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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

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Abstract

Background Glycemic control is critical for managing transcatheter aortic valve replacement (TAVR) patients, especially those in intensive care units (ICUs). Emerging metrics such as the hemoglobin glycation index (HGI), stress hyperglycemia ratio (SHR), and glycemic variability (GV) offer advanced insights into glucose metabolism. However, their prognostic implications for short- and long-term outcomes post-TAVR remain underexplored.

Methods This retrospective cohort study analyzed 3342 ICU-admitted TAVR patients via the MIMIC-IV database. Patients were stratified into tertiles for HGI, SHR, and GV levels. Survival analyses, including Kaplan–Meier curves, Cox proportional hazards models and restricted cubic splines (RCSs), were used to assess associations between glycemic control metrics and 30-day and 365-day all-cause mortality in these patients. Sensitivity analyses, subgroup assessments, and external validation were also performed to verify the study findings.

Results During follow-up, 1.6% and 6.9% of patients experienced 30-day and 365-day mortality after TAVR, respectively. In the fully adjusted cox regression model, lower HGI (HR 1.48, 95% CI 1.05–2.09, $P=0.025$) and higher SHR (HR 1.63, 95% CI 1.15–2.32, $P=0.006$) were most significantly associated with an increased risk of 365-day mortality. Higher SHR was also significantly associated with an increased risk of 30-day mortality in patients (HR 2.92, 95% CI 1.32–6.45, $P=0.008$). Both lower (HR 0.59, 95% CI 0.38–0.92, $P=0.019$) and higher GV levels (HR 1.43, 95% CI 1.06–1.93, $P=0.020$) were associated with the risk of 365-day mortality.

Conclusions In critically ill TAVR patients, glycemic control metrics are closely associated with long-term all-cause mortality. The HGI, SHR, and GV provide prognostic insights into clinical outcomes that surpass conventional glucose

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measurements. These findings highlight the importance of personalized glycemic management strategies in improving TAVR patient outcomes.

Keywords Hemoglobin glycation index, Stress hyperglycemia ratio, Glycemic variability, Transcatheter aortic valve replacement, Postoperative outcomes, ICU

Introduction

The prevalence of valvular heart disease (VHD) is increasing globally as the proportion of the population aged 60 years and over continues to grow. Aortic valve disease is one of the most common valvular heart diseases in Western countries, with no pharmacologic cure [1]. Transcatheter aortic valve replacement (TAVR) has emerged as a breakthrough treatment that reduces operative risk and is gradually becoming a noninferior surgical alternative for patients with aortic stenosis who are not suitable for surgery or who are at high surgical risk for SAVR, as well as for patients with simple degenerative aortic regurgitation [2, 3]. A substantial body of existing research has substantiated the assertion that TAVR is associated with enhanced long-term clinical outcomes and quality of life following the procedure [4, 5]. However, patients with aortic valve disease are likely to be treated in an intensive care unit (ICU) after cardiac surgery, and several perioperative clinical and procedure-related factors, such as perivalvular leakage due to intraoperative valve implantation that is too large or implantation that is too small, the development of postoperative acute kidney injury (AKI), and hyperglycemia or hypoglycemia, are likely to be short- and long-term prognostic risk factors after TAVR [6–9]. In particular, hyperglycaemia as one of the risk factors for the progression of aortic valve calcification and stenosis, which is also considered playing an instrumental role in the deterioration of the prognosis after TAVR [10]. However, tight glycaemic control tends to be associated with a high incidence of hypoglycaemia, and uncontrolled hypoglycaemia poses a higher risk of death for critically ill patients who receive cardiac surgery [11]. Therefore, monitoring and managing glycemic fluctuations during the perioperative period may be of greater clinical importance for risk prediction and prognostic assessment after TAVR.

Updated indicators related to glucose control, such as Hemoglobin Glycation Index (HGI), Stress Hyperglycemia Ratio (SHR) and Glycemic Variability (GV), have received increasing attention in recent years. The HGI refers to the discrepancy between the actual measured and predicted glycosylated hemoglobin (HbA1c) values. It has been demonstrated that the HGI is an effective means of quantifying the differences between individuals in HbA1c and the changes in the relationship between HbA1c and mean serum glucose concentration [12, 13], which is less susceptible by factors such as mean erythrocyte lifespan, enzyme abnormalities and genetic variations in hemoglobin [14, 15]. This makes it a more accurate reflection of the state of glucose metabolism. Subsequently, stress hyperglycaemia is delineated as a transient metabolic response typified by elevated blood glucose levels in emergency situations. It is postulated that an elevated SHR is a superior indicator of the acute hyperglycaemic state than absolute hyperglycemia [16]. The GV, defined as a component of glycaemic homeostasis, is used to reflect the fluctuation and control of blood glucose over a period of time [17]. It can represent one of the main manifestations of dysglycaemia in critically ill patients. In addition, many studies have shown that HGI, SHR, and GV have been identified to be associated with in-hospital mortality or major cardiovascular events in patients with a range of cardiovascular diseases, including coronary atherosclerotic heart disease, acute myocardial infarction, cardiac arrest, and hypertension [18, 19].

Controlling serum glucose during the postoperative crisis period is particularly important for the survival of TAVR patients in the ICU. However, there are still few studies on the impact of these indicators reflecting the status of serum glucose control on the prognosis of TAVR patients. Given the value of HGI, SHR, and GV in reflecting the blood glucose control status in critical conditions, this study aims to use the MIMIC-IV database to comprehensively explore the impact of the three indicators on the short-term and long-term clinical outcomes of critically ill patients after TAVR surgery. In addition, a subgroup method was used to evaluate the correlation between serum glucose control indicators and adverse postoperative prognosis in different subgroups, and to develop new risk stratification monitoring indicators for postoperative serum glucose management in TAVR patients.

Methods

Data source

The data for this study were obtained from the version 3.1 Medical Information Marketplace in Critical Care (MIMIC)-IV database (https://mimic.mit.edu/), a comprehensive, open-access, de-identified healthcare data repository comprising a total of 94,458 patients admitted to ICUs from 2008 to 2022. The shared nature of this repository has been vetted by the Institutional Review Board of Beth Israel Deaconess Medical Center [20]. One of the authors of this study (HW) obtained access to the database (ID: 59123180) and acquired the data. This study was conducted in accordance with the Declaration

of Helsinki for the identification of data from the MIMIC-IV database, and informed consent was not required as the analysed data were anonymous. In order to better verify the results of the MIMIC-IV database analysis and make some supplements, we retrospectively included the electronic medical records of patients admitted to the ICU after TAVR surgery in the Second Affiliated Hospital of Nanchang University from January 2019 to January 2023. All the operations on the patients who underwent TAVR in this center were performed by two senior professors with more than 5 years of rich experience in TAVR operations. This study has been approved by the Institutional Review Board of the Second Affiliated Hospital of Nanchang University, China, and all patients have signed informed consent. All patients have been followed up for 365 days, and the data themselves have been de-identified.

Study population

All patients included in this study underwent transcatheter aortic valve replacement (TAVR) and were admitted to the intensive care unit (ICU) for the first time. Additionally, we excluded patients based on the following criteria: medical record of readmission to the ICU (n = 29,092), age under 18 years (n = 0), lack of hemoglobin A1c and blood glucose data (n = 416), and fewer than three blood glucose measurements during the ICU stay (n = 540). The final number of patients included in the study was 2,428. A brief flowchart of the inclusion and exclusion process is presented in Fig. 1. The same inclusion and exclusion criteria were applied to single-center data collected by the Second Affiliated Hospital of Nanchang University, and a total of 122 patients admitted to the ICU after TAVR were included for external validation.

Data extraction and definitions

In this study PostgreSQL (version 16.0) and Structured Query Language (SQL) were used to retrieve and obtain baseline data on the study individuals of MIMIC-IV database, including demographic indicators, laboratory tests, critical care scores, medication use, comorbidities, history of previous surgery and survival information. In the dataset of the Second Affiliated Hospital of Nanchang University, in addition to demographic indicators, laboratory tests, intensive care unit scores, medication use, comorbidities, previous surgical history, and survival information, we also added variables such as anesthesia method, surgical route, and implanted valve model and size for analysis. Missing values for variables less than 10% were filled in using random forest interpolation. We screened patients treated TAVR by retrieving surgical records for TAVR from the list of surgical

