

Stress hyperglycemia ratio and long-term prognosis in patients with acute myocardial infarction undergoing percutaneous coronary intervention: evidence for an J-shaped association

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ABSTRACT

BACKGROUND Acute myocardial infarction (AMI) is a major cause of mortality worldwide. The stress hyperglycemia ratio (SHR), which integrates glucose and glycated hemoglobin A1c levels, better reflects acute metabolic stress. This study assessed the SHR and long-term prognosis of patients with AMI.

METHODS This study was a *post-hoc* analysis based on the prospective, multicenter OPTIMAL registry (<http://www.clinicaltrials.gov>, NCT number: NCT03084991). A total of 3384 consecutive patients who underwent percutaneous coronary intervention (PCI) at Department of Cardiology, The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China were included in the present analysis after exclusions. Patients were stratified into quartiles according to the SHR. The primary endpoint was cardiovascular death, with all-cause death and major adverse cardiovascular events as secondary endpoints. The median follow-up duration was 24.1 months, with a completion rate of 99.5%.

RESULTS Kaplan-Meier survival curves showed progressively worse survival across SHR quartiles (log-rank $P < 0.001$), with patients in Q4 (SHR ≥ 1.34) experiencing the highest risk. Multivariate Cox regression analysis confirmed that the SHR was an independent predictor of cardiovascular death [hazard ratio (HR) = 1.56], all-cause death (HR = 1.48), and major adverse cardiovascular events (HR = 1.34) for Q4 (SHR ≥ 1.34) versus Q2 (SHR: 0.93–1.11). Restricted cubic spline analysis revealed a J-shaped association between SHR and outcomes, with the lowest risk observed at an SHR of approximately 1.0.

CONCLUSIONS The SHR is an independent predictor of long-term adverse outcomes in patients with AMI undergoing PCI, supporting its use for early risk stratification and glycemic management.

Acute myocardial infarction (AMI) remains a major global health burden and one of the leading causes of death and disability. Patients with AMI frequently present with heterogeneous and complex clinical conditions, making the identification and management of prognostic factors critical for improving outcomes.

Stress hyperglycemia has been linked to an increased risk of mortality and complications, including myocardial infarction, heart failure, and cerebrovascular events in critically ill patients.^[1–3] However, the admission glucose level alone provides limited insight into chronic glycemic status and

baseline metabolic control. To address this limitation, Roberts, *et al.*^[4] proposed the stress hyperglycemia ratio (SHR) in 2015, a metric that adjusts admission blood glucose for glycated hemoglobin A1c (HbA1c), thereby providing a more accurate reflection of acute SHG.

Acute stress hyperglycemia is a complex physiological response, and a single admission blood glucose level can be confounded by pre-existing chronic dysglycemia [e.g., diabetes mellitus (DM)]. The SHR, by adjusting the acute glucose level for the patient's long-term glycemic background (as reflected by HbA1c), provides a more specific measure of the true acute stress response. This theoretically

makes it a superior biomarker for risk stratification in acute illnesses like AMI compared to glucose alone, as it helps distinguish between patients with poor chronic control and those experiencing a profound acute metabolic stress reaction.^[5-9]

Accumulating evidence indicates that an elevated SHR is independently associated with adverse cardiovascular outcomes, such as recurrent infarction and heart failure.^[10,11] However, data on its prognostic significance in patients with AMI, particularly those undergoing percutaneous coronary intervention (PCI), are limited.

Accordingly, this study aimed to evaluate the association between admission SHR and long-term outcomes in patients with AMI, including cardiovascular mortality, all-cause mortality, and major adverse cardiovascular events (MACE). Clarifying the prognostic role of SHR may help bridge the gap between metabolic disturbances and cardiovascular outcomes and provide practical implications for early risk stratification in this high-risk population.

METHODS

Study Design and Population

This study was a retrospective, single-center, *post-hoc* analysis. The primary dataset was derived from the OPTIMAL (Optical Coherence Tomography Imaging in Patients With Acute Myocardial Infarction During Primary PCI) study (<http://www.clinicaltrials.gov>, NCT number: NCT03084991), a prospective, multicenter, non-randomized, observational registry that enrolled patients with AMI requiring catheter-based PCI. The original trial enr-

olled 6000 patients with AMI, and we included those who underwent PCI at Department of Cardiology, The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China between January 2018 and January 2021 within the OPTIMAL study to investigate the prognostic value of the SHR. A total of 3744 patients diagnosed with AMI and treated with PCI were screened. After excluding 360 patients due to loss to follow-up or missing admission blood glucose/HbA1c data, 3384 patients were included in the analysis. The patient selection process and stratification into SHR quartiles are summarized in Figure 1. Consecutive eligible patients were enrolled to minimize selection bias.

