CME LIVE OPEN ACCESS

Advances
Brain Research and Neuroscience

Research Article

Stress Hyperglycemia Ratio and Glycemic Variability Predict Mortality in Critical Stroke: A Machine Learning Study

Yixiao Lu[1,2], Chengbao Yang[1*], Fuxin Yi[2], Chunguang Chen[1], Fei Meng[1] and Mingfei Xia[1]

[1]*Department of Neurosurgery, Liaoyang City Central Hospital, Liaoyang, China*

[2]*The First Affiliated Hospital of Jinzhou Medical University, Jinzhou, China*

Corresponding Author: Chengbao Yang, Department of Neurosurgery, Liaoyang City Central Hospital, No. 148, Zhonghua Street, Section 2, Baita District, Liaoyang, Liaoning, 111000, China

Received: 2026 Jan 03 **Accepted:** 2026 Feb 09 **Published:** 2026 Feb 16

Abstract

Background: *The combined prognostic value of the stress hyperglycemia ratio (SHR) and glycemic variability (GV) for mortality risk stratification across different glucose metabolic states in critically ill cerebrovascular patients remains unexplored. This study aims to evaluate its predictive utility by employing machine learning to identify critical risk predictors.*

Methods: *This retrospective cohort study analyzed data from the MIMIC-IV database and included 2,281 adult ICU patients with cerebrovascular disease stratified by glycemic status (NGR, Pre-DM, DM). The outcomes were 28-day and 90-day all-cause mortality. Associations and predictive performance of SHR and GV were evaluated via Cox regression, Kaplan–Meier analysis, and receiver operating characteristic (ROC) curves, with machine learning models (SHAP interpretation) applied for predictor identification.*

Results: *Among 2,281 patients, high levels of both SHR and GV were independently associated with increased 28-day (HR 1.53, 95% CI 1.11–2.11) and 90-day mortality (HR 1.53, 95% CI 1.15–2.03), particularly in nondiabetic subgroups. GV exhibited a nonlinear association with mortality risk. Compared with the SHR-GV model alone, the combined SHR–GV model did not significantly improve 28-day mortality prediction. For 90-day mortality in diabetic patients, the combination had a marginally greater AUC (0.584 vs. 0.557), although this difference was not statistically significant. Machine learning interpretation confirmed the SHR as the dominant predictor.*

Conclusion: *The SHR outperforms GV in predicting short-term mortality in critical cerebrovascular patients. Although combining both metrics does not significantly improve predictive accuracy, it enables practical risk stratification—particularly in people without diabetes—to guide personalized glucose management.*

Keywords: Stress–Hyperglycemia Ratio, Glycemic Variability, Mortality, Critical Care, Cerebrovascular Disorders, Machine Learning

Abbreviation

- APSIII: Acute Physiology Score
- ARV: average real variability
- BIDMC: Beth Israel Deaconess Medical Center
- BUN: blood urea nitrogen
- CAD: coronary artery disease
- CHF: Congestive Heart Failure
- COPD: chronic pulmonary disease
- CVD: cerebrovascular disease
- DBP: Diastolic Blood Pressure
- DM: diabetes mellitus
- GBM: gradient boosting machine
- GCS: Glasgow Coma Scale
- GV: glycemic variability
- Hb: hemoglobin concentration
- HbA1c: glycated hemoglobin
- HPA: Hypothalamic–pituitary–adrenal
- HR: Heart rate
- HTN: hypertension
- KM: Kaplan–Meier
- LightGBM: Light gradient boosting machine
- LR: logistic regression
- MACCEs: major adverse cardiovascular and cerebrovascular events

- MBP: mean blood pressure
- MI: myocardial infarction
- MIMIC-IV: Medical Information Mart for Intensive Care
- MINOCA: Myocardial Infarction and Nonobstructive Coro nary Artery Disease
- NGR, normal glucose regulation
- NHANES: National Health and Nutrition Examination Survey
- OASIS: Oxford Acute Severity of Illness Score
- Plt: Platelet
- Pre_DM: Prediabetes mellitus
- PT: Prothrombin time
- PTT: partial thromboplastin time
- RCS: restricted cubic splines
- RD: Renal Disease
- RF: random forest
- RI: Insulin
- ROC: receiver operating characteristic
- RR: Respiratory rate
- SAPSII: simplified acute physiology score
- SBP: Systolic Blood Pressure
- SHAP: Machine learning interpretation
- SHR: stress–hyperglycemia ratio
- SOFA: Sequential Organ Failure Assessment
- STEMI: ST-elevated myocardial infarction
- TIR: time-in-range
- VIM: variation independent of the mean
- VIF: variance inflation factor
- WBC: White blood cell

1. Introduction

Cerebrovascular disease represents a leading cause of mortality and disability worldwide, ranking as the fourth-largest contributor in the United States[1]. Survivors frequently experience persistent disability or neurological impairment. Those requiring intensive care typically present with more severe consciousness disturbances, greater clinical complexity, and elevated mortality rates [2].

Stress hyperglycemia, a transient condition triggered by inflammation and neurohormonal dysregulation during critical illness, elevates mortality risk in intensive care settings [3–5]. Pathophysiologically, critical illness activates the hypothalamic–pituitary–adrenal axis, promoting cortisol-mediated gluconeogenesis, insulin resistance, and peripheral glucose utilization defects. Exogenous nutritional support further aggravates hyperglycemia, which subsequently dysregulates inflammatory cytokines, coagulation, and immune function, accelerating disease progression [6]. However, owing to chronic glycemic status, admission glucose levels do not accurately reflect stress glucose changes. In recent years, the stress hyperglycemia ratio (SHR), combined with random glucose and glycosylated hemoglobin measurements, has been shown to more accurately capture acute stress hyperglycemia levels [7]. Concurrently, glucose variability (GV), which represents glucose fluctuations, induces endothelial dysfunction and oxidative stress more profoundly than does sustained hyperglycemia, contributing to cerebrovascular injury and cognitive decline [8, 9]. Elevated GV also correlates with increased macrovascular and microvascular risks [10, 11]. Therefore, the joint evaluation of the SHR and GV may be important for blood glucose management and disease prognosis.

Current evidence indicates a mortality disparity between diabetic and nondiabetic patients, with severely affected diabetic individuals showing reduced susceptibility to acute hyperglycemia—potentially due to chronic metabolic adaptations [12]. Nevertheless, the influence of glucose tolerance status on outcomes in critical illness patients requires further clarification.

This study aimed to assess mortality in critically ill cerebrovascular patients via the SHR, GV, and their combination across different glucose tolerance states while machine learning was employed to identify optimal predictors.

2. Methods

This study utilized data from the Medical Information Mart for Intensive Care (MIMIC-IV) database, a publicly available critical care dataset containing deidentified clinical information from over 190,000 patients and 450,000 hospital admissions at Beth Israel Deaconess Medical Center (BIDMC) in Boston, MA, USA, between 2008 and 2019[13]. The use of the MIMIC-IV was approved by the Massachusetts Institute of Technology Ethics Committee (Certification No. 70803575), which waived the requirement for informed consent owing to the retrospective nature of the analysis and the deidentification of all patient data.

Patients were included according to the primary diagnosis of cerebrovascular disease. Patients diagnosed with cerebrovascular disease by searching for ICD-9 and ICD-10 codes are shown in Table A.1. The ICD-9 and ICD-10 codes in the MIMIC-IV database are diagnostic codes perfected by clinicians at the end of a hospital stay. These codes are standardized for billing, administrative, and epidemiological purposes and reflect the final diagnosis of a particular hospital course [14]. The exclusion criteria were as follows: (1) aged less than 18 years; (2) not admitted to the ICU first; (3) had an ICU stay of less than 24 hours; and (4) had less than three blood glucose measurements or lacked HbA1c or laboratory indicators. Multiple hospitalizations were analyzed on the basis of the first ICU admission data. The patient screening process is shown in Figure 1.

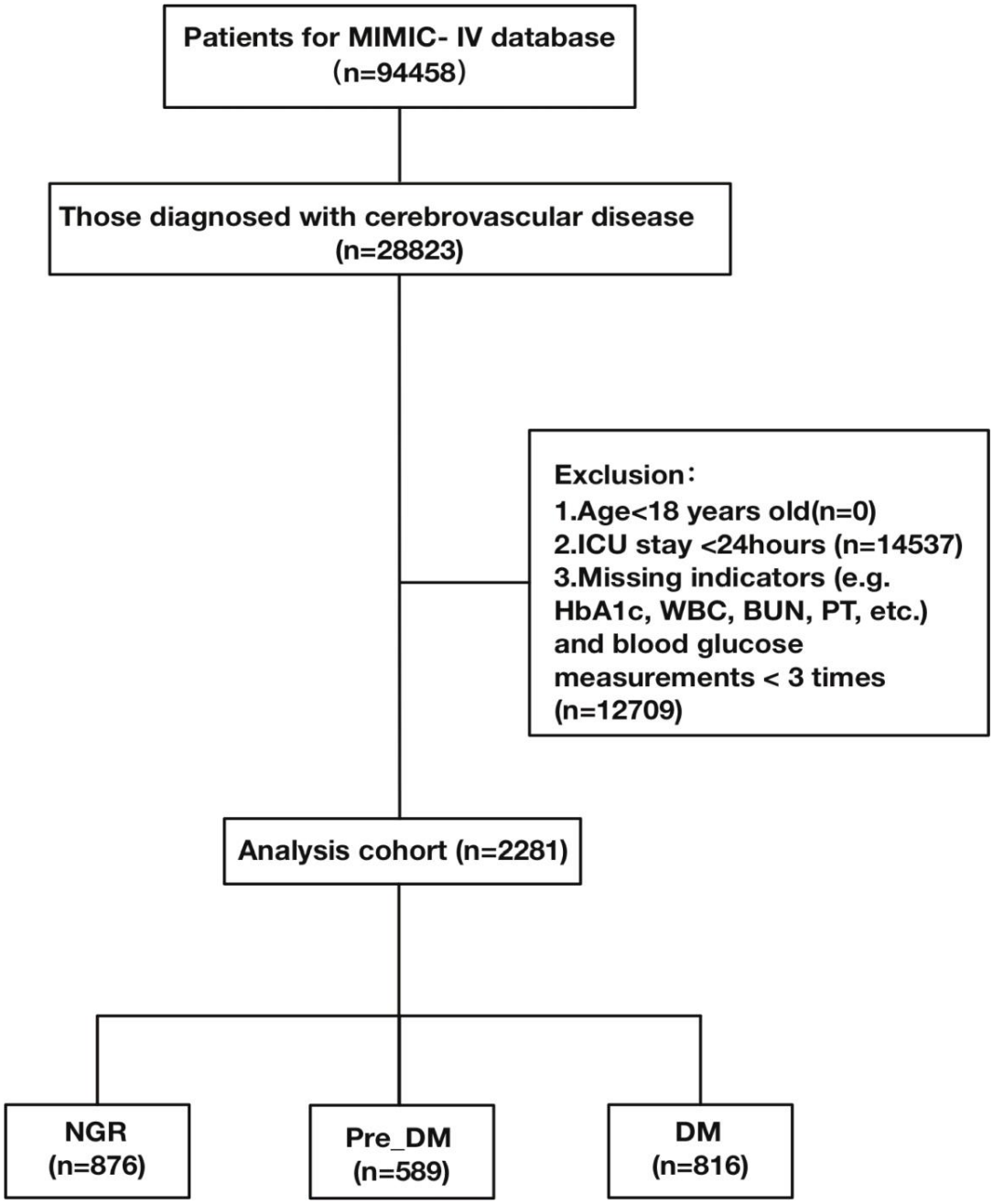

Figure 1: Flowchart of patient selection. A total of 28,823 patients with severe cerebrovascular disease from the MIMIC-IV database were screened. A total of 2281 patients who met the inclusion criteria were analyzed [exclusion conditions: age<18 years (N=0); admission <24 h (n=14537); missing information (n=12709)] and Classified into three groups according to their glycemic status: NGR (n=876), Pre_DM (n=589), and DM (n=816).

2.1. Data extraction

Data were extracted via Navicat Premium (v17.0.8) via structured query language (SQL). The following variables were collected:

- Demographics: age, sex, ICU length of stay, and time of death;
- Vital Signs: heart rate (HR), respiratory rate (RR), systolic and diastolic blood pressure (SBP/DBP), mean blood pressure (MBP), temperature, and oxygen saturation (SpO_2);
- Laboratory parameters: hemoglobin (Hb), platelet count (Plt), white blood cell count (WBC), blood urea nitrogen (BUN), glucose, glycated hemoglobin (HbA1c), prothrombin time (PT), partial thromboplastin time (PTT), and creatinine;
- Severity scores: Acute Physiology Score III (APSIII), Simplified Acute Physiology Score II (SAPSII), Oxford Acute Severity of Illness Score (OASIS), Glasgow Coma Scale (GCS), and Sequential Organ Failure Assessment (SOFA);
- Comorbidities and treatments: hypertension (HTN), diabetes, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), cerebrovascular disease (CVD), myocardial infarction (MI), renal disease (RD), atrial fibrillation (afib), mechanical ventilation, hypoglycemic agents, and insulin therapy.

SHR was calculated via the following equation: [ABG (mg/dL)/(28.7 × HbA1c (%) − 46.7)] [15]. Due to the lack of meal

times in the MIMIC-IV database, blood glucose values were measured at admission as random fasting blood glucose. We chose the coefficient of variation (CV) as the primary measure of GV because of its broad clinical applicability, simplicity of interpretation, and extensive validation in intensive care settings. The CV was calculated as the ratio of the standard deviation to the arithmetic mean of all consecutive glucose measurements obtained during intensive care unit monitoring (CV= SD/mean×100%), normalizing the variability between individuals with different baseline glucose levels.

