4.00–8.00)	6.00 (4.00–8.00)	6.00 (4.00–8.00)	< 0.001
LODS	6.00 (4.00–9.00)	6.00 (4.00–8.00)	5.00 (3.00–8.00)	6.00 (4.00–9.00)	< 0.001
SAPS II	40.00 (33.00–50.00)	39.00 (32.00–48.00)	38.00 (30.00–47.00)	40.00 (32.00–49.00)	< 0.001
Outcomes					
Hospital LOS (days)	10.02 (6.60–16.94)	9.96 (6.51–16.68)	10.82 (6.77–18.35)	12.02 (7.28–20.38)	< 0.001
ICU LOS (days)	3.90 (2.63–6.72)	4.09 (2.57–7.27)	4.44 (2.91–8.18)	4.91 (3.12–8.97)	< 0.001
In-hospital death	196 (10.52)	172 (9.22)	208 (11.16)	316 (16.95)	< 0.001

BMI body mass index, *ICU* intensive care unit, *CVICU* cardiovascular intensive care unit, *CCU* coronary care unit, *MICU* medical intensive care unit, *SICU* surgical intensive care unit, *WBC* white blood cell, *BUN* blood urea nitrogen, *pO2* partial pressure of oxygen, *pCO2* partial pressure of carbon dioxide, *AIDS* acquired immune deficiency syndrome, *CAD* coronary artery disease, *SOFA* Sequential Organ Failure Assessment, *CCI* Charlson Comorbidity Index, *LODS* Logistic Organ Dysfunction System, *SAPS* Simplified Acute Physiology Score, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MBP* mean blood pressure, *SpO2*, oxygen saturation as measured by pulse oximetry, *LOS* length of stay

[a] Other indicates race and ethnicity categories queried as American Indian or Alaska Native, unable to obtain, unknown, and other from the MIMIC-IV database

Table 2 The association between SHR and in-hospital mortality

	Model 1		Model 2		Model 3	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
SHR (continuous)	2.28 (1.85–2.83)	< 0.001	2.36 (1.90–2.93)	< 0.001	2.08 (1.66–2.61)	< 0.001
SHR (categorical)						
Q1	1.16 (0.93–1.43)	0.186	1.20 (0.96–1.48)	0.106	1.08 (0.85–1.36)	0.523
Q2	Ref		Ref		Ref	
Q3	1.24 (1.00–1.53)	0.050	1.28 (1.03–1.58)	0.024	1.24 (0.99–1.56)	0.055
Q4	2.01 (1.65–2.45)	< 0.001	2.11 (1.73–2.58)	< 0.001	1.86 (1.51–2.30)	< 0.001

SHR stress hyperglycemia ratio, *OR* odds ratio, *CI* confidence interval

pro-inflammatory mediator in sepsis pathogenesis, is associated with adverse outcomes [27] and contributes to the development of insulin resistance [28]. Similarly, IL-6 and IL-8 are multifunctional cytokines involved in inflammation and tissue injury [29]. Their levels have been linked to poor prognoses in critically ill individuals [30].

Another significant contributor to the increased mortality rate in sepsis patients is the onset of disseminated intravascular coagulation (DIC). Stress hyperglycemia induces increased mitochondrial reactive oxygen species production in endothelial cells, potentially leading to endothelial dysfunction [31]. Additionally, hyperglycemia and hyperinsulinemia have been shown to increase

