Cardiovascular Diabetology

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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

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Abstract

Background Stress hyperglycemia ratio (SHR) and glycemic variability (GV) reflect acute glucose elevation and fluctuations, which correlate with adverse outcomes in patients with atherosclerotic cardiovascular disease (ASCVD). However, the prognostic significance of combined SHR-GV evaluation for ASCVD mortality remains unclear. This study examines associations of SHR, GV, and their synergistic effects with mortality in patients with ASCVD across different glucose metabolic states, incorporating machine learning (ML) to identify critical risk factors influencing mortality.

Methods Patients with ASCVD were screened in the Medical Information Mart for Intensive Care IV (MIMIC-IV) database and stratified into normal glucose regulation (NGR), pre-diabetes mellitus (Pre-DM), and diabetes mellitus (DM) groups based on glucose metabolic status. The primary endpoint was 28-day mortality, with 90-day mortality as the secondary outcome. SHR and GV levels were categorized into tertiles. Associations with mortality were analyzed using Kaplan-Meier(KM) curves, Cox proportional hazards models, restricted cubic splines (RCS), receiver operating

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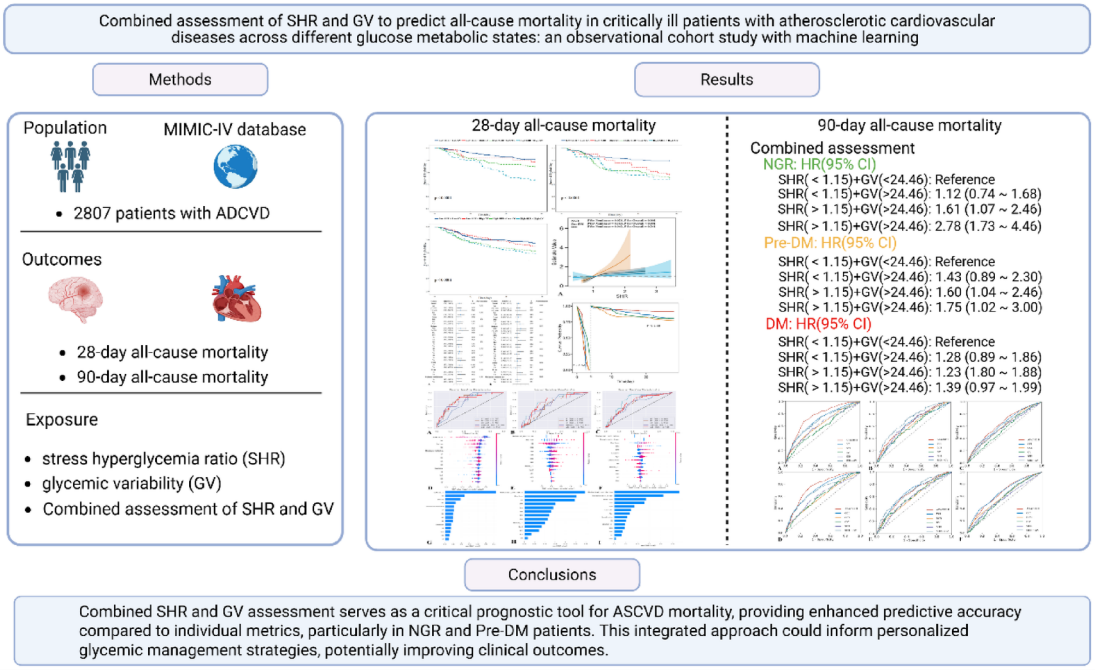
characteristic (ROC) curves, landmark analyses, and subgroup analyses. Five ML algorithms were employed for mortality risk prediction, with SHapley Additive exPlanations (SHAP) applied to identify critical predictors.

Results A total of 2807 patients were included, with a median age of 71 years, and 58.78% were male. Overall, 483 (23.14%) and 608 (29.13%) patients died within 28 and 90 days of ICU admission, respectively. In NGR and Pre-DM subgroups, combined SHR-GV assessment demonstrated superior predictive performance for 28-day mortality versus SHR alone [NGR: AUC 0.688 (0.636–0.739) vs. 0.623 (0.568–0.679), $P = 0.028$; Pre-DM: 0.712 (0.659–0.764) vs. 0.639 (0.582–0.696), $P = 0.102$] and GV alone [NGR: 0.688 vs. 0.578 (0.524–0.633), $P < 0.001$; Pre-DM: 0.712 vs. 0.593 (0.524–0.652), $P < 0.001$]. Consistent findings were observed for 90-day mortality prediction. However, in the DM subgroup, combined assessment improved prediction only for 90-day mortality vs. SHR alone [AUC 0.578 (0.541–0.616) vs. 0.560 (0.520–0.599), $P = 0.027$], without significant advantages in other comparisons.

Conclusions Combined SHR and GV assessment serves as a critical prognostic tool for ASCVD mortality, providing enhanced predictive accuracy compared to individual metrics, particularly in NGR and Pre-DM patients. This integrated approach could inform personalized glycemic management strategies, potentially improving clinical outcomes.

Graphic abstract



Keywords Atherosclerotic cardiovascular disease, Stress hyperglycemia ratio, Glycemic variability, MIMIC-IV database, Machine learning

Research insights

What is currently known about this topic?

- The Stress Hyperglycemia Ratio (SHR) and Glycemic Variability (GV) quantify acute hyperglycemic responses and glucose fluctuations, respectively, which are pathophysiologically associated with adverse clinical outcomes in patients with Atherosclerotic Cardiovascular Disease (ASCVD). Patients across distinct glucose metabolic states may exhibit differential tolerance thresholds to glycemic instability, potentially modulating the prognostic significance of these glycemic parameters in heterogeneous populations.

What is the key research question?

- Does the combined assessment of SHR and GV confer superior predictive performance for adverse clinical outcomes in ASCVD patients across varying glucose metabolic statuses?

What is new?

- The combined assessment of SHR and GV demonstrated superior predictive accuracy for adverse outcomes in ASCVD patients compared to individual parameter evaluation, with this advantage being particularly pronounced in subgroups with Normal Glucose Regulation (NGR) and Pre-Diabetes Mellitus (Pre-DM). Machine learning models significantly enhanced predictive utility and refined risk stratification, underscoring their clinical applicability in precision prognostication.

How might this study influence clinical practice?

- The study findings may inform personalized glycemic management strategies for patients with ASCVD, thereby potentially optimizing clinical outcomes through targeted metabolic intervention.

Introduction

Cardiovascular disease (CVD) remains the leading global cause of mortality and a major contributor to disability, accounting for 34.9% of worldwide deaths [1, 2]. Atherosclerotic cardiovascular disease (ASCVD), encompassing ischemic heart disease (IHD) and ischemic stroke, has emerged as a unified clinical entity within CVD classifications due to shared pathophysiological mechanisms, overlapping risk profiles, and common preventive strategies [3, 4]. Notably, the ASCVD burden has escalated markedly in recent decades, contributing to approximately 61% of CVD-related mortality [5]. Furthermore, the heightened risk of adverse cardiovascular outcomes in diabetic populations underscores substantial heterogeneity in clinical manifestations across distinct glycometabolic phenotypes [6, 7].

Stress hyperglycemia, defined as transient hyperglycemia secondary to inflammatory and neurohormonal dysregulation, is prevalent in patients with acute myocardial infarction (AMI), stroke, and multiorgan failure [8]. Its pathogenesis involves complex interactions among sympathetic nervous system activation, pro-inflammatory cytokine release, and hypothalamic-pituitary-adrenal axis hyperactivation [9]. However, admission blood glucose (ABG) levels may inadequately reflect acute hyperglycemic status due to confounding by chronic glycemic exposure [10]. Previous studies established a linear regression relationship between glycated hemoglobin (HbA1c) and average glucose (AG) levels, enabling the derivation of estimated average glucose (eAG) from HbA1c values [11]. The stress hyperglycemia ratio (SHR), derived from ABG and eAG levels, provides a quantitative measure of acute hyperglycemia relative to chronic glycemic control [12, 13]. Recent evidence demonstrates that elevated SHR independently predicts all-cause mortality in critically ill AMI and cerebrovascular disease patients, particularly in non-diabetic cohorts [14, 15]. Glycemic variability (GV), characterized by glucose fluctuations over defined intervals, serves as a marker of suboptimal glycemic control and elevated complication risks [16]. Notably, acute glucose excursions induce greater oxidative stress than sustained chronic hyperglycemia [17]. Emerging studies associate GV with adverse outcomes in diverse pathologies, including heart failure, traumatic brain injury, and cardiovascular events [9, 18–20]. Consequently, combined assessment of SHR and GV may optimize glycemic management and improve prognostication in critical care settings.

Current evidence reveals a mortality dichotomy between diabetic and non-diabetic populations, with attenuated risks of acute hyperglycemia observed in critically ill diabetic patients– a phenomenon potentially mediated by chronic metabolic adaptation [7, 21]. However, prognostic implications of ASCVD stratified by glucose metabolism status during ICU hospitalization remain poorly characterized.

This study aims to evaluate the predictive utility of SHR, GV, and their integrated metrics for all-cause mortality in ASCVD patients across glucose metabolic phenotypes, while developing machine learning (ML)-based mortality prediction models. Our findings may advance precision medicine by transitioning from uniform glycemic targets to phenotype-driven management protocols tailored to distinct glycometabolic profiles.

