Cardiovascular Diabetology

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# Association of stress hyperglycemia ratio with short-term and long-term prognosis in patients undergoing coronary artery bypass grafting across different glucose metabolism states: a large-scale cohort study

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## Abstract

**Background** Stress hyperglycemia ratio (SHR) is recognized as a reliable indicator of acute hyperglycemia during stress. Patients undergoing coronary artery bypass grafting (CABG) are at high risk of stress hyperglycemia, but little attention has been paid to this population. This study is the first to investigate the association between SHR and both short-term and long-term prognosis in CABG patients, with a further exploration of the impact of SHR across different glucose metabolic states.

**Methods** A total of 18,307 patients undergoing isolated CABG were consecutively enrolled and categorized into three groups based on SHR tertiles. The perioperative outcome was defined as a composite of in-hospital death, myocardial infarction, cerebrovascular accident, and reoperation during hospitalization. The long-term outcome was major adverse cardiovascular and cerebrovascular events (MACCEs). Restricted cubic spline and logistic regression linked SHR to perioperative risks. Kaplan–Meier and Cox regression analyses were used to determine the relationship with long-term prognosis. Subgroup analyses were further conducted based on different glucose metabolic states.

**Results** A U-shaped association was observed between SHR and perioperative outcome in the overall population (P for nonlinear < 0.001). As SHR increased, the risk of perioperative events initially decreased (OR per SD: 0.87, 95% CI 0.79–0.97, $P = 0.013$) and then elevated (OR per SD: 1.16, 95% CI 1.04–1.28, $P = 0.004$), with an inflection point at 0.79. A similar U-shaped pattern was identified in patients with normal glucose regulation. Among those with prediabetes, the association was J-shaped, while in patients with diabetes, the association became nonsignificant when SHR

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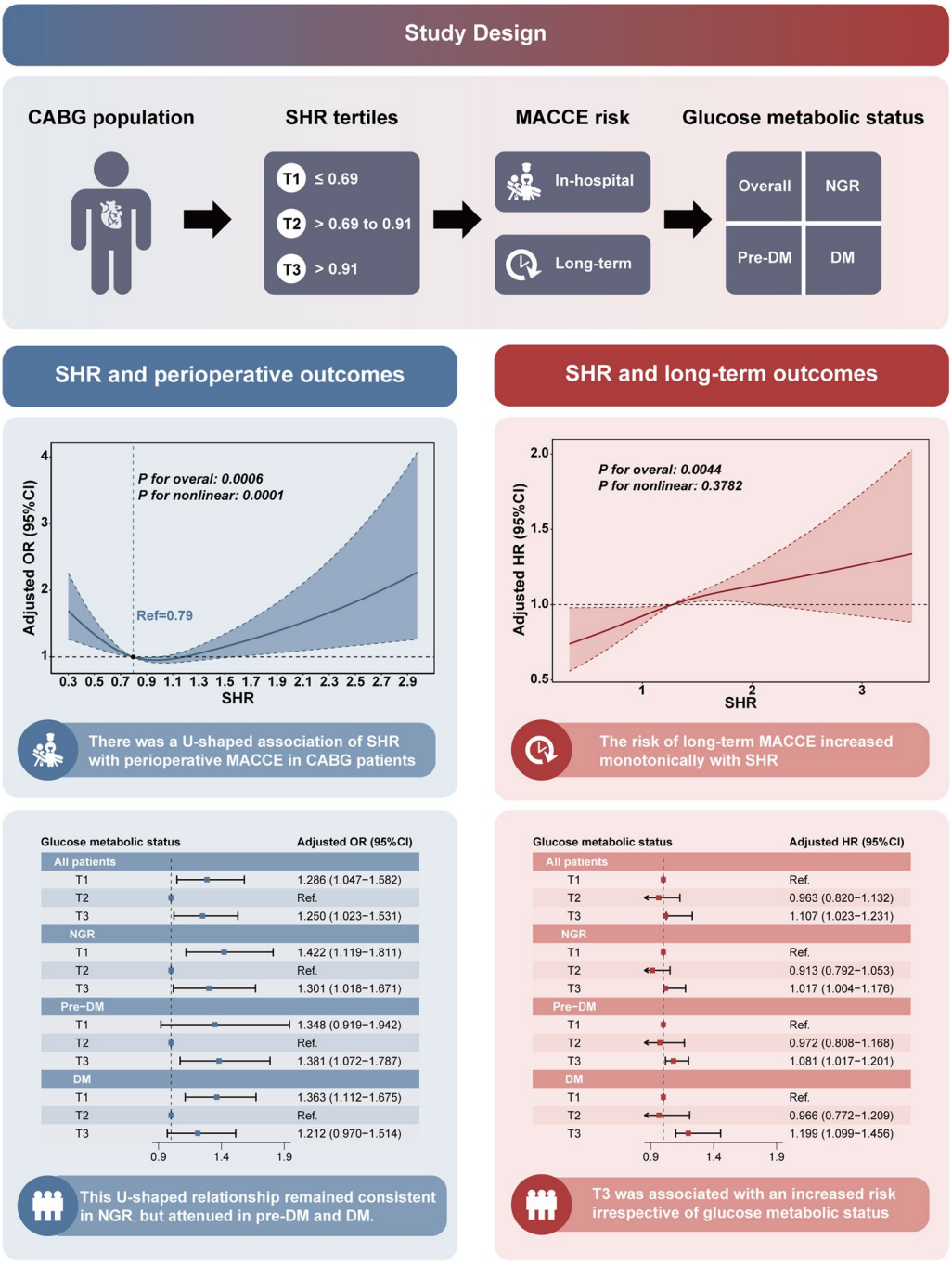
exceeded 0.76. Adding SHR to the existing risk model improved the predictive performance for perioperative outcomes in the overall population (AUC: 0.720 → 0.752, $P < 0.001$; NRI: 0.036, $P = 0.003$; IDI: 0.015, $P < 0.001$). For long-term outcomes, the risk of events was monotonically elevated with increasing SHR, regardless of glucose metabolic status. The third tertile showed a 10.7% greater risk of MACCEs (HR: 1.107, 95% CI 1.023–1.231, $P = 0.024$).

**Conclusions** SHR was significantly associated with prognosis in CABG patients, demonstrating a non-linear U-shaped relationship with short-term outcomes and a linear positive association with long-term outcomes. The in-hospital risk associated with SHR was attenuated in patients with diabetes.

**Graphical abstract** *CABG*, coronary artery bypass grafting; *CI*, confidence interval; *DM*, diabetes Mellitus; *HR*, hazard ratio; *MACCE*, major adverse cardiovascular and cerebrovascular events; *NGR*, normal glucose regulation; *OR*, odds ratio; *Pre-DM*, prediabetes; *SHR*, stress hyperglycemia ratio



**Research insights**

**What is currently known about this topic?**

- Stress hyperglycemia is common during the perioperative period in CABG patients and is linked to adverse short- and long-term outcomes.
- The stress hyperglycemia ratio (SHR) is a novel metric that accounts for baseline glycemia to better reflect acute stress-induced hyperglycemia.
- However, SHR has not been studied in the CABG population.

**What is the key research question?**

- This study is the first to investigate the association between SHR and both short-term and long-term prognosis in patients undergoing CABG, while further exploring its impact across different glucose metabolic states, categorized as normal glucose regulation, prediabetes, and diabetes.

**What is new?**

- In CABG patients, SHR shows a U-shaped relationship with perioperative events and a linear positive association with long-term outcomes, both of which are modulated by glucose metabolic status.

**How might this studyinfluence clinical practice?**

- Findings support the incorporation of SHR for risk stratification and personalized glucose management in CABG patients, ultimately improving both in-hospital and long-term prognosis.

**Keywords** Stress hyperglycemia ratio, Coronary artery disease, Coronary artery bypass grafting, Prognosis, Glucose metabolic states

## Background

Coronary artery disease (CAD) remains a major public health threat, with its global burden continuing to rise [1]. Coronary artery bypass grafting (CABG), recognized as the gold standard for coronary revascularization, is the most commonly performed major cardiac surgery worldwide, with over 600,000 procedures conducted annually [2, 3]. Despite advancements in surgical techniques, pharmacological therapies, and perioperative management, patients undergoing CABG continue to face substantial perioperative and long-term risks due to the increased severity of atherosclerosis, aging populations, and the growing complexity of disease conditions [4]. For instance, the EXCEL trial reported a perioperative major adverse event rate as high as 45.4% among CABG patients, while the SYNTAX trial demonstrated a 5-year major adverse cardiovascular and cerebrovascular event (MACCE) rate of 24% [5, 6]. Given the persistently high cardiovascular risk following CABG, it is essential to enhance the prediction and prevention of adverse events to optimize clinical outcomes.

