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ORIGINAL ARTICLE

Association between stress hyperglycemia ratio with short-term and long-term mortality in critically ill patients with ischemic stroke

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Abstract

Aims Hyperglycemia on admission is associated with poor prognosis in ischemic stroke (IS) patients. We aimed to investigate the relationship between stress hyperglycemia ratio (SHR) and short-term or long-term mortality in IS patients in the ICU and to explore whether this relationship is influenced by diabetes status.

Materials and methods We collected patients with severe IS requiring ICU admission in the Medical Information Mart for Intensive Care (MIMIC-IV) database and calculated SHR. Outcomes included 30-day, 90-day, and 1-year mortality. The association between SHR and mortality in patients with critical IS was elucidated using Multivariate Cox regression and subgroup analysis for diabetes.

Results A total of 1376 patients were recruited. After adjusting for potential confounders, patients in the third and fourth quartiles had a significantly increased risk of death at 30 days, 90 days, and 1 year compared to the first quartile of SHR (Q3 vs. Q1: HR 1.56–1.80, all $p < 0.02$; Q4 vs. Q1: HR 1.75–2.15, all $p < 0.001$; all p for trend < 0.001). In addition, the highest quartile of SHR was significantly associated with short-term or long-term mortality compared with the first quartile, regardless of diabetes status.

Conclusions Our results suggest that stress hyperglycemia, defined by the glucose/HbA1c ratio, is associated with increased short-term and long-term mortality in patients with ischemic stroke, independent of the patient's diabetes status.

Keywords Ischemic stroke · Stress hyperglycemia ratio · Diabetes · Mortality

Abbreviations

IS	Glycemic variability
SHR	Standard deviation
AUC	Area under the curves
ROC	Receiver operating characteristic

Introduction

Ischemic stroke (IS) is one of the most common types of cerebrovascular disease, accounting for about 70% of all cerebrovascular diseases and 85% of strokes [1–3], with high rates of disability and death [4], especially in critically ill patients [5]. Studies showed that up to 60% of critical stroke patients were severely disabled or died within 90 days [6]. Therefore, early identification of risk factors associated with progressive IS is particularly important for clinical management.

As one of the manifestations of stress, hyperglycemia has been proven to be associated with poor prognosis in a lot of diseases [7–10]. Hyperglycemia is seen in more than 40% of patients with acute IS [11] and is associated with poorer functional outcomes and higher mortality rates [9, 12]. In previous studies, stress hyperglycemia defined by fasting or admission blood glucose (ABG) was often confounded by diabetes-related background hyperglycemia [13, 14]. However, unlike absolute hyperglycemia levels, stress hyperglycemia assessed by glucose/glycated hemoglobin (HbA1c)

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ratio provides a more objective representation of the relative elevation of glucose levels [15] and may be useful in predicting short-term and long-term mortality in patients with IS in the intensive care unit (ICU).

In this study, we aimed to investigate the relationship between stress hyperglycemia ratio (SHR) and short-term and long-term all-cause mortality in IS patients in the ICU and to explore whether this relationship is influenced by diabetes status.

Materials and methods

Data sources and study population

Data were collected from the Medical Information Mart for Intensive Care IV (MIMIC-IV) 2.0 database, which is a large, freely available database with information from patients who had critical care unit stays at the Beth Israel Deaconess Medical Center between 2008 and 2019 [16]. One of our authors was given access to the database after completing the training (authorization code: 46032459).

In the MIMIC-IV2.0 database, 1796 patients admitted to the ICU for IS between 2008 and 2019 were included. The criteria for exclusion were as follows: (1) not the first ICU admission for each patient; (2) age < 18 years when entering ICU; (3) length of stay in ICU < 6 h; (4) Survival time after ICU admission < 48 h; (5) Missing HbA1c or glucose records. The flow diagram of our study patient selection is shown in Supplementary Fig. 1.

