Cardiovascular Diabetology

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Assessment of stress hyperglycemia ratio to predict all-cause mortality in patients with critical cerebrovascular disease: a retrospective cohort study from the MIMIC-IV database

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Abstract

Background The association between the stress hyperglycemia ratio (SHR), which represents the degree of acute stress hyperglycemic status, and the risk of mortality in cerebrovascular disease patients in the intensive care unit (ICU) remains unclear. This study aims to investigate the predictive ability of SHR for in-hospital mortality in critically ill cerebrovascular disease patients and to assess its potential to enhance existing predictive models.

Methods We extracted data from the Medical Information Mart for Intensive Care (MIMIC-IV) database for patients diagnosed with cerebrovascular disease and used Cox regression to assess the association between SHR and mortality. To investigate the nature of this association, we applied restricted cubic spline analysis to determine if it is linear. The predictive ability of SHR for mortality risk was evaluated using receiver operating characteristic (ROC) curves and the C-index.

Results We included a total of 2,461 patients, with a mean age of 70.55 ± 14.59 years, and 1,221 (49.61%) being female. Cox regression analysis revealed that SHR was independently associated with both in-hospital mortality (per standard deviation (SD) increase: hazard ratio (HR) 1.35, 95% confidence interval (CI) 1.23–1.48) and ICU mortality (per SD increase: HR 1.37, 95% CI 1.21–1.54). The risk of death increased in an approximately linear fashion when SHR exceeded 0.77–0.79. Subgroup analysis indicated the association was more pronounced in non-diabetic individuals. Additionally, incorporating SHR into existing models improved both discrimination and reclassification performance.

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Conclusion SHR serves as an independent risk factor for in-hospital mortality in cerebrovascular disease patients in the ICU. Adding SHR to existing models enhances their predictive performance, offering clinical value in the identification of high-risk patients.

Keywords Stress hyperglycemia ratio, Cerebrovascular disease, Intensive care unit, Mortality

Introduction

Cerebrovascular disease continues to be a major cause of disability and mortality worldwide and is the fifth leading cause of death in the United States [1]. Patients with cerebrovascular disease admitted to the intensive care units (ICU) often have more complex conditions and poorer prognoses, thus early identification of high-risk patients is especially critical.

Previous studies have demonstrated that acute stress hyperglycemia, a transient increase in blood glucose levels that occurs in response to acute stress conditions, in critically ill patients are closely linked to an increased risk of mortality [2]. However, both admission and fasting blood glucose measurements cannot accurately reflect acute stress hyperglycemia due to the influence of long-term chronic glycemic status. In recent years, the stress hyperglycemia ratio (SHR), which integrates blood glucose and hemoglobin A1C (HbA1c), has been shown to more accurately capture acute stress hyperglycemia levels [3]. Research has confirmed that SHR is independently associated with adverse outcomes in patients with sepsis and myocardial infarction [4, 5]. Previous research has indicated that SHR can enhance the predictive accuracy of existing models in patients with acute myocardial infarction [6] or non-cardiac surgery [7]. Nonetheless, studies investigating the impact of SHR on outcomes in cerebrovascular disease, particularly in critically ill patients, remain limited.

Therefore, this study aims to evaluate whether SHR can serve as a predictive indicator for in-hospital mortality in critically ill cerebrovascular disease patients in the ICU. Such an assessment may help clinicians identify high-risk patients for closer monitoring or early intervention.

Methods

Study design and population

This study conducts a retrospective analysis using publicly accessible data from the Medical Information Mart for Intensive Care IV (MIMIC-IV). This dataset collects clinical information from critically ill patients admitted to Beth Israel Deaconess Medical Center between 2008 and 2019. Access to these data was granted after completing the required training course provided by the National Institutes of Health (NIH) and successfully passing the Collaborative Institutional Training Initiative (CITI) program. Patient privacy is safeguarded through the de-identification of personal information within the database, which has facilitated the waiver of informed consent requirements.

We analyzed 94,458 patients aged over 18 years from the database. Patients were excluded based on the following criteria: (1) those not experiencing their first ICU admission ($n = 9,216$); (2) those with ICU stays shorter than 3 h ($n = 246$); (3) those without a diagnosis of cerebrovascular disease, as defined by specific International Classification of Diseases (ICD) codes detailed in the supplementary Table 1 ($n = 70,545$); (4) those lacking HbA1c or blood glucose measurements within the first 24 h of ICU admission ($n = 11,919$); and (5) those for whom outcome information was unavailable ($n = 71$). Ultimately, a total of 2,461 patients were included in our study (Fig. 1). And they were further divided into four groups based on quartiles of SHR: Q1 ($n = 616$), Q2 ($n = 613$), Q3 ($n = 621$), Q4 ($n = 611$).

Data collection

Data extraction, cleaning, and analysis for this study were performed using R software (version 4.4.1). The extracted variables encompassed the following categories: (1) Demographic information: age, sex; (2) Comorbid conditions: myocardial infarction, heart failure, hypertension, diabetes, chronic pulmonary disease, renal disease; (3) Laboratory findings: hemoglobin levels, platelet counts, white blood cell counts, blood urea nitrogen, creatinine, lactate; (4) Vital signs: heart rate, respiratory rate, systolic and diastolic blood pressures, mean blood pressure, body temperature, SpO_2; (5) Severity of illness scores: Acute Physiology Score III (APSIII), Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS), and Sequential Organ Failure Assessment (SOFA); (6) Length of stay (LOS) and patient outcomes. All laboratory data and severity of illness scores were derived from measurements taken within the first 24 h following ICU admission. To minimize potential bias, variables with more than 20% missing data were excluded.

Calculation of SHR

The SHR is calculated using the formula: [(admission blood glucose (mg/dL)) / (28.7 * HbA1c (%) – 46.7)] [8, 9]. All patients were divided into four groups based on SHR quartiles: Q1, Q2, Q3, and Q4, with the Q1 group designated as the reference group.