Previous studies have established a strong association between impaired glucose metabolism and CAD [7]. Compared to individuals with normal glucose regulation, those with impaired glucose metabolism typically have more complicated atherosclerosis and poorer prognosis [8–10]. While the role of chronic hyperglycemia in the progression of CAD has been extensively investigated, increasing attention has been directed toward stress hyperglycemia, characterized by an acute increase in glucose levels during illness [11]. Acute glycemic fluctuations, as compared to stable chronic hyperglycemia, have been shown to exacerbate endothelial cell apoptosis, enhance cytokine release, and increase oxidative stress in the short term, thereby promoting atherosclerotic plaque instability and rupture [12–15]. Previous studies have examined the association of stress hyperglycemia with outcomes in patients with acute coronary syndrome [16, 17]. However, little research has focused on patients undergoing CABG. Compared with non-surgical population, patients undergoing CABG typically exhibit more severe coronary lesions and experience additional stressors, such as medication use, preoperative

fasting, anesthesia, and surgery, that may elevate glucose levels. This surgical population is at high risk of adverse events mediated by stress hyperglycemia. Several studies have investigated the association of admission blood glucose (ABG) level with postoperative mortality following CABG [18–20], but the ABG alone cannot truly reflect acute hyperglycemia, as chronic glycemic status also affects absolute levels. To address the issue, the stress hyperglycemia ratio (SHR), which integrates ABG and glycated hemoglobin (HbA1c) levels, was introduced as a reliable indicator of stress hyperglycemia [21]. Investigating the association of SHR with prognosis could provide novel insights into risk stratification and glucose management in patients undergoing CABG.

Furthermore, evidence suggests that the mortality risk associated with stress hyperglycemia may be more pronounced in patients without diabetes compared to those with diabetes [16, 22], indicating that the impact of SHR may vary depending on baseline glucose metabolic states including normal glucose regulation (NGR), prediabetes mellitus (pre-DM), and diabetes mellitus (DM). This underscores the need to clarify the prognostic implications of SHR across different baseline glucose metabolism states in CABG patients.

In this study, we aimed to evaluate, for the first time, (1) the association between SHR and both in-hospital and long-term outcomes in patients undergoing CABG, and (2) whether baseline glucose metabolism status modifies the risk associated with SHR.

## Methods

### Study population and data collection

The data used in the study were from a large prospective registry-based cohort at the National Center for Cardiovascular Diseases, Fuwai Hospital in Beijing (ClinicalTrials.gov number, NCT02400125), which has been described in detail in previous studies [23, 24]. All consecutive adult patients who underwent isolated CABG with data on SHR between January 1, 2013, and December 31, 2021, were considered for inclusion in this analysis. The exclusion criteria were as follows: (1) hemoglobin (Hb) level < 100 g/L upon admission, (2) fasting blood glucose (FBG) < 3.90 mmol/L upon admission, (3) estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 $m^2$, and (4) loss to follow-up. A total of 18,307 patients met the inclusion criteria and were successfully enrolled in the study. The detailed flowchart of patient selection is provided in Supplementary Figure S1. Data on demographics, laboratory results, surgical procedures and medications were obtained from the registry and supplemented by information from electronic medical records. All variables were collected in accordance with definitions of the Society of Thoracic Surgeons National Adult Cardiac Database (http://www.sts.org/) [23, 24]. Patient follow-up was conducted through scheduled outpatient visits or telephone interviews, carried out by trained research nurses in line with institutional protocols. For reported adverse events during follow-up, patients were requested to provide relevant medical records for verification. The completeness and accuracy of these data were ensured through standardized quality control procedures as previously described [23, 24]. The institutional review board of Fuwai Hospital approved this study, waiving the requirement for written informed consent.

### Evaluation of stress hyperglycemia

Stress hyperglycemia was evaluated by SHR, which was calculated with the following formula: ABG/[(28.7 × HbA1c%)−46.7] [21, 25]. Participants were divided into three groups based on the SHR tertiles: 1st tertile, SHR ≤ 0.69; 2nd tertile, 0.69 < SHR ≤ 0.91; 3rd tertile, SHR > 0.91.

### Glucose metabolism status

According to the criteria established by the American Diabetes Association [26], pre-DM was identified by an HbA1c range of 5.7% to less than 6.5% or a FBG level between 5.6 mmol/L and less than 7.0 mmol/L. DM was defined based on any of the following: FBG of 7.0 mmol/L or higher, HbA1c of 6.5% or above, a self-reported history of physician-diagnosed diabetes, or the use of anti-diabetic medications. Patients who did not meet the criteria for DM or pre-DM were categorized as NGR.

### Laboratory measurements and clinical management

Blood samples were collected from patients after an overnight fast within 24 h of hospital admission. Glucose levels were determined using the enzymatic hexokinase method, while HbA1c was measured using the Tosoh Automated Glycohemoglobin Analyzer HLC-723G8. Lipid components and biochemical markers were analyzed with the Hitachi 7150 automatic biochemistry analyzer. Additional biomarkers were measured using standard commercial kits and validated instruments.

CABG was conducted following standardized procedures, and patient management adhered to relevant clinical practice guidelines (Supplementary Method S1). Whenever feasible, the internal thoracic artery was utilized for revascularizing the left anterior descending artery. The principal surgeon determined the use of cardiopulmonary bypass based on individual patient assessments. Postoperative secondary prevention medications were prescribed to all eligible patients in accordance with the latest guidelines available during the recruitment period [27, 28].

### Study outcomes

The study outcomes were perioperative adverse events and long-term MACCE. Perioperative adverse events was defined as a composite of all-cause death, myocardial infarction (MI), cerebrovascular accident, and reoperation during hospitalization. Long-term MACCE was defined as a composite of all-cause death, myocardial infarction (MI), cerebrovascular accident, and repeat revascularization. Detailed definitions of the outcome components are provided in the Supplementary Method S2. All outcome measures were prespecified, rigorously verified, and adjudicated by independent clinicians.

### Statistical analysis

Continuous variables with a normal distribution were presented as mean ± standard deviation (SD), whereas those with a non-normal distribution were summarized as median (interquartile range). Categorical variables were reported as counts (percentages). Comparisons of patient characteristics were performed using Welch's *t* test or the Wilcoxon rank-sum test for continuous variables, and the Chi-squared test was employed for categorical variables.

The impact of SHR on outcomes was assessed both as a categorical and as a continuous variable. For categorical analysis, patients were stratified into three groups according to SHR tertiles. In-hospital outcomes were compared using multivariate logistic regression models, adjusted for age, sex, body mass index (BMI), smoking, hypertension, hyperlipidemia, glucose metabolism status, insulin use, peripheral artery disease, atrial fibrillation, chronic obstructive pulmonary disease, cerebrovascular accident, chronic kidney disease, New York Heart Association class III/IV, left ventricular ejection fraction, alanine aminotransferase, triglycerides, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, high-sensitivity C-reactive protein, serum creatinine, European System for Cardiac Operative Risk Evaluation (EuroSCORE) II, the use of cardiopulmonary bypass (CPB), the use of intra-aortic ballon pump, left main disease and triple-vessel disease. Long-term outcomes were evaluated via Kaplan–Meier survival curves, log-rank tests, and adjusted Cox proportional hazards regression models. The Cox models were adjusted for variables previously mentioned, as well as the prescription of β-blockers, aspirin, statins, and ACEI/ARB at discharge. For continuous analysis, restricted cubic spline models were applied to examine potential nonlinear associations between SHR and outcomes, with adjustment for the same confounders as in the categorical analysis. The optimal number of knots was determined using the Akaike Information Criterion (AIC) minimum principle. The inflection point was identified as the value where the odds ratio is closest to 1 or equals 1. The discriminatory ability of the conventional model with and without SHR for predicting perioperative outcomes was evaluated using the area under the receiver-operating characteristic curve (AUC). Comparisons of AUCs were performed using DeLong test. To further assess the incremental prognostic value of adding SHR to the conventional model, the Net Reclassification Improvement (NRI) and Integrated Discrimination Improvement (IDI) were calculated.

Subgroup analyses were performed based on glucose metabolic status (NGR, pre-DM and DM) and the use of CPB to assess the consistency of the association across different populations. To test the robustness of our findings, we conducted sensitivity analyses by including patients who were initially excluded due to the following conditions: Hb level < 100 g/L, FBG < 3.90 mmol/L, or eGFR < 30 mL/min/1.73 $m^2$ upon admission.

All statistical analyses were performed via R 4.2.1 (R Development Core Team) software.