Methods

Data source

This observational cohort study retrospectively analyzed clinical data from the Medical Information Mart for Intensive Care IV (MIMIC-IV v3.1) database, a publicly accessible repository containing comprehensive clinical records of over 190,000 patients and 450,000 hospitalizations recorded at Beth Israel Deaconess Medical Center (BIDMC), Boston, Massachusetts, United States, spanning 12 years from 2008 to 2019 [22]. The MIMIC-IV database deliberately de-identifies admission timestamps (e.g., exact admission dates, hospitalization sequences) to protect patient privacy. Therefore, researchers cannot determine the specific year of admission for individual patients. Research protocol approval (Certification ID: 66829613) was granted by the Massachusetts Institute of Technology Ethics Committee with an informed consent waiver due to the de-identified nature of pre-existing medical records.

Study population

The diagnosis of ASCVD was confirmed by manually examining ICD-9 and ICD-10 codes [23–25]. The ICD-9

and ICD-10 codes in MIMIC-IV are discharge diagnosis codes assigned by clinicians at the conclusion of a hospitalization. These codes are standardized for billing, administrative, and epidemiological purposes and reflect the final diagnoses for the specific hospitalization episode [26]. Historical ASCVD codes (e.g., prior MI [I25.2]) were excluded unless they directly contributed to the current critical illness. Detailed specifications of diagnostic codes are presented in Table S1. Exclusion criteria comprised: (1) age < 18 years, (2) ICU stay < 24 h, and (3) fewer than three blood glucose measurements or missing HbA1c data [27]. For subjects with recurrent critical care admissions, analyses were restricted to the initial hospitalization episode. The flowchart of the patient inclusion process is shown in Fig. 1.

Data extraction

Data extraction was performed using Structured Query Language (SQL) via Navicat Premium (v16.3.11), focusing on five domains:

1. Demographics: age, sex, height, weight, ethnicity;
2. Clinical severity scores: Glasgow Coma Scale (GCS), Charlson Comorbidity Index (CCI); Acute Physiology and Chronic Health Evaluation II (APACHE II) score.
3. Vital signs: heart rate (HR), respiratory rate (RR), body temperature (°C);
4. Laboratory parameters: hemoglobin (Hb), red blood cell count (RBC), platelet count (Plt), white blood cell count (WBC), albumin, blood urea nitrogen (BUN), glucose, HbA1c, pH, lactate, creatinine;
5. Comorbidities and treatments: hypertension (HTN), diabetes, heart failure (HF), chronic obstructive pulmonary disease (COPD), acute kidney injury (AKI), myocardial infarction (MI), mechanical ventilation, hypoglycemic agents, and insulin therapy.

SHR was calculated by the following equation: [ABG (mg/dL)/(28.7 × HbA1c (%) – 46.7)] [11]. Due to the

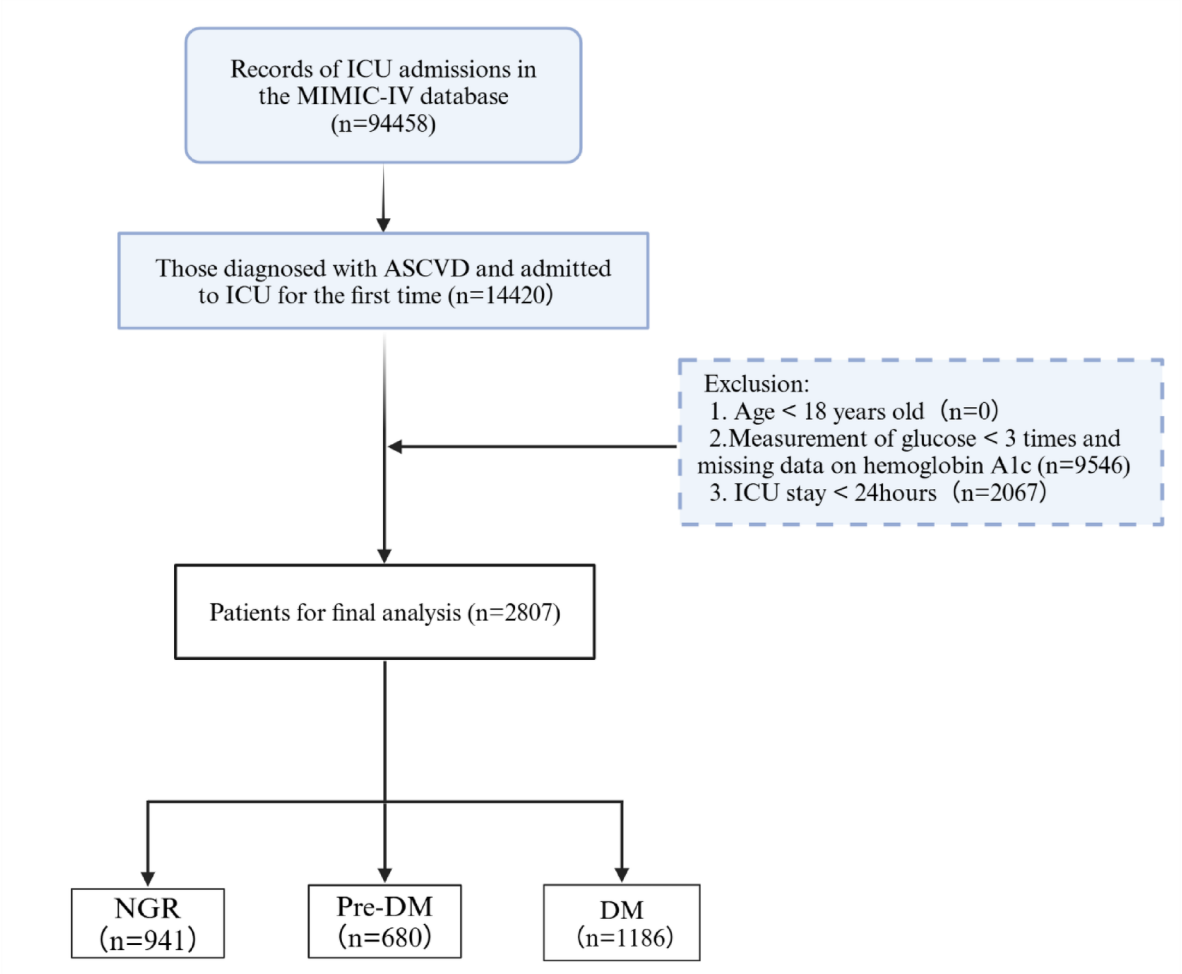


Fig. 1 Flowchart of the selection of patients

absence of meal timing in the MIMIC-IV database, our analysis incorporated all consecutive glycemic measurements obtained during ICU admissions, an approach aligning with methodological conventions established in prior critical care studies [27, 28]. We selected the coefficient of variation (CV) as the primary metric for GV due to its widespread clinical applicability, simplicity of interpretation, and extensive validation in critical care settings. CV is calculated as the percentage ratio between the standard deviation and arithmetic mean of all consecutive glycemic measurements obtained during intensive care unit monitoring (CV = SD/Mean×100%), which standardizes variability across individuals with differing baseline glucose levels [29].

Based on established diagnostic criteria for glucose metabolism, participants were stratified into three distinct cohorts: normal glucose regulation (NGR), prediabetes mellitus (Pre-DM), and diabetes mellitus (DM). The NGR group consisted of individuals with an HbA1c level < 5.7% and no prior history of diabetes. Those falling into the Pre-DM category had an HbA1c level ranging from 5.7% (inclusive) to 6.5% and no previous diabetes history. As for the DM group, it included patients who either had a history of diabetes or an HbA1c level ≥ 6.5% [30].

Vital signs (HR, RR, body temperature) and all other variables were defined using the first measured values within 24 h of ICU admission to capture baseline physiological status before any ICU interventions that might alter these parameters. Variables with ≥ 20% missing values were excluded to mitigate potential bias, while those with less than 20% missing values were populated with multiple imputations.

Outcome measures

The primary outcome of this study was 28-day all-cause mortality, while the secondary outcome was 90-day all-cause mortality.

Statistical analysis

Based on the tertiles of SHR and GV (SHR: <0.90, 0.91–1.15, > 1.15; GV: <14.92, 14.93–24.46, > 24.46), participants were classified into high and low groups. The top tertile was regarded as "high", and the lower two were regarded as "low". Normality of continuous variables was assessed using Shapiro-Wilk tests, with normally distributed variables (expressed as mean ± SD) analyzed via Student's t-tests or one-way ANOVA, and non-normally distributed variables (median [IQR]) compared using Wilcoxon rank-sum tests. Categorical variables (presented as counts and percentages) were evaluated by χ^2 or Fisher's exact tests. Multicollinearity was assessed via variance inflation factor (VIF), with variables with VIF > 5 excluded from multivariable models [31]. Kaplan-Meier (KM) curves were generated to estimate cumulative all-cause mortality risk, and Cox proportional hazards regression models were employed in three sequential steps: Model 1 (unadjusted), Model 2 (adjusted for age and sex), and Model 3 (adjusted for age and sex, GCS, CCI, APACHE II score, SpO_2, Lactate, PH, Creatinine, BUN, PT, HB, AKI, HF, Hypoglycemic drugs, Mechanical ventilation). The selection of covariates was based on clinically meaningful indicators and those demonstrating significance in univariate analysis, with collinearity controlled (VIF < 5). Restricted cubic splines (RCS) analyzed dose-effect relationships of SHR and GV, while Schoenfeld residuals validated proportional hazards assumptions. Landmark analyses evaluated temporal changes in mortality risk profiles, and receiver operating characteristic (ROC) curves compared predictive performance (AUC, sensitivity, specificity) across metrics. Subgroup analyses stratified by sex, age, comorbidities, and treatment modalities were visualized through forest plots of hazard ratios with 95% confidence intervals. Finally, sensitivity analyses were performed by excluding patients with incomplete covariate data and those who had at least one episode of hypoglycemia, to assess the robustness of the study.