Data collection and definitions

We took the first day of admission to the ICU as the baseline and extracted the following patient data: (1) demographics, including age, race, gender and body mass index (BMI); (2) comorbidities defined by the International Classification of Diseases (ICD-9-CM and ICD-10-CM) codes, including diabetes mellitus, chronic kidney disease (CKD), arterial fibrillation, myocardial infarction, peripheral vascular disease, congestive heart failure, malignant cancer, chronic pulmonary disease, and hypertension; (3) severity of illness scores at admission, including the simplified Acute Physiology Score II (SAPS-II), the Sepsis-related Organ Failure Assessment score (SOFA) and the Glasgow Coma Scale (GCS); (4) vital signs; (5) treatments, including antiplatelet (aspirin and clopidogrel) and anticoagulant (warfarin) drug use, thrombolytic therapy; (6) laboratory parameters, including HbA1c, glucose, white blood cells (WBC), platelets, red blood cells (RBC), red blood cell distribution width (RDW), hemoglobin, creatinine, serum sodium and serum potassium. Data extraction code is publicly available on GitHub (https://github.com/MIT-LCP/mimic-iv).

In the extracted data, HbA1c was the last measurement within 1 week, glucose was the first measurement after admission to the ICU, and the rest of the laboratory parameters and vital signs were averaged over the first day of admission to the ICU.

Exposure

Stress hyperglycemia was evaluated using the following formula: Glucose (mg/dl)/HbA1c (%).

Outcomes

The primary outcome indicators in our study were short-term and long-term mortality, including 30-day, 90-day, and 1-year mortality.

Statistical analysis

Eight items had varying degrees of missing data (Supplementary Table 1), except for BMI, which had a missing proportion of < 5%. We used the random forest method to interpolate data with a missing proportion < 5%. Missing data for BMI were included in the study as categorical data.

Patient characteristics were reported as mean ± SD for normally or approximately normally distributed continuous variables, median and interquartile distance for non-normally distributed continuous variables, and frequency and proportion for categorical variables. One-way ANOVA or Kruskal–Wallis test was used to compare differences between groups for continuous variables, and Fisher's exact test was used to compare differences between groups for categorical variables.

Multivariate Cox regression was used to assess the association between SHR and mortality, adjusting for potential confounders including age, gender, race, diabetes, CKD, arterial fibrillation, myocardial infarction, congestive heart failure, hypertension, SAPS-II, SOFA, GCS, antiplatelet and anticoagulant drug use, thrombolytic therapy, HbA1c, WBC, RDW, hemoglobin, creatinine, sodium and potassium. Results were shown as hazard ratios (HR) and 95% confidence intervals (CIs). Multicollinearity between continuous variables was assessed by the variance inflation factor. Survival curves were constructed by the Kaplan–Meier method and compared using the log-rank test. The area under the curves (AUC) of the receiver operating characteristic (ROC) curves was used to assess and compare the predictive ability of SHR, FBG, and HbA1c on mortality over time. We further explored the association of quartiles of SHR with diabetes status and risk of death and calculated P values for the interaction.