Patients were categorized into three groups on the basis of glucose metabolism criteria: normal glucose regulation (NGR), prediabetes (Pre_DM), and diabetes mellitus (DM). The NGR group was defined by an HbA1c level less than 5.7% and the absence of a history of diabetes. The Pre_DM group was characterized by an HbA1c level equal to or greater than 5.7% but less than 6.5%, with no prior history of diabetes. The DM group included individuals with an HbA1c level exceeding 6.5% or a documented history of diabetes.

Vital signs, clinical scores, and other laboratory parameters were measured within 24 hours of ICU admission, and variables with missing data rates greater than 20% were excluded to minimize potential bias.

2.2. Outcome Measures

The primary outcome measure was all-cause mortality at 28 days, and the secondary outcome measure was all-cause mortality at 90 days.

2.3. Statistical Methods

Continuous variables were assessed for normality via the Kolmogorov–Smirnov and Shapiro–Wilk tests. The data are presented as the means ± SDs or medians [IQRs] and were analyzed with Student's t test/ANOVA or the Mann–Whitney U test, as appropriate. Categorical variables, expressed as counts (percentages), were compared via the χ^2 test or Fisher's exact test.

Patients were stratified into tertiles on the basis of the SHR (<0.90, 0.90–1.15, >1.15) and GV (<14.92, 14.92–24.46, >24.46). Kaplan–Meier survival curves with log-rank tests were used to evaluate group differences in all-cause mortality. Three Cox regression models were constructed: unadjusted (Model 1), partially adjusted (Model 2: age, sex, HR, RR, SBP), and fully adjusted (Model 3: demographics, comorbidities, laboratory values, and severity scores). The variance inflation factor (VIF < 5) confirmed the absence of multicollinearity.

Restricted cubic splines were used to analyze dose–response relationships, whereas Schoenfeld residuals were used to test proportional hazards assumptions. ROC curves were used to compare the predictive performance of the indicators. Subgroup analyses were visualized via forest plots. Sensitivity analyses included excluding patients with hypoglycemia and those with extreme SHR/GV values to validate robustness.

On the basis of the predictions of the machine learning model, Boruta ranked the importance of features in patients who died within 28 days and randomly divided the dataset into a training subset (80%) and a test subset (20%). Five models [LR (logistic regression), GBM (gradient boosting machine), RF (random forest), XGBoost (extreme gradient boosting), and LightGBM (light gradient boosting machine)] were used to develop importance features, and the model with the best prediction performance was screened out. Finally, Shapley additive explanations (SHAPs) were used for prediction to determine key predictors. All the analytical methods were run with IBM SPSS Statistics 29.0 and R version 4.4.1, and a two-sided p value less than 0.05 indicated statistical significance.

3. Results

A total of 2281 patients, including 1100 (48.2%) females, were analyzed, with a median age of 70 years. By the 28-day and 90-day follow-ups, 1880 (82.42%) and 1758 (77.07%) patients survived, respectively. Compared with survivors, nonsurvivors were older and had a greater prevalence of most comorbidities—except for hypertension and COPD, which were less common or comparable. Nonsurvivors also received fewer hypoglycemic agents but required more mechanical ventilation and insulin. The laboratory results revealed elevated WBC, BUN, creatinine, glucose, PT, SHR, and GV in nonsurvivors, alongside lower hemoglobin and higher clinical severity scores. The patients' baseline characteristics are summarized in Table 1. The univariate Cox regression results and variance inflation factors are provided in Tables A.2 and A.3, respectively, indicating no multicollinearity.

Variable	Total (n=2281)	Survivors (n=1880)	Non-survivors (n=401)	P
Demographics				
Age, years	70(59,80)	68(58,79)	77(66,84)	<0.001
Female, n (%)	1100(48.20)	889(47.30)	211(48.20)	0.052
Comorbidities, n (%)				
MI	363(15.90)	286(15.20)	77(19.20)	0.047
CHF	543(23.80)	416(22.10)	127(31.70)	<0.001
CVD	2170(95.1)	1779(94.6)	391(97.5)	0.015

COPD	326(14.30)	276(14.70)	50(12.50)	0.251
RD	399(17.50)	303(16.10)	96(23.90)	<0.001
HTN	1279(56.10)	1074(57.10)	205(51.10)	0.028
Afib	613(26.90)	478(25.40)	135(33.70)	<0.001
Diabetes	773(33.90)	619(32.90)	154(38.40)	0.035
Glucose metabolism state, n (%)				
NGR	876(38.40)	735(39.10)	141(35.20)	0.141
Pre_DM	589(25.80)	496(26.40)	93(23.20)	0.185
DM	816(35.80)	649(34.50)	167(41.60)	0.007
Treatment, n (%)				
Antihyperglycemic drug	103(4.50)	100(5.30)	3(0.70)	<0.001
Mechanical ventilation	735(32.20)	493(26.20)	242(60.30)	<0.001
RI	1860(81.50)	1513(80.50)	347(86.50)	0.005
Vital signs				
HR, bpm	78.16(69.19,88.95)	77.43(68.75,87.96)	83.08(72.00,93.65)	<0.001
RR, bpm	18.48(16.82,20.63)	18.26(16.68,20.28)	19.54(17.57,22.04)	<0.001
SpO2, %	96.92(95.67,98.27)	96.79(95.56,98.06)	97.71(96.37,99.09)	<0.001
Temperature, °C	36.90(36.73,37.14)	36.89(36.72,37.10)	36.98(36.76,37.31)	<0.001
SBP, mmHg	132.29(121.62,143.64)	132.75(121.92,144.00)	130.26(119.08,142.25)	0.010
DBP, mmHg	70.46(62.37,79.49)	71.42(63.40,80.52)	65.48(57.83,73.70)	<0.001
MBP, mmHg	87.94(79.97,96.17)	88.56(80.89,96.62)	83.85(76.48,92.50)	<0.001
Laboratory measurements				
Hb, g/dL	12.90(11.30,14.20)	13.10(11.60,14.30)	12.10(10.40,13.50)	<0.001
Plt, $\times 10^9$/L	225.00(179.00,281.00)	225.00(181.00,280.00)	224.00(169.00,285.00)	0.190
WBC, K/μL	10.80(8.40,14.00)	10.50(8.20,13.40)	12.90(9.80,16.09)	<0.001
BUN, mg/dL	18.00(14.00,26.00)	18.00(13.00,24.00)	23.00(16.00,33.00)	<0.001
Creatinine, mg/dL	1.00(0.80,1.30)	1.0(0.8,1.2)	1.1(0.9,1.5)	<0.001
Glucose, mg/dL PT, s	12.80(11.90,14.30)	12.65(11.80,14.00)	13.60(12.30,15.80)	<0.001
PTT, s	29.60(26.90,34.50)	29.60(26.90,34.40)	30.00(27.00,34.60)	0.770
HbA1c, %	5.80(5.40,6.40)	5.80(5.40,6.40)	5.80(5.40,6.60)	0.211
SHR	1.02(0.87,1.22)	1.00(0.86,1.20)	1.13(0.94,1.38)	<0.01
GV, %	16.72(11.08,24.50)	16.23(10.79,23.49)	19.01(12.45,28.81)	<0.01
Clinical scores				
GCS	14(12,15)	14(12,15)	14(10,15)	0.074
APSIII score	35(27,46)	33(26,44)	44(34,58)	<0.001
Oasis score	31(26,36)	30(25,35)	36(31,41)	<0.001
sofa	3(1,4)	2(1,4)	4(2,6)	<0.001
SAPSII score	32(25,39)	30(24,37)	39(33,46)	<0.001

Table 1: Baseline Characteristics According to 28-day Mortality

3.1. Relationship between the SHR and survival rate

KM analysis revealed a dose-dependent decrease in survival with increasing stress–hyperglycemia ratio (SHR) across glucose metabolism strata (Figure 2A–C), although this trend was not significant in patients with diabetes (log-rank P = 0.11). According to the fully adjusted Cox model, the highest SHR tertile (T3) was associated with a 1.53-fold increased risk of 28-day mortality compared with the lowest tertile (T1) (HR = 1.53, 95% CI: 1.16–2.01, P = 0.002), with a significant dose–response trend (P-trend = 0.003). This trend was not

observed for 90-day mortality (HR = 1.24, 95% CI: 0.99–1.56, P = 0.066; P-trend = 0.068). When stratified by glucose metabolism status, the SHR was consistently associated with survival in all subgroups except those with diabetes (HR = 1.07, 95% CI: 0.73–1.58, P = 0.721; P-trend = 0.782) (Table A.4). Restricted cubic spline models revealed a linear SHR–mortality relationship in the NGR (P-nonlinear = 0.107) and DM (P-nonlinear = 0.671) groups but a nonlinear association in the pre-DM group (P-nonlinear = 0.027) (Figure A.2A). Subgroup analysis revealed a strong interaction effect between the SHR and glucose status (P-interaction < 0.001), with the highest risk observed in the NGR subgroup (HR = 5.81, 95% CI: 3.58–9.44, P < 0.001) (Figure A.3A).

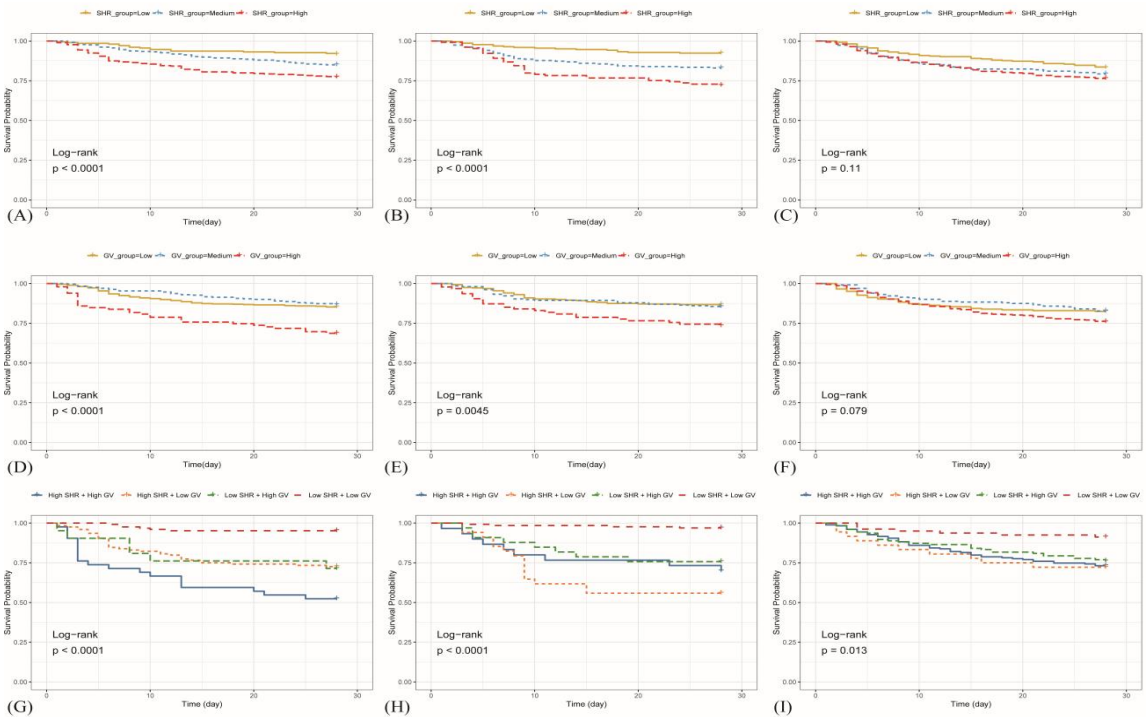

Figure 2: Kaplan–Meier curves of 28-day mortality in SHRs, GVs, and their combination. (A, D, G) patients with NGR; (B, E, H) patients with Pre-DM;(C, F, I) patients with DM

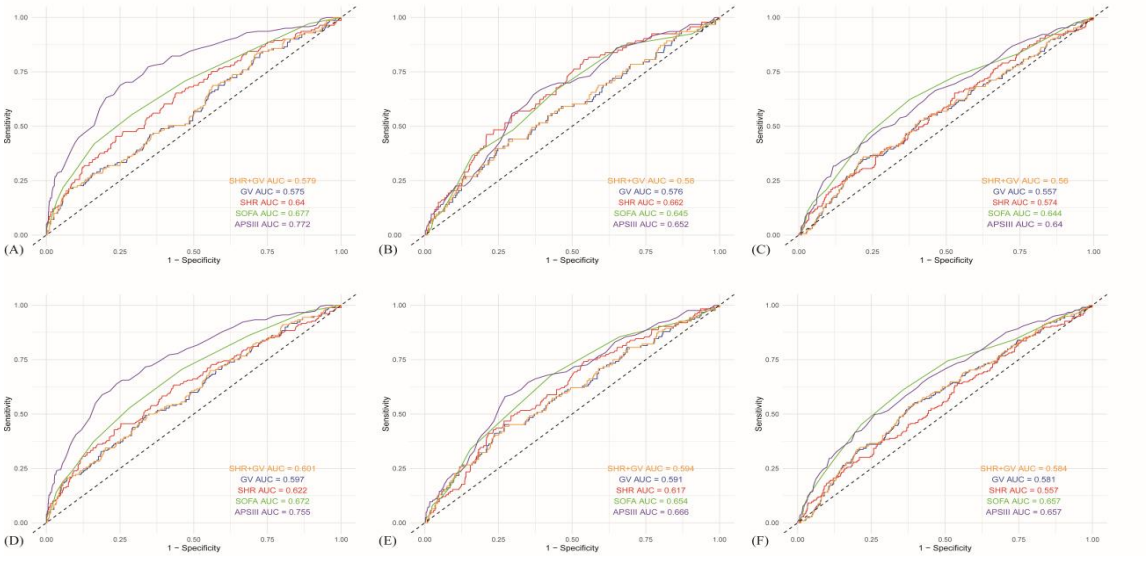

Figure 3: Receiver operating characteristic curves of the SHR and GV as biomarkers for predicting 28-day mortality (A–C) and 90- day mortality (D–F). (A) Prediction of 28-day mortality in NGR patients: SHR+GV vs. SHR, GV, APSIII, and SOFA. (B) Prediction of 28-day mortality in Pre-DM patients: SHR+GV vs. SHR, GV, APSIII, and SOFA. (C) Prediction of 28-day mortality in DM patients: SHR+GV vs. SHR, GV, APSIII, and SOFA. (D) Prediction of 90-day mortality in NGR patients: SHR+GV vs. SHR, GV, APSIII, and SOFA. (E) Prediction of 90-day mortality in Pre-DM patients: SHR+GV vs. SHR, GV, APSIII, and SOFA. (F) Prediction of 90-day mortality in DM patients: SHR+GV vs. SHR, GV, APSIII, and SOFA.