## Results

### Baseline characteristics of the study population

A total of 18,307 eligible patients were enrolled in our study (Supplementary Figure S1). The mean ± SD age of the cohort was 61.2 ± 8.58 years, 77.6% were male, 15.0% had a documented history of cerebrovascular accident, 6.54% had a prior percutaneous coronary intervention (PCI), and 73.4% had three-vessel CAD. Among the study cohort, the proportions of patients with DM and pre-DM were 48.8%, and 37.1%, respectively. All participants were divided into three groups according to their SHR tertiles (tertile 1, SHR ≤ 0.69; tertile 2, 0.69 < SHR ≤ 0.91; tertile 3, SHR > 0.91). Detailed baseline characteristics are presented in Table 1. Compared with patients in tertile 2 and tertile 3, those in tertile 1 were slightly older, more likely to be female, and had a higher BMI. They also had the highest risk of DM and the highest proportion of insulin treatment. Additionally, the HbA1c level was highest, while the FBG level was lowest in the first tertile. Patients in tertile 3 were more likely to undergo off-pump CABG.

### SHR and perioperative outcomes

During hospitalization, 707 patients (3.8%) experienced adverse events. After adjusting for potential confounders, restricted cubic spline analysis revealed a significant U-shaped association between SHR and in-hospital events in the overall population (P for nonlinear = 0.0001) (Fig. 1A). With increasing SHR, the risk of perioperative events initially decreased (OR per SD: 0.87, 95% CI 0.79–0.97, $P = 0.013$) and then increased (OR per SD: 1.16, 95% CI 1.04–1.28, $P = 0.004$), which reached the lowest risk at an SHR value of 0.79 (Fig. 1A). We further categorized participants based on their glucose metabolism status and found a similar U-shaped relationship in

**Table 1** Baseline characteristics of the Cohort by SHR tertiles

| Variables | All patients | T1 (SHR ≤ 0.69) | T2 (0.69 < SHR ≤ 0.91) | T3 (SHR > 0.91) | *P* |
|---|---|---|---|---|---|
| | N = 18,307 | N = 6104 | N = 6103 | N = 6100 | |
| Demographics | | | | | |
| Age, years | 61.2 (8.58) | 61.5 (8.33) | 61.1 (8.75) | 61.1 (8.66) | 0.005 |
| Male | 14,212 (77.6%) | 4645 (76.1%) | 4798 (78.6%) | 4769 (78.2%) | 0.002 |
| BMI | 25.9 (3.09) | 26.0 (3.08) | 25.9 (3.11) | 25.7 (3.07) | < 0.001 |
| Comorbidity status | | | | | |
| Smoking | 10,407 (56.8%) | 3437 (56.3%) | 3494 (57.3%) | 3476 (57.0%) | 0.555 |
| Prediabetes | 6795 (37.1%) | 1498 (24.5%) | 2896 (47.5%) | 2401 (39.4%) | < 0.001 |
| Diabetes | 8926 (48.8%) | 4387 (71.9%) | 2193 (35.9%) | 2346 (38.5%) | < 0.001 |
| Insulin-treated diabetes | 2576 (14.1%) | 1167 (19.1%) | 644 (10.6%) | 765 (12.5%) | < 0.001 |
| Hypertension | 12,106 (66.1%) | 4047 (66.3%) | 4019 (65.9%) | 4040 (66.2%) | 0.854 |
| Hyperlipidemia | 14,514 (79.3%) | 4764 (78.0%) | 4926 (80.7%) | 4824 (79.1%) | 0.001 |
| Previous CVA | 2753 (15.0%) | 927 (15.2%) | 857 (14.0%) | 969 (15.9%) | 0.016 |
| NYHA class III/IV | 5537 (30.2%) | 1915 (31.4%) | 1823 (29.9%) | 1799 (29.5%) | 0.057 |
| PAD | 1684 (9.20%) | 620 (10.2%) | 501 (8.21%) | 563 (9.23%) | 0.001 |
| COPD | 304 (1.66%) | 107 (1.75%) | 106 (1.74%) | 91 (1.49%) | 0.449 |
| Previous PCI | 1197 (6.54%) | 411 (6.73%) | 429 (7.03%) | 357 (5.85%) | 0.024 |
| Previous cardiac surgery | 345 (1.88%) | 138 (2.26%) | 89 (1.46%) | 118 (1.93%) | 0.005 |
| Clinical parameters | | | | | |
| HbA1C, % | 6.30 [5.80, 7.30] | 7.20 [6.30, 8.30] | 6.10 [5.70, 6.70] | 6.00 [5.60, 6.70] | < 0.001 |
| FBG, mmol/L | 5.80 [5.03, 7.30] | 5.00 [4.57, 5.64] | 5.53 [5.09, 6.27] | 7.76 [6.44, 9.80] | < 0.001 |
| Triglycerides, mmol/L | 1.46 [1.09, 1.98] | 1.47 [1.10, 2.00] | 1.45 [1.10, 1.96] | 1.47 [1.09, 1.96] | 0.093 |
| Total cholesterol, mg/dL | 151 (43.7) | 149 (43.1) | 152 (43.2) | 152 (44.7) | < 0.001 |
| LDL-C, mg/dL | 90.1 (37.0) | 88.8 (36.2) | 90.2 (36.5) | 91.3 (38.3) | 0.001 |
| HDL-C, mg/dL | 39.5 (10.7) | 38.6 (10.4) | 40.1 (10.6) | 39.8 (11.0) | < 0.001 |
| Albumin, g/L | 42.2 (4.56) | 41.7 (4.66) | 42.0 (4.41) | 43.0 (4.52) | < 0.001 |
| ALT, IU/L | 23.0 [16.0, 35.0] | 23.0 [16.0, 34.0] | 23.0 [16.0, 36.0] | 23.0 [16.0, 35.0] | 0.002 |
| Hs-CRP, mg/L | 1.39 [0.66, 3.04] | 1.49 [0.70, 3.26] | 1.31 [0.62, 2.88] | 1.37 [0.66, 3.01] | < 0.001 |
| Serum creatinine, μmol/L | 81.2 (18.0) | 81.4 (18.8) | 81.3 (17.9) | 80.9 (17.3) | 0.288 |
| LVEF, % | 60.6 (7.76) | 60.0 (8.25) | 60.8 (7.33) | 60.9 (7.63) | < 0.001 |
| Procedure characteristics | | | | | |
| Euroscore | 2.01 (1.89) | 2.04 (1.90) | 2.06 (1.91) | 1.93 (1.87) | < 0.001 |
| Euroscore II | 1.12 (0.89) | 1.07 (0.76) | 1.11 (0.86) | 1.18 (1.03) | < 0.001 |
| Emergency operation | 381 (2.08%) | 123 (2.02%) | 118 (1.93%) | 140 (2.30%) | 0.341 |
| On pump | 9223 (50.4%) | 3023 (49.5%) | 3227 (52.9%) | 2973 (48.7%) | < 0.001 |
| IABP use | 208 (1.14%) | 64 (1.05%) | 73 (1.20%) | 71 (1.16%) | 0.721 |
| LM | 3779 (20.6%) | 1138 (18.6%) | 1285 (21.1%) | 1356 (22.2%) | < 0.001 |
| TVD | 13,441 (73.4%) | 4573 (74.9%) | 4314 (70.7%) | 4554 (74.7%) | < 0.001 |
| No. of grafts | 3.20 (0.93) | 3.23 (0.93) | 3.23 (0.90) | 3.14 (0.97) | < 0.001 |
| LIMA graft | 17,177 (93.8%) | 5754 (94.3%) | 5729 (93.9%) | 5694 (93.3%) | 0.105 |
| Discharge medication | | | | | |
| Statin | 15,475 (84.5%) | 5129 (84.0%) | 5170 (84.7%) | 5176 (84.9%) | 0.402 |
| Aspirin | 17,865 (97.6%) | 5955 (97.6%) | 5954 (97.6%) | 5956 (97.6%) | 0.946 |
| DAPT | 12,567 (68.6%) | 4147 (67.9%) | 4254 (69.7%) | 4166 (68.3%) | 0.085 |
| β-Blocker | 17,006 (92.9%) | 5663 (92.8%) | 5654 (92.6%) | 5689 (93.3%) | 0.374 |
| ACEI/ARB | 1971 (10.8%) | 678 (11.1%) | 616 (10.1%) | 677 (11.1%) | 0.116 |