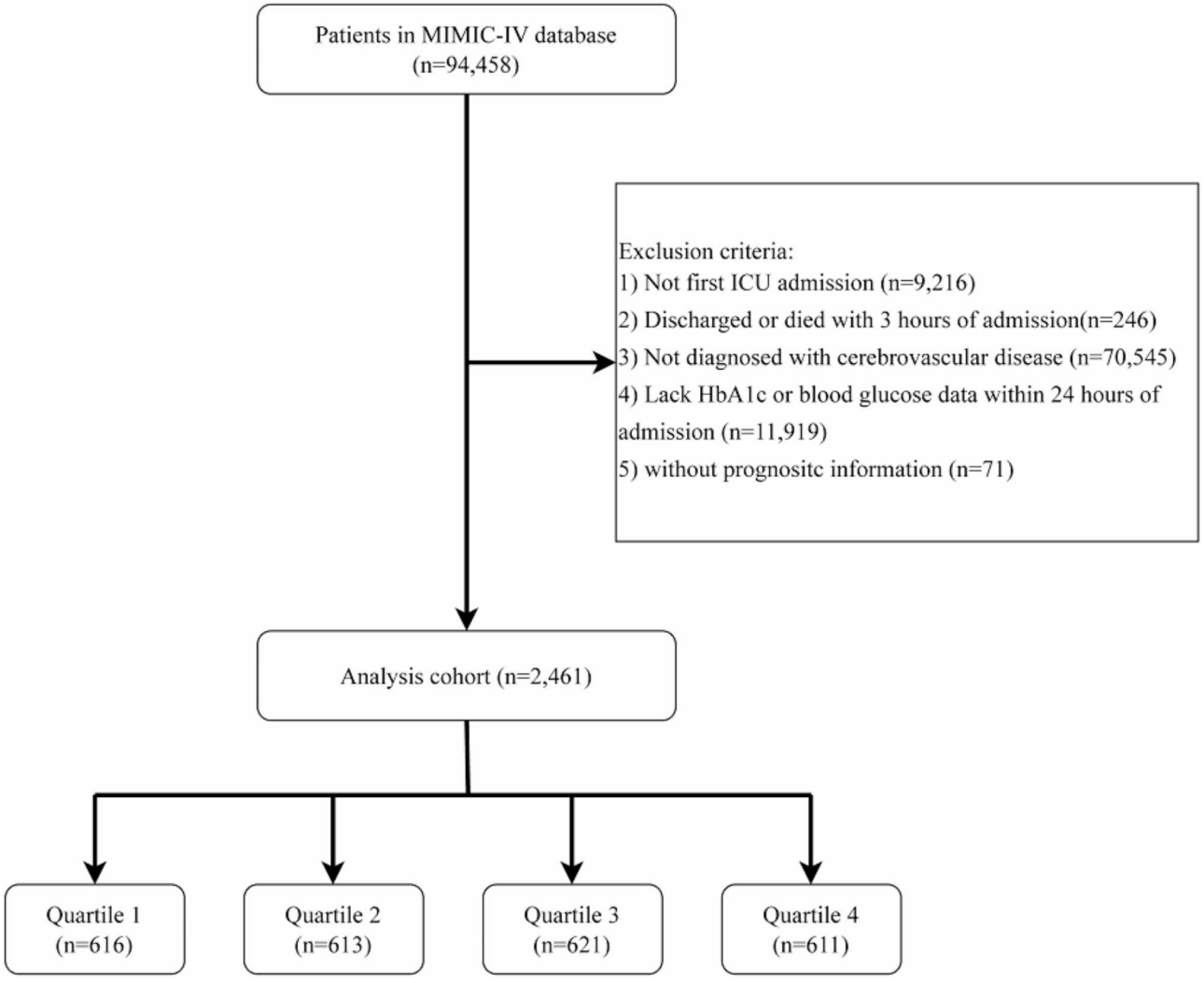

Fig. 1 Flowchart of select study population from the MIMIC-IV database

Clinical outcomes

The primary endpoints of this study were all-cause mortality during hospitalization and all-cause mortality in the ICU.

Statistical analysis

The Kolmogorov-Smirnov test was employed to evaluate whether continuous variables followed a normal distribution. Continuous variables were presented as mean ± standard deviation if normally distributed, or as median (interquartile range) if not. Categorical variables were expressed as frequencies (percentages). For the analysis of continuous variables, t-tests or ANOVA were used for normally distributed data, while the Kruskal-Wallis test or Mann-Whitney U test was applied for non-normally distributed data. Categorical variables were analyzed using chi-square tests or Fisher's exact tests, as appropriate. Kaplan-Meier survival analysis was conducted to assess the incidence of endpoint events across different SHR groups, with differences between groups evaluated using the log-rank test. We constructed three Cox proportional hazards models: Model 1 was unadjusted for any confounders; Model 2 adjusted for demographic and basic physiological factors including age, sex, heart rate, respiratory rate, mean arterial pressure, and SpO_2; Model 3 further adjusted for additional clinical conditions and laboratory findings such as hypertension, myocardial infarction, heart failure, atrial fibrillation, chronic pulmonary disease, ischemic stroke, renal disease, hemoglobin levels, platelet count, white blood cell count, and creatinine levels. SHR was analyzed both as a continuous variable and as an ordinal categorical variable, with a P for trend test performed to evaluate the linear association across categories. To examine whether a non-linear relationship existed between SHR and mortality, we employed a restricted cubic spline (RCS) regression model with four knots. If a non-linear association was detected, we further analyzed the data

using a two-piecewise Cox model on either side of the inflection point. Furthermore, stratified analyses were conducted according to age (< 60 years or ≥ 60 years), sex (male, female), and the presence of diabetes, hypertension, atrial fibrillation, renal disease, and chronic pulmonary disease. To evaluate the improvement in predictive accuracy when incorporating SHR into the existing prognostic scoring system, we employed the receiver operating characteristic (ROC) curve, quantifying the enhancement via the area under the curve (AUC). Furthermore, to assess the added value of SHR in terms of predictive performance and clinical utility, we calculated Harrell's C-index, integrated discrimination improvement (IDI), and net reclassification improvement (NRI). For all analyses, a two-sided p-value less than 0.05 was considered to indicate statistical significance.

Results

Baseline characteristics

A total of 2,461 patients were included in our study, of whom 1,402 had ischemic stroke. The mean age was 70.55 ± 14.59 years, with 1,221 (49.61%) being female. The average SHR was 1.06 ± 0.33. The length of hospital stay was 6.99 days (IQR: 3.92–13.71), whereas the duration in the ICU was 3.09 days (IQR: 1.74–6.17). Patients were categorized into four quartiles based on their SHR levels: Q1 (0.227–0.85), Q2 (0.85–0.994), Q3 (0.994–1.197), and Q4 (1.197–29.28). As illustrated in Table 1,