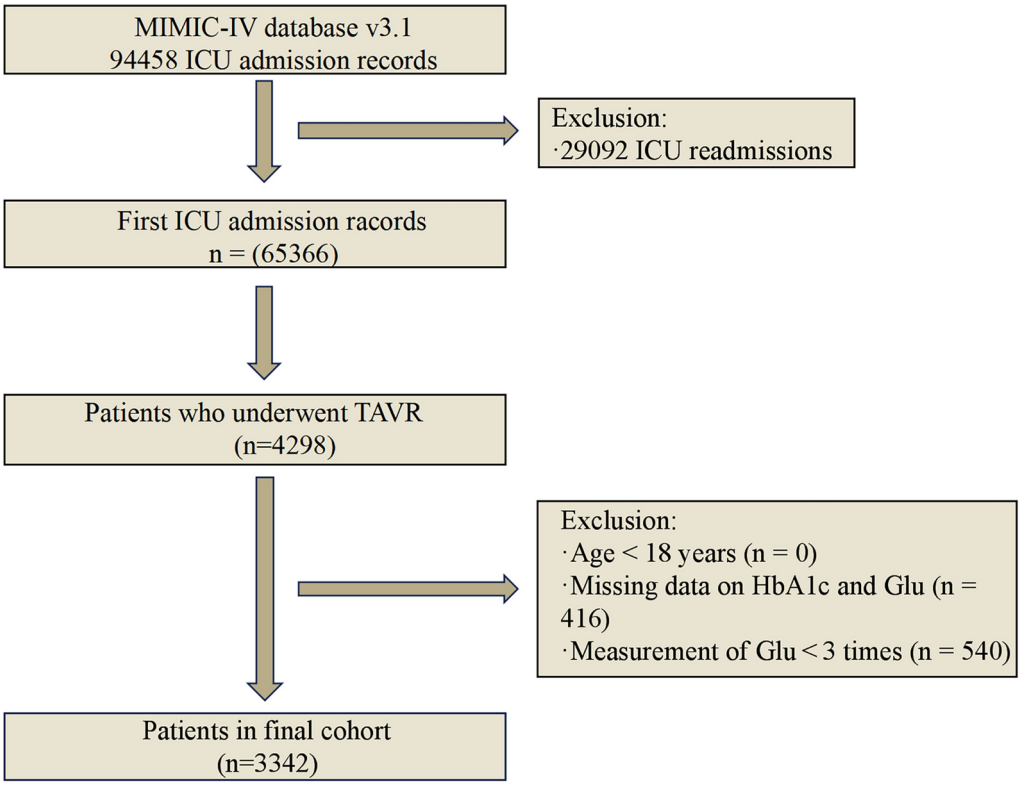

Fig. 1 Flowchart of patient inclusion and exclusion from the MIMIC-IV database. Abbreviations: MIMIC-IV, Medical Information Mart for Intensive Care-IV; ICU, intensive care unit; TAVR, Transcatheter aortic valve replacement; HbA1c, glycosylated hemoglobin; Glu, blood glucose

records in the database. The remaining comorbidities were determined based on ICD-9 and ICD-10 numbers in the International Classification of Diseases, and diabetes mellitus(DM) was identified through the Charlson comorbidity view in the MIMIC-IV database. Subsequently, CHD was defined as the sum of acute coronary syndromes, coronary artery bypass surgery, percutaneous coronary intervention, myocardial infarction, and ischaemic heart disease. The ICD diagnostic codes for cardiogenic shock(CS) included in this study include 78551, 99801, R570, T8111, T8111XA, T8111XS and T8111XD. The fasting plasma glucose (FPG) value used in this study was the first fasting blood glucose measurement after the patient was admitted to the ICU. The remaining blood glucose values may come from fingertip blood glucose, serum blood glucose, and whole blood glucose measurements. HGI represents the difference between the observed and predicted HbA1c values, where the predicted HbA1c is derived from a linear regression model based on baseline FPG. The predictive equation is given as: predicted $HbA1c = 0.009 \times FPG + 4.940$[21]. The correlation between HGI and HbA1c is shown in Fig. 2. The formula used to calculate the SHR is as follows: $SHR = FPG/(28.7 \times HbA1c - 46.7)$ [16]. GV was defined as the coefficient of variation of blood glucose, expressed as a percentage. It was calculated as the ratio of the standard deviation to the mean of all repeated blood glucose measurements during the ICU stay (standard deviation/mean × 100) [22].

Study endpoint

The key clinical outcome of this study was long-term all-cause mortality, defined as death within 365 days following ICU admission for TAVR patients. The additional clinical outcome was short-term all-cause mortality, defined as death within 30 days of ICU admission. The final follow-up for all patients included in the analysis was conducted one year after their last hospital discharge. Information regarding mortality was obtained from state or hospital death records.

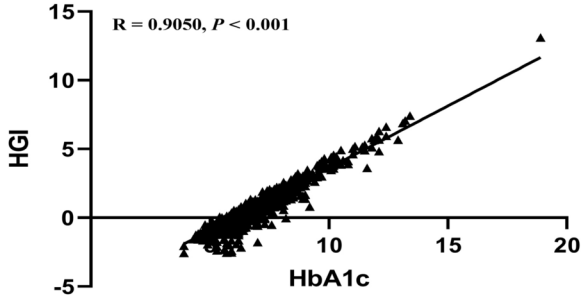

Fig. 2 Linear correlation between the HGI and HbA1c levels, HbA1c, glycosylated hemoglobin; HGI, hemoglobin glycation index

Statistical analysis

We categorized HGI, SHR, and GV into three groups based on their distribution trends (HGI: Q1:– 0.408 to 0.029, Q2: <– 0.408, Q3: > 0.029; SHR: Q1: 0.832 to 0.985, Q2: < 0.832, Q3: > 0.985; GV: Q1: 15.64% to 23.30%, Q2: < 15.64%, Q3: > 23.30%). In the baseline data analysis, continuous variables with a normal distribution were expressed as means ± standard deviation, while non-normally distributed continuous variables were presented as median (interquartile range). Categorical variables were reported as frequency (percentage). For group comparisons, we used the Mann–Whitney U test, chi-square test, and Fisher's exact test as appropriate. The Kruskal–Wallis H test was used to compare outcomes between the deceased and surviving groups. In the survival analysis, Kaplan–Meier (K–M) curves were used to illustrate survival trends over 30 days and 365 days for different HGI, SHR, and GV groups. We then conducted univariate Cox regression analysis to further elucidate the relationship between HGI, SHR, and GV levels and all-cause mortality within the 30-day and 365-day time frames. To account for potential confounders in the Cox regression models, we applied multivariate Cox regression with adjustments for various covariates. In Model 1, no adjustments were made. Model 2 adjusted for covariates including age, gender (male, female), body mass index (BMI), atrial fibrillation (AF; yes, no), DM (yes, no), myocardial infarction (MI; yes, no), CS (yes, no), AKI (yes, no), peripheral vascular disease (PVD; yes, no), malignancy (MC; yes, no), percutaneous coronary intervention (PCI; yes, no). Model 3 further adjusted for covariates such as Oxford Acute Severity of Illness Score (OASIS), use of beta-blockers (yes, no), clopidogrel (yes, no), warfarin (yes, no), insulin (yes, no), dipeptidyl peptidase-4 inhibitors (DDP-IV inhibitors; yes, no), other hypoglycemic drugs (yes, no), dopamine (yes, no), dobutamine (yes, no), loop diuretics (yes, no), heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), glycated hemoglobin (HbA1c), N-terminal pro-brain natriuretic peptide (proBNP), creatinine (Cre), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and potassium levels.. In addition, restricted cubic spline (RCS) plots with three knots and threshold effect analysis were used to identify potential inflection points to assess the linear or nonlinear relationships between clinical outcomes and the levels of HGI, SHR, and GV as continuous variables. To further determine whether the associations between HGI, SHR, and GV levels and key outcomes differed among different populations and to identify potential interactions, we performed subgroup and interaction analyses based on sex, age (< 65 years or ≥ 65 years), BMI (< 25 kg/m^2 or ≥ 25 kg/m^2), AF, DM, CHD, AKI, CS, and Oxford Acute Severity of Illness Score (OASIS) score (< 36 or ≥ 36). Forest plots were used to visualize the results, and sensitivity analyses

were performed to demonstrate the robustness of the results. Finally, we plotted time-dependent ROC curves to visualize the predictive value of single HGI, SHR, and GV indicators for short-term and long-term outcomes. All analyses were performed using the R programming environment (R Foundation for Statistical Computing, Vienna, Austria, version 4.4.0), with two-sided *P* values less than 0.05 considered statistically significant.

Results

Baseline characteristics

A total of 3342 patients were included in the analysis. The baseline characteristics of the study population are presented in Table 1. The median age of the cohort was 71 years, with 2162 patients (64.7%) identified as male. Hypertension was prevalent in 2766 patients (82.8%), while atrial fibrillation was present in 1930 patients (57.8%). Non-survivors, in comparison to survivors, were generally older, had more unstable vital signs, faster heart and respiratory rates, higher pro-BNP levels, higher OASIS scores, and lower oxygen saturation. In addition, patients who died were more likely to have comorbidities such as CHD, CS, PVD, COPD, or AKI, more likely to have a history of PCI, and less likely to use medications such as beta-blockers, diuretics, antiplatelets, and vasopressors. In addition, patients who died had higher GV, HbA1c, and blood glucose levels, and lower baseline red blood cell count, hemoglobin, serum creatinine, and HDL cholesterol levels. (Table 1). Among the 122 patients admitted to the ICU after TAVR in the Second Affiliated Hospital of Nanchang University, the median age was 72.123 years old, with 72 males and 50 females. Among them, 6 died during the 30-day follow-up period and 10 died during the 365-day follow-up period. Compared with surviving patients, deceased patients tend to have significantly higher age, pro-BNP, Cre, EuroSCORE scores and GV values, lower blood oxygen saturation, aspirin and antiplatelet drug medication rates, etc., and are more likely to have complications such as DM, CS, COPD, etc. The baseline results of the external data set can be found in Supplementary Table 4.