For machine learning-based prediction, the Boruta algorithm ranked feature importance for 28-day mortality, followed by random partitioning of the dataset into training (80%) and testing (20%) subsets. Five models—logistic regression (LR), decision tree (DT), random forest (RF), extreme gradient boosting (XGBoost), and light gradient-boosted machine (LightGBM)—were developed using selected features. Model performance was evaluated by AUC, accuracy, specificity, sensitivity, and F1-score, with the top-performing model further interpreted via SHapley Additive exPlanations (SHAP) to identify critical predictors [28]. All analyses were performed in Python 3.9.12, SPSS 26.0, and DecisionLnnc 1.0, with two-tailed p values < 0.05 considered statistically significant.

Results

Baseline characteristics

A total of 2807 patients meeting the analytical criteria were identified. The results of the univariate logistic regression are shown in Table S2. Table S3 shows the variance inflation factors, indicating that there is no multicollinearity among the variables. The baseline characteristics of the study population are presented in Table 1. Overall, the median age was 71 years, with 1650 patients (58.78%) being male. Of these patients, 2387 (85.03%) survived 28 days following ICU admission and 2199 patients (78.34%) survived for 90 days. Compared to 28-day survivors, non-survivors were older and exhibited a higher prevalence of comorbidities including AKI

Table 1 Baseline characteristics according to 28-day mortality

Variable	Overall	Survivors(*n* = 2387)	Non-survivors(*n* = 420)	*p*
Demographics				
Age (years)	71 (61–81)	70 (60–80)	77 (67–85)	< 0.01
Male, n (%)	1650 (58.78)	1430 (59.91)	220 (52.38)	< 0.01
BMI (kg/m^2)	27.34 (23.35–32.14)	27.46 (23.39–32.21)	26.82 (23.02–31.57)	0.1
Vital signs				
SpO_2 (%)	98 (95–100)	98 (95–100)	98 (95–100)	0.38
RR(bpm)	19 (16–23)	19 (16–22)	20 (16–24)	< 0.01
Temperature (℃)	36.78 (36.56–37.06)	36.78 (36.56–37.06)	36.78 (36.5-37.11)	0.16
HR (bpm)	83 (71–97)	82 (71–97)	87 (73-100.25)	< 0.01
Comorbidities				
AKI, n (%)	1009 (35.95)	793 (33.22)	216 (51.43)	< 0.01
HF, n (%)	1043 (37.16)	859 (35.99)	184 (43.81)	< 0.01
MI (%)	835 (29.75)	700 (29.33)	135 (32.14)	0.27
HTN, n (%)	1265 (45.07)	1082 (45.33)	183 (43.57)	0.54
COPD, n (%)	388 (13.82)	323 (13.53)	65 (15.48)	0.32
Glucose metabolism state				
NGR, n (%)	941 (33.52)	816 (34.19)	125 (29.76)	0.19
Pr-DM, n (%)	680 (24.23)	576 (24.13)	104 (24.76)	
DM, n (%)	1186 (42.25)	995 (41.68)	191 (45.48)	
Treatment				
Hypoglycemic drugs, n (%)	193 (6.88)	190 (7.96)	3 (0.71)	< 0.01
Mechanical ventilation, n (%)	979 (34.88)	747 (31.29)	232 (55.24)	< 0.01
RI, n (%)	953 (33.95)	812 (34.02)	141 (33.57)	0.9
Laboratory measurements				
PT(s)	13 (11.9–14.8)	12.9 (11.9–14.6)	13.7 (12.3-16.33)	< 0.01
PTT(s)	30.1 (26.8–38.3)	30 (26.7–38.7)	30.5 (26.9-36.97)	0.97
BUN(mg/dL)	19 (14–29)	18 (13–28)	25 (16-40.25)	< 0.01
Glucose(mg/dL)	132 (106–178)	130 (105–175)	146 (118–205)	< 0.01
HbA1c(%)	5.9 (5.4–6.7)	5.8 (5.4–6.7)	5.9 (5.5–6.7)	0.01
Hb(g/dL)	11.9 (10.2–13.4)	12 (10.3–13.5)	11.25 (9.5–12.9)	< 0.01
PH	7.39 (7.33–7.43)	7.39 (7.34–7.43)	7.38 (7.31–7.44)	< 0.01
Plt(10^9/L)	208 (160.5–264)	208 (162–262)	207 (152-278.25)	0.89
RBC(m/Ul)	4.01 (3.45–4.47)	4.04 (3.5–4.49)	3.8 (3.22–4.38)	< 0.01
Lactate(mmol/L)	1.6 (1.2–2.35)	1.6 (1.2–2.3)	1.8 (1.3–2.8)	< 0.01
GV(%)	19.36 (13.36–29.53)	18.91 (13.05–28.82)	22.52 (15.37–32.79)	< 0.01
SHR	1.05 (0.88–1.32)	1.04 (0.87–1.29)	1.18 (0.95–1.48)	< 0.01
WBC(K/Ul)	10.7 (8-14.1)	10.4 (7.9–13.7)	12.3 (9.28-17)	< 0.01
Creatinine(mg/dL)	1 (0.8–1.4)	1 (0.8–1.4)	1.1 (0.9–1.72)	< 0.01
Clinical scores				
APACHE II score	16 (12–21)	15 (11–20)	20 (15–25)	< 0.01
GCS	15 (13–15)	15 (13–15)	14 (11–15)	< 0.01
CCI	6 (4–8)	6 (4–8)	7 (6–9)	< 0.01

BMI body mass index; *HR* heart rate; *RR* respiratory rate; *AKI* acute kidney injury; *HF* heart failure; *HLD* hyperlipidemia; *MI* myocardial infarction; *HTN* hypertension; *COPD* chronic obstructive pulmonary disease; *NGR* normal glucose regulation; *Pre-DM* pre-diabetes mellitus; *DM* diabetes mellitus; *RI* insulin; *PT* prothrombin time; *PTT* partial thromboplastin time; *BUN* blood urea nitrogen; *HbA1c* glycated hemoglobin; *Hb* haemoglobin concentration; *Plt* platelet; *RBC* red blood cell; *GV* glycemic variability; *SHR* stress hyperglycemia ratio; *WBC* white blood cell; *APACHE II* score, acute physiology and chronic health evaluation II score; *GCS* glasgow coma scale; *CCI* Charlson comorbidity index

and HF. Notably, non-survivors were less likely to receive hypoglycemic drugs but had higher mechanical ventilation use. In deceased patients, lower levels of Hb, RBC and pH were observed, whereas elevated levels were identified in PT, PTT, HbA1c, BUN, glucose, lactate, WBC, creatinine, SHR, and GV. Moreover, compared with 28-day survivors, non-survivors demonstrated significantly higher APACHE II scores and CCI, while exhibiting lower GCS scores.