Table 1 Baseline characteristics according to quartiles of SHR

Variables	Overall ($n=1376$)	Q1 <17.5 ($n=345$)	Q2 17.5–20.0 ($n=345$)	Q3 20.0–23.8 ($n=343$)	Q4 >23.8 ($n=343$)	p value
Age, years	72.90 [61.05, 83.25]	72.00 [58.01, 82.51]	72.33 [60.83, 84.38]	73.67 [61.65, 83.23]	73.23 [62.88, 82.95]	0.544
Gender, female	722 (52.5)	188 (54.5)	165 (47.8)	174 (50.7)	195 (56.9)	0.086
BMI, kg/m^2						0.217
<30	571 (41.5)	152 (44.1)	148 (42.9)	137 (39.9)	134 (39.1)	
≥ 30	281 (20.4)	61 (17.7)	66 (19.1)	67 (19.5)	87 (25.4)	
Missing	524 (38.1)	132 (38.3)	131 (38.0)	139 (40.5)	122 (35.6)	
Ethnicity						0.461
White	873 (63.4)	220 (63.8)	227 (65.8)	208 (60.6)	218 (63.6)	
Asian	27 (2.0)	4 (1.2)	6 (1.7)	10 (2.9)	7 (2.0)	
Black	127 (9.2)	40 (11.6)	30 (8.7)	27 (7.9)	30 (8.7)	
Others	349 (25.4)	81 (23.5)	82 (23.8)	98 (28.6)	88 (25.7)	
Comorbidities						
Diabetes	437 (31.8)	91 (26.4)	77 (22.3)	93 (27.1)	176 (51.3)	<0.001
CKD	177 (12.9)	43 (12.5)	39 (11.3)	45 (13.1)	50 (14.6)	0.633
Arterial fibrillation	561 (40.8)	135 (39.1)	132 (38.3)	141 (41.1)	153 (44.6)	0.335
Myocardial infarction	158 (11.5)	43 (12.5)	34 (9.9)	26 (7.6)	55 (16.0)	0.004
Congestive heart failure	252 (18.3)	57 (16.5)	53 (15.4)	54 (15.7)	88 (25.7)	0.001
Peripheral vascular disease	147 (10.7)	41 (11.9)	35 (10.1)	44 (12.8)	27 (7.9)	0.163
Chronic pulmonary disease	215 (15.6)	54 (15.7)	48 (13.9)	51 (14.9)	62 (18.1)	0.479
Malignant cancer	87 (6.3)	17 (4.9)	19 (5.5)	24 (7.0)	27 (7.9)	0.366
Hypertension	1080 (78.5)	254 (73.6)	273 (79.1)	268 (78.1)	285 (83.1)	0.026
Score						
SAPS II	30 [23, 37]	28 [20, 34]	29 [22, 36]	30 [24, 37]	33 [26, 39]	<0.001
SOFA	3 [1, 4]	2 [1, 4]	3 [1, 4]	3 [1, 4]	4 [2, 5]	<0.001
GCS, <8	169 (12.3)	27 (7.8)	35 (10.1)	50 (14.6)	57 (16.6)	0.001
Vital signs						
Mean SBP, mmHg	136.88 ± 17.72	134.47 ± 16.92	137.01 ± 17.17	139.47 ± 18.16	136.60 ± 18.31	0.003
Mean DBP, mmHg	72.64 ± 12.25	73.07 ± 12.00	72.69 ± 11.95	72.81 ± 12.60	71.98 ± 12.46	0.683
Mean MAP, mmHg	90.06 ± 12.06	89.74 ± 11.78	90.27 ± 11.49	90.84 ± 12.45	89.40 ± 12.49	0.422
Therapy						
Antiplatelet agents	1147 (83.4)	291 (84.3)	283 (82.0)	292 (85.1)	281 (81.9)	0.579
Anticoagulation agents	330 (24.0)	89 (25.8)	85 (24.6)	80 (23.3)	76 (22.2)	0.703
Thrombolysis	213 (15.5)	50 (14.5)	56 (16.2)	62 (18.1)	45 (13.1)	0.304
Laboratory tests						
HbA1c, %	5.80 [5.40, 6.30]	5.80 [5.50, 6.20]	5.70 [5.40, 6.10]	5.70 [5.40, 6.10]	6.00 [5.50, 7.05]	<0.001
ABG, mg/dL	117.0 [100.0, 145.3]	93.0 [87.0, 99.0]	108.0 [101.0, 115.0]	125.0 [116.0, 136.0]	173.0 [147.0, 219.0]	<0.001
WBC, 10^9/L	9.50 [7.59, 11.95]	8.30 [6.95, 10.40]	9.00 [7.40, 11.45]	10.05 [8.10, 12.53]	10.70 [8.50, 13.28]	<0.001
Platelets, 10^9/L	213.0 [174.0, 263.5]	213.0 [175.0, 259.5]	213.0 [174.0, 259.3]	213.0 [176.3, 262.0]	212.5 [170.0, 274.0]	0.759
RBC, 10^9/L	4.17 [3.71, 4.56]	4.17 [3.72, 4.55]	4.22 [3.71, 4.61]	4.20 [3.77, 4.54]	4.12 [3.60, 4.51]	0.113
RDW, %	13.60 [13.00, 14.60]	13.70 [13.05, 14.63]	13.65 [13.10, 14.50]	13.50 [12.92, 14.50]	13.70 [13.00, 14.60]	0.329
Hemoglobin, g/dL	12.40 [11.05, 13.80]	12.40 [10.95, 13.80]	12.60 [11.20, 13.85]	12.65 [11.20, 13.90]	12.20 [10.82, 13.58]	0.105
Creatinine, mg/dL	0.90 [0.70, 1.10]	0.80 [0.70, 1.10]	0.90 [0.74, 1.10]	0.85 [0.70, 1.10]	0.90 [0.73, 1.17]	0.031
Sodium, mmol/L	139.61 ± 3.39	140.10 ± 3.27	139.73 ± 3.19	139.58 ± 3.52	139.03 ± 3.50	<0.001
Potassium, mmol/L	4.05 [3.77, 4.35]	4.00 [3.75, 4.30]	4.10 [3.80, 4.40]	4.00 [3.70, 4.25]	4.10 [3.80, 4.44]	0.003