Association between glycemic control metrics and endpoint events

During the 30-day follow-up, 54 patients (1.6%) died, and during the 365-day follow-up, 229 patients (6.9%) died. Kaplan–Meier survival curves based on tertiles of HGI, SHR, and GV were used to compare the incidence of key outcomes and additional outcomes between groups (Fig. 3). In the HGI analysis, the 365-day mortality rate in the Q1 group was significantly lower than that in the other two groups, and the difference was statistically significant (log-rank $P = 0.009$), suggesting that both high and low HGI levels were associated with poor long-term survival in TAVR patients, and high HGI was particularly harmful (Fig. 3D). However, there was no significant difference in 30-day mortality between groups (Fig. 3A). In contrast, both high and low SHR levels were significantly associated with higher mortality during the 30-day (log-rank $P = 0.0019$) and 365-day (log-rank $P < 0.0001$) follow-up periods (Fig. 3B and E) Furthermore, GV levels were positively correlated with both short-term and long-term mortality, with higher GV levels being associated with worse survival outcomes (log-rank $P < 0.001$), an association that remained consistent at 30- and 365-day follow-up (Fig. 3C and F). However, in the KM curve of the external validation data, we only observed a significant positive correlation between GV and 365-day mortality (log-rank $P = 0.043$). Although the trends of mortality in the HGI and SHR groups at 30 and 365 days were consistent with the KM curves of the MIMIC-IV dataset, they did not reach significant statistical differences (log-rank $P > 0.05$). The results are shown in Supplementary Fig. 3.

Comparison of the baseline characteristics of the patients revealed significant differences in the key outcomes between subgroups with different levels of HGI, SHR, and GV. Further survival analysis showed that the Q1 subgroup in HGI and SHR had the lowest mortality rate compared with other subgroups. Therefore, a Cox regression hazard model was constructed with the Q1 subgroup as the reference point to analyze the association between HGI, SHR, GV and clinical outcomes. In the unadjusted Cox proportional hazard model 1, both the HGI Q2 group (HGI < − 0.408) and the Q3 group (HGI > 0.029) were significantly associated with the key outcomes (Q1 vs. Q2: HR, 1.46 [1.04–2.06], $P = 0.028$; Q1 vs. Q3: HR, 1.66 [1.19–2.32], $P = 0.003$), but no significant association with 30-day mortality was observed. After fully adjusting for confounders, only the Q2 group remained significant (Q1 vs. Q2: HR, 1.48 [1.05–2.09], $P = 0.025$), indicating that lower HGI levels were risk factors for 365-day mortality in patients. Subsequently, in the SHR group, compared with the reference subgroup Q1 (SHR: 0.832 to 0.985), the Q3 subgroup (SHR > 0.985) showed significantly higher 30-day and 365-day mortality risks in model 1 (unadjusted), model 2 (adjusted for some confounders), and model 3 (further adjusted for other confounders). Similarly, in the GV group, the Q2 subgroup (GV < 15.64%) and Q3 subgroup (GV > 23.30%) were significantly associated with both 30-day and 365-day mortality in model 1. However, after adjusting for confounding factors in models 2 and 3, the association between the Q2 and Q3 subgroups in GV and 30-day mortality was no longer statistically significant, and the strong correlation with 365-day mortality still existed. The Q2 group of GV was negatively correlated with long-term mortality, while the Q3 group was positively correlated with long-term mortality, which indicated

Table 1 Baseline characteristics of study population

Variable	Overall (n = 3342)	30-day			365-day		
		Survivors (n = 3288)	Non-survivors (n = 54)	*p* value	Survivors (n = 3113)	Non-survivors (n = 229)	*p* value
Age (years)	71.0 (62.0, 79.0)	71.0 (62.0, 79.0)	78.0 (69.0, 83.0)	0.002	71.0 (62.0, 79.0)	77.0 (68.0, 84.0)	< 0.001
Gender (%)				0.553			0.402
Male	2162 (64.7)	2125 (64.6)	37 (68.5)		2008 (64.5)	154 (67.3)	
Female	1180 (35.3)	1163 (35.4)	17 (31.5)		1105 (35.5)	75 (32.8)	
BMI (kg/m^2)	28.2 (24.9, 32.1)	28.2 (24.9, 32.1)	27.0 (23.2, 30.1)	0.098	28.3 (25.0, 32.3)	26.4 (23.5, 30.0)	< 0.001
DM (%)				0.086			0.058
No	2222 (66.5)	2192 (66.7)	30 (55.6)		547 (17.6)	29 (12.7)	
Yes	1120 (33.5)	109 6(33.3)	24 (44.4)		2566 (82.4)	200 (87.3)	
HTN (%)				0.911			0.156
No	576 (17.2)	567 (17.3)	9 (16.7)		450 (19.8)	22 (14.7)	
Yes	2766 (82.8)	2721 (82.8)	45 (83.3)		1,828 (80.2)	128 (85.3)	
Hyperlipidemia (%)				0.059			0.218
No	919 (27.5)	898 (27.3)	21 (38.9)		848 (27.2)	71 (31.0)	
Yes	2423 (72.5)	2390 (72.7)	33 (61.1)		2265 (72.8)	158 (69.0)	
CHD (%)				< 0.001			< 0.001
No	1662 (49.7)	1649 (50.2)	13 (24.1)		1614 (51.9)	48 (21.0)	
Yes	1680 (50.3)	1639 (49.9)	41 (75.9)		1499 (48.2)	181 (79.0)	
MI (%)				0.197			< 0.001
No	3019 (90.3)	2973 (90.4)	46 (85.2)		2830 (90.9)	189 (82.5)	
Yes	323 (9.7)	315 (9.6)	8 (14.8)		283 (9.1)	40 (17.5)	
AF (%)				0.959			0.009
No	1412 (42.3)	1389 (42.3)	23 (42.6)		1334 (42.9)	78 (34.1)	
Yes	1930 (57.8)	1899 (57.8)	31 (57.4)		1779 (57.2)	151 (65.9)	
HF (%)				< 0.001			< 0.001
No	1781 (53.3)	1767 (53.7)	14 (25.9)		1727 (55.5)	54 (23.6)	
Yes	1561 (46.7)	1521 (46.3)	40 (74.1)		1386 (44.5)	175 (76.4)	
CS (%)				< 0.001			< 0.001
No	3055 (91.4)	3020 (91.9)	35 (64.8)		2880 (92.5)	175 (76.4)	
Yes	287 (8.6)	268 (8.2)	19 (35.2)		233 (7.5)	54 (23.6)	
PVD (%)				0.131			0.004
No	2353 (70.4)	2320 (70.6)	33 (61.1)		2211 (71.0)	142 (62.0)	
Yes	989 (29.6)	968 (29.4)	21 (38.9)		902 (29.0)	87 (38.0)	
MC (%)				0.897			0.004
No	3049 (91.2)	3000 (91.2)	49 (90.7)		2852 (91.6)	197 (86.0)	
Yes	293 (8.8)	288 (8.8)	5 (9.3)		261 (8.4)	32 (14.0)	
COPD (%)				0.538			< 0.001
No	2295 (68.7)	2260 (68.7)	35 (64.8)		2165 (69.6)	130 (56.8)	
Yes	1047 (31.3)	1028 (31.3)	19 (35.2)		948 (30.5)	99 (43.2)	
AKI (%)				< 0.001			< 0.001
No	2234 (66.9)	2219 (67.5)	15 (27.8)		2153 (69.2)	81 (35.4)	
Yes	1108 (33.2)	1069 (32.5)	39 (72.2)		960 (30.8)	148 (64.6)	
PCI (%)				0.649			0.016
No	3143 (94.0)	3093 (94.1)	50 (92.6)		2936 (94.3)	207 (90.4)	
Yes	199 (6.0)	195 (5.9)	4 (7.4)		177 (5.7)	22 (9.6)	
Temperature (℃)	36.7 (36.4, 36.9)	36.7 (36.4, 36.9)	36.7 (36.5, 36.9)	0.464	36.7 (36.4, 36.9)	36.6 (36.4, 36.9)	0.175
HR (bpm)	80.0 (74.0, 87.0)	80.0 (74.0, 87.0)	83.0 (79.0, 97.0)	0.004	80.0 (74.0, 87.0)	84.0 (75.0, 93.0)	< 0.001
RR (insp/min)	15.0 (13.0, 18.0)	15.0 (13.0, 18.0)	16.0 (14.0, 20.0)	< 0.001	15.0 (13.0,18.0)	16.0 (14.0, 21.0)	< 0.001
SpO2 (%)	100.0 (98.0, 100.0)	100.0 (98.0, 100.0)	99.0 (97.0, 100.0)	0.02	100.0 (98.0, 100.0)	100.0 (97.0, 100.0)	< 0.001
SBP (mmHg)	112.0 (101.0, 125.0)	112.0 (101.00, 125.0)	114.0 (105.0, 137.0)	0.188	112.0 (101.0,125.0)	112.0 (102.0, 130.0)	0.206
DBP (mmHg)	59.0 (51.0, 67.0)	59.0 (51.0, 67.0)	53.7 (47.0, 70.0)	0.245	59.0 (51.0, 67.0)	58.0 (49.0, 71.0)	0.68
Pro-BNP	2429.2 (1269.1, 4636.1)	2401.0 (1264.0, 4555.6)	5289.0 (1886.0, 9292.0)	< 0.001	2281.0 (1227.2, 4360.58)	5742.5 (2677.3, 10,438.0)	< 0.001

Table 1 (continued)