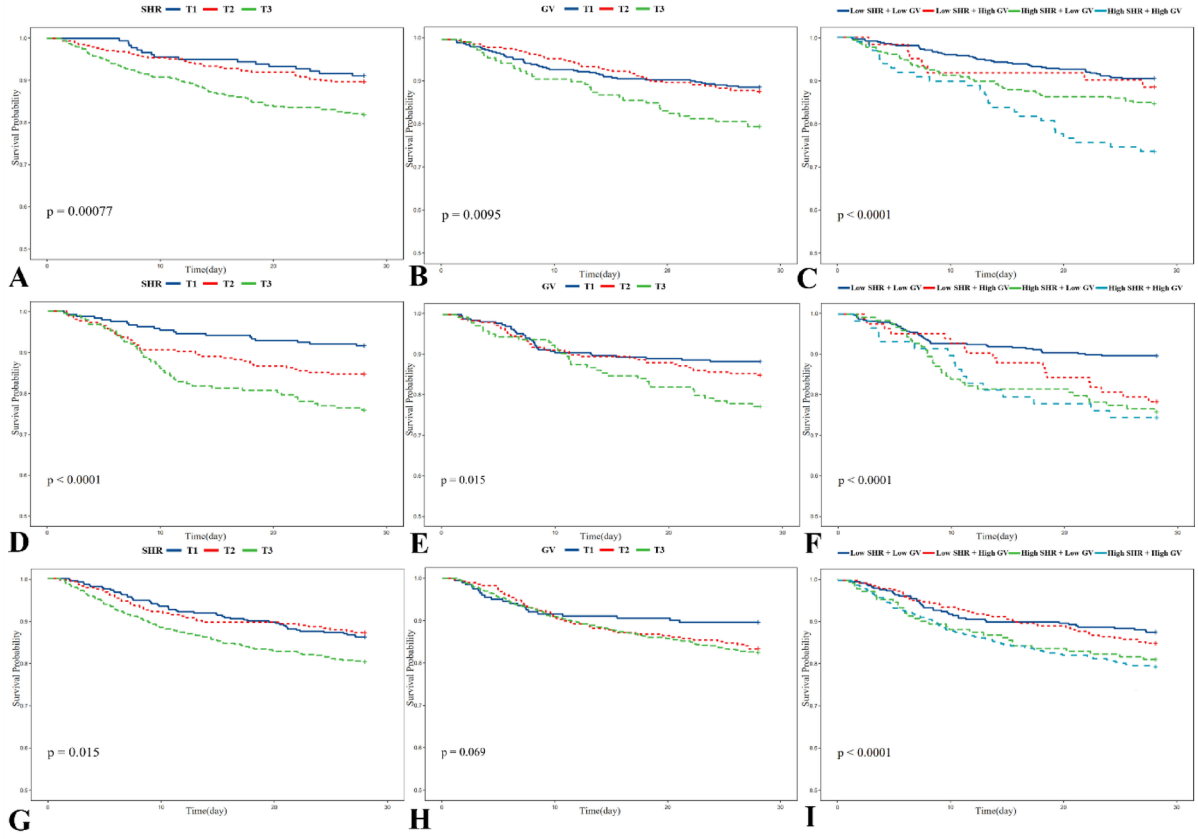


Fig. 2 Kaplan-Meier curves of SHR, GV, and their combination for 28-day mortality. (**A**–**C**) patients with NGR; (**D**–**F**) patients with Pre-DM; (**G**–**I**) patients with DM

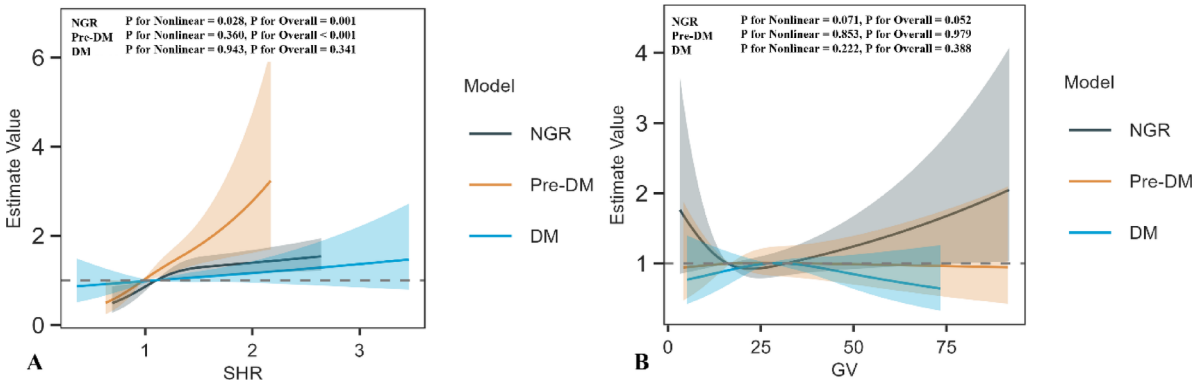


Fig. 3 Multivariable-adjusted restricted cubic spline analyses of SHR and GV for 28-day mortality. Adjusted for covariates as in Table 2. (**A**) SHR (**B**) GV

The association between SHR and mortality

K–M curves demonstrated that the 28-day survival rate progressively declined with increasing SHR quantiles across different glucose metabolic states (Fig. 2A, D, and G). In adjusted Cox proportional hazards regression analyses of the overall cohort, patients in the highest SHR tertile demonstrated a 1.24-fold increased risk of 28-day all-cause mortality (HR 1.24, 95% CI 1.10–1.41) and 1.15-fold elevated 90-day mortality risk (HR 1.15, 95% CI 1.04–1.28) compared with those in the lowest tertile. Stratified analyses across glucose metabolism subgroups indicated consistent SHR-mortality associations, with the notable exception of non-significant 28-day risk elevation in the DM population (HR 1.14, 95% CI 0.80–1.62). The complete spectrum of subgroup-specific hazard ratios with corresponding confidence intervals is detailed in Table S4. RCS analyses revealed a linear dose-response relationship between SHR and 28-day mortality in Pre-DM individuals (P for nonlinearity = 0.36) while demonstrating a nonlinear association in the NGR population

(P for nonlinearity = 0.023). However, no significant dose-response association was observed between SHR and mortality outcomes in DM patients (Fig. 3A). Furthermore, subgroup analyses revealed no statistically significant interaction effects across predefined clinical strata (all P-interaction > 0.05), confirming the robustness of the primary findings as illustrated in Fig. 6A.

The association between GV and mortality

The KM curves illustrating the association between GV and 28-day mortality are presented in Fig. 2B, E, and H. Notably, no significant survival differences were observed across GV tertiles in the DM population ($P = 0.69$). In the overall population and all glycemic subgroups, no significant association between GV and 28-day mortality was observed regardless of whether GV was modeled as a continuous variable (overall: HR 1.02 per 1% increment, 95% CI 0.89–1.17; NGR: HR 1.02 per 1% increment, 95% CI 0.78–1.33; Pre-DM: HR 1.04 per 1% increment, 95% CI 0.78–1.37; DM: HR 1.05 per 1% increment, 95% CI 0.84–1.31) or categorical variable (overall: highest vs. lowest tertile: HR 1.03, 95% CI 0.78–1.34; NGR: highest vs. lowest tertile: HR 1.07, 95% CI 0.65–1.60; Pre-DM: highest vs. lowest tertile: HR 1.07, 95% CI 0.62–1.86; DM: highest vs. lowest tertile: HR 1.17, 95% CI 0.70–1.94). Similarly, no significant association between GV and 90-day mortality was observed in the overall population and all glycemic subgroups (Table S4). RCS analyses failed to identify significant dose-response relationships between GV and clinical outcomes in any glucose metabolism subgroup (Fig. 3B). Furthermore, subgroup analysis adjusted for confounding factors revealed that GV was significantly associated with 28-day mortality only in ASCVD patients with HTN ($P = 0.032$, Fig. 6B).

The association of combined SHR and GV with mortality

The K-M curves depicting 28-day mortality for the combination of SHR and GV are shown in Fig. 2C, F, and I. Among NGR patients, those with elevated SHR (> 1.15) and GV (> 24.46) demonstrated the highest risks for 28-day mortality (HR = 2.07, 95% CI 1.23–3.48) and 90-day mortality (HR = 2.78, 95% CI 1.73–4.46). Similarly, Pre-DM individuals with high SHR/high GV showed the greatest 90-day mortality risk (HR 1.75, 95% CI 1.02–3.00), while the low SHR/high GV subgroup (SHR < 1.15, GV > 24.46) exhibited the highest 28-day mortality risk (HR = 2.08, 95% CI 1.27–3.41). However, analyses of combined SHR and GV parameters demonstrated no statistically significant associations with mortality outcomes in DM patients (all $P > 0.05$; Table 2).

Proportional hazard testing demonstrated constant risk ratios over time between SHR/GV combinations and mortality in NGR and DM subgroups [NGR: $P = 0.353$ (Table S6); DM: $P = 0.198$, (Table S7)]. However, non-constant risk ratios were observed in the Pre-DM subgroup ($P = 0.021$, Table S8), with Beta values approaching zero around day 4 (Fig. S1) (Fig. 4). As shown in Fig. 5, no significant survival differences were detected among Pre-DM patients within 4 days post-ICU admission ($P = 0.061$). Beyond day 4, however, survival disparities became evident ($P < 0.001$), with patients in the low SHR/low GV subgroup demonstrating higher 28-day survival rates compared to other combinations (Fig. 6).

ROC curve analysis

The ROC curves of SHR, GV, and their combination for predicting mortality in ASCVD patients are shown in Fig. 4 and Table S5. In the NGR and Pre-DM subgroups, the combined model outperformed SHR alone [NGR: 0.688 (0.636–0.739) vs. 0.623 (0.568–0.679), $P = 0.028$; Pre-DM: 0.712 (0.659–0.764) vs. 0.639 (0.582–0.696), $P = 0.102$] and GV alone [NGR: 0.688 (0.636–0.739) vs. 0.578 (0.524–0.633), $P < 0.001$; Pre-DM: 0.712 (0.659–0.764) vs. 0.593 (0.524–0.652), $P < 0.001$] in predicting 28-day mortality. However, no significant differences were observed between the combined model and SHR alone [0.587 (0.542–0.631) vs.. 0.577 (0.532–0.623), $P = 0.236$] or GV alone [0.587 (0.542–0.631) vs. 0.546 (0.503–0.589), $P = 0.148$] in the DM subgroup (Fig. 4A–C). Similarly, for 90-day mortality prediction, the combined model demonstrated superior performance compared to SHR and GV alone in the NGR and Pre-DM subgroups. In the DM subgroup, the combined model showed enhanced predictive ability compared to SHR alone [0.578 (0.541–0.616) vs. 0.560 (0.520–0.599), $P = 0.027$], but no significant difference was observed versus GV alone [0.578 (0.541–0.616) vs. 0.568 (0.531–0.604), $P = 0.555$] (Fig. 4D–F). Furthermore, Fig. 4 illustrates the ROC curves of SHR, GV, and their combination alongside three clinical scores (GCS, CCI, APACHE II) for predicting 28-day and 90-day mortality, respectively.