Table 1 Baseline characteristics according to SHR quartiles

Categories	Total(*n* = 2461)	Q1(*n* = 616)	Q2(*n* = 613)	Q3(*n* = 621)	Q4(*n* = 611)	*P*-value
Demographics						
Age, years	70.55 ± 14.59	71.57 ± 14.30	70.13 ± 15.02	70.67 ± 14.85	69.82 ± 14.15	0.16
Gender, female, n (%)	1221(49.61)	307(49.84)	294(47.96)	297(47.83)	323(52.86)	0.26
Comorbidity						
Hypertension	1371(55.71)	340(55.19)	344(56.12)	368(59.26)	319(52.21)	0.10
Myocardial infarction	98(3.98)	29(4.71)	15(2.45)	22(3.54)	32(5.24)	0.06
Congestive heart failure	142(5.77)	43(6.98)	27(4.40)	30(4.83)	42(6.87)	0.11
Atrial fibrillation	257(10.44)	75(12.18)	53(8.65)	72(11.59)	57(9.33)	0.12
Diabetes	804(32.67)	242(39.29)	152(24.80)	176(28.34)	234(38.30)	< 0.001
Chronic pulmonary disease	377(15.32)	100(16.23)	82(13.38)	85(13.69)	110(18.00)	0.08
Renal disease	440(17.88)	116(18.83)	91(14.85)	91(14.65)	142(23.24)	< 0.001
Vital signs						
HR mean, beats/min	79.74 ± 14.46	77.36 ± 13.77	77.65 ± 13.91	80.38 ± 15.04	83.58 ± 14.24	< 0.001
RR mean, times/min	18.92 ± 3.12	18.54 ± 2.93	18.64 ± 2.97	18.89 ± 3.01	19.62 ± 3.43	< 0.001
SBP mean, mmHg	132.77 ± 16.98	132.93 ± 16.33	133.35 ± 17.09	134.10 ± 17.07	130.68 ± 17.28	< 0.01
DBP mean, mmHg	71.18 ± 12.42	72.10 ± 12.27	72.77 ± 12.04	71.74 ± 12.99	68.07 ± 11.84	< 0.001
MBP mean, mmHg	88.49 ± 11.87	88.93 ± 11.76	89.66 ± 11.70	89.12 ± 12.32	86.22 ± 11.40	< 0.001
SpO_2 mean, %	96.86 ± 1.78	96.65 ± 1.77	96.70 ± 1.66	96.95 ± 1.78	97.16 ± 1.88	< 0.001
Laboratory indicators						
Hemoglobin min, g/dl	11.78 ± 2.16	11.94 ± 2.13	12.06 ± 2.04	11.93 ± 2.13	11.18 ± 2.22	< 0.001
Platelets min, 10^9/L	215.18 ± 79.25	225.08 ± 80.08	214.58 ± 71.90	215.49 ± 78.59	205.10 ± 84.96	< 0.001
WBC max, 10^9/L	9.70(7.50,12.70)	8.50(6.80,10.70)	8.80(7.00,11.50)	10.20(8.00,12.80)	12.05(9.38,15.70)	< 0.001
BUN max, mg/dl	16.00(12.00,23.00)	16.00(12.00,22.00)	15.00(12.00,21.00)	16.00(12.00,22.00)	19.00(13.50,29.00)	< 0.001
Creatinine max, mg/dl	0.90(0.70,1.20)	0.90(0.70,1.20)	0.90(0.70,1.10)	0.90(0.70,1.10)	1.00(0.80,1.50)	< 0.001
Disease severity score						
APSIII score	35.00(27.00,47.00)	32.00(25.00,42.00)	31.00(24.00,42.00)	36.00(27.00,47.00)	42.00(32.00,53.50)	< 0.001
SAPSII score	32.73 ± 11.54	30.51 ± 9.82	31.04 ± 11.10	32.68 ± 10.95	36.74 ± 13.07	< 0.001
OASIS score	30.84 ± 7.63	29.22 ± 7.17	29.74 ± 7.45	31.15 ± 7.25	33.26 ± 8.02	< 0.001
SOFA score	3.00(1.00,4.00)	2.00(1.00,4.00)	2.00(1.00,4.00)	3.00(2.00,4.00)	4.00(2.00,6.00)	< 0.001
Length of stay (LOS)						
LOS in hospital	6.99(3.92,13.71)	5.87(3.17,10.89)	6.12(3.70,11.53)	7.88(4.56,14.69)	9.06(4.80,16.78)	< 0.001
LOS in ICU	3.09(1.74,6.17)	2.22(1.32,4.40)	2.83(1.59,5.09)	3.33(1.88,6.51)	4.49(2.19,9.13)	< 0.001
Outcomes						
In-hospital death, n (%)	355(14.43)	45(7.31)	59(9.62)	84(13.53)	167(27.33)	< 0.001
ICU death, n (%)	225(9.14)	23(3.73)	39(6.36)	53(8.53)	110(18.00)	< 0.001

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO2, pulse blood oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; APSIII, acute physiology score; SAPSII, simplified acute physiology score; OASIS, oxford acute severity of illness score; SOFA, sequential organ failure assessment

Table 2 Baseline characteristics according to survivors and non-survivors groups

	Survivor (*n* = 2,106)	Non-survivor (*n* = 355)	*P*-value
Demographics			
Age, years	69.96 ± 14.50	74.03 ± 14.65	< 0.001
Gender, female, n (%)	1042(49.48)	179(50.42)	0.79
Comorbidity			
Hypertension	1200(56.98)	171(48.17)	< 0.01
Myocardial infarction	86(4.08)	12(3.38)	0.63
Congestive heart failure	108(5.13)	34(9.58)	< 0.01
Atrial fibrillation	209(9.92)	48(13.52)	0.05
Diabetes	678(32.19)	126(35.49)	0.24
Chronic pulmonary disease	322(15.29)	55(15.49)	0.99
Renal disease	357(16.95)	83(23.38)	< 0.01
Vital signs			
HR mean, beats/min	78.94 ± 14.04	84.47 ± 15.96	< 0.001
RR mean, times/min	18.73 ± 3.04	20.09 ± 3.33	< 0.001
SBP mean, mmHg	133.24 ± 16.63	129.98 ± 18.73	< 0.01
DBP mean, mmHg	71.85 ± 12.32	67.20 ± 12.30	< 0.001
MBP mean, mmHg	89.04 ± 11.79	85.18 ± 11.80	< 0.001
SpO_2 mean, %	96.75 ± 1.73	97.57 ± 1.92	< 0.001
Laboratory indicators			
Hemoglobin min, g/dl	11.93 ± 2.12	10.91 ± 2.17	< 0.001
Platelets min, 10^9/L	217.74 ± 79.03	199.46 ± 78.95	< 0.001
WBC max, 10^9/L	9.30(7.30,12.00)	13.00(9.60,16.80)	< 0.001
BUN max, mg/dl	16.00(12.00,22.00)	21.00(14.00,33.00)	< 0.001
Creatinine max, mg/dl	0.90(0.70,1.10)	1.00(0.80,1.60)	< 0.001
Glucose, mg/dl	133.38 ± 57.67	161.36 ± 59.96	< 0.001
HbA1c, %	6.23 ± 1.53	6.29 ± 1.53	0.50
SHR	1.02 ± 0.30	1.25 ± 0.42	< 0.001
Disease severity score			
APSIII score	34.00(26.00,44.00)	45.00(35.50,59.50)	< 0.001
SAPSII score	31.26 ± 10.77	41.49 ± 12.09	< 0.001
OASIS score	29.92 ± 7.27	36.24 ± 7.52	< 0.001
SOFA score	2.00(1.00,4.00)	4.00(2.00,6.00)	< 0.001
Length of stay (LOS)			
LOS in hospital	7.16(4.07,14.12)	5.35(2.68,10.63)	< 0.001
LOS in ICU	3.04(1.66,5.98)	3.80(2.07,7.67)	< 0.01