Variable	Overall (n = 3342)	30-day			365-day		
		Survivors (n = 3288)	Non-survivors (n = 54)	*p* value	Survivors (n = 3113)	Non-survivors (n = 229)	*p* value
RBC (m/uL)	4.3 (3.9, 4.7)	4.3 (3.9, 4.7)	4.0 (3.6, 4.4)	0.002	4.3 (3.9, 4.7)	4.0 (3.5, 4.4)	< 0.001
WBC (K/uL)	7.4 (6.0, 9.1)	7.4 (6.0, 9.1)	7.6 (6.3, 11.2)	0.085	7.3 (6.0, 9.0)	7.8 (6.3, 10.5)	0.002
PLT (K/uL)	212.0 (174.0, 259.0)	212.0 (174.0, 259.0)	207.0 (179.0, 263.0)	0.807	213.0 (174.0, 259.0)	211.0 (171.0, 271.0)	0.983
HGB (mg/dL)	13.0 (11.6, 14.2)	13.0 (11.6, 14.2)	11.8 (10.6, 13.3)	< 0.001	13.1 (11.7, 14.2)	12.0 (10.6, 13.3)	< 0.001
Cre (mg/dL)	1.0 (0.8, 1.2)	1.0 (0.8, 1.2)	1.2 (0.9, 1.5)	< 0.001	1.0 (0.8, 1.2)	1.1 (0.9, 1.5)	< 0.001
HDL (mg/dL)	45.2 (44.2, 45.2)	45.2 (44.4, 45.2)	45.2 (38.0, 45.2)	0.025	45.2 (44.6, 45.2)	45.2 (41.0, 45.2)	0.002
LDL (mg/dL)	71.5 (71.5, 84.3)	71.5 (71.5, 84.3)	71.5 (65.0, 82.0)	0.11	71.5 (71.5, 85.0)	71.5 (69.0, 80.2)	0.003
HbA1c (%)	5.7 (5.4, 6.2)	5.7 (5.4, 6.2)	5.9 (5.7, 6.6)	0.015	5.7 (5.4, 6.2)	5.9 (5.6, 6.5)	0.001
Glu (mmo/L)	5.9 (5.3, 6.9)	5.9 (5.3, 6.9)	6.9 (5.7, 8.7)	0.001	5.8 (5.3, 6.9)	6.4 (5.3, 8.2)	< 0.001
Sodium (mEq/L)	140.0 (138.0, 141.0)	140.0 (138.0, 141.0)	140.0 (137.0, 142.0)	0.94	140.0 (138.0, 141.0)	139.0 (137.0, 141.0)	0.203
Potassium (mEq/L)	4.2 (3.9, 4.5)	4.2 (3.9, 4.5)	4.1 (3.9, 4.6)	0.989	4.2 (3.9, 4.5)	4.3 (3.9, 4.7)	0.006
HGI	−0.209 (−0.522, 0.212)	−0.209 (−0.521, 0.209)	−0.167 (−0.555, 0.550)	0.687	−0.211 (−0.522, 0.195)	−0.134 (−0.515, 0.368)	0.314
SHR	0.903 (0.791, 1.043)	0.903 (0.792, 1.035)	1.005 (0.781, 1.294)	0.02	0.902 (0.792, 1.034)	0.930 (0.768, 1.138)	0.037
GV (%)	19.0 (14.3, 26.6)	18.9 (14.2, 26.4)	26.4 (18.8, 36.9)	< 0.001	18.7 (14.0, 25.9)	24.6 (18.5, 34.2)	< 0.001
OASIS	31.0 (26.0, 36.0)	31.0 (26.0, 36.0)	34.0 (29.0, 41.0)	0.003	31.0 (26.0, 36.0)	33.0 (28.0, 39.0)	< 0.001
Beta-blockers (%)				< 0.001			< 0.001
No	124 (3.7)	117 (3.6)	7 (13.0)		106 (3.4)	18 (7.9)	
Yes	3218 (96.3)	3171 (96.4)	47 (87.0)		3007 (96.6)	211 (92.1)	
Statins (%)				0.929			0.072
No	1753 (52.5)	1725 (52.5)	28 (51.9)		1646 (52.9)	107 (46.7)	
Yes	1589 (47.5)	1563 (47.5)	26 (48.2)		1467 (47.1)	122 (53.3)	
ACEIs/ARBs (%)				0.754			0.694
No	1724 (51.6)	1695 (51.6)	29 (53.7)		1603 (51.5)	121 (52.8)	
Yes	1618 (48.4)	1593 (48.5)	25 (46.3)		1510 (48.5)	108 (47.2)	
Loop_diuretics (%)				0.004			0.002
No	67 (2.0)	63 (1.9)	4 (7.4)		56 (1.8)	11 (4.8)	
Yes	3275 (98.0)	3225 (98.1)	50 (92.6)		3057 (98.2)	218 (95.2)	
Aspirin (%)				< 0.001			0.238
No	23 (0.7)	20 (0.6)	3 (5.6)		20 (0.6)	3 (1.3)	
Yes	3319 (99.3)	3268 (99.4)	51 (94.4)		3093 (99.4)	226 (98.7)	
Clopidogrel (%)				0.003			< 0.001
No	2555 (76.5)	2523 (76.7)	32 (59.3)		2413 (77.5)	142 (62.0)	
Yes	787 (23.6)	765 (23.3)	22 (40.7)		700 (22.5)	87 (38.0)	
Warfarin (%)				0.18			0.259
No	1740 (52.1)	1707 (51.9)	33 (61.1)		1629 (52.3)	111 (48.5)	
Yes	1602 (47.9)	1581 (48.1)	21 (38.9)		1484 (47.7)	118 (51.5)	
NOAC (%)				0.844			0.366
No	3135 (93.8)	3084 (93.8)	51 (94.4)		2917 (93.7)	218 (95.2)	
Yes	207 (6.2)	204 (6.2)	3 (5.6)		196 (6.3)	11 (4.8)	
Insulin (%)				0.906			0.059
No	765 (22.9)	753 (22.9)	12 (22.2)		701 (22.5)	64 (28.0)	
Yes	2577 (77.1)	2535 (77.1)	42 (77.8)		2412 (77.5)	165 (72.1)	
DPP_IV(%)				0.434			0.095
No	3172 (94.9)	3122 (95.0)	50 (92.6)		2960 (95.1)	212 (92.6)	
Yes	170 (5.1)	166 (5.1)	4 (7.4)		153 (4.9)	17 (7.4)	
Hypoglycemic_ drugs (%)				0.396			0.169
No	2764 (82.7)	2717 (82.6)	47 (87.0)		2567 (82.5)	197 (86.0)	
Yes	578 (17.3)	571 (17.4)	7 (13.0)		546 (17.5)	32 (14.0)	
Dopamine (%)				0.02			< 0.001
No	3225 (96.5)	3176 (96.6)	49 (90.7)		3017 (96.9)	208 (90.8)	

Table 1 (continued)

Variable	Overall (n = 3342)	30-day			365-day		
		Survivors (n = 3288)	Non-survivors (n = 54)	*p* value	Survivors (n = 3113)	Non-survivors (n = 229)	*p* value
Yes	117 (3.5)	112 (3.4)	5 (9.3)		96 (3.1)	21 (9.2)	
HGI group (%)				0.344			0.009
Q1	1113 (33.3)	1100 (33.5)	13 (24.1)		1057 (34.0)	56 (24.5)	
Q2	1115 (33.4)	1095 (33.3)	20 (37.0)		1034 (33.2)	81 (35.4)	
Q3	1114 (33.3)	1093 (33.2)	21 (38.9)		1022 (32.8)	92 (40.2)	
SHR group (%)				0.002			< 0.001
Q1	1112 (33.3)	1104 (33.6)	8 (14.8)		1064 (34.2)	48 (21.0)	
Q2	1117 (33.4)	1100 (33.5)	17 (31.5)		1036 (33.3)	81 (35.4)	
Q3	1113 (33.3)	1084 (33.0)	29 (53.7)		1013 (32.5)	100 (43.7)	
GV group (%)				< 0.001			< 0.001
Q1	1114 (33.3)	1098 (33.4)	16 (29.6)		1046 (33.6)	68 (29.7)	
Q2	1114 (33.3)	1110 (33.8)	4 (7.4)		1084 (34.8)	30 (13.1)	
Q3	1114 (33.3)	1080 (32.8)	34 (63.0)		983 (31.6)	131 (57.2)	

Continuous numerical variables are expressed as medians (interquartile spacing) and categorical variables are expressed as numbers (percentages)

BMI, body mass index; DM, diabetes mellitus, CHD, coronary heart disease, MI, acute myocardial infarction, AF, atrial fibrillation, CS, cardiogenic shock, MC, malignant cancer, HTN, hypertension, AKI, acute kidney injury, HF, heart failure; PVD, peripheral vascular disease; COPD, chronic obstructive pulmonary disease; PCI, percutaneous coronary intervention; OASIS, oxford acute severity of illness score; HR, heart rate, RR, respiratory rate, SBP, systolic blood pressure, DBP, diastolic blood pressure, SpO2, oxyhemoglobin saturation, RBC, red blood cells, WBC, white blood cells, PLT, platelets, HGB, hemoglobin, Cre, creatinine, HDL, high-density lipoprotein, LDL, low-density lipoprotein, HbA1c, glycosylated hemoglobin, Glu, glucose, HGI, hemoglobin glycation index; SHR, stress hyperglycemia ratio; GV, glycemic variability, ACEI, angiotensin-converting enzyme inhibitions, ARB, angiotensin receptor blockers; NOAC, new oral anticoagulants; DPP_IV, dipeptidyl peptidase IV