3.2. Relationship between GV and survival rate

KM curves for GV and 28-day survival, stratified by glucose status, are shown in Figure 2D–F. Like in SHRs, GV was not significantly associated with 28-day survival in patients with diabetes (log-rank P = 0.079). In adjusted Cox models, GV was not significantly predictive of 28-day mortality in the overall population or in any glucose subgroup, either as a continuous variable (all HRs included 1) or as tertiles (T3 vs T1, all confidence intervals crossed 1). However, the intermediate GV tertile was associated with a significantly lower mortality risk than the low GV tertile in most subgroups, although not in the pre-DM cohort (HR = 0.77, 95% CI: 0.47–1.26, P = 0.297; Table A.4). Restricted cubic spline analysis revealed a linear GV–survival relationship in the NGR (P-nonlinear = 0.822) and pre-DM (P-nonlinear = 0.245) groups but a nonlinear association in the DM group (P-nonlinear = 0.009; Figure A.2B). Subgroup analysis further revealed significant interaction effects for GV in patients with cerebrovascular disease among those with myocardial infarction (P-interaction = 0.010) or renal disease (P-interaction = 0.043; Figure A.3B).

3.3. Association of combined SHR and GV with mortality

The results of the Kaplan–Meier analysis of the combined SHR and GV data are presented in Figure 2G–I. Elevated SHR (>1.15) was consistently associated with higher 28-day mortality across glucose metabolism strata. In the NGR subgroup, high SHR combined with high GV (>24.46) significantly increased both 28-day (HR=2.69, 95% CI: 1.51–4.80, P=0.001) and 90-day mortality (HR=2.54, 95% CI: 1.49–4.34, P=0.001). Conversely, among Pre-DM patients, high SHR with low GV (<24.46) had the strongest association with 28-day mortality (HR=2.57, 95% CI: 1.53–4.33, P<0.001) and 90-day mortality (HR=1.72, 95% CI: 1.07–2.77, P=0.026). No significant associations were observed in the DM subgroup (Table 2).

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
28-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.81(1.36~2.39)	<0.001	1.66(1.25~2.20)	0.001	1.25(0.92~1.70)	0.146
Group 3	1.74(1.36~2.24)	<0.001	1.58(1.23~2.04)	<0.001	1.28(0.99~1.66)	0.061
Group 4	2.79(2.12~3.66)	<0.001	2.55(1.93~3.38)	<0.001	1.53(1.11~2.11)	0.010
P for trend	1.37(1.26~1.49)	<0.001	1.32(1.21~1.44)	<0.001	1.14(1.03~1.25)	0.008
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.73(0.91~3.30)	0.093	1.54(0.80~2.94)	0.195	1.15(0.58~2.31)	0.685
Group 3	1.73(1.19~2.52)	0.004	1.60(1.10~2.34)	0.015	1.30(0.88~1.93)	0.189
Group 4	5.56(3.36~9.22)	<0.001	4.89(2.87~8.32)	<0.001	2.69(1.51~4.80)	0.001
P for trend	1.52(1.30~1.77)	<0.001	1.45(1.24~1.70)	<0.001	1.25(1.07~1.47)	0.006
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)			
Group 2	2.61(1.47~4.65)	0.001	2.29(1.28~4.11)	0.005	1.79(0.97~3.29)	0.061
Group 3	2.87(1.76~4.68)	<0.001	2.64(1.59~4.37)	<0.001	2.57(1.53~4.33)	<0.001
Group 4	3.23(1.57~6.63)	0.001	2.81(1.35~5.85)	0.006	2.36(1.06~5.27)	0.036
P for trend	1.57(1.31~1.88)	<0.001	1.50(1.24~1.81)	<0.001	1.45(1.18~1.78)	<0.001
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.28(0.85~1.92)	0.238	1.25(0.83~1.89)	0.278	0.93(0.60~1.44)	0.735
Group 3	1.15(0.71~1.86)	0.562	1.04(0.64~1.68)	0.873	0.77(0.47~1.29)	0.323
Group 4	1.72(1.16~2.55)	0.007	1.68(1.13~2.51)	0.011	1.03(0.65~1.61)	0.913
P for trend	1.18 (1.03~1.34)	0.002	1.16(1.02~1.32)	0.028	0.99(0.86~1.15)	0.938
90-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.94(1.53~2.46)	<0.001	1.77(1.39~2.25)	<0.001	1.36(1.05~1.77)	0.019
Group 3	1.56(1.25~1.96)	<0.001	1.41(1.12~1.76)	0.003	1.16(0.92~1.47)	0.196
Group 4	2.67(2.09~3.40)	<0.001	2.39(1.87~3.06)	<0.001	1.53(1.15~2.03)	0.004
P for trend	1.33(1.24~1.44)	<0.001	1.28(1.18~1.38)	<0.001	1.11(1.02~1.21)	0.014

Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.97(1.15~3.37)	0.013	1.77(1.03~3.04)	0.040	1.32(0.74~2.37)	0.345
Group 3	1.69(1.21~2.35)	0.002	1.55(1.11~2.16)	0.011	1.32(0.94~1.87)	0.113
Group 4	4.90(3.05~7.86)	<0.001	4.33(2.64~7.10)	<0.001	2.54(1.49~4.34)	0.001
P for trend	1.46(1.28~1.68)	<0.001	1.39(1.21~1.60)	<0.001	1.24(1.07~1.43)	0.004
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	2.37(1.44~3.88)	0.001	1.93(1.17~3.19)	0.010	1.59(0.94~2.69)	0.081
Group 3	2.12(1.36~3.30)	0.001	1.74(1.10~2.77)	0.019	1.72(1.07~2.77)	0.026
Group 4	2.99(1.61~5.54)	0.001	2.28(1.21~4.29)	0.011	1.80(0.91~3.54)	0.091
P for trend	1.45 (1.24~1.71)	<0.001	1.32 (1.11~1.57)	0.001	1.26 (1.05~1.51)	0.012
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.47(1.04~2.09)	0.029	1.46(1.03~2.07)	0.034	1.07(0.73~1.55)	0.738
Group 3	1.08(0.70~1.67)	0.720	0.99(0.64~1.53)	0.958	0.75(0.47~1.18)	0.213
Group 4	1.79(1.26~2.54)	0.001	1.76(1.23~2.50)	0.002	1.08(0.73~1.60)	0.706
P for trend	1.17(1.05~1.31)	0.005	1.16(1.03~1.29)	0.013	0.99(0.87~1.13)	0.902

Table 2: The Associations of the Combinations of SHR and GV with All-Cause Mortality

Proportional hazards assumptions were maintained in the Pre-DM (P=0.525) and DM (P=0.586) subgroups but violated in the NGR subgroup. The Schoenfeld residuals indicated stabilization of the beta coefficients around day 5 (Table A.5, Figure A.1). Landmark analysis confirmed superior survival in NGR patients with low SHR and low GV throughout follow-up (Figure A.4).

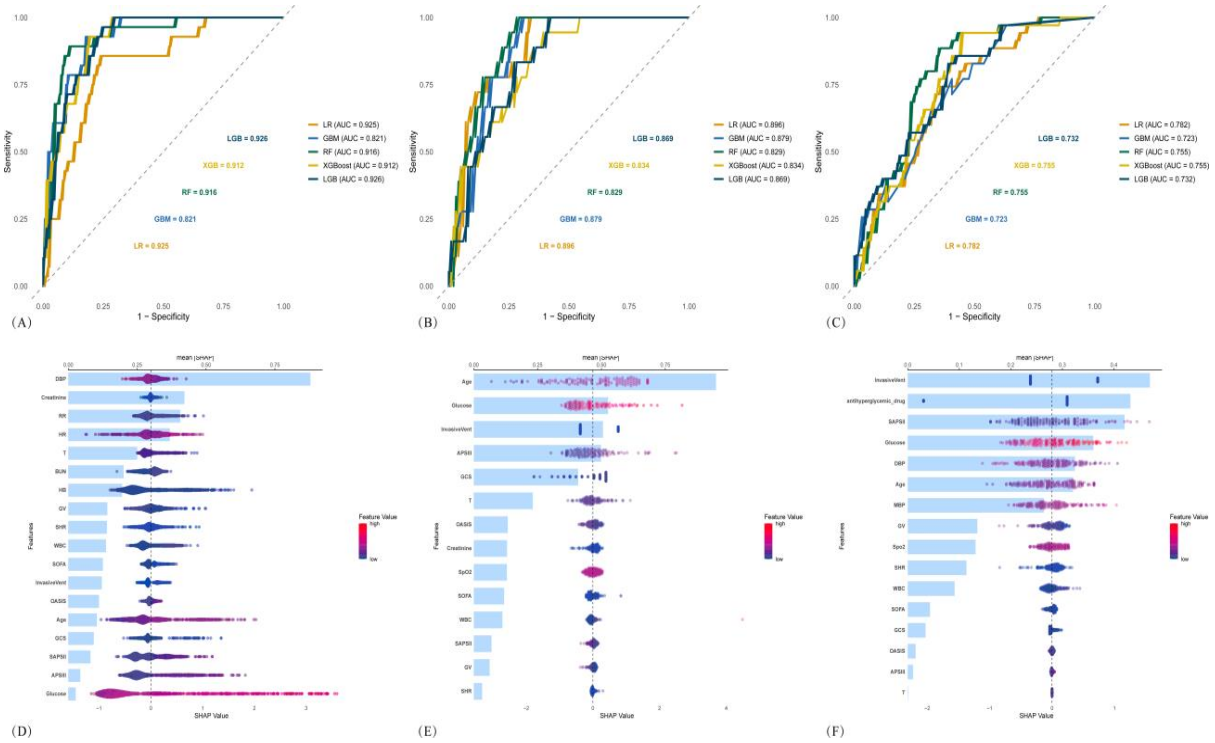

Figure 4: Receiver operating characteristic curves and SHAP interpretations of the ML-based 28-day mortality prediction models. (A, D) Patients with NGR; (B, E) patients with Pre-DM; (C, F) patients with DM. LR, logistic regression; GBM, gradient boosting machine; RF, random forest; XGBoost, extreme gradient boosting; LightGBM, light gradient boosting machine.

3.4. ROC curve analysis

ROC analysis was used to assess the predictive performance of the SHR, GV, and their combination for mortality in patients with cerebrovascular diseases (Table A.8, Figure 3). For 28-day mortality in the NGR and Pre-DM groups, the combined model had a significantly greater AUC than GV alone (0.579 vs. 0.575, $P < 0.001$) but was not superior to the SHR alone (0.579 vs. 0.640, $P = 0.094$). In the DM group, all models showed reduced discriminative ability, with the combined model achieving an AUC of 0.560, similar to that of SHR (0.574) and GV (0.557) alone.

For 90-day mortality, the combined model again outperformed GV in the NGR and Pre-DM subgroups but not in the SHR subgroup. Notably, in the DM group, the combined model exhibited a greater AUC than both the SHR (0.584 vs. 0.557, $P = 0.372$) and GV (0.584 vs. 0.581, $P = 0.002$) models did, although the improvement over the SHR model was not statistically significant. Significant differences between the models for 28-day mortality were observed only in the NGR and Pre-DM groups. Figure 3 additionally compares the investigational metrics with the SOFA and APSIII scores for the prediction of 28- and 90-day mortality.

3.5. Sensitivity analysis

Sensitivity analyses confirmed the robustness of our primary findings. After excluding 82 patients with ICU-acquired hypoglycemia, the Cox regression results remained consistent with those of the main analysis (Table A.9). Similarly, the exclusion of 195 subjects with extreme SHR or GV values did not alter the associations between these metrics and cerebrovascular outcomes (Table A.10).

3.6. Machine learning

Feature selection via the Boruta algorithm identified 18, 14, and 16 mortality predictors in the NGR, Pre-DM, and DM groups, respectively, with predictor importance decreasing from right to left (Figure A.5B–D; overall population results in Figure A.5A).

The predictive performance of the models varied across subgroups (Table A.11). LightGBM achieved the highest AUC (0.926) in the NGR cohort (Figure 4A), whereas logistic regression performed best in both the Pre-DM (AUC = 0.893) and DM (AUC = 0.782) groups (Figure 4B, C). The overall population results are provided in Table A.11 and Figure A.6.

SHAP analysis (Figure 4D–F) revealed that SHR and GV contributed the least to predictions in the Pre-DM subgroup (Figure 4E). Although GV had marginally greater overall importance than SHR across subgroups, SHAP plots revealed that both variables were concentrated in the SHAP > 0 region, with SHR showing denser clustering, indicating a stronger positive association with mortality risk. The full population SHAP results are shown in Figure A.7.