HR, heart rate; RR, respiratory rate; SBP, systolic blood pressure; DBP, diastolic blood pressure; MBP, mean blood pressure; SpO2, pulse blood oxygen saturation; WBC, white blood cell; BUN, blood urea nitrogen; HbA1c, hemoglobin A1c; SHR, stress hyperglycemia ratio; APSIII, acute physiology score; SAPSII, simplified acute physiology score; OASIS, oxford acute severity of illness score; SOFA, sequential organ failure assessment; LOS, length of stay

when compared to the Q1 group, patients in the Q4 group exhibited faster heart rates and respiratory rates but lower systolic, diastolic, and mean blood pressures; however, their SpO_2 levels were higher. Additionally, both the hospital length of stay and ICU length of stay were notably prolonged for the Q4 group compared to the Q1 group (all $P < 0.001$). Notably, the mortality risk was markedly increased in the Q4 group compared to other groups: in-hospital mortality rates were 7.31%, 9.62%, 13.53%, and 27.33% respectively across the quartiles ($P < 0.001$); similarly, in-ICU mortality rates were 3.73%, 6.36%, 8.53%, and 18.00% respectively ($P < 0.001$). The baseline characteristics of patients with ischemic stroke and those with non-ischemic stroke are detailed in Supplementary Tables 2 and 3, respectively.

The baseline characteristics of patients in the survival and mortality groups during hospitalization are summarized in Table 2. Patients in the mortality group were generally older, though there was no significant difference in gender distribution. Of particular note, the SHR level was markedly higher in the mortality group (1.25 ± 0.42) than in the survival group (1.02 ± 0.30), with a statistically significant difference ($P < 0.001$).

SHR and clinical outcomes

We utilized Kaplan-Meier survival analysis curves to examine the incidence of in-hospital and ICU mortality across the four SHR quartile groups (Fig. 2), revealing that patients in the Q4 group had a significantly higher risk of both in-hospital and ICU mortality (log-rank $P < 0.001$). To further investigate the relationship between SHR and mortality, we conducted Cox proportional hazards regression models (Table 3). The results demonstrated that each standard deviation (SD) increase in SHR was associated with a 45% higher risk of in-hospital mortality in the unadjusted model (HR 1.45, 95% CI 1.34–1.57, $P < 0.001$), which attenuated to 34% in the partially adjusted model (HR 1.34, 95% CI 1.23–1.45, $P < 0.001$) and 35% in the fully adjusted model (HR 1.35, 95% CI 1.23–1.48, $P < 0.001$). When SHR was categorized as an ordinal variable, patients in the Q4 group showed a 178% higher risk of mortality compared to the Q1 group in the unadjusted model (HR 2.78, 95% CI 2.00-3.87, $P < 0.001$), which reduced to 137% in the partially adjusted model (HR 2.37, 95% CI 1.70–3.32, $P < 0.001$) and 152% in the fully adjusted model (HR 2.52, 95% CI 1.75–3.63, $P < 0.001$), with a significant trend towards increasing risk as SHR increased (P for trend < 0.001).

Similar trends were observed for ICU mortality: each SD increase in SHR corresponded to HR of 1.43 (95% CI 1.30–1.58, $P < 0.001$) in the unadjusted model, 1.33 (95% CI 1.19–1.47, $P < 0.001$) in the partially adjusted model, and 1.37 (95% CI 1.21–1.54, $P < 0.001$) in the fully adjusted model. Patients in the Q4 group exhibited

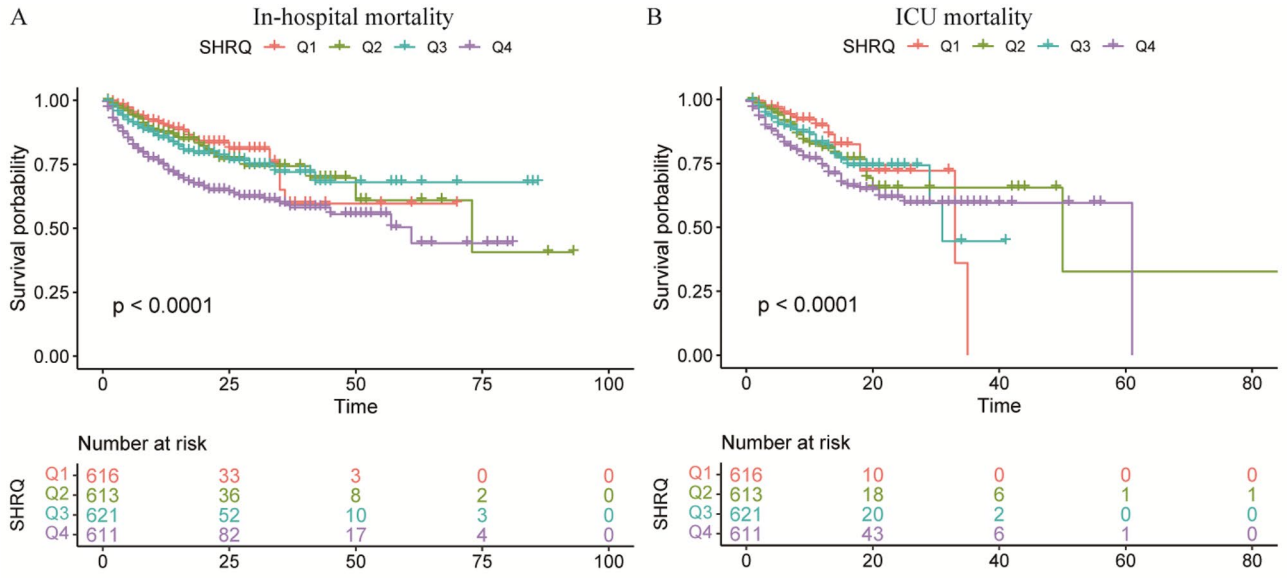

Fig. 2 Kaplan-Meier survival analysis curves for all-cause mortality. **A** In-hospital mortality; **B** ICU mortality