Table 1 (continued)

Variables	Overall ($n=1376$)	Q1 <17.5 ($n=345$)	Q2 17.5–20.0 ($n=345$)	Q3 20.0–23.8 ($n=343$)	Q4 >23.8 ($n=343$)	p value
Death						
30-day mortality	210 (15.3)	30 (8.7)	32 (9.3)	63 (18.4)	85 (24.8)	<0.001
90-day mortality	260 (18.9)	44 (12.8)	38 (11.0)	75 (21.9)	103 (30.0)	<0.001
1-year mortality	322 (23.4)	60 (17.4)	52 (15.1)	92 (26.8)	118 (34.4)	<0.001

Data are presented as n (%), mean ± SD, or median [interquartile range]. Q1–Q4 indicate quartiles of SHR, *SHR* stress hyperglycemia ratio, *BMI* body mass index, *CKD* chronic kidney disease, *SAPS II* simplified acute physiology score II, *SOFA* sepsis-related Organ failure assessment score, *GCS* Glasgow Coma Scale, *SBP* systolic blood pressure, *DBP* diastolic blood pressure, *MAP* mean arterial pressure, *HbA1c* glycated hemoglobin, *ABG* admission blood glucose, *WBC* white blood cells, *RBC* red blood cells, *RDW* red blood cell distribution width

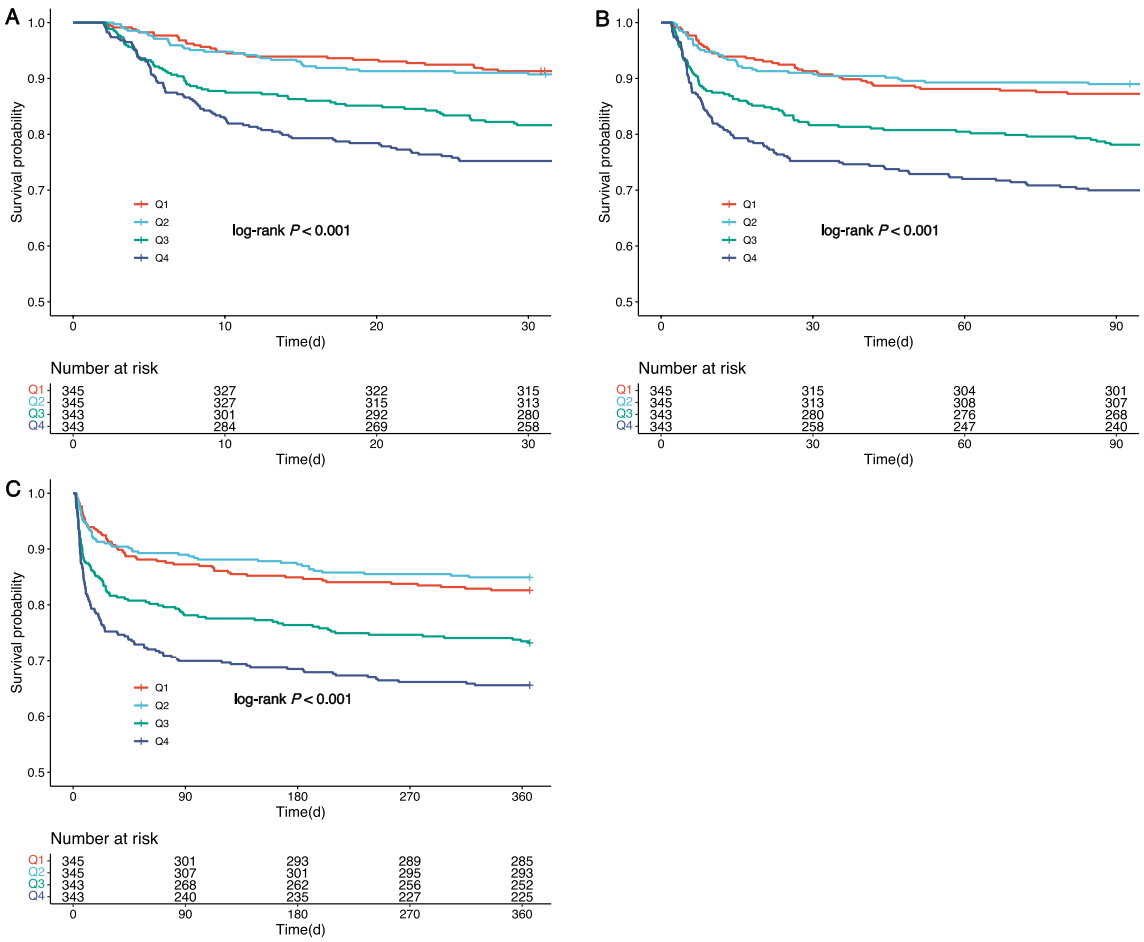

Fig. 1 Kaplan–Meier curves for short-term and long-term mortality according to quartiles (Q1-4) of SHR. **A** 30-day mortality; **B** 90-day mortality; **C** 1-year mortality