4. Discussion

In this cohort study of cerebrovascular disease patients, the SHR demonstrated a stronger and more consistent association with short-term mortality than did the GV. Cox regression identified the SHR as a significant predictor in the nondiabetic groups (NGR and Pre-DM), whereas GV exhibited a nonlinear relationship with mortality, with moderate levels conferring a protective effect. The highest 28-day mortality risk was observed in NGR patients with high SHR and high GV and in Pre-DM patients with high SHR and low GV. Although the combined SHR–GV model did not outperform the SHR alone in ROC analysis, it provided incremental predictive value for 90-day mortality in diabetic patients. SHAP analysis from machine learning models confirmed that SHR contributed more substantially than GV did to prediction stability and overall performance. The superior predictive utility of the SHR may stem from its reflection of illness severity, as an elevated SHR is correlated with higher clinical scores and more intensive treatments. In contrast, GV—which solely captures glucose fluctuations—showed a complex nonlinear relationship with outcomes and did not enhance the stability of the combined models, likely because of its susceptibility to confounding clinical factors.

Current evidence suggests that the SHR and GV are significant prognostic markers in critical care. The SHR, which integrates acute glucose levels with chronic glycemic status (HbA1c), has been consistently associated with disease severity and mortality in patients with cardiovascular and cerebrovascular conditions [16–19]. Meta-analyses and cohort studies have demonstrated that elevated SHR predicts adverse outcomes in acute myocardial infarction, ST-elevation myocardial infarction, and ischemic stroke, particularly among nondiabetic individuals. Similar results have also been reported for myocardial infarction and nonobstructive coronary artery disease (MINOCA) and three-vessel disease [20-23]. Furthermore, for acute ischemic stroke due to large vessel occlusion, the RESCUE BT test revealed a linear relationship between elevated SHR and poor functional outcomes [24]. Duan et al. reported that elevated SHR was associated with early neurological deterioration after thrombolysis in acute stroke, while NHANES data revealed a J/u relationship between SHR and mortality from all cardiovascular diseases [25,26]. In these studies, we observed a positive association between SHR and cardiovascular adverse events, which is consistent with our findings. Glucose variability was also associated with adverse outcome events.

A retrospective analysis of 4809 critically ill patients with cerebrovascular disease by Cai W. et al. revealed that glucose variability was approximately linearly associated with severe cognitive decline and in-hospital mortality in CVD patients [27]. GV was demonstrated to be an independent risk factor for adverse outcomes in patients with acute stroke in a prospective multicenter study combined with an animal model in a GLIAS-III translational study. He HM. et al. high SHR/GV combination levels in individuals without diabetes with CAD were found to predict poor prognosis, whereas high SHR and low GV combination levels in individuals with diabetes were associated with increased mortality [28]. Wang Feng et al. reached the same conclusion

and verified the predictive accuracy of the combined SHR and GV index model [29]. These findings underscore the clinical importance of comprehensive SHR-GV assessment in cerebrovascular disease. Further research should explore their combined utility in guiding personalized glucose management strategies for critically ill patients.

Stress-induced hyperglycemia is caused mainly by excessive activation of sympathetic nerves and the release of large amounts of glucocorticoids such as cortisol which also drives inflammatory cytokine regulation and the amplification of oxidative stress [30-31]. On the other hand, stress hyperglycemia may exacerbate acute heart disease in a variety of ways, including exacerbating microvascular obstruction accelerating endothelial cell damage and impairing platelet nitric oxide responsiveness (nitric oxide deficiency causes sustained vasoconstriction, accelerates vascular sclerosis, and increases the risk of thrombosis and vascular inflammation [32-36]. In addition, other vascular injury mechanisms mediated by hyperglycemia are promoted. Stress hyperglycemia may also disrupt the blood–brain barrier through intracellular acidosis, leading to mitochondrial dysfunction, energy depletion, and apoptosis, further driving adverse outcomes after stroke [37]. Glycemic variability reflects changes in blood glucose fluctuations, which can lead to endothelial dysfunction and oxidative stress further exacerbating plaque vulnerability [33] and promoting cardiovascular and cerebrovascular diseases [38,39].

Studies indicate that glycated hemoglobin (A1C) can be converted to estimated average glucose (eAG), reflecting mean glycemic levels over 8–12 weeks [40, 41]. Unlike absolute hyperglycemia, relative hyperglycemia—assessing acute glucose changes—remains independent of baseline glucose levels in critical illness patients [42]. The stress hyperglycemia ratio (SHR) integrates acute glucose levels with A1C to differentiate stress-induced hyperglycemia from chronic dysglycemia, thereby improving the assessment of acute glycemic impact on clinical outcomes. Furthermore, glycemic variability (GV) captures short-term glucose fluctuations, complementing the temporal limitations of SHRs.

The combined assessment of SHR and GV provides a rational approach for evaluating stress-mediated hyperglycemia and acute glucose fluctuations in critically ill patients. This study confirmed the prognostic value of SHR-GV integration for 28-day mortality in the NGR and Pre-DM subgroups but not in diabetic patients. Previous evidence indicates greater susceptibility to acute glucose variations in nondiabetic individuals than in diabetic individuals potentially due to long-term adaptive responses to oxidative stress and increased glycemic tolerance thresholds in diabetic patients [29,43-45]. Additionally, ongoing hypoglycemic therapies in diabetic patients may attenuate acute glycemic effects [46]. Thus, diabetes-specific factors likely confound the interpretation of the SHR and GV metrics.

Notably, high GV levels were not significantly associated with poor prognosis in cerebrovascular disease patients. This may stem from methodological limitations, as the quantitative CV index might interfere with GV expression, compounded by the MIMIC-IV database's lack of meal timing data. Furthermore, Cox regression revealed a nonlinear relationship, with moderate GV levels serving as a protective factor, which is consistent with reported threshold effects in critical illness patients [47, 48]. These findings suggest that maintaining GV within an optimal range may prove more beneficial than indiscriminate minimization. Future studies should incorporate advanced GV metrics (e.g., TIR, VIM, ARV) to validate these observations.

The combined assessment of the SHR and GV provides complementary risk stratification for acute cerebrovascular disease. The SHR captures acute-on-chronic glycemic stress, whereas the GV reflects acute glucose instability—which is particularly relevant in nondiabetic patients (NGR/Pre-DM) who lack adaptive hyperglycemic responses. Although the combined model did not outperform the SHR alone in terms of predictive performance, machine learning interpretation (SHAP) confirmed the stronger overall contribution of the SHR to mortality prediction, whereas GV was more important in specific metabolic subgroups. This suggests that GV may introduce interference rather than synergistic improvement in the combined model. Nevertheless, integrating the SHR and GV—especially in nondiabetic patients—offers a clinically valuable framework for glycemic risk stratification in neurocritical care. Further validation across diverse cerebrovascular cohorts is needed.

This study has several limitations. First, despite adjusting for available confounders, residual confounding may persist due to unmeasured variables such as lifestyle factors. Second, the exclusion of patients with missing HbA1c or insufficient glucose measurements may have introduced selection bias. Third, the predominantly white nature of the study population limits its generalizability to other ethnic groups. Fourth, the analysis did not account for differences in treatment strategies between the ischemic and hemorrhagic stroke subtypes. Finally, the retrospective design precludes causal inference. Further prospective studies are needed to validate these findings across diverse cerebrovascular disease populations.

5. Conclusion

The SHR is a stronger predictor of short-term mortality than GV is in critically ill cerebrovascular patients. While combining SHR and GV does not significantly enhance predictive modeling, it offers practical risk stratification—particularly in the group without diabetes—which may guide personalized glucose management strategies in neurocritical care.

Acknowledgments

This study acknowledges the MIT Computational Physiology Laboratory and Beth Israel Deaconess Medical Centre for providing and maintaining the invaluable public resource

MIMIC-IV. Moreover, the author expresses sincere gratitude for the technical support of Liaoyang Central Hospital, the First Affiliated Hospital of Jinzhou Medical University, and all individuals involved in this study.

Funding

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Ethics Approval and Consent to Participate

This study utilized data from the Medical Information Mart for Intensive Care IV (MIMIC-IV) database, a publicly available, de-identified critical care database. The establishment of the MIMIC-IV database was approved by the Institutional Review Board (IRB) of the Massachusetts Institute of Technology (Cambridge, MA, USA) (Certification No. 70803575). All original data were de-identified to protect patient privacy, and the requirement for individual patient consent was waived by the approving IRB.

References

1. Ahmad, F. B., Cisewski, J. A., & Anderson, R. N. (2024). Leading causes of death in the US, 2019-2023. *JAMA, 332*(12), 957-958.
2. Chang, C. W., Provençal, J. J., & Shah, S. (2021). Neurological critical care: the evolution of cerebrovascular critical care. *Crit Care Med, 49*(6), 881-900.
3. Godinjak, A., Iglica, A., Burekovic, A., Jusufovic, S., Ajanovic, A., Tancica, I., & Kukuljac, A. (2015). Hyperglycemia in critically ill patients: management and prognosis. *Med Arch, 69*(3), 157.
4. Dungan, K. M., Braithwaite, S. S., & Preiser, J. C. (2009). Stress hyperglycaemia. *The Lancet, 373*(9677), 1798-1807.
5. Huang, Y. W., Yin, X. S., & Li, Z. P. (2022). Association of the stress hyperglycemia ratio and clinical outcomes in patients with stroke: a systematic review and meta-analysis. *Front Neurol, 13*, 999536.
6. Dombrowski, N. C., & Karounos, D. G. (2013). Pathophysiology and management strategies for hyperglycemia for patients with acute illness during and following a hospital stay. *Metabolism, 62*(3), 326-336.
7. Yang, Y., Kim, T. H., Yoon, K. H., Chung, W. S., Ahn, Y., Jeong, M. H., ... & Chang, K. (2017). The stress hyperglycemia ratio, an index of relative hyperglycemia, as a predictor of clinical outcomes after percutaneous coronary intervention. *Int J Cardiol, 241*, 57-63.
8. Ceriello, A., Monnier, L., & Owens, D. (2019). Glycaemic variability in diabetes: clinical and therapeutic implications. *Lancet Diabetes Endocrinol, 7*(3), 221-230.
9. Ceriello, A., Esposito, K., Piconi, L., Ihnat, M. A., Thorpe, J. E., Testa, R., ... & Giugliano, D. (2008). Oscillating glucose is more deleterious to endothelial function and oxidative stress than mean glucose in normal and type 2 diabetic patients. *Diabetes, 57*(5), 1349-1354.
10. Echouffo-Tcheugui, J. B., Zhao, S., Brock, G., Matsouaka, R. A., Kline, D., & Joseph, J. J. (2019). Visit-to-visit glycemic variability and risks of cardiovascular events and all-cause mortality: the ALLHAT study. *Diabetes Care, 42*(3), 486-493.
11. Shuai, W. L., Zhang, H. J., Wang, N., Zhang, H. C., Zeng, Q. T., Wang, R., & Dong, Y. F. (2025). Association of glycemic variability with short and long-term mortality among critically ill patients with heart failure: analysis of the MIMIC-IV database. *Diabetes Res Clin Pract, 221,* 112009.
12. Egi, M., Bellomo, R., Stachowski, E., French, C. J., Hart, G. K., Hegarty, C., & Bailey, M. (2008). Blood glucose concentration and outcome of critical illness: the impact of diabetes. *Crit Care Med, 36*(8), 2249-2255.
13. Johnson, A. E., Bulgarelli, L., Shen, L., Gayles, A., Shammout, A., Horng, S., ... & Mark, R. G. (2023). MIMIC-IV, a freely accessible electronic health record dataset. *Scientific data, 10*(1), 1.
14. Yu, Q., Fu, Q., Ma, X., Wang, H., Xia, Y., Chen, Y., ... & Wu, Y. (2025). Impact of glycemic control metrics on short- and long-term mortality in transcatheter aortic valve replacement patients: a retrospective cohort study from the MIMIC-IV database. *Cardiovascular Diabetology, 24*(1), 135.
15. Cheng, S., Shen, H., Han, Y., Han, S., & Lu, Y. (2024). Association between stress hyperglycemia ratio index and all-cause mortality in critically ill patients with atrial fibrillation: a retrospective study using the MIMIC-IV database. *Cardiovascular Diabetology, 23*(1), 363.
16. ADAG, S., Nathan, D. M., Kuenen, J., Borg, R., Zheng, H., Schoenfeld, D., & Heine, R. J. (2008). Translating the A1C assay into estimated average glucose values (A1c-Derived Average Glucose Study Group). Diabetes Care.
17. Lee, T. F., Drake, S. M., Roberts, G. W., Bersten, A., Stranks, S. N., Heilbronn, L. K., ... & Burt, M. G. (2020). Relative hyperglycemia is an independent determinant of in-hospital mortality in patients with critical illness. *Critical care medicine, 48*(2), e115-e122.
18. Lipton, J. A., Barendse, R. J., Van Domburg, R. T., Schinkel, A. F. L., Boersma, H., Simoons, M. L., & Akkerhuis, K. M. (2013). Hyperglycemia at admission and during hospital stay are independent risk factors for mortality in high risk cardiac patients admitted to an intensive cardiac care unit. *European Heart Journal: Acute Cardiovascular Care, 2*(4), 306-313.
19. Yan, F., Chen, X., Quan, X., Wang, L., Wei, X., & Zhu, J. (2024). Association between the stress hyperglycemia ratio and 28-day all-cause mortality in critically ill patients with sepsis: a retrospective cohort study and predictive model establishment based on machine learning. *Cardiovascular diabetology, 23*(1), 163.
20. Karakasis, P., Stalikas, N., Patoulias, D., Pamporis, K., Karagiannidis, E., Sagris, M., ... & Giannopoulos, G. (2024). Prognostic value of stress hyperglycemia ratio in patients with acute myocardial infarction: a systematic review with Bayesian and frequentist meta-analysis. *Trends Cardiovasc Med, 34*(7), 453-465.
21. Kojima, T., Hikoso, S., Nakatani, D., Suna, S., Dohi, T., Mizuno, H., ... & Osaka Acute Coronary Insufficiency Study (OACIS) Group. (2020). Impact of hyperglycemia on long-term outcome in patients with ST-segment elevation myocardial infarction. *Am J Cardiol, 125*(6), 851-859.
22. Paolisso, P., Foà, A., Bergamaschi, L., Angeli, F., Fabrizio,

M., Donati, F., ... & Pizzi, C. (2021). Impact of admission hyperglycemia on short and long-term prognosis in acute myocardial infarction: MINOCA versus MIOCA. *Cardiovasc Diabetol, 20*(1), 192.