Data are presented as mean (SD), median (interquartile range), or n (%). *ACEI* angiotensin-converting enzyme inhibitor, *ALT* alanine aminotransferase, *ARB* angiotensin II receptor blocker, *BMI* body mass index, *COPD* chronic obstructive pulmonary disease, *CVA* cerebrovascular accident, *DAPT* dual antiplatelet therapy, *EuroSCORE* European System for Cardiac Operative Risk Evaluation, *FBG* fasting blood glucose, *HbA1c* hemoglobin A1c, *HDL-C* high-density lipoprotein cholesterol, *Hs-CRP* high-sensitivity C-reactive protein, *IABP* intra-aortic balloon pump, *LDL-C* low-density lipoprotein cholesterol, *LIMA* left internal mammary artery, *LM* left main disease, *LVEF* left ventricular ejection fraction, *NYHA* New York Heart Association, *PAD* peripheral artery disease, *PCI* percutaneous coronary intervention, *SHR* stress hyperglycemia ratio, *TVD* triple-vessel disease

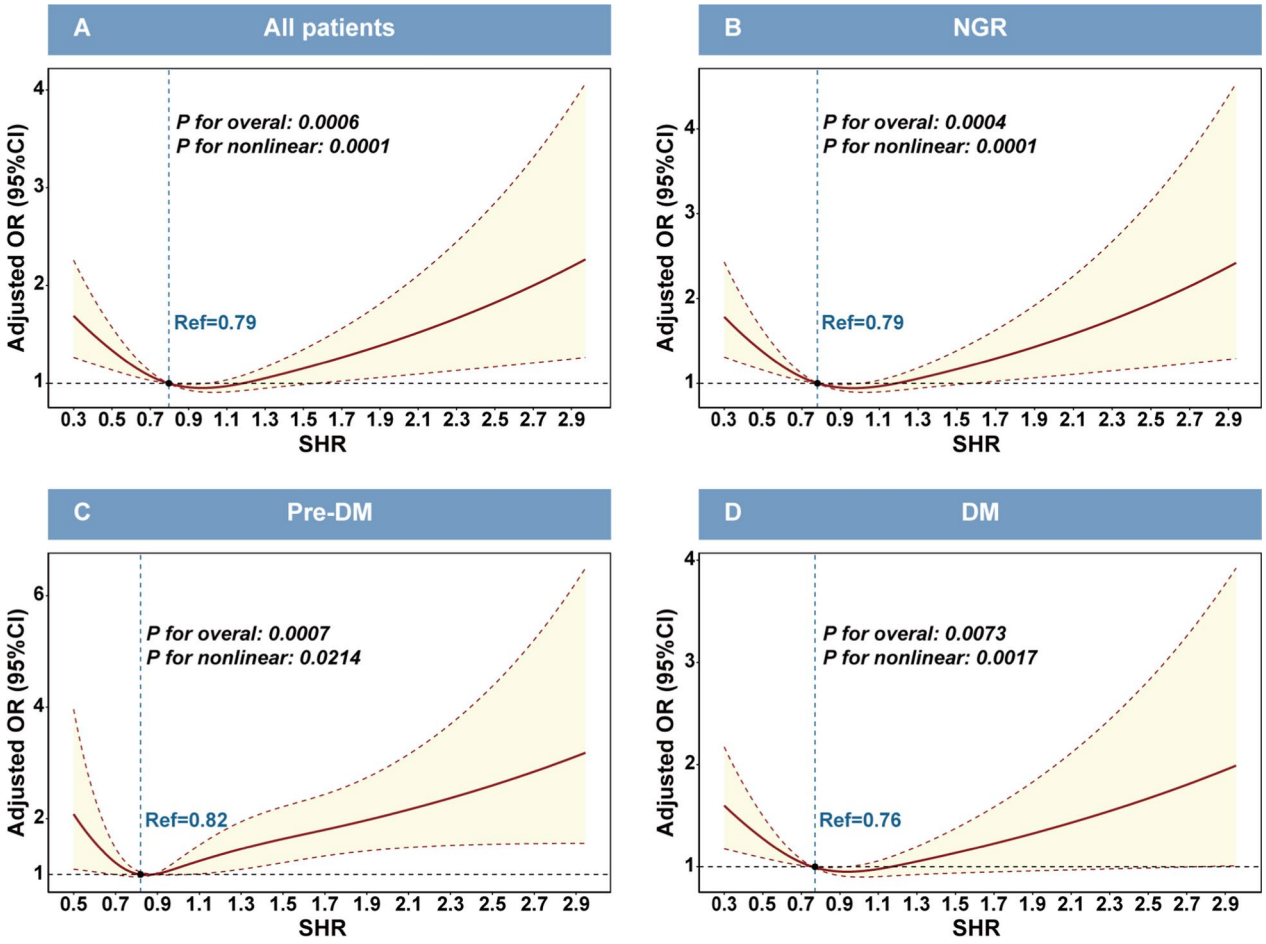



**Fig. 1** Nonlinear associations of stress hyperglycemia ratio with in-hospital outcomes. Associations of SHR with in-hospital outcomes across different glucose metabolic status. **A** All patients. **B** Patients with NGR. **C** Patients with Pre-DM. **D** Patients with DM. The solid red line represents the adjusted OR, and the yellow shaded area indicates the 95% CI. The horizontal dashed line represents the reference line (OR = 1). The vertical blue dashed line indicates the inflection point of the curve (Ref). P for overall indicates the significance of the whole curve, and P for nonlinear represents the significance of the nonlinear component. CI, confidence interval; DM, diabetes mellitus; NGR, normal glucose regulation; OR, odds ratio; Pre-DM, pre-diabetes mellitus; SHR, stress hyperglycemia ratio

patients with NGR (P for nonlinear = 0.0001) (Fig. 1B). Among patients with pre-DM, a J-shaped relationship was observed with an inflection point of 0.82 (P for nonlinear = 0.0214) (Fig. 1C). In the DM group, the risk of in-hospital events also first decreased with increasing SHR (OR per SD: 0.90, 95% CI 0.82–0.99, $P = 0.029$). However, the association was no longer significant when SHR value exceeded 0.76 (OR per SD increase: 1.18, 95% CI 0.95–1.44, $P = 0.12$) (Fig. 1D).

To further examine the association between SHR tertiles and outcomes, the logistic regression model was performed, with the second tertile as the reference group (Table 2). After multiple adjustments, the results showed increased risks of adverse outcomes in tertile 1 (OR: 1.286, 95% CI 1.047–1.582, $P = 0.017$) and tertile 3 (OR: 1.250, 95% CI 1.023–1.531, $P = 0.030$). The SHR-associated risk remained present in patients with NGR (tertile 1, OR: 1.422, 95% CI 1.119–1.811, $P = 0.004$; tertile 3, OR: 1.301, 95% CI 1.018–1.671, $P = 0.037$). Among participants with pre-DM, SHR > 0.91 (tertile 3) was associated with a higher risk of adverse outcomes (OR: 1.381, 95% CI 1.072–1.787, $P = 0.013$), whereas no significant difference was observed between tertile 1 and the reference group (OR: 1.348, 95% CI 0.919–1.942, $P = 0.117$). In contrast, patients with DM in tertile 1 showed an elevated risk (OR: 1.363, 95% CI 1.112–1.675, $P = 0.003$), but no significant association was found in tertile 3 (OR: 1.212, 95% CI 0.970–1.514, $P = 0.090$).

Crude OR represents unadjusted analysis results. Adjusted OR was calculated after controlling for potential confounding factors including age, sex, BMI, smoking, hypertension, hyperlipidemia, glucose metabolism status, insulin use, PAD, atrial fibrillation, COPD, CVA, chronic kidney disease, NYHA class III/IV, LVEF, ALT, TG, LDL-C, HDL-C, hs-CRP, serum creatinine, EuroSCORE, the use of cardiopulmonary bypass, the use of IABP, LM and

**Table 2** Stress hyperglycemia ratio and perioperative outcomes

| Group | Crude OR (95% CI) | *P* | Adjusted OR | *P* |
|---|---|---|---|---|
| All patients | | | | |
| T1 | 1.412 (1.172–1.705) | < 0.001 | 1.286 (1.047–1.582) | 0.017 |
| T2 | Reference | | | |
| T3 | 1.185 (0.977–1.439) | 0.086 | 1.250 (1.023–1.531) | 0.030 |
| NGR | | | | |
| T1 | 1.509 (1.214–1.88) | < 0.001 | 1.422 (1.119–1.811) | 0.004 |
| T2 | Reference | | | |
| T3 | 1.234 (0.973–1.572) | 0.086 | 1.301(1.018–1.671) | 0.037 |
| Pre-DM | | | | |
| T1 | 1.385 (0.945–1.993) | 0.086 | 1.348 (0.919–1.942) | 0.117 |
| T2 | Reference | | | |
| T3 | 1.382 (1.073–1.786) | 0.013 | 1.381(1.072–1.787) | 0.013 |
| DM | | | | |
| T1 | 1.350 (1.111–1.644) | 0.003 | 1.363 (1.112–1.675) | 0.003 |
| T2 | Reference | | | |
| T3 | 1.190 (0.96–1.476) | 0.112 | 1.212 (0.97–1.514) | 0.090 |

TVD (Abbreviations as in Table 1). $P < 0.05$ was considered statistically significant. *CI*, confidence interval; *DM*, diabetes mellitus; *NGR*, normal glucose regulation; *OR*, odds ratio; *Pre-DM*, pre-diabetes mellitus.