Table 2 Association of SHR and the risk of short-term or long-term mortality

SHR	Model1		Model2		Model3	
	HR (95% CI)	*p*	HR (95% CI)	*p*	HR (95% CI)	*p*
30-day death						
Q1	1 (ref)		1 (ref)		1 (ref)	
Q2	1.06 (0.65–1.75)	0.812	1.05 (0.64–1.73)	0.852	0.92 (0.55–1.53)	0.746
Q3	2.34 (1.51–3.62)	< 0.001	2.37 (1.53–3.66)	< 0.001	1.80 (1.14–2.85)	0.012
Q4	3.17 (2.09–4.82)	< 0.001	3.08 (2.02–4.71)	< 0.001	2.15 (1.38–3.34)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
90-day death						
Q1	1 (ref)		1 (ref)		1 (ref)	
Q2	0.86 (0.55–1.32)	0.486	0.85 (0.55–1.32)	0.485	0.76 (0.49–1.19)	0.238
Q3	1.92 (1.32–2.79)	< 0.001	1.97 (1.36–2.87)	< 0.001	1.59 (1.08–2.36)	0.019
Q4	2.67 (1.87–3.81)	< 0.001	2.57 (1.79–3.68)	< 0.001	1.94 (1.33–2.82)	< 0.001
p for trend		< 0.001		< 0.001		< 0.001
1-year death						
Q1	1 (ref)		1 (ref)		1 (ref)	
Q2	0.84 (0.58–1.22)	0.371	0.85 (0.59–1.24)	0.405	0.77 (0.53–1.13)	0.182
Q3	1.77 (1.27–2.45)	< 0.001	1.84 (1.33–2.56)	< 0.001	1.56 (1.11–2.20)	0.011
Q4	2.32 (1.70–3.17)	< 0.001	2.19 (1.59–3.01)	< 0.001	1.75 (1.26–2.44)	< 0.001
P for trend		< 0.001		< 0.001		< 0.001

Model 1: adjusted for age, gender and race. Model 2: adjusted for age, gender, race, diabetes, CKD, arterial fibrillation, myocardial infarction, congestive heart failure and hypertension. Model 3: adjust for age, gender, race, diabetes, CKD, arterial fibrillation, myocardial infarction, congestive heart failure, hypertension, SAPS-II, SOFA, GCS, antiplatelet and anticoagulant drug use, thrombolytic therapy, HbA1c, WBC, RDW, hemoglobin, creatinine, sodium and potassium

Two-tailed values of $p < 0.05$ was considered statistically significant. All analyses were performed with R statistical software version 4.2.2 (The R Foundation).

Results

Baseline characteristics

Of the 1376 patients who fulfilled the inclusion criteria, the median age was 72.9 years, of whom 47.5% were male and 63.4% were white; 210 (15.3%), 260 (18.9%), and 322 (23.4%) patients died within 30 days, 90 days, and 1 year after ICU admission, respectively. The characteristics of participants according to quartiles of SHR are shown in Table 1. The group with higher SHR had a higher proportion of patients with a history of diabetes, myocardial infarction and cancer, a higher SAPS-II, SOFA score, proportion of comatose patients, HbA1c, and glucose compared to the lower group. As the SHR increased, there was a gradual increase in the short-term and long-term mortality of the patients.

SHR and the risk of short-term or long-term mortality

The association of SHR with short-term or long-term mortality is shown in Table 2. The risk of death adjusted for different models increased significantly with increasing quartiles of SHR. Model 3 showed that after adjusting for potential confounders, patients in the third and fourth quartiles had a significantly increased risk of death at 30 days, 90 days, and 1 year compared to the first quartile of SHR (Q3 vs. Q1: HR 1.56–1.80, all $p < 0.02$; Q4 vs. Q1: HR 1.75–2.15, all $p < 0.001$; all p for trend < 0.001). Kaplan–Meier survival curves revealed that patients had a significantly higher risk of death in both the short and long terms with increasing quartiles of SHR (Fig. 1).