23. Qiao, Z., Bian, X., Song, C., Zhang, R., Yuan, S., Lin, Z., ... & Dou, K. (2024). High stress hyperglycemia ratio predicts adverse clinical outcome in patients with coronary three-vessel disease: a large-scale cohort study. *Cardiovasc Diabetol, 23*(1), 190.
24. Peng, Z., Song, J., Li, L., Guo, C., Yang, J., Kong, W., ... & Yang, Q. (2023). Association between stress hyperglycemia and outcomes in patients with acute ischemic stroke due to large vessel occlusion. *CNS Neurosci Ther, 29*(8), 2162-2170.
25. Duan, Z. W., Li, Z. N., Zhai, Y. J., Liu, T. F., Zhang, C. C., Hu, T., ... & Liu, H. Y. (2025). Effects of glycemic indicators on early neurological outcomes in patients with acute ischemic stroke treated with intravenous thrombolysis. *World J Diabetes, 16*(3), 94491.
26. Cao, B., Guo, Z., Li, D. T., Zhao, L. Y., Wang, Z., Gao, Y. B., & Wang, Y. X. (2025). The association between stress-induced hyperglycemia ratio and cardiovascular events as well as all-cause mortality in patients with chronic kidney disease and diabetic nephropathy. *Cardiovasc Diabetol, 24*(1), 55.
27. Cai, W., Li, Y., Guo, K., Wu, X., Chen, C., & Lin, X. (2023). Association of glycemic variability with death and severe consciousness disturbance among critically ill patients with cerebrovascular disease: analysis of the MIMIC-IV database. *Cardiovasc Diabetol, 22*(1), 315.
28. He, H. M., Zheng, S. W., Xie, Y. Y., Wang, Z., Jiao, S. Q., Yang, F. R., ... & Sun, Y. H. (2024). Simultaneous assessment of stress hyperglycemia ratio and glycemic variability to predict mortality in patients with coronary artery disease: a retrospective cohort study from the MIMIC-IV database. *Cardiovasc Diabetol, 23*(1), 61.
29. Wang, F., Guo, Y., Tang, Y., Zhao, S., Xuan, K., Mao, Z., ... & Zhu, X. (2025). Combined assessment of stress hyperglycemia ratio and glycemic variability to predict all-cause mortality in critically ill patients with atherosclerotic cardiovascular diseases across different glucose metabolic states: an observational cohort study with machine learning. *Cardiovasc Diabetol, 24*(1), 199.
30. Shamoon, H., Hendler, R., & Sherwin, R. S. (1981). Synergistic interactions among antiinsulin hormones in the pathogenesis of stress hyperglycemia in humans. *J Clin Endocrinol Metab, 52*(6), 1235-1241.
31. Esposito, K., Marfella, R., & Giugliano, D. (2003). Stress hyperglycemia, inflammation, and cardiovascular events. *Diabetes care, 26*(5), 1650.
32. Jensen, C. J., Eberle, H. C., Nassenstein, K., Schlosser, T., Farazandeh, M., Naber, C. K., ... & Bruder, O. (2011). Impact of hyperglycemia at admission in patients with acute ST-segment elevation myocardial infarction as assessed by contrast-enhanced MRI. *Clin Res Cardiol, 100*(8), 649-659.
33. Monnier, L., Mas, E., Ginet, C., Michel, F., Villon, L., Cristol, J. P., & Colette, C. (2006). Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA, 295*(14), 1681-1687.
34. Worthley, M. I., Holmes, A. S., Willoughby, S. R., Kucia, A. M., Heresztyn, T., Stewart, S., ... & Horowitz, J. D. (2007). The deleterious effects of hyperglycemia on platelet function in diabetic patients with acute coronary syndromes: mediation by superoxide production, resolution with intensive insulin administration. *J Am Coll Cardiol, 49*(3), 304-310.
35. Violi, F., Pastori, D., Pignatelli, P., & Carnevale, R. (2020). Nutrition, thrombosis, and cardiovascular disease. *Circ Res, 126*(10), 1415-1442.
36. Yan, G., Zhang, X., Liu, Y., Guo, P., Liu, Y., Li, X., ... & Xue, M. (2024). Integrative insights into cerebrometabolic disease: Understanding, management, and future prospects. *Journal of Neurorestoratology, 12*(2), 100107.
37. Martini, S. R., & Kent, T. A. (2007). Hyperglycemia in acute ischemic stroke: a vascular perspective. *J Cereb Blood Flow Metab, 27*(3), 435-451.
38. Chen, X. M., Zhang, Y., Shen, X. P., Huang, Q., Ma, H., Huang, Y. L., ... & Wu, H. J. (2010). Correlation between glucose fluctuations and carotid intima-media thickness in type 2 diabetes. *Diabetes Res Clin Pract, 90*(1), 95-99.
39. Kuroda, M., Shinke, T., Sakaguchi, K., Otake, H., Takaya, T., Hirota, Y., ... & Hirata, K. I. (2015). Effect of daily glucose fluctuation on coronary plaque vulnerability in patients pre-treated with lipid-lowering therapy: a prospective observational study. *JACC Cardiovasc Interv, 8*(6), 800-811.
40. ADAG, S., Nathan, D. M., Kuenen, J., Borg, R., Zheng, H., Schoenfeld, D., & Heine, R. J. (2008). Translating the A1C assay into estimated average glucose values (A1c-Derived Average Glucose Study Group). *Diabetes Care*.
41. Nathan, D. M., Turgeon, H., & Regan, S. (2007). Relationship between glycated haemoglobin levels and mean glucose levels over time. *Diabetologia, 50*(11), 2239-2244.
42. Roberts, G. W., Quinn, S. J., Valentine, N., Alhawassi, T., O'Dea, H., Stranks, S. N., ... & Doogue, M. P. (2015). Relative hyperglycemia, a marker of critical illness: introducing the stress hyperglycemia ratio. *J Clin Endocrinol Metab, 100*(12), 4490-4497.
43. Liu, J., Zhou, Y., Huang, H., Liu, R., Kang, Y., Zhu, T., ... & Gao, F. (2023). Impact of stress hyperglycemia ratio on mortality in patients with critical acute myocardial infarction: insight from American MIMIC-IV and the Chinese CIN-II study. *Cardiovasc Diabetol, 22*(1), 281.
44. Rau, C. S., Wu, S. C., Chen, Y. C., Chien, P. C., Hsieh, H. Y., Kuo, P. J., & Hsieh, C. H. (2017). Higher mortality in trauma patients is associated with stress-induced hyperglycemia, but not diabetic hyperglycemia: a cross-sectional analysis based on a propensity-score matching approach. *Int J Environ Res Public Health, 14*(10), 1161.
45. Kerby, J. D., Griffin, R. L., MacLennan, P., & Rue III, L. W. (2012). Stress-induced hyperglycemia, not diabetic hyperglycemia, is associated with higher mortality in trauma. *Ann Surg, 256*(3), 446-452.
46. Bahadoran, Z., Mirmiran, P., & Ghasemi, A. (2020). Role of nitric oxide in insulin secretion and glucose metabolism.

Trends Endocrinol Metab, 31(2), 118-130.

47. Liu, Y., Fu, H., Wang, Y., Sun, J., Zhang, R., Zhong, Y., ... & Wang, H. (2025). U− shaped association between the glycemic variability and prognosis in hemorrhagic stroke patients: a retrospective cohort study from the MIMIC-IV database. *Frontiers in Endocrinology, 16*, 1546164.
48. Wang, D., He, C., Zou, S., Yu, L., Han, B., He, L., ... & Li, Q. (2025). Glycemic variability and its association with short and long term clinical outcomes in critically ill patients with cerebral hemorrhage. *Sci Rep, 15*(1), 7820.

Supplementary Materials

Table A.1: Disease codes included in the study

haemorrhagic stroke	ICD9	430,431,436,4320,4321,4329
	ICD10	I6001, I6002, I6010, I6011, I6012, I602, I6020, I6021, I6022 I6031, I6032, I604, I6051, I6052, I606, I607, I608, I609, I610, I611, I612, I613, I614, I615, I616, I618, I619, I6200, I6201, I6202, I6203, I621, I629
ischaemic stroke	ICD9	43300，43301，43310，43311，43320，43321，43330，43331，43380，43381，43390，43391，43400，43401，43410，43411，43490，43491
	ICD10	I6300, I63011, I63012, I63013, I6302, I63031, I63032, I63039, I6309, I6310, I63111, I63112, I63113, I63119, I6312, I63131, I63132, I63133, I63139, I6319, I6320, I63211, I63212, I63213, I63219, I6322, I63231, I63232, I63233, I63239, I6329, I6330, I63311, I63312, I63313, I63319, I63321, I63322, I63331, I63332, I63333, I63341, I63342, I63343, I63349, I6339, I6340, I63411, I63412, I63413, I63419, I63421, I63422, I63423, I63429, I63431, I63432, I63433, I63439, I63441, I63442, I63443, I63449, I6349, I6350, I63511, I63512, I63513, I63521, I63522, I63523, I63529, I63531, I63532, I63533, I63539, I63541, I63542, I63543, I63549, I6359, I636, I638, I6381, I6389, I639, I6501, I6502, I6503, I6509, I651, I6521, I6522, I6523, I6529, I658, I659, I6601, I6602, I6609, I6611, I6612, I6613, I6621, I6622, I6623, I663, I668, I669
Stroke not specified as haemorrhage or infarction	ICD9	436，4370，4371，4372，4373，4374，4375，4376，4377，4378，4379

Table A.2: Univariate Cox regression results

Characteristics	Number (%)	Hazard Ratio (HR)	95% CI Lower	95% CI Upper	P
Age	-	1.036	1.028	1.044	0
Male	1181(51.80)	0.825	0.678	1.004	0.055
MI	363(15.90)	1.262	0.984	1.618	0.066
CHF	543(23.80)	1.530	1.240	1.889	0
CVD	2170(95.1)	2.099	1.120	3.932	0.021
COPD	326(14.30)	0.841	0.625	1.131	0.251
RD	399(17.50)	1.529	1.215	1.923	0
HTN	1279(56.10)	0.809	0.665	0.984	0.033
Afib	613(26.90)	1.424	1.157	1.751	0
Diabetes	773(33.90)	1.230	1.006	1.505	0.043
diabetes					
NGR	876(38.40)				
Pre_DM	589(25.80)	0.985	0.758	1.280	0.909
DM	816(35.80)	1.302	1.040	1.629	0.021
Antihyperglycemic drug,	103(4.50)	0.145	0.047	0.452	0
Mechanical ventilation,	735(32.20)	3.758	3.076	4.591	0
RI	1860(81.50)	1.505	1.130	2.004	0.005
HR	-	1.019	1.012	1.025	0
RR	-	1.119	1.088	1.151	0
SpO2	-	1.278	1.204	1.357	0
Temperature	-	1.756	1.391	2.218	0
SBP	-	0.992	0.986	0.998	0.008
DBP	-	0.966	0.959	0.974	0
MBP	-	0.972	0.964	0.980	0
Hb	-	0.848	0.811	0.887	0
Plt	-	0.999	0.998	1.000	0.241
WBC	-	1.016	1.011	1.020	0
BUN	-	1.016	1.012	1.020	0
Creatinine	-	1.126	1.071	1.183	0
Glucose	-	1.010	1.009	1.012	0

PT	-	1.019	1.011	1.027	0
PTT	-	0.998	0.994	1.002	0.420
HbA1c	-	1.028	0.968	1.092	0.370
SHR	-	1.834	1.568	2.145	0
SHR tertiles					
Low	703(30.86)				
Mid	830(36.39)	1.552	1.181	2.040	0.002
High	747(32.75)	2.324	1.785	3.027	0
GV	-	1.016	1.010	1.022	0
GV tertiles					
Low	969(42.48)				
Mid	740(32.44)	0.984	0.768	1.261	0.900
High	572(25.08)	1.829	1.453	2.301	0
Group					
1	1217(53.33)				
2	334(14.63)	1.737	1.309	2.304	0
3	483(21.17)	1.731	1.345	2.226	0
4	247(10.82)	2.765	2.103	3.635	0
GCS	-	0.907	0.878	0.937	0
APSIII	-	1.035	1.030	1.040	0
OASIS	-	1.087	1.075	1.100	0
SOFA	-	1.195	1.158	1.234	0
SAPSII	-	1.062	1.055	1.070	0

Abbreviations: APSIII, Acute Physiology Score; BUN, Blood Urea Nitrogen; CHF, Congestive Heart Failure; COPD, Chronic Pulmonary Disease; CVD, Cerebrovascular Disease; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; GCS, Glasgow Coma Scale; GV, Glycemic Variability; Hb, Hemoglobin Concentration; HbA1c, Glycated Hemoglobin; HR, Heart Rate; HTN, Hypertension; MBP, Mean Blood Pressure; MI, Myocardial Infarction; NGR, Normal Glucose Regulation; OASIS, Oxford Acute Severity of Illness Score; Plt, platelet; Pre_DM, Pre-Diabetes Mellitus; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RD, Renal Disease; RI, Insulin; RR, Respiratory Rate; SAPSII, Simplified Acute Physiology Score; SBP, Systolic Blood Pressure; SHR, Stress Hyperglycemia Ratio; SOFA, Sequential Organ Failure Assessment; WBC, White Blood Cell

Group 1: Low SHR and Low GV (SHR < 1.15 and GV < 24.46); **Group 2:** Low SHR and High GV (SHR < 1.15 and GV > 24.46); **Group 3:** High SHR and Low GV (SHR > 1.15 and GV < 24.46); **Group 4:** High SHR and High GV (SHR > 1.15 and GV > 24.46)