Ethical Approval

This study complied with the Declaration of Helsinki and was approved by the Ethics Committee of The 2nd Affiliated Hospital of Harbin Medical University, Harbin, China (No. KY2019-012-01). It also adhered to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines.

Data Collection and Definition of SHR

Baseline demographic, clinical, laboratory, and angiographic data were retrieved from electronic medical records. SHR was calculated as:

$$\text{SHR} = \frac{\text{Admission Blood Glucose}}{(1.59 \times \text{HbA1c}) - 2.59}$$

Data collection was performed independently by two investigators, and discrepancies were adjudicated by a third reviewer.

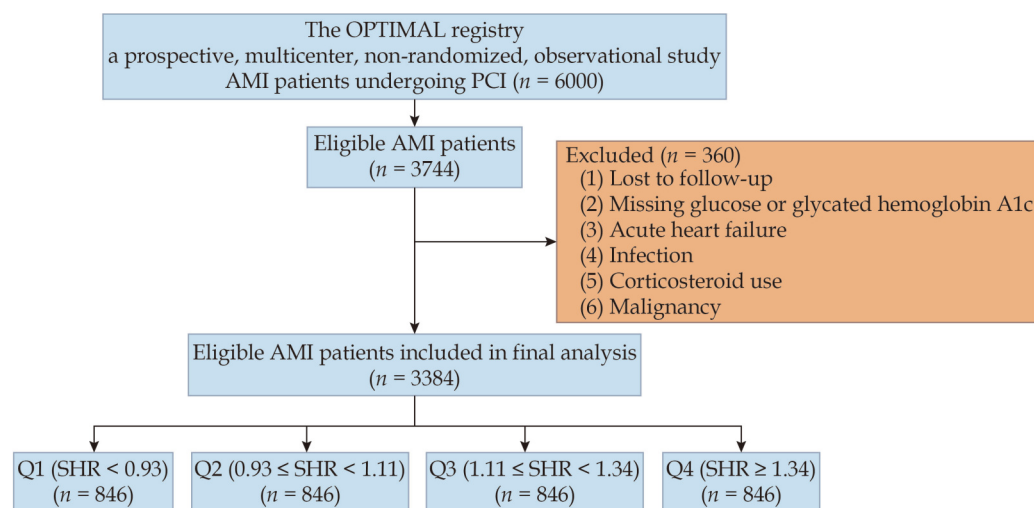


Figure 1 Flow diagram of AMI patient inclusion and SHR quartile stratification. AMI: acute myocardial infarction; PCI: percutaneous coronary intervention; SHR: stress hyperglycemia ratio.



Eligibility Criteria and Grouping

The inclusion criteria were as follows: (1) age ≥ 18 years; (2) confirmed diagnosis of AMI, including ST-segment elevation myocardial infarction (STEMI) or non-ST-segment elevation myocardial infarction (NSTEMI); and (3) planned PCI during the index hospitalization. The exclusion criteria were as follows: (1) absence of follow-up data; (2) uncontrolled or acute decompensated heart failure; (3) missing admission blood glucose or HbA1c values; and (4) severe infection, corticosteroid use, malignancy, or other systemic illnesses likely to affect glycemic status. Patients were stratified into quartiles according to SHR: Q1 (< 0.93), Q2 ($0.93\text{--}1.11$), Q3 ($1.11\text{--}1.34$), and Q4 (≥ 1.34).

Follow-up and Endpoints

Follow-ups were conducted at 1, 6, 12, 24, and 36 months after discharge through structured telephone interviews, outpatient visits, or review of hospital records. The primary endpoint was cardiovascular death, and the secondary endpoints were all-cause death and MACE. Patients without valid follow-up information or with missing baseline glucose/HbA1c data were excluded from the final analysis. The follow-up completion rate was calculated as the proportion of patients with available follow-up information among the final study population. The primary endpoint was cardiovascular death. Secondary endpoints included all-cause death and MACE, defined as a composite of recurrent myocardial infarction, cardiovascular death, coronary revascularization, rehospitalization for cardiovascular causes, bleeding, or ischemic stroke. The bleeding endpoint in our study was defined as clinically significant bleeding events, classified as the Bleeding Academic Research Consortium (BARC) types 2, 3, or 5.