Sensitivity analysis

We conducted several sensitivity analyses to assess the robustness of our findings. First, after excluding 84 patients who experienced at least one hypoglycemic episode during their ICU hospitalization, the results of the Cox proportional hazards regression analysis remained consistent with those from the primary analysis (Table S9). Second, upon excluding 1264 participants with missing data, the association between the combination of SHR and GV and the prognosis of patients with ASCVD continued to align with the primary outcomes (Table S10). These sensitivity analyses corroborate the reliability and generalizability of the principal findings.

Table 2 The association of the combination of SHR and GV with all-cause mortality

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	1.50 (1.13–2.01)	0.006	1.50 (1.12–2.00)	0.006	1.10 (0.81–1.48)	0.555
Group 3	1.80 (1.39–2.34)	< 0.001	1.81 (1.40–2.35)	< 0.001	1.49 (1.15–1.94)	0.003
Group 4	2.23 (1.74–2.88)	< 0.001	2.26 (1.76–2.92)	< 0.001	1.45 (1.10–1.90)	0.007
P for trend	1.30 (1.20–1.41)	< 0.001	1.31 (1.21–1.42)	< 0.001	1.15 (1.06–1.25)	0.001
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.23(0.56–2.73)	0.608	1.10 (0.50–2.44)	0.819	0.89 (0.39–2.04)	0.791
Group 3	1.69(1.12–2.54)	0.012	1.64 (1.09–2.47)	0.018	1.41 (0.92–2.17)	0.116
Group 4	3.03(1.87–4.91)	< 0.001	3.01 (1.86–4.87)	< 0.001	2.07 (1.23–3.48)	0.006
P for trend	1.40(1.20–1.63)	< 0.001	1.39 (1.19–1.63)	< 0.001	1.25 (1.06–1.48)	0.007
Patients with pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)			
Group 2	2.15 (1.23–3.74)	0.007	1.96 (1.14–3.46)	0.016	1.27 (0.69–2.32)	0.438
Group 3	2.50 (1.56–4.00)	< 0.001	2.58 (1.61–4.12)	< 0.001	2.08 (1.27–3.41)	0.004
Group 4	2.66 (1.47–4.81)	0.001	2.72 (1.50–4.93)	0.001	1.95 (1.03–3.72)	0.041
P for trend	1.44 (1.22–1.69)	< 0.001	1.46 (1.23–1.72)	< 0.001	1.32 (1.10–1.58)	0.003
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.21 (0.79–1.84)	0.376	1.28 (0.84–1.95)	0.251	0.96 (0.61–1.51)	0.862
Group 3	1.59 (0.98–2.56)	0.059	1.55 (0.96–2.50)	0.074	1.17 (0.71–1.91)	0.541
Group 4	1.74 (1.19–2.56)	0.005	1.79 (1.22–2.63)	0.003	1.19 (0.78–1.81)	0.421
P for trend	1.21 (1.07–1.36)	0.002	1.21 (1.07–1.36)	0.002	1.08 (0.95–1.23)	0.264
90-day mortality						
Overall						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.63 (0.90–2.96)	0.107	1.46 (0.80–2.65)	0.216	1.14 (0.62–2.12)	0.671
Group 3	1.79 (1.27–2.51)	0.001	1.74 (1.24–2.44)	< 0.001	1.50 (1.05–2.14)	0.025
Group 4	2.90 (1.92–4.40)	< 0.001	2.87 (1.89–4.34)	< 0.001	1.88 (1.21–2.94)	0.005
P for trend	1.39 (1.22–1.58)	< 0.001	1.38 (1.21–1.57)	< 0.001	1.23 (1.08–1.41)	0.002
Patients with NGR						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.04 (0.70–1.55)	0.847	1.04 (1.70–1.54)	0.858	1.12 (0.74–1.68)	0.592
Group 3	1.57 (1.08–2.29)	0.018	1.57 (1.06–2.29)	0.02	1.61 (1.07–2.46)	0.023
Group 4	2.91(1.96–4.33)	< 0.001	2.91 (1.95–4.37)	< 0.001	2.78 (1.73–4.46)	< 0.001
P for trend	1.39(1.22–1.58)	< 0.001	1.38 (1.21–1.57)	< 0.001	1.23 (1.08–1.41)	0.002
Patients with Pre-DM						
Group 1	1.00 (Reference)		1.00 (Reference)			
Group 2	2.25 (1.47–3.49)	< 0.001	2.07 (1.33–3.20)	0.001	1.43 (0.89–2.30)	0.142
Group 3	1.81 (1.20–2.74)	0.005	1.87 (1.23–2.82)	0.003	1.60 (1.04–2.46)	0.034
Group 4	2.30 (1.39–3.79)	0.001	2.31 (1.10–3.82)	0.001	1.75 (1.02–3.00)	0.042
P for trend	1.20 (1.09–1.33)	< 0.001	1.21 (1.09–1.33)	< 0.001	1.09 (0.98–1.21)	0.117
Patients with DM						
Group 1	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Group 2	1.59 (1.12–2.25)	0.009	1.70 (1.20–2.41)	0.003	1.28 (0.89–1.86)	0.183
Group 3	1.59 (1.05–2.41)	0.029	1.55 (1.02–2.35)	0.039	1.23 (1.80–1.88)	0.35

Table 2 (continued)

Variables	Model 1		Model 2		Model 3	
	HR (95%CI)	*P*	HR (95%CI)	*P*	HR (95%CI)	*P*
Group 4	1.92 (1.38–2.67)	< 0.001	1.99 (1.43–2.76)	< 0.001	1.39 (0.97–1.99)	0.073
P for trend	1.26 (1.16–1.36)	< 0.001	1.24 (1.15–1.35)	< 0.001	1.12 (1.03–1.22)	0.011

Model 1: unadjusted;

Model 2: adjusted for age and sex

Model 3: adjusted for Model 2 plus GCS, CCI, APACHE II score, SpO_2, Lactate, PH, Creatinine, BUN, PT, HB, AKI, HF, Hypoglycemic drugs, Mechanical ventilation

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);

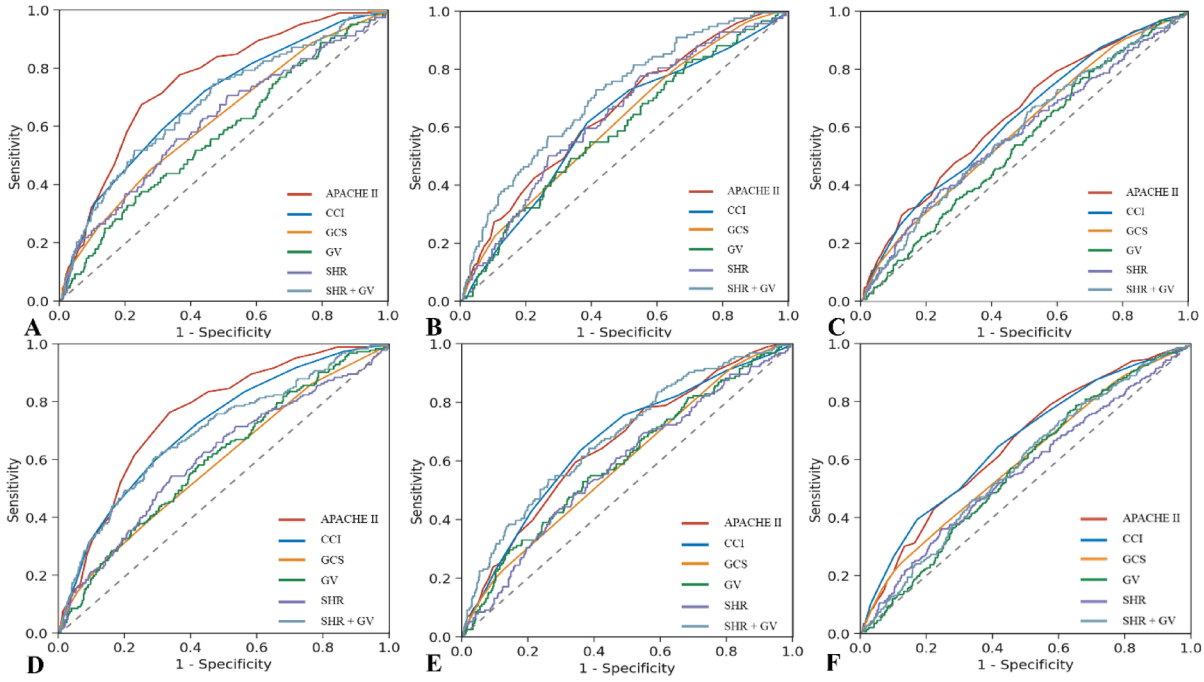


Fig. 4 The ROC curves of SHR and GV as biomarkers for predicting 28-day mortality(**A**–**C**) and 90-day mortality(**D**–**F**). **A** SHR versus GV versus SHR+GV versus APACHE II, CCI, and GCS in NGR patients for predicting 28-day mortality. **B** SHR versus GV versus SHR+GV versus APACHE II, CCI, and GCS in Pre-DM patients for predicting 28-day mortality. **C** SHR versus GV versus SHR+GV versus APACHE II, CCI, and GCS in DM patients for predicting 28-day mortality. **D** SHR versus GV versus SHR+GV versus APACHE II, CCI, and GCS in NGR patients for predicting 90-day mortality. **E** SHR versus GV versus SHR+GV versus APACHE II, CCI, and GCS in Pre-DM patients for predicting 90-day mortality. **F** SHR versus GV versus SHR+GV versus APACHE II, CCI, and GCS in DM patients for predicting 90-day mortality.