Table A.3: Variance inflation factor between variables

Variable	unadjusted		adjusted	
	Tolerances	VIF	Tolerances	VIF
Gender	.819	1.221	.819	1.221
Age	.428	2.338	.430	2.326
GCS	.468	2.139	.468	2.139
APSIII	.257	3.886	.260	3.844
OASIS	.356	2.806	.356	2.806
SOFA	.372	2.689	.372	2.688
SAPSII	.217	4.617	.220	4.551
HR	.639	1.566	.639	1.566
SBP	.198	5.050	.555	1.802
DBP	.069	14.512	.452	2.215
MBP	.046	21.888	-	-
RR	.768	1.302	.771	1.297
T	.798	1.253	.798	1.253
Spo2	.712	1.405	.712	1.404
HB	.670	1.492	.671	1.490
Plt	.859	1.164	.860	1.163
WBC	.836	1.196	.836	1.196
BUN	.444	2.253	.445	2.248
Creatinine	.502	1.994	.502	1.994
Glucose	.319	3.131	.319	3.131
PT	.855	1.169	.855	1.169
PTT	.871	1.148	.879	1.137
GV	.621	1.611	.621	1.611
SHR	.622	1.607	.624	1.603
HbA1c	.380	2.632	.381	2.626
MI	.819	1.222	.821	1.218
CHF	.691	1.447	.692	1.445
CVD	.850	1.177	.850	1.177
COPD	.925	1.081	.925	1.081
Diabetes	.504	1.985	.504	1.985
RD	.533	1.877	.533	1.876

HTN	.630	1.588	.630	1.586
Afib	.792	1.263	.794	1.259
InvasiveVent	.516	1.936	.520	1.925
Insulin	.856	1.168	.856	1.168
antihyperglycemic drug	.868	1.152	.868	1.152

Abbreviations: APSIII, Acute Physiology Score; BUN, Blood Urea Nitrogen; CHF, Congestive Heart Failure; COPD, Chronic Pulmonary Disease; CVD, Cerebrovascular Disease; DBP, Diastolic Blood Pressure; DM, Diabetes Mellitus; GCS, Glasgow Coma Scale; GV, Glycemic Variability; Hb, Hemoglobin Concentration; HbA1c, Glycated Hemoglobin; HR, Heart Rate; HTN, Hypertension; MBP, Mean Blood Pressure; MI, Myocardial Infarction; NGR, Normal Glucose Regulation; OASIS, Oxford Acute Severity of Illness Score; Plt, platelet; Pre_DM, Pre-Diabetes Mellitus; PT, Prothrombin Time; PTT, Partial Thromboplastin Time; RD, Renal Disease; RI, Insulin; RR, Respiratory Rate; SAPSII, Simplified Acute Physiology Score; SBP, Systolic Blood Pressure; SHR, Stress Hyperglycemia Ratio; SOFA, Sequential Organ Failure Assessment; WBC, White Blood Cell

Table A.4: The association of the SHR and GV with 28-day and 90-day mortality

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
28-day mortality						
Overall						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.55(1.18~2.04)	0.002	1.54(1.17~2.02)	0.002	1.38(1.04~1.82)	0.024
T3	2.32(1.79~3.03)	<0.001	2.13(1.63~2.78)	<0.001	1.53(1.16~2.01)	0.002
P for trend	1.52(1.34~1.73)	<0.001	1.45(1.27~1.65)	<0.001	1.22(1.07~1.39)	0.003
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	0.98(0.77~1.26)	0.9	0.86(0.67~1.10)	0.238	0.62(0.48~0.81)	<0.001
T3	1.83(1.45~2.30)	<0.001	1.60(1.27~2.03)	<0.001	0.92(0.70~1.22)	0.579
P for trend	1.35(1.20~1.53)	<0.001	1.18(1.04~1.33)	0.011	0.95(0.82~1.10)	0.520
Patients with NGR						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.83(1.06~3.15)	0.03	1.70(0.99~2.93)	0.056	1.41(0.81~2.45)	0.225
T3	3.09(1.82~5.26)	<0.001	2.70(1.58~4.62)	<0.001	1.90(1.10~3.31)	0.022
P for trend	1.74(1.37~2.21)	<0.001	1.63(1.28~2.07)	<0.001	1.37(1.07~1.76)	0.014

GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	0.88(0.60~1.30)	0.516	0.61(0.41~0.91)	0.015	0.55(0.36~0.84)	0.005
T3	2.41(1.58~3.68)	<0.001	1.70(1.09~2.65)	0.018	1.39(0.86~2.24)	0.175
P for trend	1.41(1.13~1.78)	0.003	1.15(0.89~1.47)	0.282	1.02(0.78~1.32)	0.900
Patients with Pre-DM						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	2.38(1.35~ 4.20)	0.003	2.25(1.27~3.96)	0.005	1.71(0.96~3.04)	0.070
T3	4.15(2.33~7.41)	<0.001	3.68(2.03~6.66)	<0.001	3.09(1.68~5.70)	<0.001
P for trend	1.99(1.52~2.61)	<0.001	1.88(1.42~2.49)	<0.001	1.77(1.30~2.39)	<0.001
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.11(0.69~1.79)	0.679	0.91(0.56~1.48)	0.690	0.77(0.47~1.26)	0.297
T3	2.20(1.33~3.64)	0.002	1.74(1.03~2.93)	0.038	1.25(0.71~2.22)	0.435
P for trend	1.45(1.11~1.89)	0.006	1.28(0.97~1.69)	0.078	1.08(0.80~1.45)	0.624
Patients with DM						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.28(0.86~1.92)	0.226	1.32(0.88~1.98)	0.177	1.27(0.84~1.92)	0.251
T3	1.49(1.03~2.16)	0.033	1.43(0.99~2.08)	0.057	1.07(0.73~1.58)	0.721
P for trend	1.22(1.02~1.46)	0.033	1.19(0.99~1.43)	0.061	1.03(0.85~1.24)	0.782
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	0.95(0.61~1.49)	0.823	0.94(0.60~1.47)	0.778	0.62(0.38~1.00)	0.049
T3	1.38(0.94~2.02)	0.106	1.38(0.93~2.04)	0.109	0.79(0.51~1.24)	0.308
P for trend	1.21(0.99~1.46)	0.057	1.21(0.99~1.47)	0.058	0.94(0.75~1.17)	0.569
90-day mortality						
Overall						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	

T2	1.26(1.00~1.58)	0.046	1.24(0.99~1.56)	0.062	1.15(0.91~1.45)	0.249
T3	1.84(1.48~2.30)	<0.001	1.66(1.33~2.07)	<0.001	1.24(0.99~1.56)	0.066
P for trend	1.37(1.23~1.53)	<0.001	1.29(1.16~1.44)	<0.001	1.11(0.99~1.24)	0.068
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.18(0.95~1.47)	0.136	1.03(0.83~1.28)	0.794	0.77(0.61~0.96)	0.022
T3	2.10(1.71~2.57)	<0.001	1.83(1.48~2.25)	<0.001	1.14(0.89~1.46)	0.295
P for trend	1.45(1.31~1.62)	<0.001	1.36(1.22~1.52)	<0.001	1.07(0.94~1.21)	0.318
Patients with NGR						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.38(0.89~2.14)	0.151	1.29(0.83~2.00)	0.260	1.14(0.73~1.79)	0.564
T3	2.32(1.51~3.56)	<0.001	2.01(1.31~3.11)	0.002	1.57(1.00~2.45)	0.050
P for trend	1.56(1.27~1.92)	<0.001	1.45(1.18~1.79)	<0.001	1.28(1.03~1.59)	0.026
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.10(0.79~1.54)	0.569	0.93(0.66~1.31)	0.680	0.70(0.49~1.00)	0.052
T3	2.58(1.75~3.78)	<0.001	2.16(1.45~3.22)	<0.001	1.32(0.85~2.05)	0.216
P for trend	1.51(1.24~1.85)	<0.001	1.36(1.10~1.68)	0.004	1.05(0.84~1.33)	0.658
Patients with Pre-DM						
SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.71(1.10~2.66)	0.018	1.62(1.04~2.53)	0.033	1.26(0.80~1.99)	0.325
T3	2.68(1.68~4.29)	<0.001	2.14(1.32~3.48)	0.002	1.79(1.08~2.96)	0.024
P for trend	1.64(1.30~2.06)	<0.001	1.46(1.15~1.85)	0.002	1.34(1.04~1.73)	0.025
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.26(0.84~1.91)	0.266	0.97(0.64~1.48)	0.883	0.78(0.51~1.20)	0.259
T3	2.38(1.53~3.70)	<0.001	1.71(1.08~2.71)	0.021	1.23(0.75~2.02)	0.419
P for trend	1.52(1.21~1.91)	<0.001	1.28(1.01~1.63)	0.043	1.08(0.83~1.40)	0.583
Patients with DM						

SHR						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.14(0.80~1.61)	0.469	1.15(0.81~1.64)	0.423	1.15(0.81~1.64)	0.427
T3	1.32(0.96~1.81)	0.084	1.26(0.92~1.73)	0.153	0.97(0.69~1.35)	0.839
P for trend	1.15(0.98~1.35)	0.082	1.12(0.96~1.31)	0.155	0.98(0.83~1.15)	0.799
GV						
T1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
T2	1.14(0.76~1.71)	0.524	1.14(0.76~1.72)	0.520	0.78(0.51~1.20)	0.263
T3	1.70(1.19~2.42)	0.003	1.72(1.20~2.46)	0.003	1.02(0.69~1.52)	0.918
P for trend	1.33(1.12~1.58)	0.001	1.34(1.13~1.60)	0.001	1.05(0.86~1.29)	0.604

Model1: unadjusted
Model2: adjusted for age, gender, HR, RR, SBP
Model3: adjusted for Model 2 plus MI, CHF, RD, HTN, Afib, DM, Hb ,BUN, Creatinine, PT, Mechanical ventilation, RI, SOFA, APSIII

Table A.5: Results of the proportional hazards test (Cox model) in the NGR population

Variable Name	P
SHR	0.0093
GV	0.7019
age	0.0002
gender	0.8692
HR	0.4370
RR	0.2528
SDP	0.3542
HB	0.0201
BUN	0.8843
Creatinine	0.7582
pt	0.8206
CHF	0.0616
MI	0.1196
RD	0.0680
HTN	0.1429
afib	0.0102
InvasiveVent	0.0010
Insulin	0.8074
sofa	0.8608
apsiii	0.5181
Group	0.0185
GLOBAL	0.0037

Table A.6: Results of the proportional hazards test (Cox model) in the Pre_DM population

Variable Name	P
SHR	0.542
GV	0.896
Age	0.528
Gender	0.080
HR	0.486
RR	0.881
SDP	0.432
HB	0.959
BUN	0.660
Creatinine	0.944
pt	0.069
CHF	0.813
MI	0.922
HTN	0.396
afib	0.925
InvasiveVent	0.318
Insulin	0.803
sofa	0.334
apsiii	0.975
Group	0.525
GLOBAL	0.585

Table A.7: Results of the proportional hazards test (Cox model) in the DM population

Variable Name	P
SHR	0.599
GV	0.162
age	0.513
gender	0.265
HR	0.519
RR	0.812
SDP	0.452
HB	0.074
BUN	0.432
Creatinine	0.572
PT	0.836
CHF	0.133
MI	0.040
RD	0.230
Afib	0.613
HTN	0.162
Afib	0.613

Diabetes	0.018
InvasiveVent	0.348
Insulin	0.859
sofa	0.765
apsiii	0.932
Group	0.586
GLOBAL	0.420

Table A.8: Discrimination of each predictive model for outcomes

Models	AUC (95% CI)	Sensitivity	Specificity	P
28-day mortality				
NGR				
SHR+GV	0.579(0.526-0.632)	0.206	0.932	1.00 (Reference)
SHR	0.640(0.588-0.691)	0.454	0.765	0.094
GV	0.575(0.522-0.628)	0.213	0.924	<0.001
SOFA	0.677(0.628-0.727)	0.553	0.710	0.002
APSIII	0.772(0.728-0.816)	0.688	0.750	<0.001
Pre-DM				
SHR+GV	0.580(0.515-0.644)	0.398	0.758	1.00 (Reference)
SHR	0.662(0.603-0.722)	0.806	0.460	0.070
GV	0.576(0.510-0.642)	0.441	0.716	0.000
SOFA	0.645(0.584-0.705)	0.667	0.554	0.128
APSIII	0.652(0.592-0.712)	0.645	0.631	0.055
DM				
SHR+GV	0.560(0.510-0.610)	0.359	0.781	1.00 (Reference)
SHR	0.574(0.524-0.623)	0.653	0.471	0.686
GV	0.557(0.507-0.607)	0.347	0.783	0.000
SOFA	0.644(0.596-0.692)	0.623	0.624	0.010
APSIII	0.640(0.592, 0.688)	0.491	0.718	0.010
90-day mortality				
NGR				
SHR+GV	0.601(0.554-0.648)	0.494	0.659	1.00 (Reference)
SHR	0.622(0.574-0.670)	0.456	0.747	0.519
GV	0.597(0.550-0.645)	0.494	0.664	0.001

SOFA	0.672(0.629-0.716)	0.528	0.718	0.013
APSIII	0.755(0.714-0.795)	0.639	0.761	<0.001
Pre-DM				
SHR+GV	0.594(0.528-0.647)	0.444	0.729	1.00 (Reference)
SHR	0.617(0.562-0.673)	0.742	0.460	0.555
GV	0.591(0.533-0.649)	0.452	0.729	0.022
SOFA	0.654(0.600-0.707)	0.677	0.572	0.104
APSIII	0.666(0.612-0.720)	0.581	0.727	0.032
DM				
SHR+GV	0.584(0.540-0.628)	0.534	0.625	1.00 (Reference)
SHR	0.557(0.512-0.602)	0.639	0.459	0.372
GV	0.581(0.537-0.625)	0.553	0.603	0.002
SOFA	0.657(0.614-0.700)	0.612	0.642	0.010
APSIII	0.657(0.614-0.700)	0.498	0.739	0.007