Covariates

Data on demographic (age, sex, body mass index, and smoking status) and the following comorbidities were extracted: DM, use of antidiabetic medication including insulin and oral antidiabetic drugs, hypertension, prior myocardial infarction, prior PCI, renal dysfunction, and clinical presentation (STEMI or NSTEMI). Laboratory covariates included low-density lipoprotein cholesterol (LDL-C), total cholesterol, triglyceride, and high-density lipoprotein cholesterol, hemoglobin, cardiac troponin I, HbA1c, glucose, fasting blood glucose (FBG), and left ventricular ejection fraction (LVEF). Medication covariates included aspirin, clopidogrel, ticagrelor, statins, beta-blockers, and angiotensin-

converting enzyme inhibitors or angiotensin II receptor blockers, mineralocorticoid receptor antagonists. Angiographic and procedural covariates included culprit vessel distribution (left anterior descending artery), left circumflex artery, right coronary artery, or left main, pre-PCI TIMI flow grade, number of diseased vessels (single-vessel disease vs. multivessel disease), and stent implantation status (any vs. ≥ 2 stents).

Statistical Analysis

Continuous variables were presented as mean $\pm$ SD or medians (interquartile range) and compared using one-way analysis of variance (ANOVA) or Kruskal-Wallis *H* tests, as appropriate. Categorical variables were expressed as counts (percentages) and compared using the Pearson's chi-squared test. Survival was assessed using Kaplan-Meier curves with log-rank tests. The Cox proportional hazard models were fitted to estimate hazard ratio (HR) with 95% CI, with three levels of adjustment: Model 1 (age, sex, and body mass index); Model 2 (Model 1 plus smoking, DM, hypertension, prior myocardial infarction, and clinical presentation); and Model 3 (Model 2 plus LVEF, multivessel disease, ≥ 2 stents, statin, LDL-C, stent implantation, and cardiac troponin I). The proportional hazards assumption was verified using the Schoenfeld residuals.

Restricted cubic spline models with knots at the 5th, 35th, 65th, and 95th percentiles were applied to examine the dose-response and potential nonlinear associations between SHR and outcomes. Sensitivity analyses were also performed to evaluate the robustness of the findings, including stratification by age, sex, clinical presentation (STEMI vs. NSTEMI), DM, hypertension, and presence of multivessel disease. Interaction terms were tested to explore potential heterogeneity across subgroups. To further evaluate the prognostic performance of FBG in comparison with the SHR, we conducted additional analyses including multivariate Cox regression, restricted cubic spline model, and time-dependent receiver operating characteristic analyses. The area under the curves (AUCs) were compared using the DeLong's test.

The proportion of missing data was $< 5\%$ for most variables, with the highest levels observed for LVEF (14.2%) and LDL-C (8.5%) (supplemental material, Table 1S). A multivariate single imputation method for missing data based on an iterative imputation was implemented using a Bayesian ridge model as the estimator at each step of the round-robin imputation.

All analyses were performed using R statistical softw-



are (version 4.2.2, R Foundation for Statistical Computing, Boston, MA, USA) and the Free Statistics Analysis Platform (version 2.1, <http://www.clinicalscintists.cn/freestatistics>).^[12] A two-tailed *P*-value < 0.05 was considered statistically significant.

RESULTS

Of the 3744 patients initially screened, 360 patients were excluded because of loss to follow-up or missing baseline glucose/HbA1c data, leaving 3384 patients in the final cohort. During a median follow-up of 24.1 months (interquartile range: 12.2–35.8 months), a total of 191 cardiovascular deaths, 263 all-cause deaths, and 535 MACE events were recorded. In the final study population, 3366 patients had valid follow-up information, with a follow-up completion rate of 99.5%.

Baseline Characteristics

A total of 3384 patients with AMI who underwent PCI

were stratified into quartiles according to SHR levels. Baseline demographic, clinical, laboratory, and angiographic characteristics are presented in Tables 1 & 2.

Patients in the higher SHR quartiles were generally older and more likely to have DM, renal dysfunction, and lower LVEF (all *P* < 0.001). By contrast, the prevalence of smoking, hypertension, and prior myocardial infarction did not differ significantly between groups. Laboratory findings showed a stepwise increase in admission glucose, fasting glucose, HbA1c, and cardiac troponin I levels with higher SHR, consistent with greater metabolic stress. Lipid parameters varied modestly but without clear trends.

Medication use at discharge was broadly comparable among the groups; however, patients in the high SHR strata were more likely to receive beta-blockers and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers therapy, reflecting a high burden of baseline cardiac dysfunction. Angiographic findings indicated no significant differences in culprit vessel distribution, multivessel disease, or stent implantation rates.