Machine learning: SHR, GV and 28-day mortality

The final variables incorporated into the machine learning models were determined through Boruta algorithm analysis (Fig. 7), with variable importance ranked in descending order from right to left. The Boruta algorithm selected 14, 13, and 14 features as optimal predictors of mortality from the NGR, Pre-DM, and DM subgroups, respectively. Results of the Boruta algorithm in the overall population are presented in Fig. S2.

The RF model demonstrated superior performance in the NGR population (AUC = 0.804; sensitivity: 0.880, specificity: 0.671, accuracy: 0.873, F1-score: 0.504) (Fig. 8A). The LR model exhibited the best predictive capability in the Pre-DM subgroup (AUC = 0.757; sensitivity: 0.714, specificity: 0.757, accuracy: 0.654, F1-score: 0.574) (Fig. 8B). For the DM cohort, the LR model achieved optimal performance (AUC = 0.794; sensitivity: 0.921, specificity: 0.655, accuracy: 0.697, F1-score: 0.636) (Fig. 8C). Detailed sensitivity, specificity, and accuracy metrics for other models are provided in Table S11. The results of the ROC curve analysis in the total population are presented in Fig. S3.

Figure 8D–I present scatter plots of mortality-associated risk factors and average importance bar plots for the optimal models. The results demonstrate that GV exhibited the lowest contribution weight in the NGR subgroup (Fig. 8D, G) and the Pre-DM subgroup (Fig. 8E, H). Interestingly, both GV and SHR showed minimal contribution weights in the DM subgroup (Fig. 8F, I). The interpretability of the 28-day mortality prediction model in the

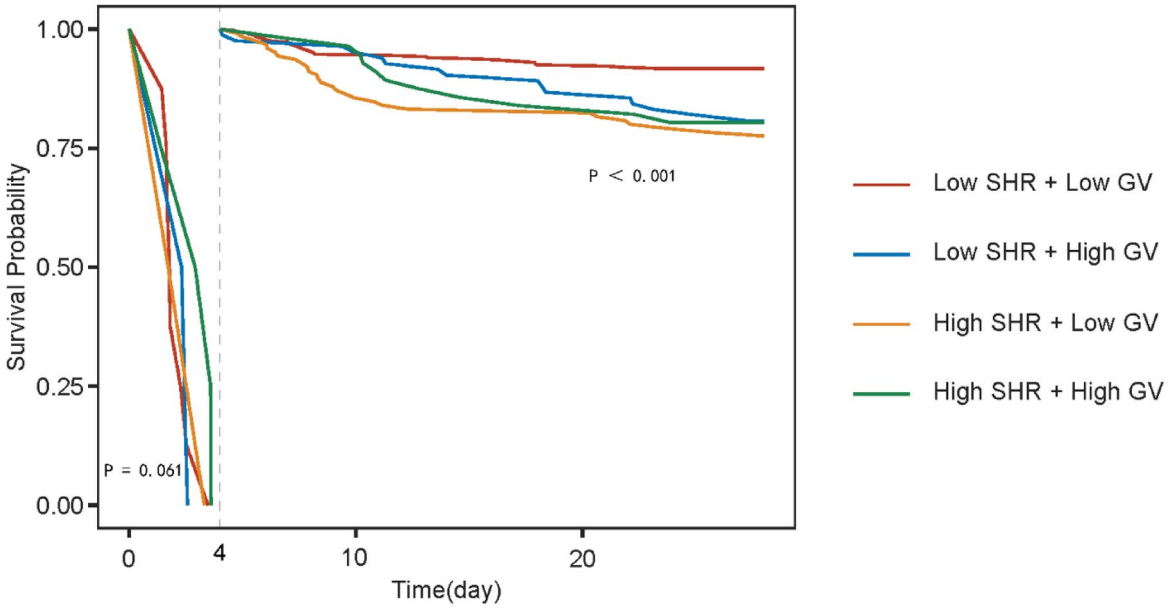


Fig. 5 Landmark survival analysis of 28-day mortality with combined SHR and GV assessment in Pre-DM patients. Low SHR: SHR < 1.15; High SHR: SHR > 1.15; Low GV: GV < 24.46; High GV: GV > 24.46

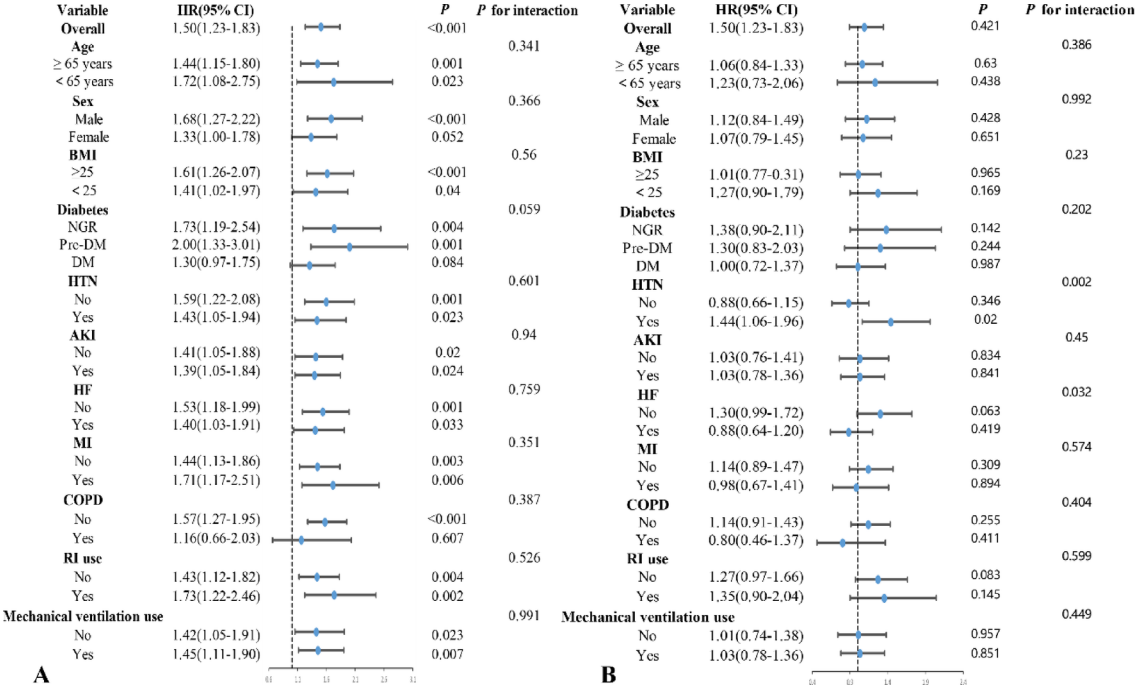


Fig. 6 Forest plots for subgroup analyses of **A** SHR and **B** GV with 28-day mortality

overall patient population is presented in Fig. S4. To validate the models' interpretability, Fig. S5 provides a comparative visualization of clinical parameters influencing mortality risk predictions between representative non-survivors (Fig. S5A, C, E) and survivors (Fig. S5B, D, F).

Discussion

In this study, we evaluated the associations of stress hyperglycemia ratio SHR, GV, and their combined effects on 28-day and 90-day all-cause mortality in ASCVD patients. Notably, Cox proportional hazards models showed that SHR was significantly associated with mortality in the NGR and Pre-DM subgroups, but not in DM patients. No significant associations were observed