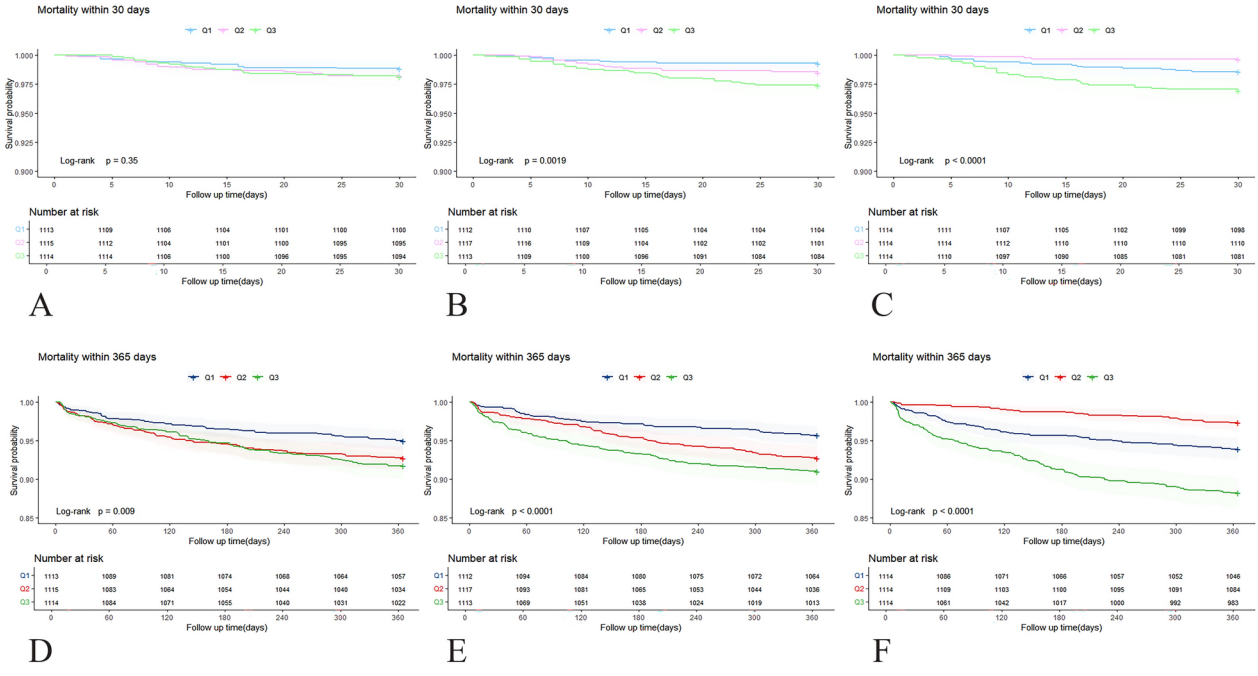

Fig. 3 Kaplan–Meier curves of HGI, SHR, and GV for all-cause mortality. **A**–**C** Showing comparison of mortality within 30 days across groups; **D**–**F** Showing comparison of mortality within 365 days across groups. A and D refer to the HGI groups, B and E refer to the SHR groups, C and F refer to the GV groups

that the risk of 365-day mortality in patients after TAVR increased significantly with the increase of GV level (Table 2). Through multivariate cox regression analysis, we found that HGI, SHR and GV were significantly associated with the risk of 365-day death in patients after TAVR. To better reflect the predictive value of the three single indicators for 365-day death, we drew a time-dependent ROC curve and placed it in the Supplementary Fig. 2. In the figure, we observed that GV as a single variable had the strongest predictive ability for long-term

Table 2 Multivariate cox regression analysis of 30-day and 365-day all-cause mortality in the HGI groups, SHR groups, and GV groups

Outcomes exposure	Model 1 HR (95% CI, *P*)	Model 2 HR (95% CI, *P*)	Model 3 HR (95% CI, *P*)
30-day mortality			
HGI group			
Q1	Ref	Ref	Ref
Q2	1.54 (0.77–3.10, *P* = 0.226)	1.57 (0.78–3.17, *P* = 0.210)	1.65 (0.80–3.43, *P* = 0.176)
Q3	1.62 (0.81–3.23, *P* = 0.174)	1.16 (0.55–2.44, *P* = 0.699)	0.99 (0.43–2.27, *P* = 0.981)
SHR group			
Q1	Ref	Ref	Ref
Q2	2.12 (0.92–4.92, *P* = 0.079)	1.57 (0.67–3.66, *P* = 0.295)	1.54 (0.66–3.60, *P* = 0.315)
Q3	**3.65 (1.67–7.98, *P* = 0.001)**	**2.94 (1.34–6.45, *P* = 0.007)**	**2.92 (1.32–6.45, *P* = 0.008)**
GV group			
Q1	Ref	Ref	Ref
Q2	**0.25 (0.08–0.74, *P* = 0.013)**	0.38 (0.13–1.17, *P* = 0.092)	0.41 (0.13–1.24, *P* = 0.115)
Q3	**2.14 (1.18–3.88, *P* = 0.012)**	1.64 (0.90–2.99, *P* = 0.107)	1.60 (0.88–2.91, *P* = 0.125)
365-day mortality			
HGI group			
Q1	Ref	Ref	Ref
Q2	**1.46 (1.04–2.06, *P* = 0.028)**	**1.54 (1.09–2.17, *P* = 0.014)**	**1.48 (1.05–2.09, *P* = 0.025)**
Q3	**1.66 (1.19–2.32, *P* = 0.003)**	1.27 (0.89–1.82, *P* = 0.190)	1.17 (0.82–1.69, *P* = 0.385)
SHR group			
Q1	Ref	Ref	Ref
Q2	**1.70 (1.19–2.43, *P* = 0.004)**	1.29 (0.90–1.86, *P* = 0.166)	1.21 (0.83–1.75, *P* = 0.323)
Q3	**2.14 (1.52–3.03, *P* < 0.001)**	**1.80 (1.27–2.55, *P* = 0.001)**	**1.63 (1.15–2.32, *P* = 0.006)**
GV group			
Q1	Ref	Ref	Ref
Q2	**0.43 (0.28–0.66, *P* < 0.001)**	**0.60 (0.39–0.94, *P* = 0.024)**	**0.59 (0.38–0.92, *P* = 0.019)**
Q3	**1.99 (1.48–2.67, *P* < 0.001)**	**1.65 (1.23–2.22, *P* = 0.001)**	**1.43 (1.06–1.93, *P* = 0.020)**

Bold represents statistically significant correlation with the outcome and *p*-value less than 0.05.

Model 1: no covariates were adjusted,

Model 2: adjusted for age, gender (male, female), body mass index (BMI), atrial fibrillation (AF; yes, no), diabetes mellitus (DM; yes, no), myocardial infarction (MI; yes, no), cardiogenic shock (CS; yes, no), acute kidney injury (AKI; yes, no), peripheral vascular disease (PVD; yes, no), malignancy (MC; yes, no), percutaneous coronary intervention (PCI; yes, no)

Model 3: adjusted for Model 2 plus Oxford Acute Severity of Illness Score (OASIS), use of beta-blockers (yes, no), clopidogrel (yes, no), warfarin (yes, no), insulin (yes, no), dipeptidyl peptidase-4 inhibitors (DDP-IV inhibitors; yes, no), other hypoglycemic drugs (yes, no), dopamine (yes, no), dobutamine (yes, no), loop diuretics (yes, no), heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), glycated hemoglobin (HbA1c), N-terminal pro-brain natriuretic peptide (proBNP), creatinine (Cre), high-density lipoprotein (HDL), low-density lipoprotein (LDL), and potassium levels

death in patients (AUC = 0.629). In the external data, we also performed univariate and multivariate cox regression analyses, and adjusted for surgical route, valve type, size, and anesthesia compared to the analysis in the MIMIC-IV data. Unfortunately, HGI, SHR, and GV did not show significant associations with 30-day and 365-day mortality, although their overall trends were similar to those obtained in MIMIC-IV (Supplementary Table 5).

Restricted cubic spline

We used restricted cubic spline analysis to evaluate the relationships between HGI, SHR, GV, and both 30-day and 365-day mortality. The analysis was adjusted for various confounding factors, including age, sex, body mass index, atrial fibrillation, diabetes mellitus, OASIS score, heart rate, respiratory rate, oxygen saturation, proBNP, HbA1c, creatinine, beta-blocker use, and other relevant clinical variables. As illustrated in Fig. 4, both HGI and SHR exhibited a linear, inverted'L'-shaped relationship with short-term and long-term mortality risk in TAVR patients, with non-linearity *P* values consistently exceeding 0.05 (Fig. 4A, D and B, E). In contrast, GV displayed a distinct non-linear'S'-shaped association with key outcomes (non-linearity *P* value: 0.015), while maintaining a linear'S'-shaped relationship with additional outcomes (non-linearity *P* value > 0.05) (Fig. 4C and F).

Threshold effect analysis identified critical inflection points: HGI at -0.199, SHR at 0.876 and 0.934, and GV at 19.03%, all within subgroup Q1. Beyond these thresholds, HGI, SHR, and GV each significantly influenced 365-day mortality (Supplementary Table 1). The segmented Cox regression analysis further highlights critical thresholds for HGI, SHR, and GV in relation to 365-day mortality, revealing distinct risk shifts and predictive trends across short- and long-term outcomes. HGI displayed variability at lower values but stabilized over time, SHR showed a sustained increase in risk beyond its threshold, and GV displayed a clear positive trend, with higher values consistently associated with increased predicted effects (Supplementary Fig. 1).