Table 3 Cox proportional hazard models for in-hospital and in-ICU all-cause mortality

Categories	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value	HR (95%CI)	*P*-value
In-hospital mortality						
Per SD increase	1.45(1.34,1.57)	< 0.001	1.34(1.23,1.45)	< 0.001	1.35(1.23,1.48)	< 0.001
Quartiles						
Q1	Ref		Ref		Ref	
Q2	1.26(0.85,1.85)	0.25	1.29(0.87,1.90)	0.20	1.4(0.92,2.15)	0.12
Q3	1.52(1.06,2.19)	0.02	1.45(1.01,2.08)	0.04	1.61(1.08,2.38)	0.02
Q4	2.78(2.00,3.87)	< 0.001	2.37(1.70,3.32)	< 0.001	2.52(1.75,3.63)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	
ICU mortality						
Per SD increase	1.43(1.30,1.58)	< 0.001	1.33(1.19,1.47)	< 0.001	1.37(1.21,1.54)	< 0.001
Quartiles						
Q1	Ref		Ref		Ref	
Q2	1.41(0.84,2.37)	0.19	1.42(0.85,2.38)	0.18	1.68(0.93,3.04)	0.08
Q3	1.67(1.02,2.72)	0.04	1.56(0.95,2.55)	0.08	1.89(1.08,3.31)	0.03
Q4	2.66(1.69,4.18)	< 0.001	2.21(1.40,3.49)	< 0.001	2.65(1.57,4.47)	< 0.001
P for trend	< 0.001		< 0.001		< 0.001	

Model 1: no adjustment

Model 2: adjusted for age, sex, heart rate, respiratory rate, mean blood pressure, SpO_2

Model 3: further adjusted for hypertension, myocardial infarction, heart failure, atrial fibrillation, diabetes, chronic pulmonary disease, renal disease, hemoglobin, platelet, white blood cell, creatinine

significantly higher ICU mortality risks compared to the Q1 group, with HR of 2.66 (95% CI 1.69–4.18) in the unadjusted model, 2.21 (95% CI 1.40–3.49, $P < 0.001$) in the partially adjusted model, and 2.65 (95% CI 1.57–4.47, $P < 0.001$) in the fully adjusted model, all showing a significant upward trend (P for trend < 0.001).

Additionally, we evaluated the potential non-linear relationship between SHR and mortality using RCS model. The results (Fig. 3) showed that in the fully adjusted model, the P values for non-linear relationships between SHR and both in-hospital and ICU mortality were not statistically significant (non-linear $P > 0.05$). However, threshold effects were observed (Supplementary Table 4): for in-hospital mortality, the SHR threshold point was identified at 0.77, beyond which each unit increase in SHR was associated with a significant rise in mortality risk (HR 2.41, 95% CI 1.77–3.30, $P < 0.001$). Similarly, for ICU mortality, the SHR threshold point was 0.79; when SHR exceeded this value, there was also

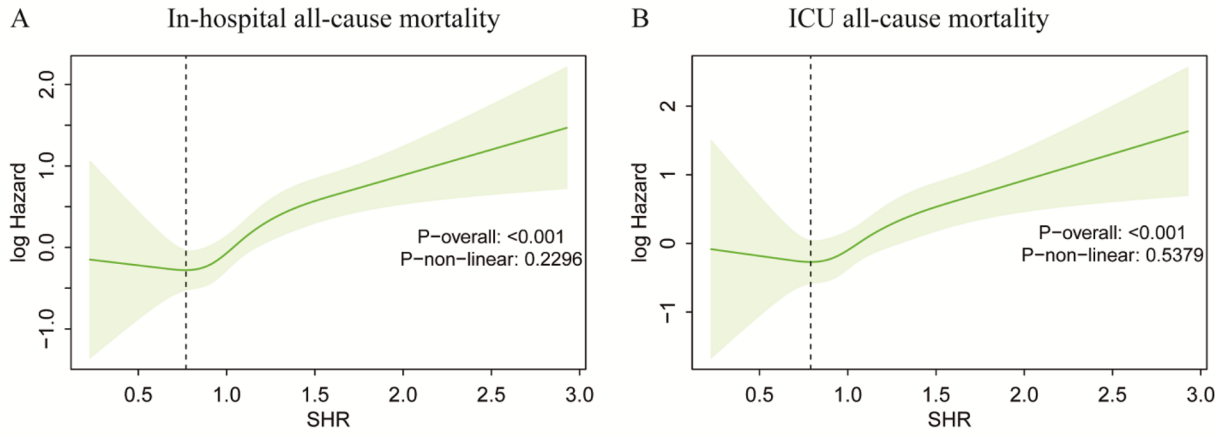

Fig. 3 RCS analysis of SHR with all-cause mortality. **A** In-hospital mortality; **B** ICU mortality

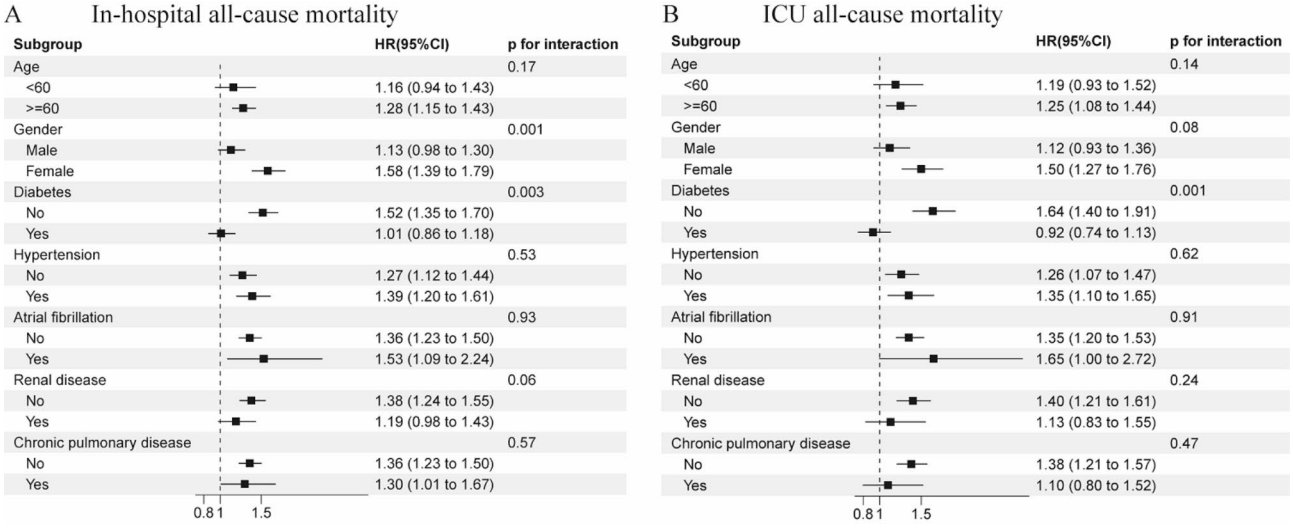

Fig. 4 Subgroup forest plot for all-cause mortality. **A** In-hospital mortality; **B** ICU mortality

a significant increase in mortality risk (HR 1.96, 95% CI 1.29–2.98, $P = 0.002$).