The predictive value of SHR, glucose, and HbA1c for mortality

The ROC analyses showed that SHR (AUC: 30-day 0.643, 90-day 0.631, 1-year 0.612) was a better predictor of mortality risk than glucose (AUC: 30-day 0.624, 90-day 0.614, 1-year 0.602) and HbA1c (AUC: 30-day 0.514, 90-day

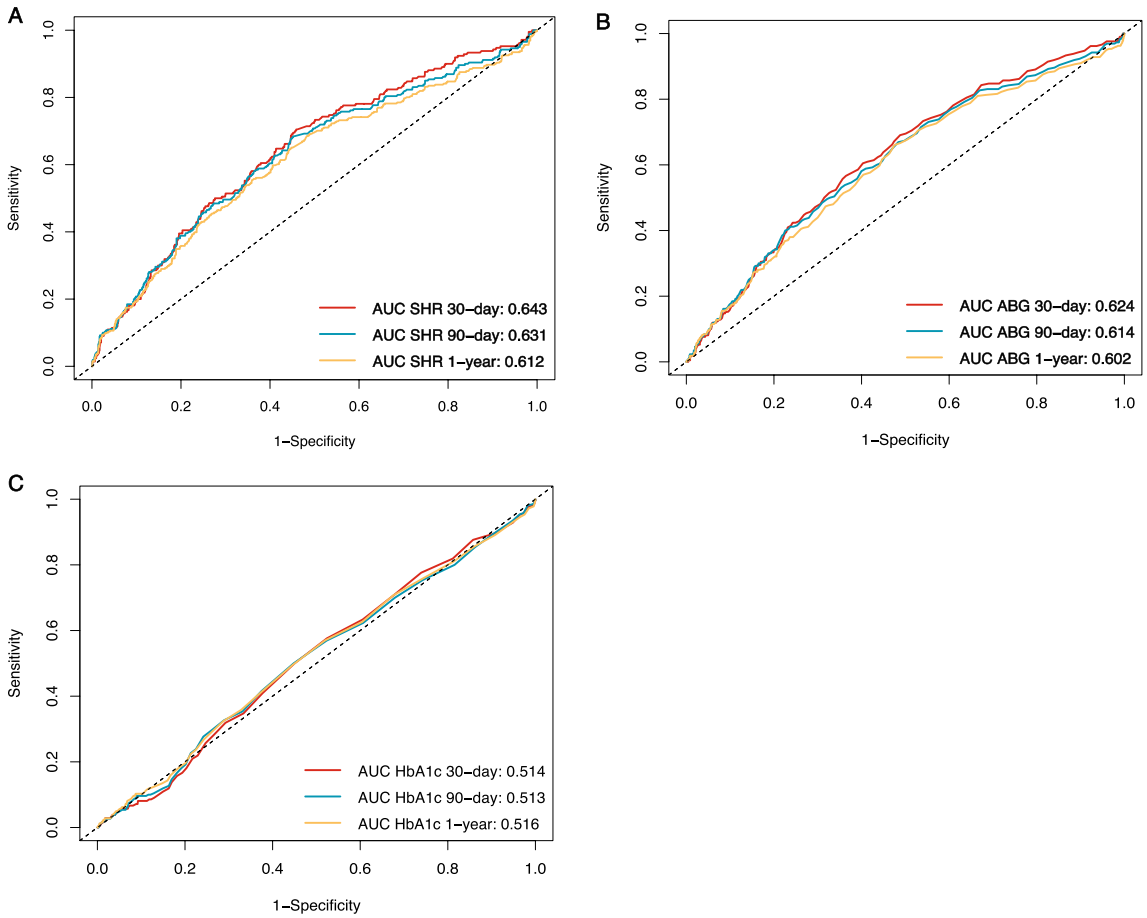

Fig. 2 Receiver operating curves (ROC) of short-term and long-term mortality on multiple glucose indicators. **A** ROC for SHR; **B** ROC for ABG; **C** ROC for HbA1c

0.513, 1-year 0.516) for both short-term and long-term mortality (Fig. 2).