#### Incremental prognostic value of SHR over EuroSCORE II for perioperative outcomes

To assess whether SHR could improve the predictive performance of the traditional risk model, we compared the discriminatory ability between the EuroSCORE II model with and without the addition of SHR. In the overall population, adding SHR to the EuroSCORE II model significantly improved the prediction of in-hospital outcomes (AUC: 0.720 vs. 0.752, $P < 0.001$) (Fig. 2A). This improvement was consistently observed across different glucose metabolic states. In the NGR group, the addition of SHR increased the AUC from 0.704 to 0.746 ($P < 0.001$) (Fig. 2B). Similarly, for patients with pre-DM, incorporating SHR improved the discrimination of the traditional model (AUC: 0.712 vs. 0.749, $P < 0.001$) (Fig. 2C). In the DM group, although the magnitude of improvement was relatively smaller, adding SHR still significantly enhanced the predictive ability, with the AUC rising from 0.737 to 0.756 ($P = 0.004$) (Fig. 2D). Furthermore, the incorporation of SHR into the traditional model significantly improved both risk reclassification and overall discrimination ability (NRI: 0.036, $P = 0.003$; IDI: 0.015, $P < 0.001$) (Supplementary Table S1).

#### SHR and long-term outcomes

Over a median follow-up of 2.5 years, 1529 patients (8.4%) developed MACCE. The risk of long-term adverse cardiovascular events increased monotonically with rising SHR values, showing no significant nonlinear relationship in the study population, irrespective of glucose metabolic status (All P for nonlinear > 0.05) (Fig. 3). Kaplan–Meier survival curves revealed that patients with SHR > 0.91 (tertile 3) had the highest MACCE rate (Fig. 4). Cox regression analyses (Table 3) demonstrated that participants in tertile 3 had a 10.7% higher risk of MACCE compared to the reference group (HR: 1.107, 95% CI 1.023–1.231, $P = 0.024$). No significant differences were observed between the second tertile and reference group (HR: 0.963, 95% CI 0.820–1.132, $P = 0.651$). The results remained consistent among patients with and without glucose metabolism dysfunction.

Crude HR represents unadjusted analysis results. Adjusted HR was calculated after controlling for potential confounding factors including age, sex, BMI, smoking, hypertension, hyperlipidemia, glucose metabolism status, insulin use, PAD, atrial fibrillation, COPD, CVA, chronic kidney disease, NYHA class III/IV, LVEF, ALT, TG, LDL-C, HDL-C, hs-CRP, serum creatinine, EuroSCORE, the use of cardiopulmonary bypass, the use of IABP, LM, TVD, the prescription of β-blockers, aspirin, statins, and ACEI/ARB at discharge (Abbreviations as in Table 1). $P < 0.05$ was considered statistically significant. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; NGR, normal glucose regulation; Pre-DM, pre-diabetes mellitus.

#### Subgroup analyses and sensitivity analyses

We performed subgroup analyses based on two key variables: glucose metabolic status (DM, pre-DM, and NGR) and the use of CPB, to assess the association between SHR and both perioperative and long-term outcomes across different patient populations. The results of the subgroup analysis based on glucose metabolic status have been presented above. Subgroup analysis by CPB use showed that the association between SHR and both perioperative and long-term outcomes remained consistent in both groups (Supplementary Figure S2 and Figure S3). The U-shaped relationship between SHR and perioperative outcomes was significant in both groups. The risk of long-term MACCE in the third tertile of SHR was significantly elevated in both groups.

To further validate the robustness of the association between SHR and adverse outcomes, we conducted a sensitivity analysis by including patients who were previously excluded due to the following criteria: (1) Hb level < 100 g/L upon admission, (2) FBG < 3.90 mmol/L upon admission, and (3) eGFR < 30 mL/min/1.73 $m^2$. After incorporating these patients into the analysis, the results of the restricted cubic spline modeling and Cox regression analysis remained consistent with those of the primary analysis (Supplementary Figure S4 and Figure S5).

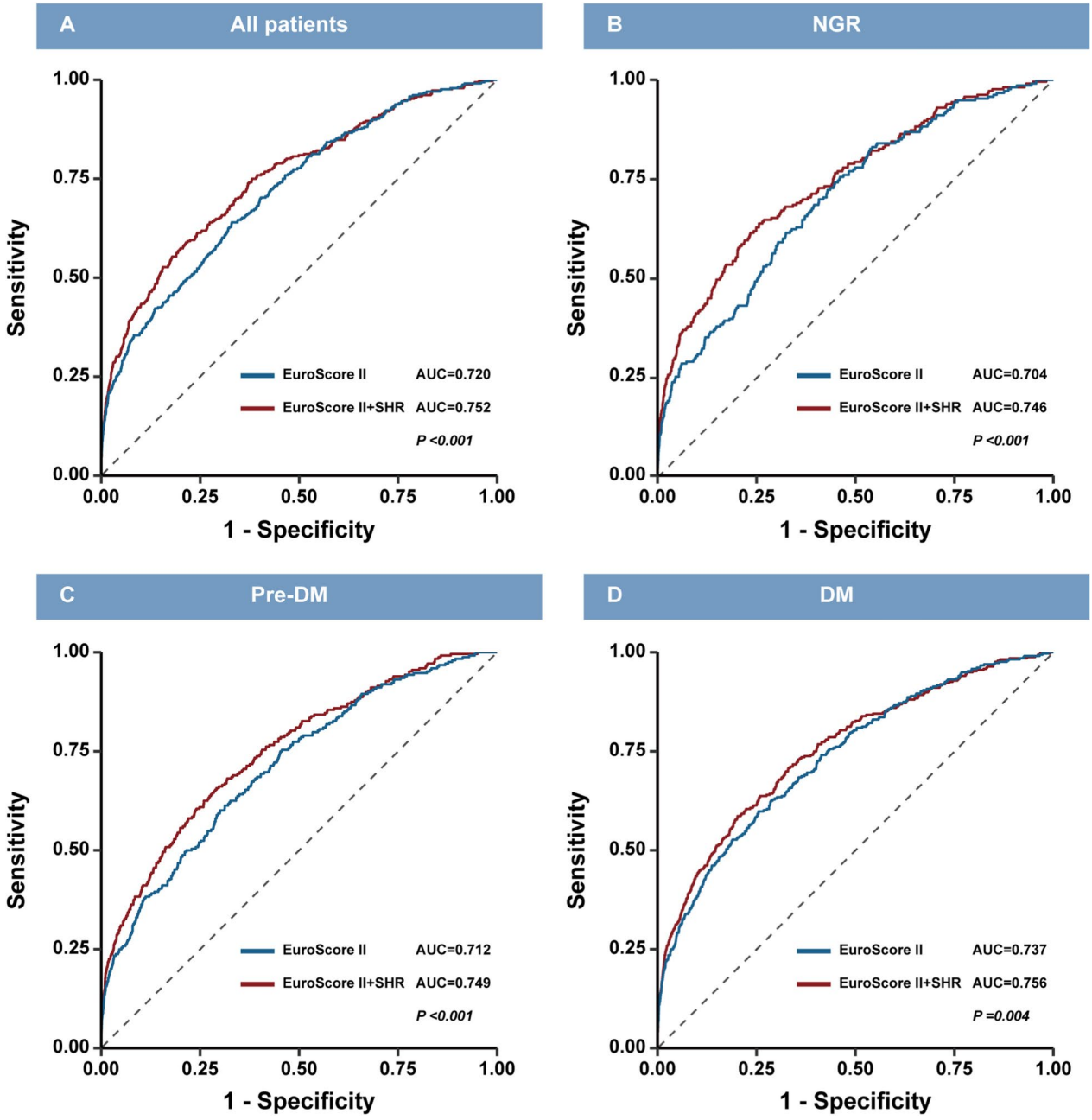



**Fig. 2** Comparison of ROC curves between EuroSCORE II with and without stress hyperglycemia ratio. The discriminatory performance of EuroSCORE II and EuroSCORE II + SHR was evaluated in **A** all patients, **B** patients with NGR, **C** patients with Pre-DM, and **D** patients with DM. P values for comparisons of the two models were calculated using the DeLong test. *AUC*, area under the curve; *DM*, diabetes mellitus; *EuroSCORE II*, European System for Cardiac Operative Risk Evaluation II; *NGR*, normal glucose regulation; *Pre-DM*, pre-diabetes mellitus; *SHR*, stress hyperglycemia ratio