Subgroup analyses

In addition, we also performed risk subgroup analysis and interaction analysis of outcomes in patients after TAVR according to sex, age (< 65 years or ≥ 65 years), BMI (< 25 kg/m^2 or ≥ 25 kg/m^2), AF, DM, CHD, AKI, CS, and OASIS score (< 36 or ≥ 36). In the subgroup analysis of HGI and key outcomes, we observed that lower HGI levels were significantly associated with an increased risk of long-term mortality. Specifically, this relationship was significant in women, patients aged ≥ 65 years, and those without atrial fibrillation or diabetes or coronary heart disease or cardiogenic shock, as well as patients with lower OASIS scores. In overweight or obese people,

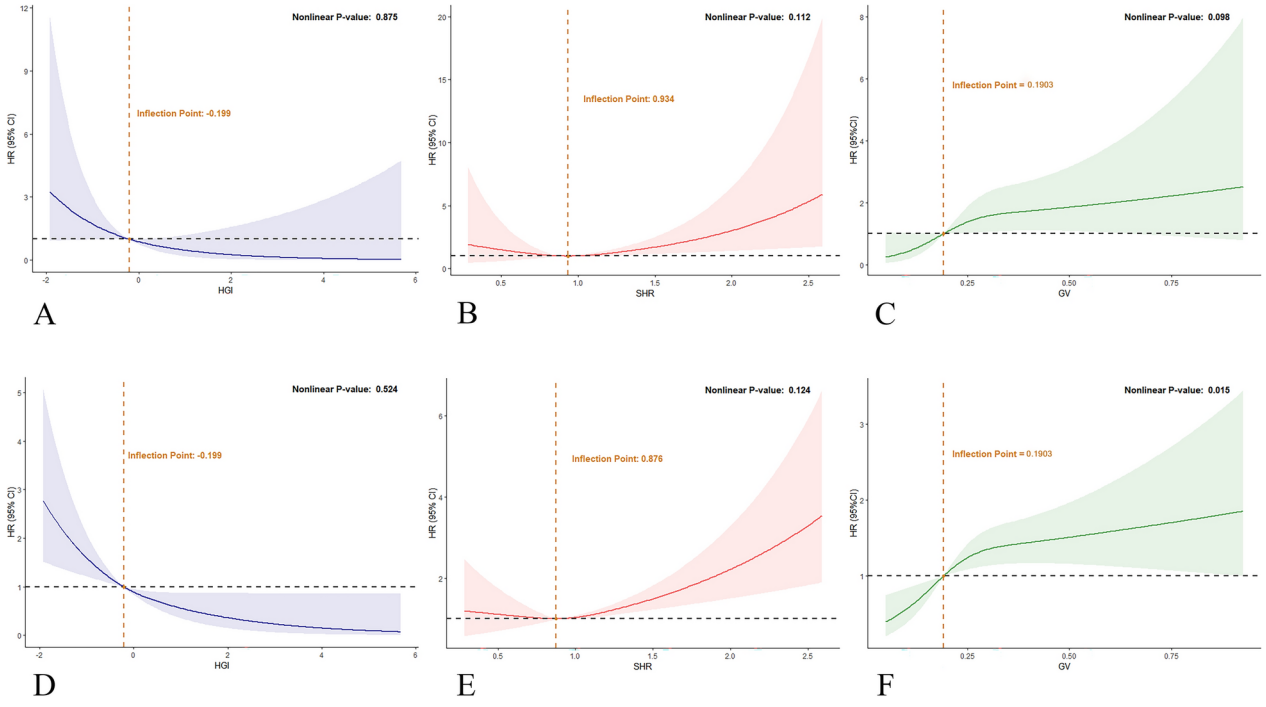

Fig. 4 Association of HGI, SHR and GV with all-cause mortality among patients who treated with TAVR. **A**–**C** Restricted Cubic Spline Curve for the all-cause mortality rate of patients within 30 days; **D**–**F** Restricted Cubic Spline Curve for the all-cause mortality rate of patients within 365 days. Fully adjusted HRs are indicated by blue lines for HGI cohort, by red lines for SHR cohort, and by green lines for GV cohort, shaded areas indicate 95% CIs. Vertical orange lines indicate inflection points, horizontal dashed hazard ratio 1. Abbreviations: *CI* confidence interval, *HR* hazard ratio, *HGI* hemoglobin glycation index, *SHR* stress hyperglycemia ratio, *GV* glycemic variability

higher HGI was more strongly associated with the risk of long-term mortality (Fig. 5). In the subgroup analysis of HGI and 30-day mortality, except for the group aged ≥ 65 years, where both lower and higher HGI had a risk effect on the outcome, the other groups were not significant. In addition, higher SHR levels were significantly associated with an increased risk of death within 365 days, especially in male patients, patients under 65 years of age, and patients without DM, AF, and AKI. Similarly, higher SHR levels were also significantly associated with an increased risk of death within 30 days, especially in male patients, patients under 65 years of age, and patients without AF and CS (Fig. 6). In the subgroup analysis of GV and 365-day mortality, high GV levels were significantly associated with an increased risk of long-term mortality in male patients, obese and overweight patients, AF patients, non-DM patients, CHD patients, and AKI patients, while low levels of GV had the opposite effect (Fig. 5). In the subgroup relationship between GV and 30-day mortality, no significant association was observed in any subgroup. Overall, we only observed a significant interaction between GV and 365-day mortality in the CHD subgroup (P for interaction = 0.006). This indicates that in patients without CHD, maintaining a low GV can reduce the risk of long-term death, while in patients with CHD, a higher GV will directly lead to an increase in long-term risk. In addition, the effects of the remaining covariate groups on the short-term or long-term mortality risk of patients at different levels of HGI, SHR and GV did not show significant differences (the P values of the interaction analysis results were all > 0.05).

Sensitivity analyses

Sensitivity analyses further confirmed the robustness of the results. In multivariable Cox regression models investigating the associations between HGI, SHR, GV, and the risk of 30-day and 365-day mortality, we employed various data handling methods, such as removing missing values, using multiple imputations, and excluding outliers, to compare the analysis results. The findings indicated that the relationships between HGI, SHR, GV, and both key and additional outcomes remained largely consistent across different data processing approaches. After excluding outliers from the cohort, significant associations with key outcomes were observed in the HGI Q2, SHR Q3, and GV Q2 and Q3 subgroups. Specifically, the HGI Q2 subgroup was associated with a significantly increased risk (HR: 1.544, 95% CI 1.092–2.183, $P = 0.0139$), as was the SHR Q3 subgroup (HR: 1.760, 95% CI 1.241–2.497, $P = 0.0015$). Additionally, the GV Q2 subgroup showed a protective effect (HR: 0.581, 95% CI 0.373–0.905, $P = 0.0163$), while the GV Q3 subgroup

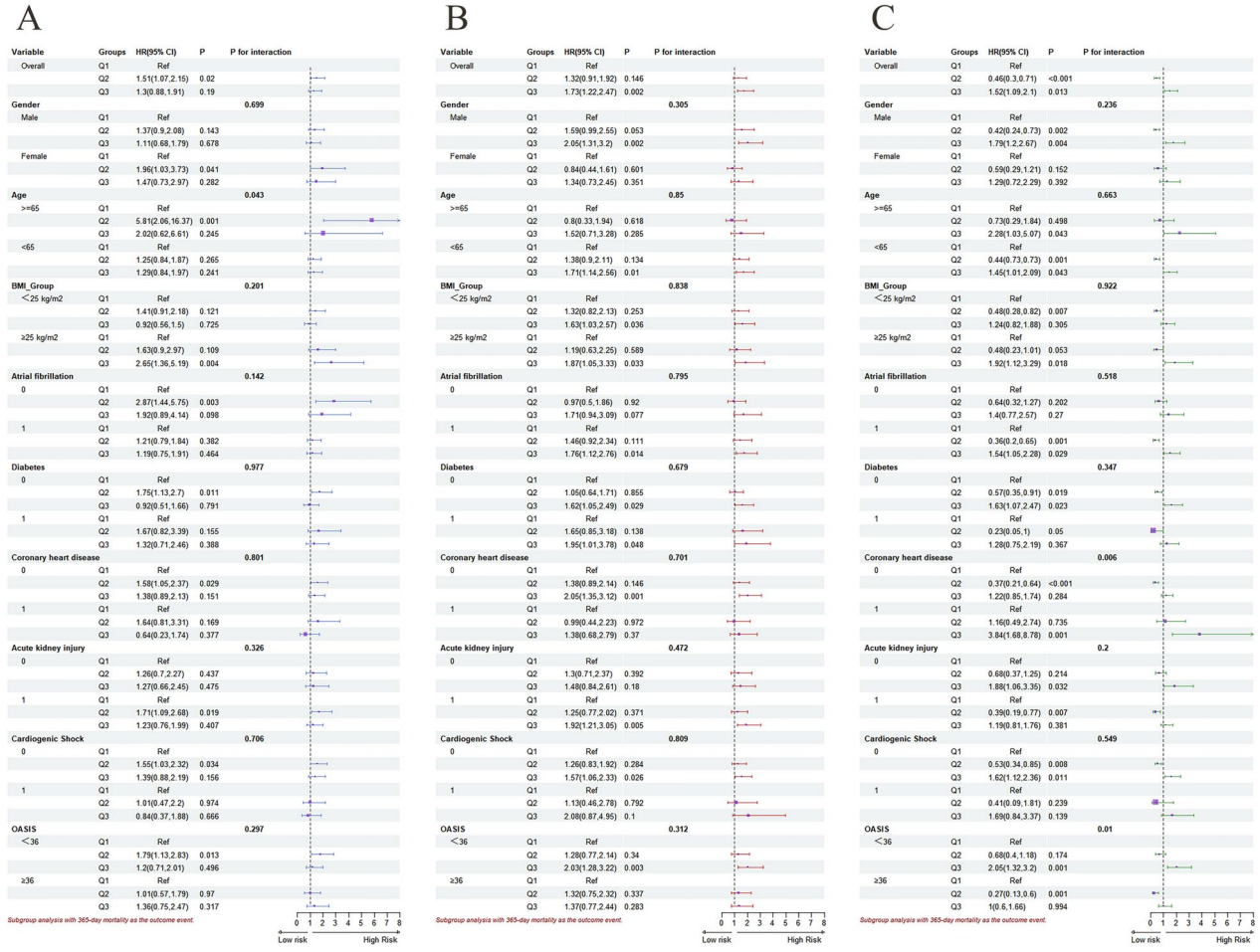

Fig. 5 Forest plots for subgroup analyses of HGI, SHR and GV with 365-day all-cause mortality

was linked to a significantly higher risk (HR: 1.633, 95% CI 1.183–2.254, $P = 0.0029$). These associations remained robust after adjusting for potential confounders, including OASIS score, glycated hemoglobin, Pro-BNP, SpO2, heart rate, creatinine, β-blockers, insulin, HDL cholesterol, and other relevant variables (Supplementary Table 2).