Abbreviations: SHR, Stress hyperglycemia ratio; GV, Glycemic variability; APSIII, Acute Physiology Score; SOFA, Sequential Organ Failure Assessment

Table A.9: The association of the combination of SHR and GV with all-cause mortality after excluding individuals with hypoglycemic episodes

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
28-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.59(1.17~2.17)	0.003	1.49(1.09~2.03)	0.012	1.14(0.82~1.59)	0.424
Group 3	1.73(1.34~2.23)	<0.001	1.56(1.21~2.02)	<0.001	1.26(0.97~1.63)	0.089
Group 4	2.72(2.04~3.62)	<0.001	2.49(1.86~3.34)	<0.001	1.51(1.08~2.10)	0.016
P for trend	1.37(1.25~1.49)	<0.001	1.32(1.20~1.44)	<0.001	1.14(1.03~1.25)	0.010
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.60(0.79~3.23)	0.187	1.54(0.76~3.12)	0.229	1.12(0.51~2.43)	0.782
Group 3	1.73(1.18~2.53)	0.005	1.56(1.06~2.29)	0.024	1.25(0.83~1.87)	0.284
Group 4	4.91(2.86~8.42)	<0.001	4.32(2.45~7.62)	<0.001	2.67(1.44~4.98)	0.002

P for trend	1.48(1.26~1.73)	<0.001	1.40(1.19~1.65)	<0.001	1.23(1.04~1.45)	0.018
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	2.24(1.18~4.26)	0.014	2.01(1.05~3.83)	0.035	1.53(0.77~3.03)	0.221
Group 3	2.88(1.76~4.70)	<0.001	2.65(1.60~4.41)	<0.001	2.57(1.52~4.35)	<0.001
Group 4	3.00(1.41~6.40)	0.004	2.58(1.19~5.59)	0.016	2.37(1.04~5.41)	0.040
P for trend	1.56(1.29~1.88)	<0.001	1.48(1.22~1.80)	<0.001	1.46(1.18~1.80)	<0.001
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.13(0.73~1.74)	0.593	1.10(0.71~1.70)	0.669	0.88(0.55~1.41)	0.595
Group 3	1.12(0.69~1.83)	0.637	1.01(0.62~1.64)	0.974	0.75(0.45~1.26)	0.275
Group 4	1.74(1.16~2.61)	0.008	1.70(1.13~2.57)	0.011	1.02(0.64~1.62)	0.942
P for trend	1.19(1.04~1.36)	0.013	1.17(1.02~1.34)	0.026	0.99(0.85~1.15)	0.904
90-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.77(1.37~2.29)	<0.001	1.64(1.27~2.13)	<0.001	1.29(0.98~1.70)	0.075
Group 3	1.57(1.25~1.97)	<0.001	1.40(1.12~1.76)	0.004	1.15(0.91~1.46)	0.227
Group 4	2.57(1.99~3.32)	<0.001	2.31(1.78~2.99)	<0.001	1.50(1.12~2.01)	0.007
P for trend	1.32(1.23~1.43)	<0.001	1.27(1.17~1.37)	<0.001	1.11(1.02~1.21)	0.019
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.81(1.00~3.25)	0.049	1.73(0.96~3.13)	0.069	1.27(0.66~2.44)	0.467
Group 3	1.73(1.24~2.42)	0.001	1.55(1.11~2.18)	0.011	1.31(0.92~1.87)	0.129
Group 4	4.40(2.66~7.27)	<0.001	3.94(2.33~6.66)	<0.001	2.44(1.38~4.33)	0.002
P for trend	1.44(1.25~1.66)	<0.001	1.37(1.19~1.58)	<0.001	1.22(1.05~1.42)	0.008
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	2.16(1.26~3.69)	0.005	1.82(1.06~3.13)	0.029	1.48(0.84~2.61)	0.180
Group 3	2.11(1.35~3.30)	0.001	1.72(1.08~2.74)	0.023	1.69(1.05~2.74)	0.032
Group 4	2.82(1.49~5.36)	0.002	2.09(1.08~4.04)	0.028	1.76(0.88~3.53)	0.110

P for trend	1.44(1.22~1.70)	<0.001	1.30(1.09~1.55)	0.003	1.25(1.04~1.51)	0.018
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.34(0.93~1.94)	0.114	1.33(0.92~1.92)	0.130	1.04(0.70~1.54)	0.863
Group 3	1.06(0.69~1.64)	0.790	0.96(0.62~1.49)	0.855	0.74(0.46~1.17)	0.196
Group 4	1.75(1.22~2.52)	0.002	1.73(1.20~2.50)	0.003	1.07(0.71~1.61)	0.741
P for trend	1.17(1.04~1.32)	0.009	1.15(1.02~1.30)	0.018	0.99(0.87~1.13)	0.883

Model1: unadjusted
Model2: adjusted for age, gender, HR, RR, SBP
Model3: adjusted for Model 2 plus MI, CHF, RD, HTN, Afib, DM, Hb, BUN, Creatinine, PT, Mechanical ventilation, RI, SOFA, APSIII
Group 1: Low SHR and Low GV (SHR < 1.15 and GV < 24.46); Group 2: Low SHR and High GV (SHR < 1.15 and GV > 24.46); Group 3: High SHR and Low GV (SHR > 1.15 and GV < 24.46); Group 4: High SHR and High GV (SHR > 1.15 and GV > 24.46)

Table A.10: The association of the combination of SHR and GV with all-cause mortality after excluding extreme value

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	P	HR (95%CI)	P	HR (95%CI)	P
28-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.59(1.16~2.18)	0.004	1.49(1.08~2.04)	0.014	1.07(0.76~1.51)	0.681
Group 3	1.61(1.24~2.10)	<0.001	1.47(1.13~1.92)	0.004	1.22(0.93~1.59)	0.158
Group 4	2.41(1.70~3.42)	<0.001	2.24(1.57~3.18)	<0.001	1.47(0.99~2.17)	0.056
P for trend	1.31(1.19~1.44)	<0.001	1.26(1.14~1.40)	<0.001	1.12(1.01~1.25)	0.035
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.55(0.74~3.23)	0.247	1.50(0.71~3.15)	0.288	1.13(0.50~2.58)	0.763
Group 3	1.59(1.07~2.37)	0.022	1.51(1.01~2.25)	0.045	1.39(0.91~2.11)	0.124
Group 4	3.40(1.69~6.86)	0.001	3.20(1.52~6.75)	0.002	2.51(1.08~5.84)	0.033
P for trend	1.34(1.13~1.59)	0.001	1.30(1.09~1.55)	0.004	1.23(1.03~1.48)	0.026
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	2.63(1.43~4.81)	0.002	2.28(1.23~4.24)	0.009	1.95(1.01~3.77)	0.046
Group 3	2.81(1.71~4.61)	<0.001	2.58(1.55~4.30)	<0.001	2.51(1.47~4.29)	<0.001
Group 4	2.11(0.76~5.87)	0.155	1.93(0.68~5.44)	0.214	1.95(0.67~5.69)	0.222
P for trend	1.52(1.25~1.85)	<0.001	1.46(1.18~1.79)	<0.001	1.45(1.16~1.81)	0.001

Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.05(0.67~1.65)	0.833	1.06(0.67~1.66)	0.817	0.70(0.42~1.15)	0.155
Group 3	0.98(0.58~1.66)	0.938	0.88(0.52~1.49)	0.625	0.68(0.39~1.18)	0.169
Group 4	1.72(1.08~2.74)	0.023	1.67(1.05~2.68)	0.032	0.99(0.59~1.66)	0.967
P for trend	1.15(0.99~1.35)	0.068	1.13(0.97~1.32)	0.127	0.98(0.83~1.16)	0.792
90-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.77(1.37~2.30)	<0.001	1.63(1.25~2.12)	<0.001	1.21(0.91~1.61)	0.194
Group 3	1.45(1.14~1.83)	0.002	1.31(1.03~1.66)	0.026	1.11(0.87~1.41)	0.411
Group 4	2.54(1.89~3.42)	<0.001	2.29(1.69~3.09)	<0.001	1.61(1.15~2.25)	0.005
P for trend	1.29(1.19~1.41)	<0.001	1.24(1.14~1.35)	<0.001	1.11(1.01~1.22)	0.027
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.93(1.08~3.47)	0.028	1.83(1.01~3.31)	0.047	1.41(0.74~2.71)	0.297
Group 3	1.59(1.12~2.24)	0.008	1.47(1.04~2.09)	0.029	1.39(0.97~1.99)	0.077
Group 4	2.92(1.51~5.64)	0.001	2.67(1.34~5.32)	0.005	2.09(0.96~4.53)	0.063
P for trend	1.31(1.13~1.52)	<0.001	1.26(1.08~1.47)	0.003	1.20(1.03~1.41)	0.024
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	2.47(1.48~4.12)	0.001	1.91(1.13~3.23)	0.016	1.66(0.95~2.89)	0.075
Group 3	2.08(1.33~3.27)	0.001	1.70(1.07~2.73)	0.026	1.65(1.01~2.69)	0.046
Group 4	2.55(1.17~5.57)	0.019	2.17(0.98~4.77)	0.055	1.90(0.83~4.34)	0.126
P for trend	1.43(1.20~1.70)	<0.001	1.31(1.09~1.58)	0.005	1.27(1.05~1.54)	0.016
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.25(0.86~1.83)	0.243	1.26(0.86~1.86)	0.229	0.83(0.55~1.27)	0.396
Group 3	0.88(0.54~1.43)	0.616	0.80(0.49~1.31)	0.378	0.64(0.39~1.06)	0.083
Group 4	1.97(1.32~2.94)	<0.001	1.90(1.27~2.85)	0.002	1.16(0.75~1.81)	0.505
P for trend	1.18(1.04~1.35)	0.014	1.16(1.01~1.32)	0.033	1.01(0.87~1.17)	0.911

Model1: unadjusted
Model2: adjusted for age, gender, HR, RR, SBP
Model3: adjusted for Model 2 plus MI, CHF, RD, HTN, Afib, DM, Hb, BUN, Creatinine, PT, Mechanical ventilation, RI, SOFA, APSIII
Group 1: Low SHR and Low GV (SHR < 1.15 and GV < 24.46); Group 2: Low SHR and High GV (SHR < 1.15 and GV > 24.46); Group 3: High SHR and Low GV (SHR > 1.15 and GV < 24.46); Group 4: High SHR and High GV (SHR > 1.15 and GV > 24.46)

Table A.11: The performance comparison of each ML model in predicting 28-day mortality

	AUC	Sensitivity	Specificity	Accuracy	F1
Overall					
LR	0.846	0.974	0.486	0.568	0.432
GBM	0.828	0.475	0.878	0.807	0.463
RF	0.879	0.377	0.931	0.838	0.439
XGBoost	0.895	0.649	0.873	0.836	0.571
LGB	0.890	0.662	0.873	0.838	0.580
NGR					
LR	0.922	0.96	0.720	0.754	0.528
GBM	0.821	0.46	0.884	0.817	0.448
RF	0.919	0.48	0.940	0.874	0.522
XGBoost	0.911	0.64	0.907	0.869	0.582
LGB	0.926	0.68	0.893	0.863	0.586
Pre-DM					
LR	0.893	0.947	0.745	0.778	0.581
GBM	0.879	0.611	0.909	0.863	0.579
RF	0.846	0.316	0.969	0.863	0.429
XGBoost	0.846	0.579	0.837	0.795	0.478
LGB	0.880	0.421	0.908	0.829	0.444
DM					
LR	0.782	0.943	0.422	0.534	0.465
GBM	0.732	0.371	0.867	0.761	0.400
RF	0.755	0.343	0.867	0.755	0.375
XGBoost	0.755	0.400	0.836	0.742	0.400
LGB	0.732	0.029	0.992	0.785	0.054

Abbreviations: LR, logistic regression; GBM, Gradient Boosting Machine; RF, Random Forest; XGBoost, Extreme Gradient Boosting; LightGBM, Light Gradient Boosting Machine.