## Discussion

In this large-scale cohort study, we investigated the association of SHR with in-hospital and long-term prognosis in patients undergoing CABG. The key findings were as follows: (1) SHR was significantly associated with adverse events during hospitalization in CABG patients, exhibiting a U-shaped relationship; (2) This non-linear association was attenuated in patients with pre-DM and DM; (3) The addition of SHR significantly improved the discriminatory performance of the traditional risk model for perioperative outcomes. (4) The risk of long-term MACCE increased monotonically with SHR, with no significant nonlinear relationship identified in the study population, irrespective of glucose metabolic status. These findings suggest that both very low and elevated SHR indicate increased perioperative risk in patients after CABG, while for long-term outcomes, higher SHR values consistently predict worse prognosis across all

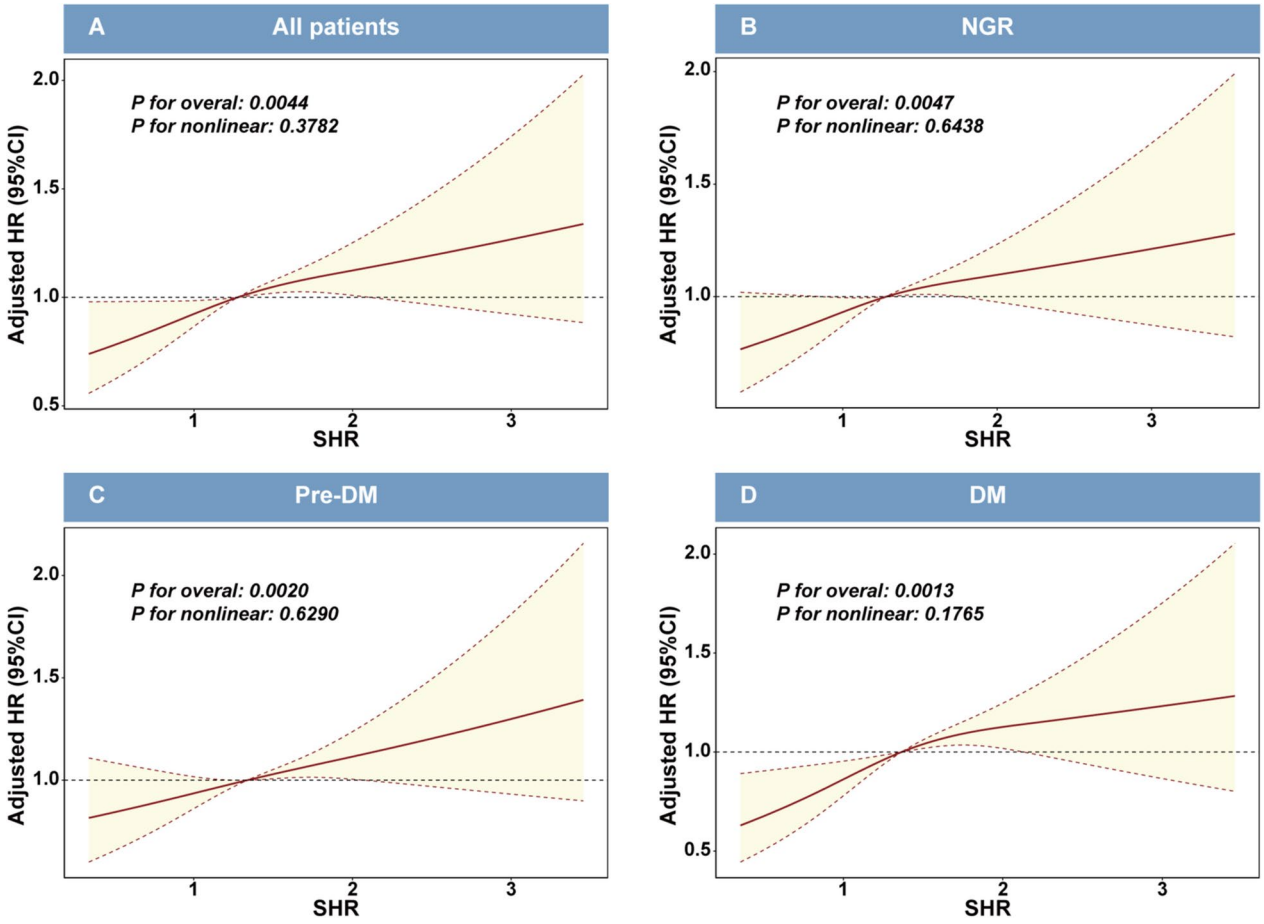



**Fig. 3** Restricted cubic spline curves of the association between stress hyperglycemia ratio and long-term MACCE risk. Associations of SHR with long-term MACCE across different glucose metabolic status. **A** All patients. **B** Patients with NGR. **C** Patients with Pre-DM. (D) Patients with DM. The solid red line represents the adjusted HR, and the yellow shaded area indicates the 95% CI. The horizontal dashed line represents the reference line (HR = 1). P for overall indicates the significance of the whole curve, and P for nonlinear represents the significance of the nonlinear component. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; NGR, normal glucose regulation; Pre-DM, pre-diabetes mellitus; SHR, stress hyperglycemia ratio

patient groups. Attention should be paid to patients with these SHR values, who may require more intensive monitoring and management. To our knowledge, this is the first study to evaluate the prognostic value of SHR in both perioperative and long-term outcomes in patients undergoing CABG, and the first to elucidate its differential impact across varying states of glucose metabolism.

Stress hyperglycemia refers to the relative increase in blood glucose levels caused by inflammatory and neurohormonal disturbances during severe illness [11]. This acute relative hyperglycemia indicates the severity of illness and poor glucose control, increasing the risk of acute or chronic cardiovascular complications through the following mechanisms. First, acute glucose fluctuation induces much greater endothelial dysfunction and cytokines release compared to sustained chronic hyperglycemia [12–15]. It is well established that endothelial dysfunction and inflammatory activation are critical factors in the progression of atherosclerosis and are closely related to an increased risk of cardiovascular events [29]. Furthermore, hyperglycemia attenuates platelet nitric oxide responsiveness [30], which promotes thrombosis. Therefore, attention should be devoted not only to chronic and mean glucose concentrations but also to stress hyperglycemia.

Several studies have examined the impact of preoperative glucose levels on short-term outcomes in patients undergoing CABG, but with inconsistent findings [18–20, 22]. Zindrou et al. found that ABG was an independent risk factor for female patients without diabetes after CABG, but did not modify mortality risk in males [18]. However, later studies observed that ABG was significantly related to short-term mortality but did not identify sex differences [19, 20, 22]. The possible reason for this inconsistency may be the ambiguous clinical significance of ABG. Absolute glucose levels cannot accurately reflect acute hyperglycemia, as the chronic glucose status also affects absolute values. Therefore, a single