In addition, we performed a sensitivity analysis of the effect of glycemic control targets on mortality in diabetic and non-diabetic patients. Blood glucose control indicators (HGI, SHR, and GV) exert a greater influence on mortality in non-diabetic (Non-DM) patients than in those with diabetes (DM). In Non-DM patients, high SHR (Q3) significantly increased both 30-day (HR = 2.88, $P = 0.031$) and 365-day mortality (HR = 1.74, $P = 0.012$), while high HGI (Q2) was associated with higher 365-day mortality (HR = 1.88, $P = 0.006$), and high GV (Q3) also increased 365-day mortality risk (HR = 1.68, $P = 0.014$). However, in DM patients, none of these factors showed statistically significant associations with mortality (Supplementary Table 3). This suggests that blood sugar management is particularly important for non-DM patients because they are less resistant to high blood sugar and blood sugar fluctuations than DM patients, which may amplify the side effects caused by blood sugar fluctuations and thus increase their short-term and long-term mortality risks.

Discussion

This study elucidates the relationship between glycemic control parameters and adverse outcomes in ICU-treated TAVR patients. To our knowledge, this is the first study to simultaneously evaluate the effects of HGI, SHR, and GV on 30-day and 365-day all-cause mortality in critically ill TAVR patients. The results showed that (1) Lower HGI was associated with an increased risk of long-term mortality in critically ill TAVR patients. The HGI level was linearly associated with the hazard ratio of key outcome events, with the best inflection point being -0.199. However, there was no consistent result in terms of short-term mortality outcomes in patients, and neither high nor low HGI was associated with short-term mortality. (2) Elevated SHR levels were significantly associated with increased risks of both short-term and

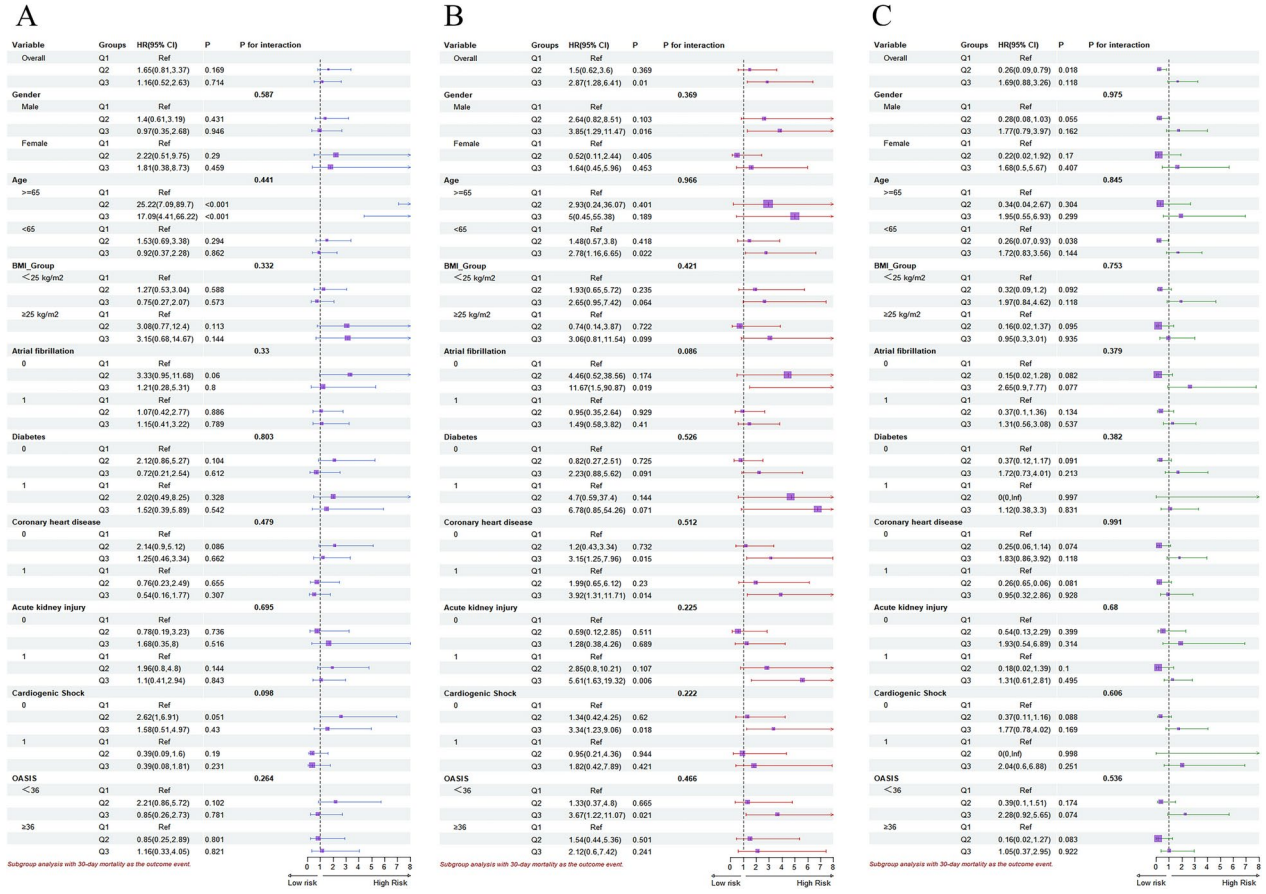

Fig. 6 Forest plots for subgroup analyses of HGI, SHR and GV with 30-day all-cause mortality

long-term mortality, while low SHR levels were not significantly associated with mortality outcomes. In addition, the association between SHR and outcome events showed a inverted 'L'-shaped trend, and the best binary cutoff values of SHR and short-term and long-term all-cause mortality were 0.934 and 0.876, respectively. (3) Compared with low GV levels, high GV levels before discharge were nonlinearly associated with increased long-term all-cause mortality. However, the association between high GV levels and short-term mortality was only observed in the univariate Cox model and lost statistical significance after adjustment for confounders. The data analysis results in our center showed the same correlation trend as the analysis results of the MIMIC-IV database, although it did not reach statistical significance. (4) Comorbidity variables such as BMI, age, and DM did not show significant interactions on the associations between HGI, SHR, and GV and mortality risk. These findings highlight the complex interactions between glycemic control indicators and clinical outcomes, emphasizing the importance of personalized management strategies for this critically ill population.

TAVR has become the standard treatment for patients with severe aortic stenosis who are inoperable or at high surgical risk. However, several perioperative clinical and procedural factors have been shown to significantly impact postoperative clinical outcomes and quality of life, particularly factors related to cardiometabolic conditions such as diabetes [23]. Previous studies have demonstrated that perioperative blood glucose levels and glycemic variability play a critical role in predicting outcomes following cardiac surgery [24, 25]. Poor glycemic control during the perioperative period has been associated with increased risks of postoperative complications, including prolonged mechanical ventilation (6%), arrhythmias (10.5%), sepsis (3.9%) and mortality (2%) [26]. Hemoglobin A1c (HbA1c), as an essential indicator of average glycemic exposure over the preceding 2–3 months, is widely regarded as the gold standard for monitoring long-term glycemic control [27]. Studies have shown that elevated HbA1c levels in patients undergoing TAVR are indicative of poor glycemic management and may be associated with higher mortality rates during long-term follow-up [28]. However, with advancements in glucose monitoring technologies, increasing evidence has revealed that HbA1c is susceptible to biological variability unrelated to mean blood glucose (MBG) levels [29]. Consequently,

relying solely on HbA1c to assess glycemic control may lead to inappropriate clinical decision-making.

HGI introduced by Hempe et al. [21] in 2002, reflects individual variability in the relationship between MBG and HbA1c, and is considered an important marker for identifying the risk of microvascular complications [30]. Over the past two decades, numerous studies have investigated the association between HGI and various cardiovascular disease risks. For instance, Wang Y et al., in a large national prospective cohort study examining the relationship between diabetes, its complications, and cancer, reported a "U-shaped" association between HGI and 5-year major adverse cardiovascular events (MACEs), where both low and high HGI values were associated with increased MACE risk [12]. Similarly, another study demonstrated that both low and high HGI were linked to poor long-term outcomes in critically ill patients with coronary artery disease [13]. Furthermore, study also found that elevated HGI levels over a 4-year period significantly increased the risk of coronary artery calcification events, regardless of baseline HbA1c levels [31]. This study is the first to reveal that regardless of the diabetes status, too low HGI will significantly affect the long-term prognosis of critically ill TAVR patients, and too high HGI also shows a trend of endangering the long-term prognosis of patients, which is consistent with the results of previous studies. Other studies have shown that whether or non-DM has no effect on the prognosis of patients after TAVR surgery, which is also consistent with the conclusion of this study [32]. Studies have shown that perioperative blood glucose management strategies targeting moderate blood glucose control are more effective in reducing postoperative mortality and stroke rates than less stringent blood glucose control methods, while more stringent blood glucose control does not bring additional benefits [33]. Therefore, we propose that HGI, as a novel biomarker of glucose metabolism, may mitigate the influence of HbA1c variability, offering a more reliable tool for clinical research and diagnostic support.