Subgroup analysis

The association between SHR and mortality remained significant in both ischemic and non-ischemic stroke patients (Supplementary Tables 5 and 6). This relationship was consistent across various subgroups, including different age groups and patients with hypertension, atrial fibrillation, renal disease, or chronic lung disease, with no significant interactions observed (Fig. 4). Interestingly, SHR demonstrated a more pronounced predictive value for in-hospital mortality in female patients compared to male patients (female HR 1.58, 95% CI 1.39–1.79 vs. male HR 1.13, 95% CI 0.98–1.30, p for interaction = 0.001). Notably, in patients without diabetes, SHR exhibited a more prominent predictive value: for in-hospital mortality (non-diabetic HR 1.52, 95% CI 1.35–1.70 vs. diabetic HR 1.01, 95% CI 0.86–1.18, P for interaction = 0.003) and for ICU mortality (non-diabetic HR 1.64, 95% CI 1.40–1.91 vs. diabetic HR 0.92, 95% CI 0.74–1.13, P for interaction = 0.001).

Predictive value and incremental effect of SHR

We evaluated the impact of adding SHR to existing scoring models on the prediction of in-hospital mortality by calculating the AUC. The results (Fig. 5) demonstrated that incorporating SHR consistently improved the predictive ability for in-hospital mortality across all examined scores: APSIII (from 0.707(0.678, 0.736) to 0.748(0.722, 0.775)), SAPSII (from 0.746(0.721, 0.772) to 0.780(0.757, 0.803)), OASIS (from 0.730(0.703, 0.758) to 0.766(0.740, 0.791)), and SOFA (from 0.678(0.647, 0.708) to 0.728(0.700, 0.756)). Specifically, as presented in Table 4, for the APSIII score, the C-index increased from 0.647 (95% CI 0.614, 0.680) to 0.695 (95% CI 0.665, 0.725)

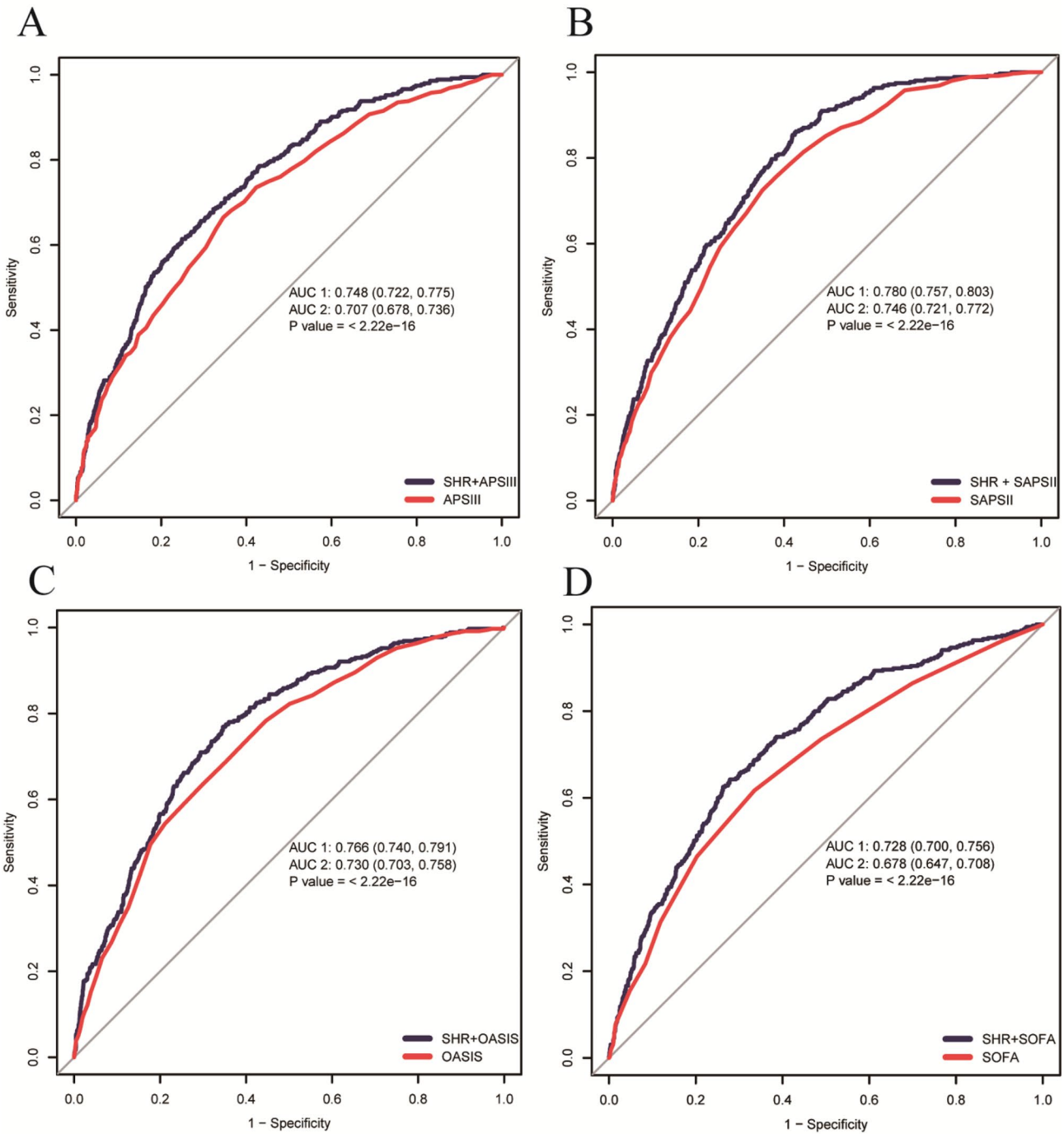

Fig. 5 ROC curve analysis of the incremental effect of SHR on in-hospital all-cause mortality. **A** APSIII score + SHR; **B** SAPSII score + SHR; **C** OASIS score + SHR; **D**SOFA score + SHR