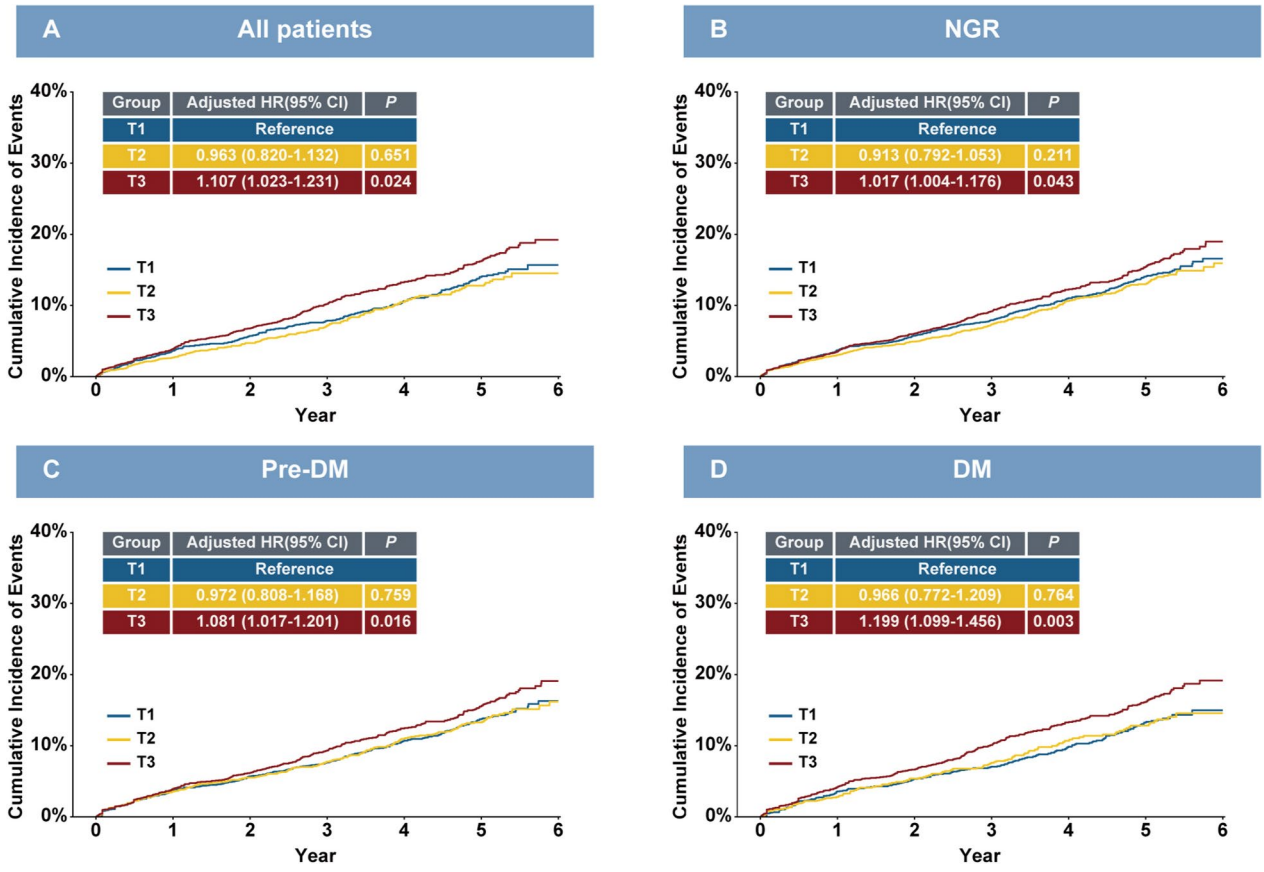



**Fig. 4** Kaplan–Meier analyses for long-term MACCE. Kaplan–Meier curves depict the cumulative incidence of events stratified by tertiles of stress hyperglycemia ratio: T1 (blue), T2 (yellow), and T3 (red). The results are shown for **A** all patients, **B** patients with NGR, **C** patients with Pre-DM, and **D** patients with DM. CI, confidence interval; DM, diabetes mellitus; HR, hazard ratio; MACCE, major adverse cardiovascular and cerebrovascular events; NGR, normal glucose regulation; Pre-DM, pre-diabetes mellitus; SHR, stress hyperglycemia ratio

**Table 3** Stress hyperglycemia ratio and long-term outcomes

| Group | Crude HR (95% CI) | *P* | Adjusted HR (95% CI) | *P* |
|---|---|---|---|---|
| All patients | | | | |
| T1 | Reference | | | |
| T2 | 0.997 (0.849–1.170) | 0.969 | 0.963 (0.820–1.132) | 0.651 |
| T3 | 1.159 (1.024–1.335) | 0.031 | 1.107 (1.023–1.231) | 0.024 |
| NGR | | | | |
| T1 | Reference | | | |
| T2 | 0.907 (0.792–1.038) | 0.157 | 0.913 (0.792–1.053) | 0.211 |
| T3 | 1.116 (1.009–1.245) | 0.046 | 1.017 (1.004–1.176) | 0.043 |
| Pre-DM | | | | |
| T1 | Reference | | | |
| T2 | 0.993 (0.827–1.192) | 0.940 | 0.972 (0.808–1.168) | 0.759 |
| T3 | 1.154 (1.018–1.345) | 0.029 | 1.081(1.017–1.201) | 0.016 |
| DM | | | | |
| T1 | Reference | | | |
| T2 | 1.011 (0.811–1.261) | 0.922 | 0.966 (0.772–1.209) | 0.764 |
| T3 | 1.310 (1.101–1.559) | 0.002 | 1.199(1.099–1.456) | 0.003 |

preoperative glucose measurement is neither representative for stress hyperglycemia nor sufficient to define the chronic states of patients. To address this limitation, Roberts et al. proposed the SHR, calculated by both ABG and HbA1c, which considers both acute fluctuations and chronic levels simultaneously [21]. Recent studies have highlighted the prognostic value of SHR in non-surgical CAD patients such as acute coronary syndrome [31], multivessel or triple-vessel disease [32, 33] and chronic total occlusion [34]. The association of SHR with adverse events has exhibited various forms across different CAD populations, including non-linear U-shaped, J-shaped, and linear positive relationships. Researchers also observed that SHR was significantly related to the CAD severity, function and microvascular obstruction [35, 36]. Compared with non-surgical individuals, patients undergoing CABG experience greater oxidative stress induced by surgery, which may exacerbate the adverse effects associated with hyperglycemia. Furthermore, patients who underwent CABG often have more complicated atherosclerosis and are more susceptible to complications secondary to stress hyperglycemia. Therefore, it

is of significance to clarify the impact of SHR on CABG patients and explore the specific relationship with both in-hospital and long-term prognosis.

As far as we know, the current study is the first to examine the prognostic role of SHR in individuals who underwent CABG. We also identified, for the first time, a non-linear relationship between SHR and perioperative outcomes, as well as a linear relationship with long-term MACCE risk after CABG. Specifically, as SHR increased, the risk of in-hospital events initially increased and then decreased, with an inflection point observed at 0.79. Similar to our findings, a study on patients with acute coronary syndrome found the inflection point of SHR for poor prognosis was 0.78 [17]. Other studies also demonstrated a U-shaped curve of SHR-related risk in surgical or non-surgical populations [37–40]. These findings suggested that mild to moderate stress hyperglycemia might be harmless or even beneficial in certain patients. However, the underlying mechanisms are not yet fully understood. Previous studies have provided evidence showing that acute glucose-loading contributes to significant improvement in myocardial function and a subsequent rise in cardiac output in animals and patients [41, 42]. The beneficial effects of mild to moderate stress hyperglycemia might be attributed to enhanced glucose utilization during ischemia–reperfusion, especially in cardiac tissues where glucose becomes the preferred metabolic substrate under stress conditions [43]. At the molecular level, mild to moderate hyperglycemia may activate protective signaling pathways such as the PI3K/Akt pathway, which has been shown to improve myocardial recovery following ischemic insult [44]. Therefore, mild stress-induced hyperglycemia in critical illness has been thought to be an adaptive and defensive response [45]. Given the importance of perioperative hemodynamics on outcomes following CABG, it is reasonable to speculate that adaptive stress hyperglycemia may reduce the risk of adverse events during hospitalization. However, once glucose levels exceed the threshold for adaptive response, excessive hyperglycemia triggers pathological mechanisms including increased oxidative stress through overproduction of reactive oxygen species, activation of protein kinase C, and increased formation of advanced glycation end products [46]. These mechanisms collectively induce endothelial dysfunction, impair coronary microcirculation, and promote a prothrombotic state that can worsen myocardial ischemia and reduce the benefits of surgical revascularization [47]. Furthermore, the first tertile exhibited a greater risk of diabetes compared with the other groups. This group also had the highest proportion of insulin use, indicating tight glycemic control. Consequently, the first tertile had the highest HbA1c level but the lowest FBG value as shown in Table 1. It is reasonable to speculate that the higher rates of perioperative adverse outcomes in the first tertile may be attributed to hypoglycemic episodes during hospitalization. Hypoglycemia can trigger inflammatory responses, which in turn lead to the increased risk of in-hospital complications and lengthened ICU stays after CABG [48, 49]. Recent evidence suggests that hypoglycemia induces endothelial dysfunction through increased expression of adhesion molecules, impaired nitric oxide production, and enhanced platelet aggregation [50]. Additionally, hypoglycemia activates the sympathoadrenal system, resulting in catecholamine release that can induce cardiac arrhythmias and increase myocardial oxygen demand at a time when the post-CABG myocardium is particularly vulnerable [51]. From this perspective, an SHR below 0.79 may indicate tight or excessive glucose control in our study population, while an SHR above 0.79 suggests poor glucose control. Given the unique and significant impact of SHR on perioperative outcomes, we further investigated its clinical value in the risk prediction model. Our analysis revealed that incorporating SHR into the EuroSCORE II model significantly improved its predictive performance for in-hospital adverse events, both in the overall population and across different glucose metabolism states.