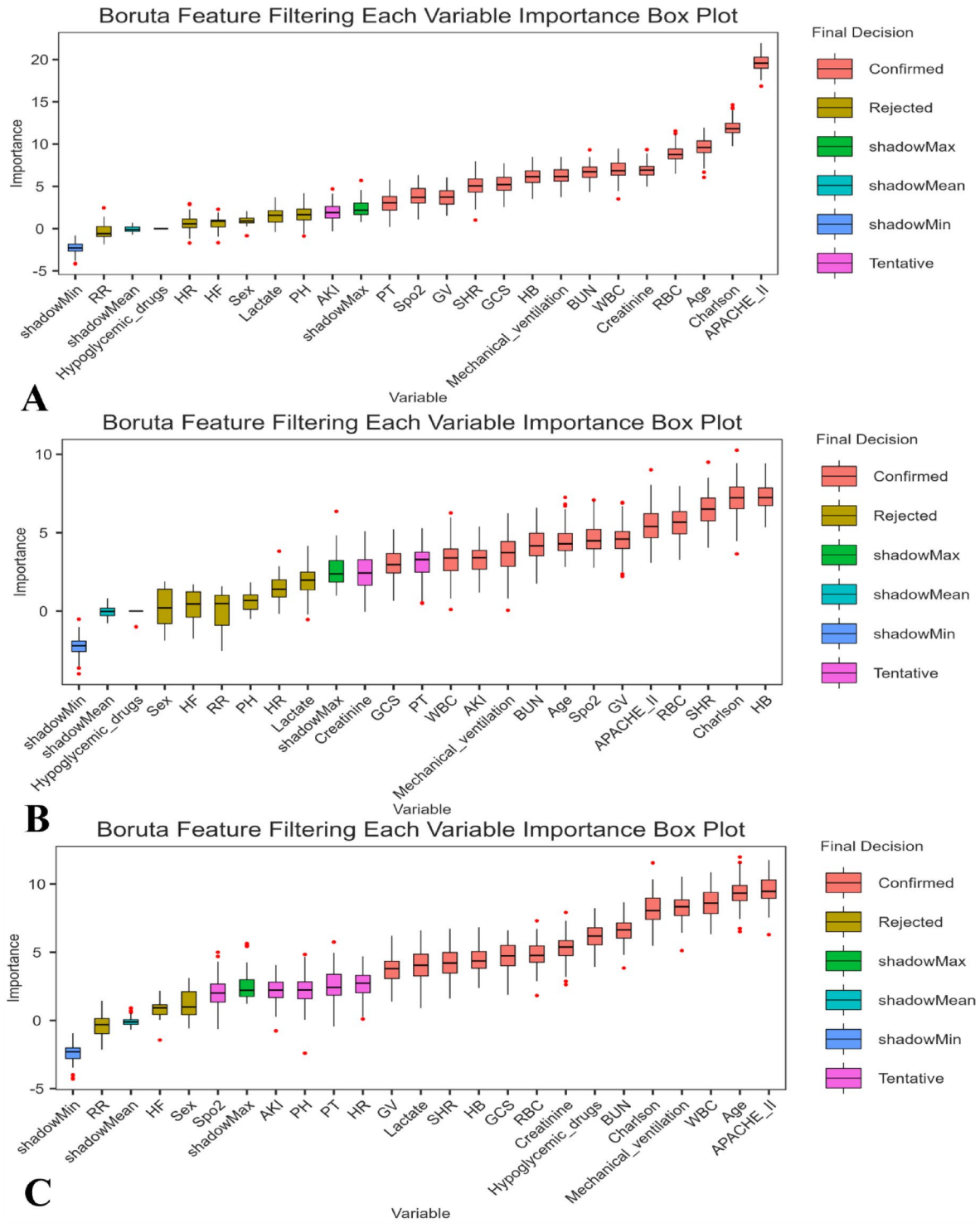


Fig. 7 The Boruta algorithm ranks the importance of potential risk factors for 28-day mortality.The x-axis delineates parameter nomenclature, whereas the y-axis quantifies standardized scores (Z-scores) across variables. Boxplot distributions graphically depict the dispersion characteristics of normalized values during model computation cycles. **A** patients with NGR **B** patients with Pre-DM **C** patients with DM

between GV and mortality across all subgroups. Intriguingly, the highest 28-day mortality risks were identified in NGR patients with high SHR/high GV profiles and Pre-DM patients with low SHR/high GV profiles. In contrast, combined SHR-GV metrics lacked prognostic significance in the DM subgroup. ROC analysis showed that in the NGR and Pre-DM cohorts, the combination of SHR and GV outperformed SHR alone or GV alone in

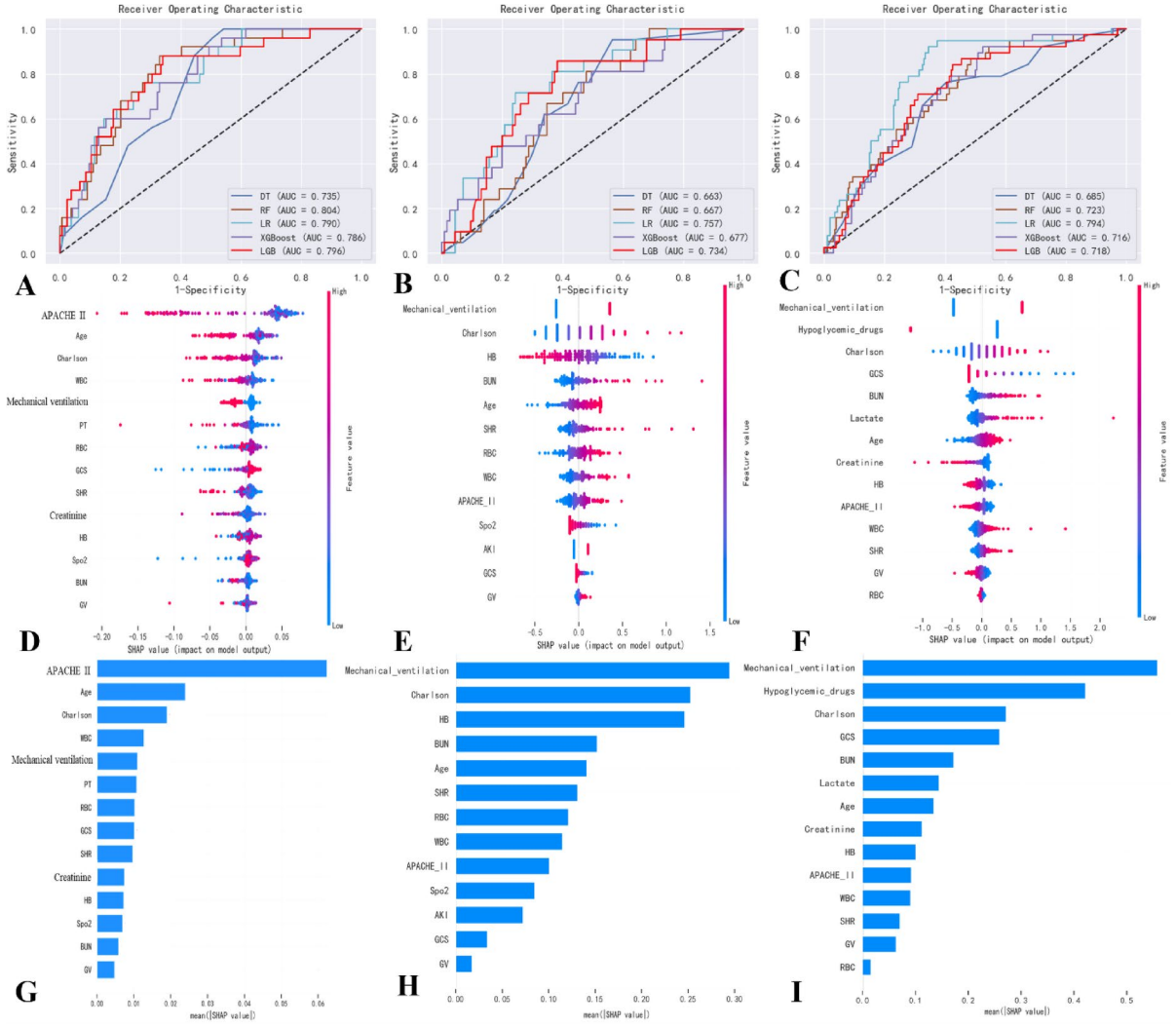


Fig. 8 ROC curves and SHAP interpretation of ML-based 28-day mortality prediction models. **A**, **D**, **G** patients with NGR; **B**, **E**, **H** patients with Pre-DM; **C**, **F**, **I** patients with DM. LR, logistic regression; DT, decision tree; RF, random forest; XGBoost, extreme gradient boosting; LightGBM, light gradient boosting machine

predictive performance, while in DM patients, the combined assessment was only superior to SHR in predicting 90-day mortality. Landmark survival analysis further demonstrated that combined metrics gained statistical significance after day 4 of ICU admission in Pre-DM patients. SHAP-based interpretation of machine learning models corroborated these findings, underscoring the clinical utility of dual SHR-GV assessment for risk stratification and glycemic management in heterogeneous populations.

Current evidence predominantly focuses on SHR and GV in critically ill cohorts. Stress hyperglycemia, a hallmark of disease severity in critical illness [32, 33], drives inflammatory cytokine modulation and oxidative stress amplification [34]. Chen et al. [15] identified SHR as an independent predictor of ICU mortality in cerebrovascular patients, particularly non-diabetics. Duan et al. [35] linked elevated SHR to early neurological deterioration post-thrombolysis in acute stroke, while NHANES data revealed J-/U-shaped SHR-mortality relationships for all-cause and cardiovascular deaths [36]. Cheng et al. [37] reported U-shaped associations between SHR and mortality up to 365 days in severe atrial fibrillation. A meta-analysis of 87,974 AMI patients demonstrated increased major adverse cardio-cerebrovascular events (MACCE) risks with upper-quartile SHR [38, 39]. Zhihan Lyu further associated elevated SHR with adverse events in 12,899 non-cardiac surgical patients, especially non-diabetic [40]. Glycemic variability has similarly been implicated in adverse outcomes. Su et al. [41] identified high GV as an independent in-hospital mortality predictor in 17,756 ICU patients, correlating with hypoglycemic/hyperglycemic events. He et al. [27] demonstrated that non-diabetic CAD patients with elevated SHR/GV faced

the poorest prognoses, whereas diabetic patients with high SHR but low GV exhibited highest mortality. Cumulatively, these findings advocate for integrated SHR-GV assessment to refine risk prediction and personalize glycemic management in critical care.