Associations of SHR with outcomes in patients with and without diabetes

Regardless of the patient's diabetes status, the highest quartile of the SHR was consistently and significantly associated with an increased risk of death in both the short and long term compared to the lowest quartile. The Associations of SHR with outcomes in patients with and without diabetes are shown in Table 3. In patients with diabetes, the highest quartile of SHR was significantly associated with an increased risk of short-term and long-term mortality compared with the lowest quartile (HR: 30-day 2.57, 90-day 2.33, 1-year 1.82; all $p < 0.05$; all p for trend ≤ 0.005), and a similar relationship was found in those without diabetes (HR: 30-day 2.04, 90-day 1.94, 1-year 1.87; all $p < 0.02$; all p for trend ≤ 0.001).

Discussion

This 12-year retrospective observational study demonstrated that elevated SHR is an independent predictor of higher mortality in patients with critical IS, and this result remains for both short-term and long-term mortality risk. Although SHR was a mediocre predictor of short-term and long-term mortality risk, it was consistently slightly better than blood glucose and better than Hba1c. In addition, the highest quartile of SHR was remarkably associated with short-term or long-term mortality compared with the first quartile, regardless of diabetes status. This suggests that SHR may be useful in identifying more patients in need of more aggressive treatment and patients at high risk of death during follow-up.

Previous studies have shown that stress hyperglycemia is associated with poor outcomes in patients with IS [17, 18]. However, due to the presence of high background glucose in diabetic patients, the association between glucose and adverse outcomes was often contradictory among patients with different diabetes states [13, 19]. Therefore, Roberts et al. [15] proposed a stress hyperglycemia ratio that takes

Table 3 Associations of SHR with outcomes in patients with and without diabetes

Participants	Outcomes	SHR	Events/patients (%)	HR[a] (95% CI)	*p*-value	*p* for trend
With diabetes	30-day death	Q1	9/91 (9.9)	1 (ref)		0.005
		Q2	13/117 (11.1)	0.67 (0.19–2.36)	0.535	
		Q3	10/53 (18.9)	2.60 (1.06–6.41)	0.037	
		Q4	39/176 (22.2)	2.57 (1.15–5.76)	0.022	
	90-day death	Q1	14/91 (15.4)	1 (ref)		0.001
		Q2	16/117 (13.7)	0.67 (0.24–1.89)	0.450	
		Q3	10/53 (18.9)	2.00 (0.91–4.40)	0.084	
		Q4	49/176 (27.8)	2.33 (1.19–4.58)	0.014	
	1-year death	Q1	20/91 (22.0)	1 (ref)		0.004
		Q2	19/117 (16.2)	0.63 (0.27–1.49)	0.292	
		Q3	13/53 (24.5)	1.61 (0.81–3.20)	0.174	
		Q4	57/176 (32.4)	1.82 (1.02–3.25)	0.043	
Without diabetes	30-day death	Q1	21/254 (8.3)	1 (ref)		0.001
		Q2	46/377 (12.2)	0.92 (0.51–1.67)	0.794	
		Q3	26/141 (18.4)	1.63 (0.93–2.85)	0.086	
		Q4	46/167 (27.5)	2.04 (1.16–3.59)	0.013	
	90-day death	Q1	30/254 (11.8)	1 (ref)		< 0.001
		Q2	54/377 (14.3)	0.79 (0.47–1.32)	0.372	
		Q3	33/141 (23.4)	1.57 (0.97–2.53)	0.065	
		Q4	54/167 (32.3)	1.94 (1.19–3.16)	0.008	
	1-year death	Q1	40/254 (15.7)	1 (ref)		< 0.001
		Q2	70/377 (18.6)	0.82 (0.53–1.29)	0.393	
		Q3	42/141 (29.8)	1.66 (1.09–2.52)	0.018	
		Q4	61/167 (36.5)	1.87 (1.21–2.89)	0.005	

p for interaction: all > 0.5

[a]Adjust for age, gender, race, diabetes, CKD, arterial fibrillation, myocardial infarction, congestive heart failure, hypertension, SAPS-II, SOFA, GCS, antiplatelet and anticoagulant drug use, thrombolytic therapy, HbA1c, WBC, RDW, hemoglobin, creatinine, sodium and potassium

into account background blood glucose levels to quantify this acute stress condition. Li and Yuan et al. [20, 21] showed that SHR was an independent risk factor for hemorrhagic transformation and neurologic deficit in IS patients and regardless of diabetes status. This is similar to our findings. In addition, in our study, the relationship between SHR and mortality at different times in critically ill IS patients was also simultaneously explored, and diabetes status was stratified to provide additional clinical support for this view.