with the addition of SHR, accompanied by an IDI of 1.40 (95% CI 0.40, 3.00), and an NRI of 10.90 (95% CI 2.30, 16.90). For the SAPSII score, the C-index rose from 0.706 (95% CI 0.678, 0.734) to 0.738 (95% CI 0.712, 0.764), with an IDI of 1.20 (95% CI 0.20, 2.40), and an NRI of 5.90 (95% CI -2.20, 11.80). For the OASIS score, the C-index improved from 0.692 (95% CI 0.663, 0.722) to 0.729 (95% CI 0.702, 0.757), with an IDI of 1.70 (95% CI 0.50, 3.30), and an NRI of 7.70 (95% CI 0.90, 14.30). Lastly, for the SOFA score, the C-index enhanced from 0.625 (95% CI 0.591, 0.659) to 0.686 (95% CI 0.656, 0.716), with an IDI of 1.80 (95% CI 0.60, 3.60), and an NRI of 8.00 (95% CI 1.60, 15.50).

Table 4 Improvement in discrimination and risk reclassification for in-hospital all-cause mortality after addition of SHR

	C-index (95%CI)	IDI (%) (95%CI)	*P*-value	NRI (%) (95%CI)	*P*-value
APSIII	0.647(0.614, 0.680)	Ref	Ref	Ref	Ref
APSIII + SHR	0.695(0.665, 0.725)	1.40(0.40, 3.00)	0.007	10.90(2.30, 16.90)	0.020
SAPSII	0.706(0.678, 0.734)	Ref	Ref	Ref	Ref
SAPSII + SHR	0.738(0.712, 0.764)	1.20(0.20, 2.40)	0.007	5.90(-2.20, 11.80)	0.159
OASIS	0.692(0.663, 0.722)	Ref	Ref	Ref	Ref
OASIS + SHR	0.729(0.702, 0.757)	1.70(0.50,3.30)	< 0.001	7.70(0.90, 14.30)	0.040
SOFA	0.625(0.591, 0.659)	Ref	Ref	Ref	Ref
SOFA + SHR	0.686(0.656, 0.716)	1.80(0.60,3.60)	< 0.001	8.00(1.60, 15.50)	0.027

IDI, integrated discrimination improvement; NRI, net reclassification improvement; APSIII, acute physiology score; SHR, stress hyperglycemia ratio; SAPSII, simplified acute physiology score; OASIS, oxford acute severity of illness score; SOFA, sequential organ failure assessment

Discussion

In this study, we have, for the first time, elucidated the association between SHR and mortality in critically ill patients with cerebrovascular disease, and evaluated the predictive value of SHR for prognosis. Our findings demonstrate that elevated SHR levels are a significant independent risk factor for both in-hospital and ICU mortality in these patients, even after adjusting for potential confounders. The results also indicate a linear association between SHR and mortality. Additionally, incorporating SHR into existing risk scores significantly enhances the models' ability to predict clinical outcomes.

SHR, which is composed of blood glucose and HbA1c, is considered a potential marker reflecting the degree of stress-induced hyperglycemia. Several clinical studies have confirmed the association between SHR and the risks of mortality and adverse outcomes in specific patient populations. Jie et al. reported that, in a cohort of 5,562 patients with acute coronary syndrome followed for an average of more than two years, SHR was independently associated with major adverse cardiovascular events (MACE) [5]. Similar results were also observed in patients with acute ST-elevation myocardial infarction (STEMI) [6], myocardial infarction and non-obstructive coronary arteries (MINOCA) [10], three-vessel disease [11], and chronic total occlusion [12]. Additionally, Zhihan et al. reported that in a cohort of 12,899 patients undergoing non-cardiac surgery, SHR was significantly associated with the risk of perioperative MACE [13]. Similar results were also observed in patients with severe sepsis [14], heart failure [15, 16], atrial fibrillation [8], and pulmonary infections [17]. In this study, we observed a significant positive correlation between SHR levels and in-hospital mortality in critically ill patients with cerebrovascular disease, findings that align with previous research. Specifically, for acute ischemic stroke due to large vessel occlusion, the RESCUE BT trial found that elevated SHR levels are strongly associated with poor functional outcomes [18]. Xiaolei et al. also reported that in patients with large ischemic stroke undergoing endovascular therapy, SHR levels were negatively correlated with neurological recovery at 90 days. However, no such association was observed between SHR and neurological recovery in patients receiving standard medical treatment [19]. Donghua et al. also reported that, in their analysis of the Chinese Stroke Center Alliance database, elevated SHR levels were significantly associated with an increased risk of in-hospital mortality in patients with acute ischemic stroke and diabetes [20]. Zhong et al. also found that, in patients with acute stroke, stress hyperglycemia was associated not only with all-cause mortality at 12 months but also with infectious complications and functional deficits [21]. In this study, we performed the first evaluation of the association between SHR and mortality in critically ill patients with cerebrovascular disease, extending beyond ischemic stroke. Our results indicate that SHR is an independent risk factor for in-hospital mortality in patients with both ischemic and non-ischemic cerebrovascular diseases. This may be attributed to the association between abnormal blood glucose levels and angiogenesis [22, 23], which plays a critical role in cerebrovascular diseases. Future studies could assess the predictive value of angiogenic markers [24, 25] in the prognosis of cerebrovascular events and investigate whether these markers mediate the relationship between SHR and adverse outcomes.

Previous studies have debated whether a linear relationship exists between SHR and adverse clinical events. Jie et al. observed a U-shaped relationship between SHR and MACE in patients with acute coronary syndrome, suggesting that both excessively low and high glucose levels may pose risks to patients [5]. In patients with chronic total occlusion, however, Yanjun et al. found a linear association between SHR and both cardiovascular mortality and MACE [12]. Xiangming et al. also reported that in patients with severe aortic stenosis undergoing transcatheter aortic valve replacement (TAVR) treatment, SHR was linearly associated with all-cause mortality, cardiovascular mortality, and MACE [26]. In patients undergoing non-cardiac surgery, SHR exhibited a linear relationship with perioperative MACE in diabetic patients, whereas it demonstrated a U-shaped relationship with perioperative MACE in patients without diabetes [13]. These findings suggest that the relationship between SHR and prognosis may differ across various patient populations. Yongle

et al. observed a U-shaped relationship between SHR and stroke recurrence in patients with acute minor ischemic stroke [27]. Guangyong et al., however, found that in patients with acute ischemic stroke receiving thrombolytic therapy, SHR was linearly associated with poor neurological recovery at 3 months [28]. In this study, we observed that in critically ill patients with cerebrovascular disease, SHR exhibited a linear relationship with both in-hospital and ICU mortality, with a threshold ranging from 0.77 to 0.79.