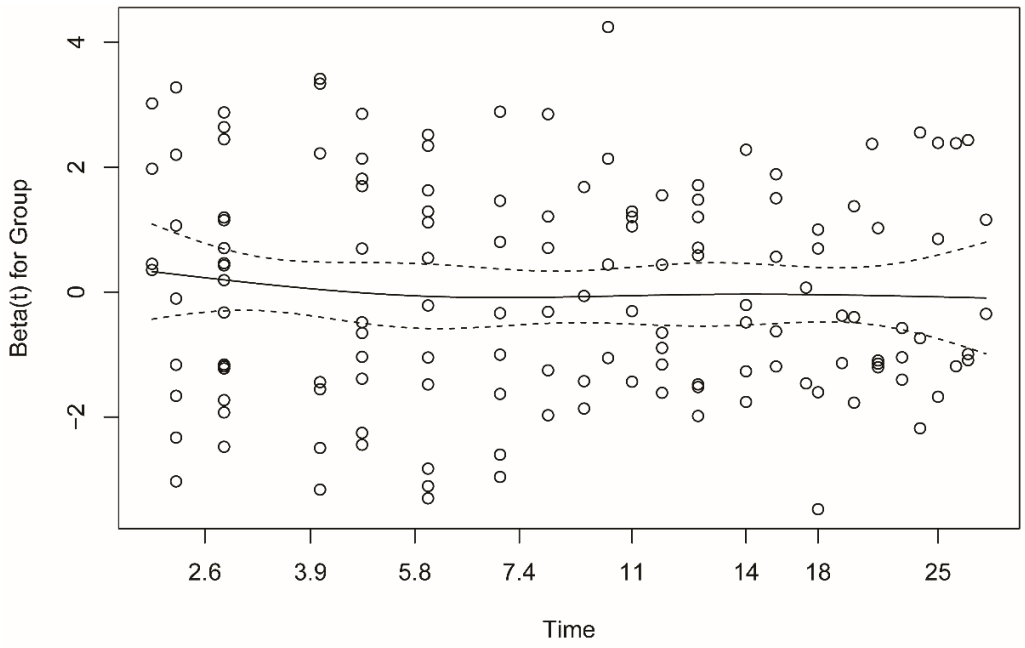

Figure A.1: The trends of the proportional - hazards assumption test based on the COX regression model

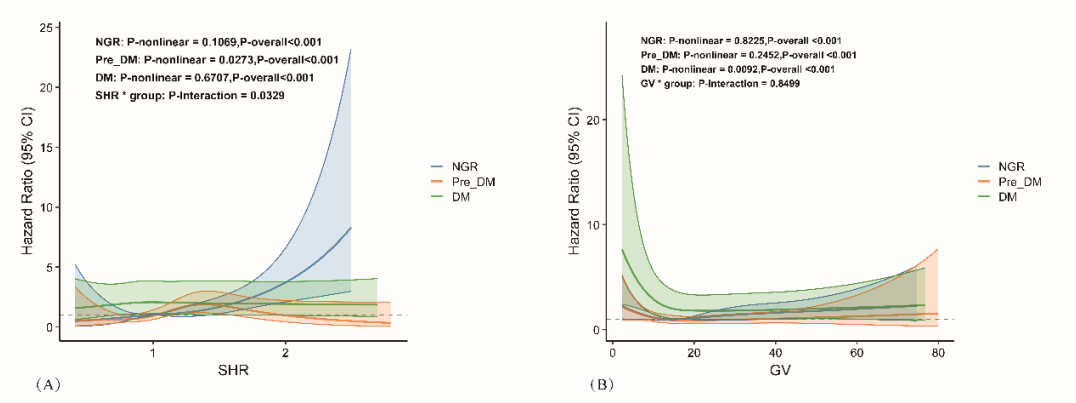

Figure A.2: Multivariable-adjusted restricted cubic spline analyses of SHR and GV for 28-day mortality. (A) SHR (B) GV

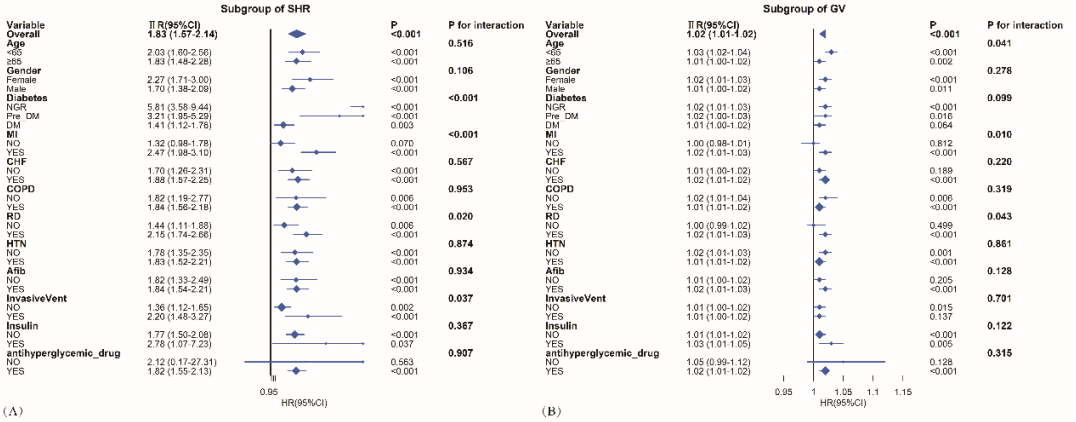

Figure A.3: Forest plots for subgroup analyses of A SHR and B GV with 28-day mortality

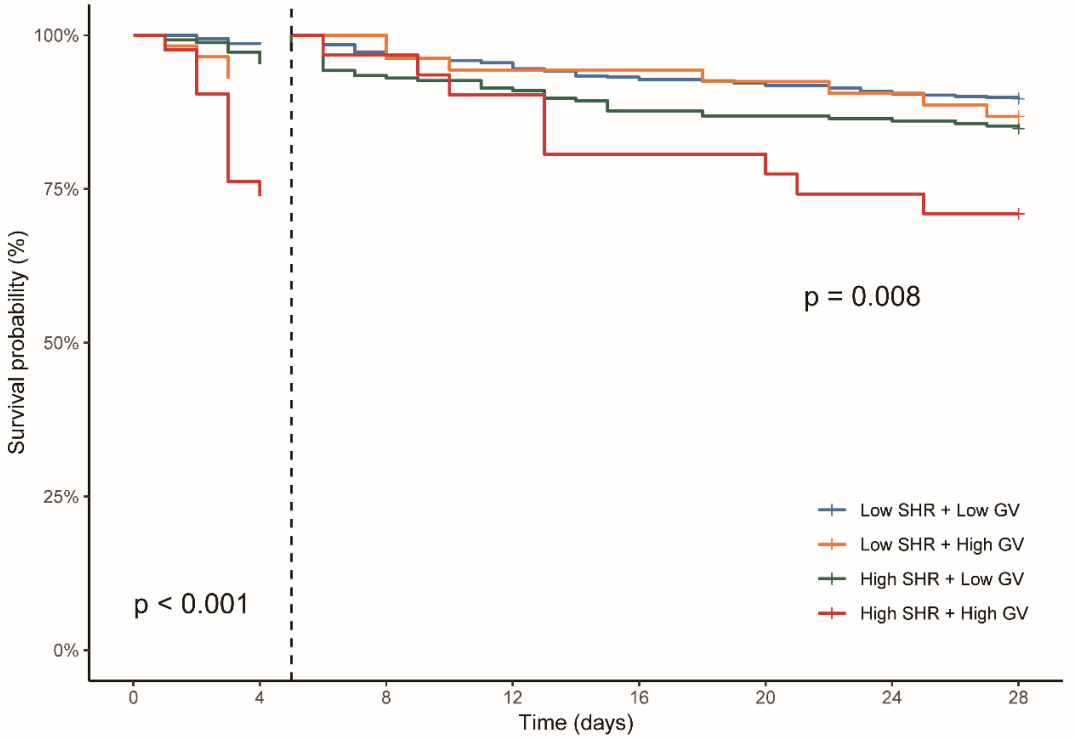

Figure A.4: Landmark survival analysis of 28-day mortality with combined SHR and GV assessment in NGR patients. Low SHR: SHR < 1.15; High SHR: SHR > 1.15; Low GV: GV < 24.46; High GV: GV > 24.46

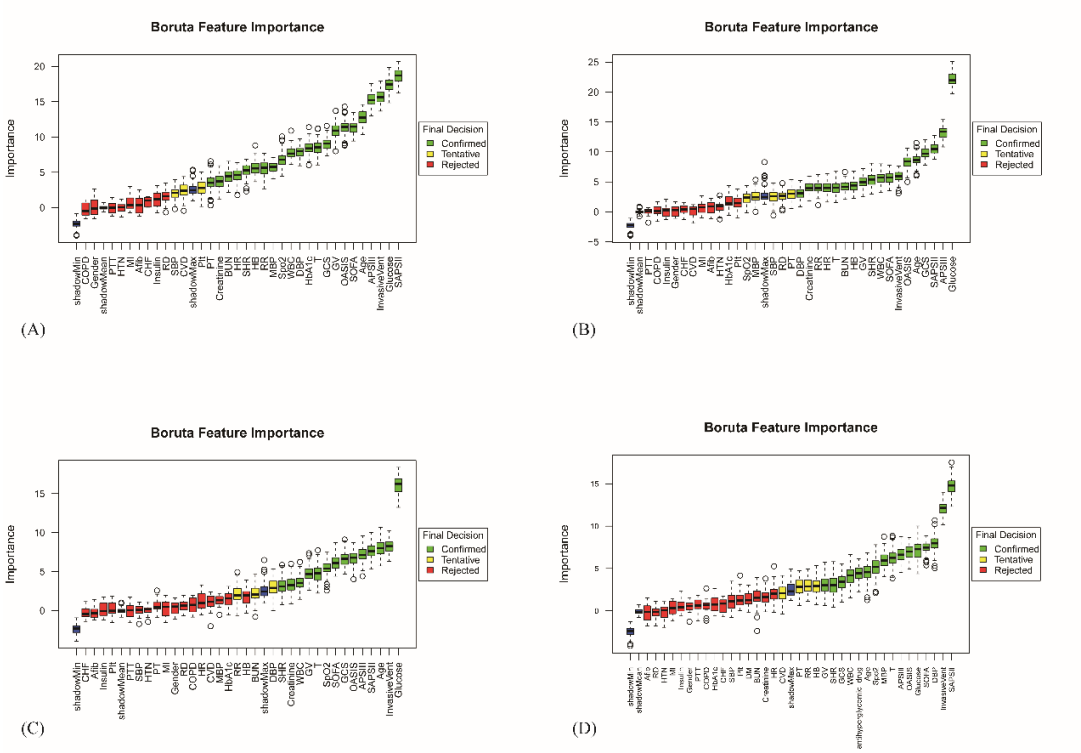

Figure A.5: The Boruta feature selection algorithm was employed to rank the importance of potential risk factors for 28-day mortality. The x-axis indicates the parameter names, and the y-axis represents the normalized importance score (Z-score). The box plots visualize the distribution of importance scores across all Boruta iterations. A. Patients with overall. B. Patients with normal glucose regulation (NGR). C. Patients with prediabetes (Pre-DM). D. Patients with diabetes mellitus (DM)

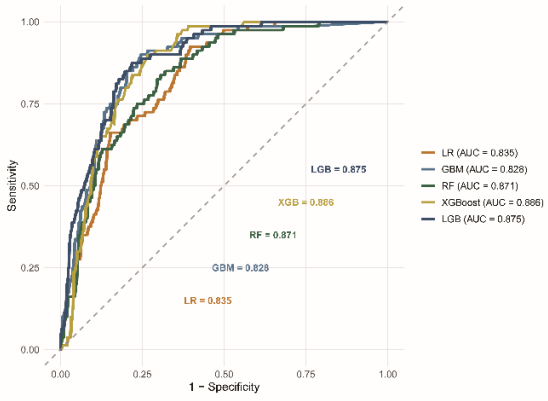

Figure A.6: Receiver operating characteristic curve of five ML models for predicting 28-day mortality in overall patients

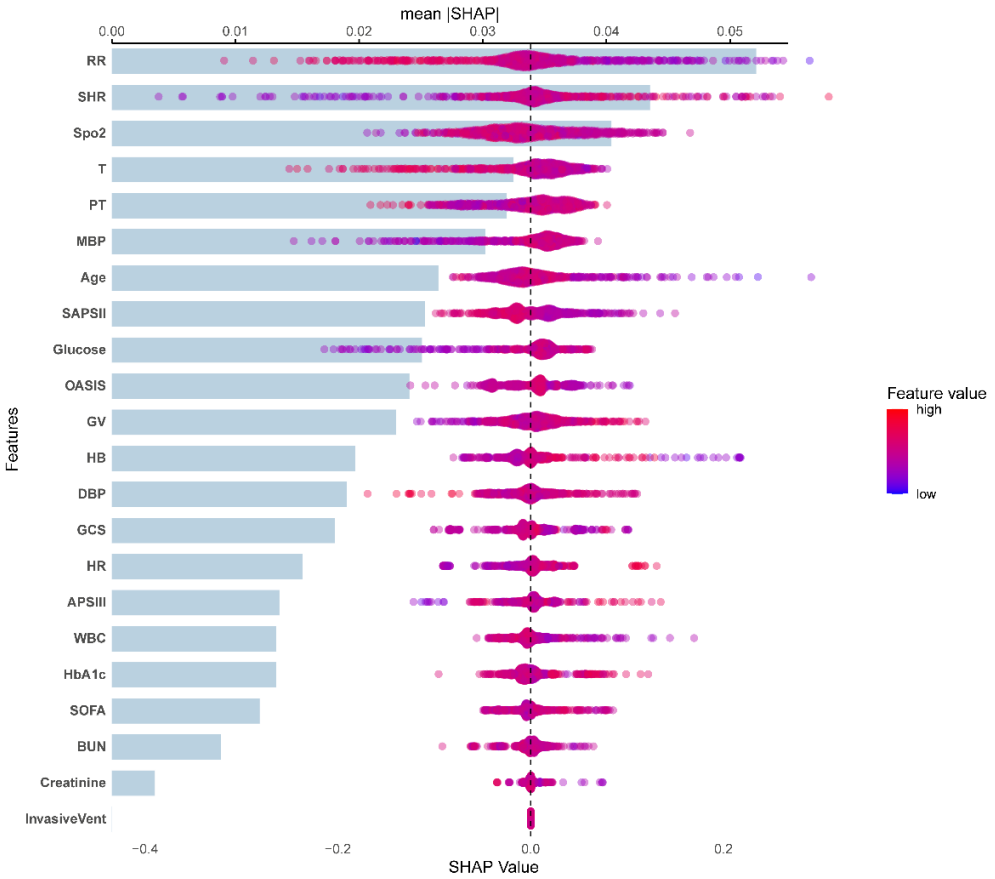

Figure A.7: SHAP interpretation of ML-based 28-day mortality prediction models in overall patients

Citation: Lu, Y., Yang, C., Yi, F., Chen, C., Meng, F., et al. (2026). Stress Hyperglycemia Ratio and Glycemic Variability Predict Mortality in Critical Stroke: A Machine Learning Study. *Adv Brain Res Neurosci, 2*(1), 01-32.