GV is regarded as an alternative metric for evaluating glycemic control [34]. Compared to mean HbA1c levels, GV tends to reflect glucose fluctuations and appears to be more effective in assessing the risk of future microvascular and macrovascular complications in patients with type 2 diabetes [35]. Recent studies have consistently demonstrated that GV is an independent risk factor and predictor of poor cardiovascular outcomes. Data from the Korean Acute Heart Failure Registry indicated that higher GV was significantly associated with increased all-cause mortality during a 1-year follow-up in patients with acute heart failure, particularly among those without diabetes [22]. Su et al. reported that high GV is an independent risk factor for in-hospital mortality in ICU patients, with the increased risk of ventricular arrhythmias partially mediating the relationship between GV and in-hospital mortality [36]. In a study analyzing the impact of GV on short-term outcomes after TAVR, researchers observed that early postoperative GV was significantly associated with the higher incidence of major adverse events within 30 days post-surgery, whereas high glucose levels and mean glucose values during the first two postoperative days were not correlated with these outcomes [37]. Our findings demonstrated that high GV significantly increased the long-term mortality risk in TAVR patients, even after adjusting for strong confounders. These results underscore the importance of managing GV in ICU patients undergoing TAVR to improve long-term outcomes. Interestingly, this study also revealed that while GV significantly influenced long-term mortality in critically ill TAVR patients, its association with short-term mortality were not evident. We speculate that immediate clinical interventions might overshadow the direct impact of glycemic control in the short term, whereas the role of glycemic management appears to be more critical over the long term.

In addition to HbA1c, HGI, and GV, the fasting SHR is another valuable metric for reflecting poor perioperative glycemic control. SHR, akin to fasting blood glucose levels prior to admission, often occurs in the context of normal glucose homeostasis being disrupted by acute illness, representing a transient physiological response to concurrent illnesses [16]. The significance of stress-related states is particularly pronounced in patients with severe cardiovascular and cerebrovascular diseases, and SHR, adjusted for baseline glucose levels, is considered a more effective biomarker for stress hyperglycemia than absolute blood glucose [38]. In previous studies, SHR has been identified as a strong predictor of adverse cardiovascular outcomes and increased in-hospital mortality, especially in cases of acute myocardial infarction and acute heart failure [39, 40]. Notably, Huang et al., in a multicenter observational study, investigated the relationship between SHR and clinical deterioration in patients with secondary mitral regurgitation (sMR), finding that elevated SHR was significantly associated with an increased risk of heart failure exacerbation in this population [41]. This study provides more robust evidence for a potential association between SHR and prognosis in patients with valvular heart disease, particularly demonstrating that elevated SHR in ICU-admitted patients undergoing their first TAVR is significantly linked to higher short-term and long-term mortality. Furthermore, this study defined the critical SHR thresholds for predicting short-term and long-term adverse outcomes as 0.876 and 0.934, respectively, facilitating more precise identification of high-risk patients.

The mechanisms underlying the association between HGI, SHR, and GV and adverse outcomes in TAVR

patients may be closely related to pronounced inflammation and oxidative stress. In patients undergoing TAVR, the aortic valve disease itself is characterized by subendothelial lipid and lipoprotein deposition and oxidative stress-induced endothelial injury, leading to aortic valve sclerosis and eventual deformation [42]. Furthermore, poor glycemic control is significantly associated with accelerated progression of valvular disease [43]. Hyperglycemia can exacerbate systemic pro-inflammatory and fibrotic responses in pressure-overloaded myocardium through interactions between vascular and inflammatory cells, thereby inducing or worsening valvular calcification [44]. The pathophysiological mechanisms likely involve activation of NF-κB-mediated signaling pathways that drive inflammation, excessive synthesis of pro-inflammatory phospholipids, activation of coagulative functions in valvular interstitial cells, and accelerated accumulation of advanced glycation end-products (AGEs) on the valve [45, 46]. These factors may explain why patients with aortic valve disease and poor glycemic control often exhibit worse clinical outcomes even after TAVR, particularly in critically ill ICU settings. Our results showed that low HGI significantly affected the long-term mortality of critically ill TAVR patients, while high HGI also showed a trend of increasing the risk of death [47]. Moreover, high HGI has been found to be associated with increased levels of AGEs [48]. AGEs may bind to their receptors and initiate signaling cascades that suppress mitochondrial respiration, activate NF-κB-mediated inflammatory responses and oxidative stress, and accelerate cardiomyocyte aging [49]. Similarly, excessive SHR has been shown to promote oxidative stress and inflammation, increase pro-thrombotic and pro-aggregatory states, and directly damage myocardial tissue [50]. In addition, the hyperactivity of the adrenergic and renin-angiotensin systems, hyperglucagonemia, and elevated circulating free fatty acids associated with high SHR are not fully reversible by insulin therapy, further contributing to poor patient outcomes [51]. We also found that in obese patients, large fluctuations in serum glucose are more likely to lead to an increased risk of death, which seems to be inconsistent with the obesity paradox. In fact, it may be because obese patients already have higher levels of basal inflammation and oxidative stress, which are further aggravated by the rapid fluctuations in serum glucose, ultimately increasing the risk of death [52]. While GV reflects glucose fluctuations, oscillatory glucose levels may exert greater harmful effects on endothelial cells through oxidative stress and inflammation than sustained hyperglycemia, promoting monocyte adhesion to endothelial cells and accelerating endothelial apoptosis [53]. This can also explain why, compared with DM patients, excessively high GV and SHR in non-DM patients are more likely to lead to an increased risk of long-term mortality, that is, the internal environment of non-DM patients is more difficult to adapt to the inflammation and oxidative stress response caused by a sudden increase in serum glucose. Overall, changes in HGI, SHR, and GV may exacerbate clinical outcomes in ICU-admitted TAVR patients. Therefore, perioperative assessment and management of glycemic control in TAVR patients should be a priority for clinicians. The insights provided by this study may facilitate more rational management of glycemic control in critically ill TAVR patients, potentially improving their outcomes.

This is the first study to explore the effects of HGI, SHR, and GV on the 30-day and 365-day clinical outcomes of TAVR patients based on a large sample of public intensive care unit databases with follow-up data. A large number of covariates that may interfere with the results were collected and included in the cox regression analysis, and strict subgroup analysis and sensitivity analysis were used to reduce potential bias and ensure the robustness of the results. In addition, this study also included data from another single center for external validation, and obtained similar correlation trends, further improving the universality of the results. However, the limitations of this study cannot be ignored. First, as a single-center retrospective cohort study, the external validity and universality of the study results are limited, and causal relationships cannot be inferred. Although external validation was performed, the sample size of the validation data was small and the results were not significantly different, which made the validation power poor. In the future, a larger prospective multicenter study is needed to externally validate the results. Secondly, due to the limitations of the MIMIC-IV public database data, we were unable to include relevant variables such as perioperative data, surgical records, cardiac ultrasound and angiography, and were unable to accurately assess the patient's condition and timing of hospitalization. This causes potential deviations in the study results, and the conclusions need to be verified in a cohort with a better design and more comprehensive data in the future. Third, this study only included patients after TAVR who were admitted to the ICU, and did not consider other patients after TAVR who bypassed the ICU. In the future, it is necessary to explore the relationship between blood glucose control indicators and the prognosis of patients after TAVR who did not enter the ICU, and compare them with patients in the ICU. Finally, due to the lack of data on inflammatory markers and oxidative stress indicators, the intrinsic mechanism of the association between HGI, SHR and GV and mortality outcomes cannot be inferred. Further basic experimental research is needed to clarify the specific mechanisms, as well as key signaling pathways and targets.

Conclusion

In conclusion, this study showed that HGI, SHR, and GV were significantly associated with one-year all-cause mortality in critically ill patients who underwent TAVR surgery for the first time and were admitted to the ICU. As easily accessible indicators of blood glucose control, HGI, SHR, and GV can conveniently provide valuable prognostic evidence in clinical practice, thereby providing accurate risk stratification for TAVR patients. These indicators address the limitations of traditional FPG and HbA1c indicators in assessing mortality risk and help clinicians to take personalized intervention measures for serum glucose control in critically ill patients during hospitalization. However, more studies are needed to verify the correlation between HGI, SHR, and GV and the prognosis of critically ill TAVR patients and to clarify the potential mechanisms involved.

Supplementary Information

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Supplementary Material1

Supplementary Material2

Supplementary Material3

Supplementary Material4

Supplementary Material5

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Author contributions
Qingyun Yu and Qingan Fu conceptualized and designed this study. Xiaowei Ma and Huijian Wang performed the data extraction and initial analysis. Qingyun Yu, Qingan Fu and Penghui Li assisted in the data cleaning, data proofreading, and statistical analysis. Yunlei Xia, Yue Chen and Yue Li contributed to figure plotting. Qingyun Yu prepared the initial manuscript draft. Yanqing Wu participated in the critical revision of the manuscript and supervised the study. All the authors participated in editing, reviewing, and approving the final manuscript.

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Availability of data and materials
No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate
The data in the MIMIC-IV public database have passed the ethical review of the original study, and no further ethical review and informed consent is required. The data from the Second Affiliated Hospital of Nanchang University have been reviewed by the Biomedical Research Ethics Committee of the Second Affiliated Hospital of Nanchang University (approve no. 2022-07), and all participants have signed the informed consent form.

Consent for publication
All authors have consented to the publication of the paper.

Competing interests
The authors declare no competing interests.

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