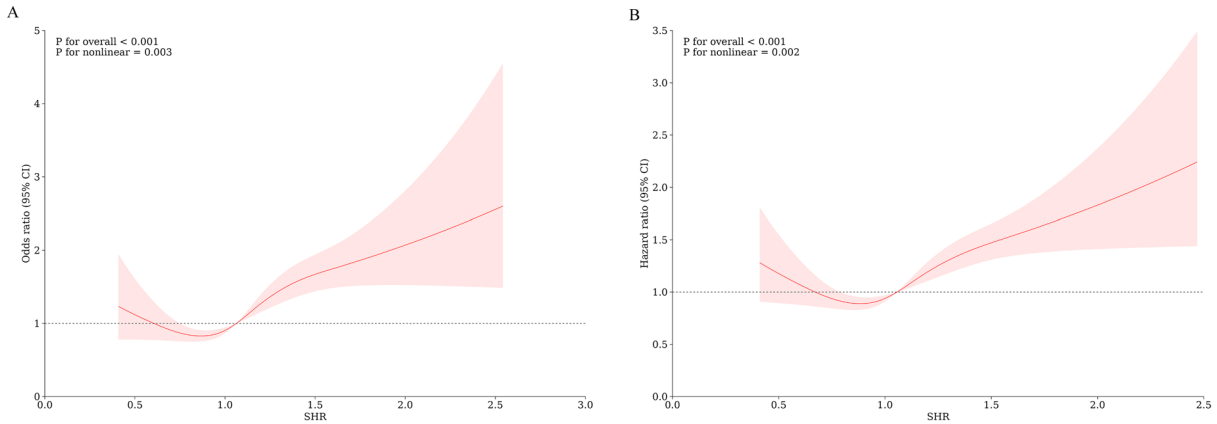

Fig. 2 The nonlinear relationship for SHR with in-hospital and 1-year mortality. **A** Restricted cubic spline for in-hospital mortality. **B** Restricted cubic spline for 1-year mortality. The solid red line represents odds ratio/hazard ratio, and the red area represents 95% confidence intervals. The median value of SHR was used as the reference. SHR, stress hyperglycemia ratio

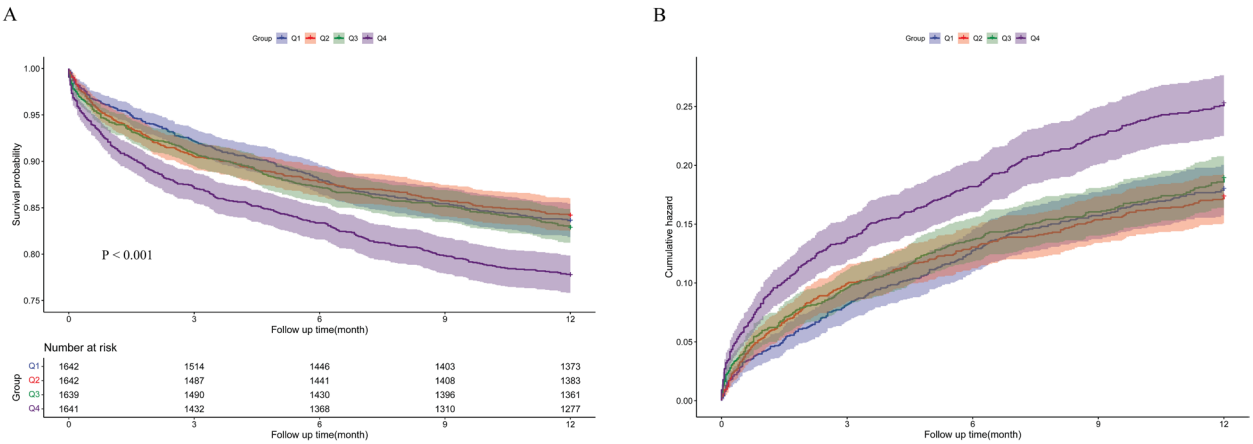

Fig. 3 **A** Kaplan–Meier survival plot and **B** cumulative Incidence for all-cause mortality according to various stress hyperglycemia ratio (SHR) level groups

Table 3 Cox regression analysis for 1-year all-cause mortality

	Model 1		Model 2		Model 3	
	HR (95% CI)	***P*-value**	**HR (95% CI)**	***P*-value**	**HR (95% CI)**	***P*-value**
SHR (continuous)	1.61 (1.34–1.93)	< 0.001	1.75 (1.45–2.11)	< 0.001	1.70 (1.42–2.04)	< 0.001
SHR (categorical)						
Q1	1.03 (0.87–1.22)	0.747	1.09 (0.92–1.29)	0.323	0.97 (0.81–1.16)	0.722
Q2	Ref		Ref		Ref	
Q3	1.09 (0.92–1.29)	0.328	1.16 (0.98–1.37)	0.094	1.13 (0.95–1.34)	0.159
Q4	1.46 (1.25–1.71)	< 0.001	1.63 (1.39–1.91)	< 0.001	1.44 (1.23–1.69)	< 0.001

SHR stress hyperglycemia ratio, *HR* hazard ratio, *CI* confidence interval

tissue factor coagulant activity, promoting a pro-thrombotic state [32]. These processes drive inflammation and thrombogenesis, culminating in DIC development [33], which profoundly impacts sepsis prognosis [34]. The mechanisms outlined above likely underlie the