In the subgroup analysis, we observed that the association between SHR and mortality in cerebrovascular disease patients was more pronounced in non-diabetic individuals. This phenomenon may be attributed to the fact that in individuals without diabetes, a sudden short-term spike or fluctuation in blood glucose levels can markedly exacerbate oxidative stress and lead to endothelial dysfunction [29]. Conversely, patients with diabetes, who experience chronic hyperglycemia, might have developed a reduced sensitivity to such acute glucose variations. Previous studies have reported inconsistent findings regarding the impact of SHR on prognosis in diabetic versus non-diabetic patients. Kongyong et al. found that in patients with acute myocardial infarction, SHR was significantly associated with in-hospital mortality, irrespective of diabetic status [30]. Zhihan et al. found that in patients undergoing non-cardiac surgery, the association between SHR and perioperative complications was more pronounced in non-diabetic patients than in diabetic patients [13]. However, Wei et al. found that SHR was associated with in-hospital mortality in patients with coronary heart disease and either diabetes or prediabetes, but not in non-diabetic patients [31]. This difference may be attributable to the lower number of in-hospital mortality events among non-diabetic patients in their study, which could have resulted in insufficient statistical power. Yu et al. also found that in patients with triple-vessel disease from acute coronary syndrome, the prognostic value of SHR was significant only in diabetic patients, but not in non-diabetic patients [32]. Fuad et al. also observed similar findings in patients with MINOCA [33]. This suggests that the impact of diabetes on SHR may differ across various patient populations, highlighting the need for further research to clarify how diabetes or the absence of diabetes influences SHR and prognosis in patients with cerebrovascular disease.

Additionally, in this study, we also examined the improvement in predicting in-hospital mortality for cerebrovascular disease patients by adding SHR to existing risk scores. The results demonstrated that incorporating SHR consistently enhanced the predictive ability of all evaluated models. Currently, there are limited studies on the improvement of prognostic models for cerebrovascular disease by incorporating SHR; most research has focused on patients with myocardial infarction. Side et al. found that in patients with MINOCA, SHR demonstrated superior prognostic predictive ability compared to blood glucose and HbA1c. Furthermore, adding SHR to the TIMI score enhanced the prediction of MACE [34]. In patients with acute myocardial infarction, incorporating SHR into the GRACE score also enhances its predictive ability for in-hospital mortality and long-term MACE [35, 36]. Jingfang et al. also found that in patients undergoing non-cardiac surgery, incorporating SHR into existing predictive models enhanced the model's ability to predict MACE and cardiac death [7]. Clinically, the ease of obtaining blood glucose and HbA1c data makes the application of SHR for predicting adverse patient outcomes more feasible.

In summary, this study demonstrates that SHR significantly influences the prognosis of critically ill patients with cerebrovascular disease. However, several limitations should be acknowledged. Firstly, as all hospitalized patients were from a U.S. population, the results may not be generalizable to other populations. Secondly, due to the limitations of the public databases used, while we adjusted for certain confounding factors, other potential confounders such as patients' dietary habits, physical activity, smoking status, alcohol consumption, and data from electrocardiograms and echocardiograms were not included in this analysis. Thirdly, As demonstrated in Table 4, the inclusion of SHR into existing models (APSIII, SAPSII, OASIS, SOFA) results in only modest improvements in their ability to predict in-hospital mortality, with the final improved AUC remaining below the threshold of ≥ 0.80. Moreover, while the enhancements in IDI and NRI are statistically significant, they are relatively minor. Although SHR improves risk stratification at the population level, its incremental clinical benefit for individual predictions may be limited. Consequently, the transformative clinical value of incorporating SHR into these models might be restricted. Lastly, given the retrospective observational nature of this study, establishing a definitive causal relationship is challenging; therefore, further prospective studies with larger sample sizes are necessary to confirm these findings.

Conclusion

This study found that SHR is an independent risk factor for mortality in critically ill patients with cerebrovascular disease, exhibiting an approximately linear relationship. Additionally, SHR demonstrates predictive value for in-hospital mortality, which could enhance the accuracy of identifying patients at risk for adverse outcomes. Future research will require larger prospective cohort studies or randomized controlled trials to further validate the relationship and predictive value of SHR in patients with cerebrovascular disease, as well as to determine whether

early intervention targeting SHR can improve patient outcomes.

Abbreviations

AUC	Area under the curve.
APSIII	Acute Physiology Score III.
CI	Confidence interval.
CITI	Collaborative Institutional Training Initiative.
HR	Hazard ratio.
IDI	Integrated discrimination improvement.
ICU	Intensive care units.
LOS	Length of stay.
MACE	Major adverse cardiovascular events.
MINOCA	Myocardial infarction and non-obstructive coronary arteries.
MIMIC-IV	Medical Information Mart for Intensive Care IV.
NIH	National Institutes of Health.
NRI	Net reclassification improvement.
OASIS	Oxford Acute Severity of Illness Score.
RCS	Restricted cubic spline.
ROC	Receiver operating characteristic.
SAPSII	Simplified Acute Physiology Score II.
SD	Standard deviation.
SHR	Stress hyperglycemia ratio.
SOFA	Sequential Organ Failure Assessment.
STEMI	ST-elevation myocardial infarction.
TAVR	Transcatheter aortic valve replacement.

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02613-y .

Supplementary Material 1

Supplementary Material 2

Supplementary Material 3

Supplementary Material 4

Supplementary Material 5

Supplementary Material 6

Acknowledgements
We acknowledge the contributions of the MIMIC-IV program registry for their work in creating and maintaining the MIMIC IV database.

Author contributions
Qucheng Wei and Bingchen Liu designed the study. Data extraction was performed by Jian Xu, Anan Huang and Jie Wang, while data analysis was conducted by Yuwen Chen and Fan He. Yuwen Chen and Jian Xu wrote the initial draft of the manuscript, which was subsequently revised by Qucheng Wei and Bingchen Liu. All authors approved the final version of the manuscript.

Funding
None.

Availability of data and materials
This study utilized publicly available datasets, which can be accessed at https://mimic.mit.edu/.

Declarations

Ethical approval and consent to participate
The MIMIC-IV project received approval from the Institutional Review Boards of both the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Patient information was anonymized, thereby obviating the need for informed consent from individual patients for this study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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Received: 27 December 2024 / Accepted: 24 January 2025
Published online: 07 February 2025

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