Stress-induced hyperglycemia is primarily driven by sympathetic nervous system hyperactivation, triggering substantial release of epinephrine, norepinephrine, and cortisol. These hormones promote glycogenolysis and gluconeogenesis, elevating blood glucose levels [42]. Concurrently, they exacerbate oxidative stress, accelerate atherosclerosis, and induce endothelial injury—key mechanisms amplifying cardiovascular pathogenesis [17, 36, 43]. In diabetic patients, elevated plasminogen activator inhibitor-1 (PAI-1) levels and impaired nitric oxide (NO)-mediated antiplatelet responses contribute to platelet dysfunction, partially explaining hypercoagulability and heightened thrombotic risk under hyperglycemia [44, 45]. Stress hyperglycemia may also disrupt the blood-brain barrier via intracellular acidosis, leading to mitochondrial dysfunction, energy depletion, and apoptosis—critical drivers of adverse post-stroke outcomes [46]. GV exacerbates plaque vulnerability through inflammatory pathway activation and oxidative stress [47], while promoting cardiac fibrosis, adverse ventricular remodeling, and sympatho-adrenal-mediated ischemic events [27].

HbA1c serves as a well-validated biomarker of cumulative glycemic exposure over the preceding 8–12 weeks, which can be translated into eAG concentrations for this period [48]. In contrast to absolute hyperglycemia, the association between relative hyperglycemia (defined as acute glucose elevation contextualized against chronic glycemic baselines) and critical illness outcomes remains independent of background glucose status [49]. The SHR operationalizes this concept by integrating chronic glycemic status (derived from HbA1c) with acute glucose dysregulation, thereby allowing it to distinguish acute stress-mediated hyperglycemia (e.g., triggered by systemic inflammation or endocrine activation during critical illness) from chronic hyperglycemia (e.g., diabetes-related dysregulation). By quantifying the magnitude of acute glucose excursions beyond chronic baselines, SHR specifically captures the added mortality risk attributable to transient metabolic crises that directly exacerbate short-term outcomes in critically ill populations.

Given the prognostic significance of stress-induced hyperglycemia and acute glycemic fluctuations, integrated evaluation of SHR and GV may refine risk stratification in critically ill populations. This study demonstrated significant associations between combined SHR-GV metrics and adverse outcomes in NGR and Pre-DM subgroups with ASCVD, whereas no such associations were observed in the DM cohort. These findings corroborate the hypothesis that non-diabetic individuals exhibit heightened vulnerability to glycemic variability-related complications compared with diabetic patients [37, 50–52]. Mechanistically, diabetic patients may develop adaptive tolerance to glucose fluctuations through chronic oxidative stress exposure and expanded harm thresholds (lower hypoglycemia/higher hyperglycemia limits) [27, 51], while insulin-treated diabetics may retain superior anti-inflammatory resilience [53, 54]. In non-diabetic individuals, acute glycemic fluctuations significantly exacerbate oxidative stress and induce endothelial dysfunction [55]. Conversely, patients with diabetes—owing to chronic hyperglycemia—may exhibit diminished sensitivity to acute glucose fluctuations [15]. Furthermore, DM patients more frequently receive intensive glucose management (e.g., insulin protocols, oral hypoglycemics), which may artificially suppress SHR values and obscure its prognostic signal.

Notably, GV alone showed no mortality association after multivariable adjustment, potentially attributable to the following: (1) This study introduces a novel application of CV-quantified GV to assess mortality risk in patients with ASCVD. Importantly, GV demonstrated no prognostic value in either diabetic or non-diabetic subgroups, despite the predictive utility of SHR. This aligns with findings by Yoo et al. [56], who reported no association between 10-year ASCVD risk and traditional GV metrics, suggesting that GV itself may have limited pathophysiological relevance in this context rather than reflecting data artifacts. (2) The MIMIC-IV database does not include meal timing, making it impossible to distinguish pre-prandial versus post-prandial glucose measurements. Unstandardized sampling could introduce noise from non-physiological fluctuations. Intriguingly, while GV alone showed limited predictive utility, its integration with SHR improved risk stratification in NGR/Pre-DM subgroups, consistent with prior evidence in coronary artery disease cohorts. Combining SHR-GV assessment enhanced risk stratification, suggesting synergistic prognostic effects through distinct pathways—acute metabolic dysregulation versus chronic glycemic oscillations [27]. Future studies should explore additional GV metrics [e.g., variation independent of mean (VIM), average real variability (ARV)] to further validate these findings.

Our findings demonstrate that the combined assessment of SHR and GV provides synergistic prognostic value through complementary pathophysiological mechanisms: SHR quantifies acute hyperglycemic stress relative to chronic glycemic control, while GV captures destabilizing glucose fluctuations that exacerbate oxidative damage [10, 16]. This interaction is particularly pronounced in non-diabetic (NGR/Pre-DM) patients, in whom the absence of chronic hyperglycemic adaptation amplifies the mortality risk of acute dysregulation.

Statistically, the SHR + GV model demonstrated superior discrimination in these subgroups. Machine learning validation and SHAP analysis further confirmed GV's incremental prognostic contribution, despite its lower feature weight relative to SHR. Methodologically, the absence of multicollinearity supports robust variable independence. Notably, our results align with recent evidence from He et al. [27], who reported extreme mortality risks (OR 10.83 for in-hospital death; HR 5.83 for 1-year mortality) in non-diabetic coronary patients with elevated SHR/GV. The integration of GV with SHR provides a clinically actionable framework for glycemic risk stratification in critically ill patients with ASCVD without diabetes. Landmark survival analysis demonstrated limited prognostic utility of combined SHR-GV assessment for mortality during the initial 4 days of ICU admission in Pre-DM patients. However, divergent mortality risks emerged post-day 4, potentially mediated by early stress response mechanisms. During this critical phase, catecholamine and cortisol surges may drive transient hyperglycemia to prioritize energy allocation to vital organs [57], with elevated SHR reflecting preserved metabolic adaptability rather than glucose dysregulation. Early interventions (e.g., vasoactive agents, fluid resuscitation) may induce hemodynamic instability-linked glycemic fluctuations, though such perturbations are often transient and physiologically contained without cumulative damage.

Strengths and limitations

Our study advances critical care metabolomics research through three innovations. First, we demonstrate that glycemic phenotype modifies the prognostic utility of SHR and GV, a novel finding overlooked in prior unstratified ICU analyses. The synergistic mortality prediction improvement from combined SHR-GV assessment in NGR/Pre-DM patients contrasts sharply with the attenuated associations observed in diabetics, compellingly arguing for phenotype-tailored glucose monitoring protocols. Second, the SHAP-based machine learning framework extends beyond conventional Cox regression by providing visually intuitive quantification of variable-specific contributions to clinical outcomes. Third, landmark analysis was applied to evaluate time-dependent variations in the prognostic impact of SHR and GV across different hospitalization durations in patients with ASCVD.

However, this study has several limitations. First, while our methods aimed to minimize bias, residual confounding from unmeasured variables may persist. Second, selection bias might have been introduced by excluding patients with missing HbA1c data or inadequate glycemic measurements. Third, this study uses a cross-sectional design, which precludes assessing dynamic changes in clinical parameters over time. Future longitudinal studies integrating serial measurements are needed to characterize the temporal trajectories of therapeutic responses in the critically ill population. Fourth, although comprehensive analytical methods were employed, the cohort predominantly comprised White (non-Hispanic) participants, limiting the generalizability of our findings to other racial and ethnic populations.

Conclusion

This study demonstrates that combined assessment of SHR and GV serves as a robust prognostic tool for mortality risk stratification in patients with ASCVD, with significantly enhanced predictive accuracy observed in NGR and Pre-DM subgroups. These findings advocate for personalized glycemic management strategies tailored to individual metabolic phenotypes, providing a framework to optimize clinical outcomes through precision medicine approaches.

Abbreviations

AKI	Acute kidney injury
AMI	Acute myocardial infarction
APACHE II	Acute physiology and chronic health evaluation II
ASCVD	Atherosclerotic cardiovascular disease
AUC	Area under the curve
ARV	Average real variability
BUN	Blood urea nitrogen
CAD	Coronary artery disease
CCI	Charlson comorbidity index
CI	Confidence interval
COPD	Chronic obstructive pulmonary disease
CVD	Cardiovascular disease
DM	Diabetes mellitus
GCS	Glasgow coma scale
GV	Glycemic variability
HbA1c	Glycated hemoglobin
HF	Heart failure
HR	Hazard ratio
HTN	Hypertension
ICU	Intensive care unit
IHD	Ischemic heart disease
MACCE	Major adverse cardio-cerebrovascular events
MIMIC-IV	Medical information mart for intensive care IV
ML	Machine learning
NGR	Normal glucose regulation
PAI-1	Plasminogen activator inhibitor-1
Pre-DM	Pre-diabetes mellitus
RBC	Red blood cell
RCS	Restricted cubic splines
ROC	Receiver operating characteristic
SHR	Stress hyperglycemia ratio
SHAP	Shapley additive explanations
SOFA	Sequential Organ Failure Assessment
VIM	Variation independent of mean
WBC	White blood cell

Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02762-0.

Supplementary Material 1

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None.

Author contributions
FXW designed the study and analyzed the data.YG and YRT drafted the manuscript. SMZ, KGX and ZM proposed significant revisions to the manuscript. RGL, RYH and XYZ proofread the article and performed the technical review. All authors contributed to the manuscript and approved the submitted version. All authors read and approved the final manuscript.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
This study was carried out in accordance with the guidelines of the Helsinki Declaration. The utilization of the MIMIC-IV database obtained approval from the review committee of Massachusetts Institute of Technology and Beth Israel Deaconess Medical Center. Since the data is publicly accessible within the MIMIC-IV database, the ethical approval statement and the need for informed consent were exempted for this particular study.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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