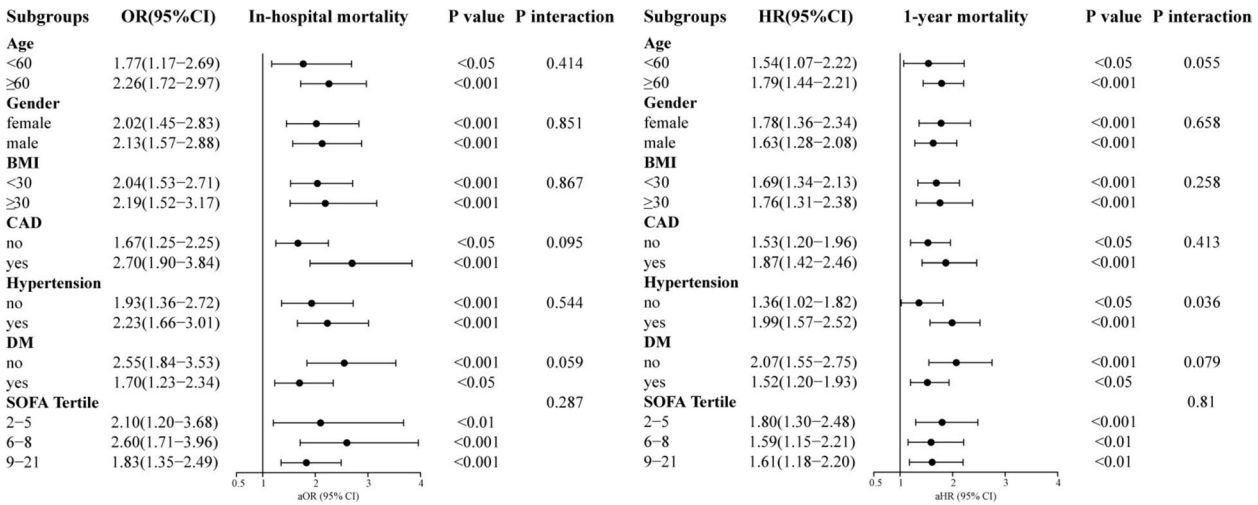

Fig. 4 Subgroup analyses for the association of stress hyperglycemia ratio (SHR) with in-hospital mortality and 1-year mortality. *OR* odds ratio, *HR* hazard ratio, *CI* confidence interval, *BMI* body mass index, *CAD* coronary artery disease, *DM* diabetes mellitus, *SOFA* Sequential Organ Failure Assessment

poor outcomes observed in sepsis patients with stress hyperglycemia.

The stress hyperglycemia ratio (SHR), an index of relative glycemia, was first developed by Roberts et al. to investigate the impact of acute hyperglycemia on mortality in hospitalized patients [11]. Over time, SHR has proven to be a robust predictor of mortality and morbidity across various clinical conditions, including acute myocardial infarction (AMI) [16], acute ischemic stroke [35], and acute kidney injury [36]. Several studies have explored the association between high SHR and the severity and outcomes of sepsis. Fabbri et al. found that diabetic patients with SHR exceeding 1.14 faced an increased mortality risk. However, their analysis, which utilized a linear regression model, failed to capture potential nonlinear relationships [9]. Ji et al. examined 4460 sepsis patients (with and without diabetes) and identified a "J-shaped" association between SHR and 90-day mortality. Nevertheless, their findings were limited by insufficient adjustments for confounding variables [19]. In this study, after rigorous adjustment for confounders, high SHR was found to be significantly associated with the risk of in-hospital and 1-year all-cause mortality. Patients in the highest SHR quartile experienced an 86% higher risk of in-hospital mortality and a 44% higher risk of 1-year mortality compared to those in quartile 2.

In our study, two cohorts comprising 7456 and 6564 patients were analyzed, with the population stratified into four groups based on SHR quartiles. Notably, only patients in the highest SHR quartile exhibited an elevated risk of all-cause mortality. These findings align with previous research. For instance, Liu et al. reported that patients with AMI in the highest SHR quartile faced a heightened risk of 1-year and long-term mortality compared to those in the reference quartile, whereas the risk was not increased in the mild-to-moderate SHR quartile. They proposed that high SHR induces inflammation and oxidative stress, exacerbates endothelial dysfunction, and promotes a pro-thrombotic condition, ultimately contributing to a higher mortality risk [16]. While there is no universally accepted classification for SHR, we hypothesize that mild-to-moderate SHR may play a protective role by enhancing cell survival mechanisms in sepsis patients.