Several plausible explanations exist for the association of stress hyperglycemia with poor prognosis in patients with IS. First, activation of the hypothalamic–pituitary–adrenal axis, the sympathetic adrenomedullary system, the glucose regulatory center, and humoral factors under stress together induce stress hyperglycemia, which accordingly represents a more severe neuroendocrine response [22, 23]. Second, acute glucose elevation and glucose fluctuations induce greater endothelial dysfunction, more endothelial apoptosis, and an oxidative stress response cascade worsening the progression of the disease [24, 25]. Moreover, stress hyperglycemia may directly damage ischemic brain tissues and accelerate the transformation of the ischemic penumbra into infarct regions by increasing lactate accumulation and intracellular acidosis through anaerobic glucose metabolism [26, 27]. In addition, hyperglycemia may provoke chronic cardiac metabolic changes, which may enlarge the sympathetic tone dysfunction and cardiac denervation, leading to cardiovascular damage [28]; interfere with vascular remodeling and apoptosis via multiple pathways, promoting atherosclerosis and leading to plaque instability and rupture [29]; and induce oxidative stress and increase intestinal barrier permeability to promote thrombosis. These may lead to increased all-cause mortality in patients [30–32].

In the context of IS, stress hyperglycemia has been measured in a variety of ways, including admission random glucose, admission fasting glucose, glucose gap, stress hyperglycemia index, and glucose variability [33]. Nevertheless, without knowing the state of diabetes and its glycemic control, which is the best glycemic indicator and its threshold remains undetermined. Although several recent studies have shown that the stress hyperglycemia ratio provides better prognostic insights than other metrics [34, 35], more

prospective studies are still needed to assess and compare the clinical feasibility of various glycemic metrics or to try to apply them in combination.

Currently, there is no evidence to support the positive impact of early glycemic control in stroke patients. This may be due to the fact that appropriately elevated glucose under stress provides sufficient substrate for energy metabolism, maximizing the guarantee of cellular metabolism [36, 37]. It also promoted the generation of cell survival proteins, such as heat shock protein 27 and phosphorylated endothelial nitric oxide synthase, which somewhat reduced the infarct area [38]. Current prospective studies of acute stroke patients receiving islets to control stress hyperglycemia were designed using admission glucose as the definition and have not yet produced the desired results [39–43]. However, given the differences in the timing and duration of patient treatment, glycemic control criteria, and whether or not to differentiate between stroke type and diabetes status across studies, further research is needed in the future.

Our study has some potential limitations. First, because this was a retrospective observational study, it is difficult to demonstrate a causal relationship between exposure and outcome, and the use of all-cause mortality as an outcome ignores effects due to other causes of death. Second, we had no access to patients' use of insulin and oral antidiabetic medications, there was less information in the database about changes in blood glucose levels in subsequent patients, and some of the laboratory indicators with a large proportion of missing data were excluded by us, which are potential confounders. Thirdly, it was difficult to differentiate between types of IS in this study and further stratification of analyses by type of IS was not possible. Finally, because only deaths of patients within 1 year were recorded in the database, we were not able to know the follow-up over a longer period of time. In the future, well-designed multicenter prospective studies should be conducted to validate our findings.

Conclusion

Our results suggest that stress hyperglycemia, defined by the Glucose/HbA1c ratio, is associated with higher short-term and long-term mortality in patients with IS, independent of the patient's diabetes status. Thus, the calculation of SHR can contribute to early identification and intervention in treating patients at high risk of death after IS.

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Author contributions HP contributed to conceptualization, methodology, and software. HP and YX done data curation and writing—original draft preparation. HP, YX, and YH helped in visualization and investigation. YH and JZ helped in supervision. JZ and HW done software and validation. HW helped in writing—reviewing and editing.

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Data availability MIMIC-IV database v2.0 is freely-available on PhysioNet (https://doi.org/10.13026/7vcr-e114). The code for data query and extraction is available from the MIMIC Code Repository (https://github.com/MIT-LCP/mimic-code).

Declarations

Conflict of interest The authors declare that they have no competing interests.

Consent for publication Not applicable.

Ethics approval and consent to participate This study was performed by the principals of the Declaration of Helsinki. The use of the MIMIC-IV database was approved by the review committee of the Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. The data is publicly available (in the MIMIC-IV database) hence ethical approval statements and informed consent are not required for the study.

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