For long-term outcomes, the U-shaped association of SHR no longer existed. The long-term MACCE rates increased progressively with higher SHR levels. There was no significant prognostic difference between tertile 2 and the reference group (tertile 1). However, SHR > 0.91 (tertile 3) increased the risk of in-hospital outcomes by 10.7%. Our findings on long-term outcomes were consistent with previous research by Abdu et al. [52], who demonstrated that patients in the highest SHR tertile (tertile 3) were independently associated with a 2.465-fold increased risk of long-term MACE in individuals with myocardial infarction with non-obstructive coronary arteries (MINOCA). The consistency of SHR's prognostic value across both surgical and non-surgical populations strengthens its clinical utility as a risk stratification tool. This linear relationship of long-term prognosis suggests differences in the mechanisms underlying acute and chronic complications related to stress hyperglycemia. The transition from a U-shaped short-term relationship to a linear long-term relationship may reflect different pathophysiological processes over time. While acute adaptive responses might provide short-term hemodynamic benefits, chronic exposure to stress hyperglycemia likely promotes sustained endothelial dysfunction, vascular inflammation, and accelerated atherosclerosis [53]. Elevated SHR may indicate impaired glucose homeostasis and metabolic inflexibility that, over time, contributes to progressive vascular damage through chronic oxidative stress, mitochondrial dysfunction, and epigenetic modifications that persist even after the initial stress resolves [54]. Additionally, high SHR might identify patients with

underlying subclinical insulin resistance who are particularly susceptible to adverse cardiovascular events following CABG [55]. Furthermore, the impact of SHR was more pronounced on perioperative outcomes compared with long-term prognosis. Specifically, the protective effects of adaptive stress hyperglycemia may not extend to long-term prognostic benefits for CABG patients. As mentioned above, the beneficial effects of adaptive response are primarily attributed to hemodynamic improvements. Since stress hyperglycemia is a transient response and usually resolves spontaneously after discharge [11], the hemodynamic benefits may not persist over time. Despite this distinction, the findings demonstrated that patients with SHR > 0.91 were consistently at high risk of poor prognosis.

Several studies have highlighted that the risk of adverse outcomes associated with stress hyperglycemia may be heightened in patients without diagnosed diabetes [16, 40, 56, 57]. Lyu et al. observed a statistically significant U-shaped association between SHR and MACCE risk within 30 or 90 days after non-cardiac surgery in non-diabetes group. However, no significant relationship was found in patients with diabetes [40]. Another study on critical acute myocardial infarction divided patients into four groups based on SHR quartiles, and found that the fourth quartile had a greater mortality risk among non-diabetes patients, with no significant relationship identified in diabetes group [56]. The results of our study align partially with previous findings. We found that SHR-related perioperative risks were consistent in patients with NGR, but attenuated in those with DM. Although the protective effects of the adaptive response still existed, there was no significant relationship with in-hospital outcomes in diabetes group when SHR > 0.79. Previous evidence suggests that chronic hyperglycemia may establish a pattern of cellular conditioning to reduce the harmful effects of stress hyperglycemia. Long-term exposure to hyperglycemia contributes to a series of compensatory responses, including antioxidant production, glucose transporters downregulation, increased survival factors and angiogenesis [11, 58–60]. These responses enable the body to manage acute hyperglycemia more effectively and reduce the associated risks. However, it is worth mentioning that glucose metabolism status did not modify the long-term risk associated with stress hyperglycemia. This finding again underscores the distinctions of the mechanisms between short-term and long-term complications. As previously discussed, the acute protective effects may not persist in discharged patients. Similarly, it can be inferred that the antagonistic effect between acute harm and compensatory responses may also disappear after discharge. Consequently, the third tertile consistently had increased rates of long-term MACCE regardless of glucose metabolism status.

Perioperative glucose control remains a critical concern for patients undergoing CABG. Previous studies have identified the harmful effects of hyperglycemia and attempted to determine optimal glucose targets during the intraoperative or postoperative periods [61–64]. However, there is limited data regarding the management of preoperative hyperglycemia in CABG patients. Our study was the first to highlight the prognostic significance of SHR, indicating the importance of preoperative glucose management in this population. Given its prognostic significance, an important consideration is the role of glucose-lowering medications that might influence SHR and potentially modify outcomes in CABG patients. Insulin therapy, while effective for immediate glucose control, may increase the risk of hypoglycemia and has been associated with increased mortality in some studies of critically ill patients [65]. In contrast, agents such as glucagon-like peptide 1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter 2 (SGLT2) inhibitors offer promising alternatives to provide cardiovascular protection [66, 67]. These agents may attenuate ischemia–reperfusion injury and reduce infarct size. Their additional benefits on cardiac function, congestion reduction, and cardiometabolic parameters could improve perioperative outcomes [68]. However, a comprehensive review by Karakasis et al. highlights important considerations regarding SGLT2 inhibitors in acute cardiac settings [68]. Despite established cardiovascular benefits in patients with type 2 diabetes, current evidence does not firmly support their use in acute coronary syndrome, and safety concerns such as hypotension, hypovolemia, or ketoacidosis require careful attention [68, 69]. This suggests caution may be warranted when considering these agents in the perioperative period of CABG. Nevertheless, SGLT2 inhibitors appear promising for the long-term prevention of adverse cardiovascular events after CABG, with studies demonstrating significant reduction in MACCE in patients with diabetes after surgical revascularization [70]. Future studies are warranted to explore effective strategies to reduce the risk of adverse events associated with stress hyperglycemia, particularly investigating the impact of different antidiabetic medications on SHR-related risks in patients undergoing CABG.

The study has several limitations. First, our study was conducted in a Chinese cohort, which may limit the generalizability of our findings to other populations and ethnicities. The prognostic value of SHR in diverse ethnic groups requires further investigation, and future multi-ethnic studies are warranted to validate our results. Second, the SHR was calculated with ABG and HbA1c. Blood glucose levels may fluctuate dynamically during hospitalization due to the various stressors such as surgical stress, medication use, and postoperative recovery. The study could not account for these dynamic changes

in SHR throughout hospitalization, which might affect the accuracy of our findings. Future studies incorporating multiple SHR measurements over time would likely provide more comprehensive prognostic insights. Third, detailed information on hypoglycemic agents was not obtained. Given that certain medications, such as GLP-1 RAs, and SGLT2 inhibitors, have demonstrated cardiovascular benefits, future studies should explore the impact of anti-diabetic medications on stress hyperglycemia-related risks. Finally, despite adjusting for major confounding variables, residual confounding may exist from unmeasured biomarkers (e.g., NT-proBNP, troponin), and factors such as nutritional status, psychological stress, and quality of postoperative care.

## Conclusions

In conclusion, the study demonstrated a non-linear U-shaped association of SHR with adverse events during hospitalization, as well as a linear positive relationship with long-term prognosis in patients undergoing CABG. The inflection point of the SHR value observed in the U-shaped curve was at 0.79. Our study was the first to identify the prognostic significance of SHR in CABG patients. Future therapeutic strategies aiming at stress hyperglycemia should be explored to improve the prognosis of individuals undergoing CABG.

### Abbreviations

| | |
|---|---|
| SHR | Stress hyperglycemia ratio |
| MACCE | Major adverse cardiac and cerebrovascular events |
| MI | Myocardial infarction |
| CAD | Coronary artery disease |
| CABG | Coronary artery bypass grafting |
| CI | Confidence interval |
| CPB | Cardiopulmonary bypass |
| HbA1c | Glycated hemoglobin |
| ABG | Admission blood glucose |
| TC | Total cholesterol |
| TG | Triglycerides |

## Supplementary Information

The online version contains supplementary material available at https://doi.org/10.1186/s12933-025-02682-z.

Additional file1 (DOCX 946 KB)

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### Author contributions

Concept and design: Z.L., R.C., Z.Z., H.Z., Z.Z.; Acquisition, analysis, or interpretation of data: Z.L., R.C., P.W., Z.Z.; Drafting of the manuscript: Z.L., R.C.; Critical review of the manuscript for important intellectual content: Z.L., R.C., Z.Z., H.Z., Z.Z.; Statistical analysis: Z.L., R.C.; Administrative, technical, or material support: C.Y., S.Y., X.S., Y.Z.; Supervision: H.Z., Z.Z.

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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

This study was approved by the institutional review board at Fuwai Hospital and the requirement for written informed consent was waived.

### Consent for publication

All participants provided written informed consent for publication.

### Competing interests

The authors declare no competing interests.

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