In the sub-analysis, it was noteworthy that sepsis patients without DM had worse outcomes compared to those with DM, including higher in-hospital and 1-year mortality. This finding contrasts with the trends observed in patients with CAD and hypertension. The observed difference may be explained by prior glycemic-lowering treatments administered to sepsis patients with DM [37, 38]. Diabetic patients often undergo more rigorous glucose monitoring and management during hospitalization, potentially attenuating the adverse effects of stress hyperglycemia on sepsis outcomes. In contrast, non-diabetic patients are less likely to receive comparable glycemic management, potentially contributing to worse outcomes. Moreover, a phenomenon analogous to ischemic preconditioning in the myocardium may provide an additional explanation. Patients with DM might develop a "preconditioning effect" in response to acute stress-induced hyperglycemia. This response could enhance antioxidant defenses, safeguarding tissues against oxidative stress triggered by such episodes

[39–41]. In contrast, non-diabetic patients lack this adaptive mechanism, making them more vulnerable to the acute metabolic and inflammatory consequences of stress-induced hyperglycemia. This heightened vulnerability could exacerbate immune dysfunction, endothelial injury, and oxidative stress, thereby exacerbating the severity of sepsis outcomes. Given these findings, we propose that non-diabetic sepsis patients may require closer monitoring and intervention, even at comparable SHR levels, to mitigate their increased risk of adverse outcomes.

One of the main strengths of this study is the use of an established measure, SHR, to define stress hyperglycemia and predict its impact on the outcomes of patients with sepsis. Since glucose and HbA1c are routinely measured in clinical practice, calculating SHR is straightforward and easily implementable. Another advantage is the application of RCS. RCS allows for the modeling of complex nonlinear relationships without imposing a rigid functional form, making it well-suited for exploring the association between SHR and mortality. By applying smooth constraints, RCS generates interpretable curves that depict changes in risk across different SHR levels while avoiding overfitting.

However, there are several limitations to consider in this study. First, the study is based exclusively on data from the MIMIC-IV database, limiting its generalizability. Further external validation across diverse populations is necessary to reduce selection bias and enhance the robustness of the findings. Second, glucose metabolism in patients with sepsis is highly influenced by pharmacological and nutritional interventions, such as glucose-lowering medications, steroid therapy, and parenteral nutrition. Future studies with more granular data on treatment interventions are essential to adjust for potential confounding factors. Third, it is hard to distinguish whether a lower SHR value results from strict glucose control interventions or reflects a lower degree of stress hyperglycemia. Fourth, the optimal cut-off value of SHR for the prognostic evaluation of sepsis patients has not yet been standardized. Lastly, the lack of dynamic measurements of SHR limits our understanding of whether changes over time in SHR during hospitalization influence the prognosis of sepsis patients. Future studies focused on the fluctuations in SHR are warranted to be explored.

Conclusions

Our research demonstrates a robust correlation between SHR and heightened in-hospital as well as 1-year all-cause mortality in critically ill sepsis patients. SHR is an important risk predictor of patient prognosis in sepsis. Nonetheless, further investigations are necessary to explore the effect of glycemic control on predicting and improving outcomes among sepsis patients.

Abbreviations

SH	Stress hyperglycemia
DM	Diabetes mellitus
ICU	Intensive care unit
HbA1c	Glycated hemoglobin
SHR	Stress hyperglycemia ratio
MIMIC-IV	Medical Information Mart for Intensive Care IV
SOFA	Sequential Organ Failure Assessment
MI	Myocardial infarction
CAD	Coronary artery disease
CHF	Congestive heart failure
LOS	Length of stay
IQR	Interquartile range (IQR)
OR	Odds ratio
CI	Confidence intervals
HR	Hazard ratio
BMI	Body mass index
RCS	Restricted cubic splines
IL	Interleukin
TNF-α	Tumor necrosis factor-alpha
AMI	Acute myocardial infarction
DIC	Disseminated intravascular coagulation

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s40001-025-02281-4.

Supplementary Material 1: **Table S1.** Missing rate for clinical variables extracted from the database after patient selection. **Table S2.** Baseline characteristics and outcomes of patients of cohort 2. **Table S3.** The association between SHR and LOS of hospital and ICU.

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Author contributions

SJZ, HCS: study design; HCS, YCW, MN, JHZ: data collection; SJZ, XYL, YC: statistical analysis; SJZ, HCS: manuscript drafting; WQG and TL: manuscript reviewing and editing. All authors review and approve the final manuscript.

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Availability of data and materials

No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

All the authors gave their consent to publication.

Competing interests

The authors declare no competing interests.

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