Table 1 Baseline characteristics by SHR quartiles.

Variables	Total (<i>n</i> = 3384)	SHR				<i>P</i> -value
		Q1 (< 0.93) (<i>n</i> = 846)	Q2 (0.93–1.11) (<i>n</i> = 846)	Q3 (1.11–1.34) (<i>n</i> = 846)	Q4 (≥ 1.34) (<i>n</i> = 846)	
Demographics and clinical features						
Age, yrs	61.7 ± 11.4	60.7 ± 11.5	60.8 ± 11.7	62.0 ± 11.0	63.2 ± 11.1	< 0.001
Male	2378 (70.3%)	619 (73.2%)	624 (73.8%)	582 (68.8%)	553 (65.4%)	< 0.001
Body mass index, kg/m ²	25.1 ± 3.8	25.3 ± 4.0	25.3 ± 3.6	25.0 ± 3.7	24.7 ± 3.7	0.007
Current smoking	1404 (41.5%)	372 (44.0%)	364 (43.0%)	339 (40.1%)	329 (38.9%)	0.110
Diabetes mellitus	845 (25.0%)	193 (22.8%)	137 (16.2%)	212 (25.1%)	303 (35.8%)	< 0.001
Anti-diabetic drug	724 (21.4%)	167 (19.7%)	116 (13.7%)	183 (21.6%)	258 (30.5%)	< 0.001
Insulin	323 (9.5%)	65 (7.7%)	49 (5.8%)	84 (9.9%)	125 (14.8%)	< 0.001
Oral antidiabetic drugs	455 (13.4%)	111 (13.1%)	77 (9.1%)	111 (13.1%)	156 (18.4%)	< 0.001
Hypertension	1682 (49.7%)	408 (48.2%)	402 (47.5%)	438 (51.8%)	434 (51.3%)	0.198
Prior myocardial infarction	197 (5.8%)	50 (5.9%)	42 (5.0%)	53 (6.3%)	52 (6.1%)	0.657
Prior PCI	207 (6.1%)	52 (6.1%)	49 (5.8%)	56 (6.6%)	50 (5.9%)	0.898
Renal dysfunction	33 (1.0%)	10 (1.2%)	8 (0.9%)	7 (0.8%)	8 (0.9%)	0.901
NSTEMI	1200 (35.6%)	433 (51.5%)	288 (34.1%)	232 (27.4%)	247 (29.3%)	< 0.001
STEMI	2173 (64.4%)	407 (48.5%)	556 (65.9%)	614 (72.6%)	596 (70.7%)	< 0.001
LVEF, %	55.8 ± 8.6	56.9 ± 8.4	56.2 ± 8.2	55.8 ± 8.3	54.2 ± 9.1	< 0.001
Laboratory findings						
LDL-C, mmol/L	3.1 ± 1.0	3.1 ± 1.0	3.2 ± 1.0	3.1 ± 1.0	3.0 ± 1.0	0.003
High-density lipoprotein cholesterol, mmol/L	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	1.1 ± 0.3	< 0.001
Total cholesterol, mmol/L	4.8 ± 1.2	4.7 ± 1.2	4.8 ± 1.2	4.8 ± 1.1	4.7 ± 1.2	0.034
Triglyceride, mmol/L	1.2 (0.9–1.8)*	1.3 (0.9–1.9)*	1.2 (0.9–1.8)*	1.2 (0.9–1.8)*	1.2 (0.8–1.8)*	0.029



Continued

Variables	Total (n = 3384)	SHR				P-value
		Q1 (< 0.93) (n = 846)	Q2 (0.93–1.11) (n = 846)	Q3 (1.11–1.34) (n = 846)	Q4 (≥ 1.34) (n = 846)	
Hemoglobin, g/L	153.3 ± 57.3	153.9 ± 63.3	155.9 ± 54.2	154.2 ± 56.1	149.1 ± 4.8	0.099
Cardiac troponin I, ng/mL	7.6 (1.4–36.2)*	4.2 (0.9–18.0)*	8.0 (1.4–37.6)*	8.3 (1.3–42.0)*	11.0 (2.1–57.5)*	< 0.001
HbA1c, %	6.5 ± 1.5	6.5 ± 1.5	6.3 ± 1.3	6.5 ± 1.5	6.7 ± 1.6	< 0.001
Glucose, mmol/L	9.1 ± 4.4	6.1 ± 2.0	7.5 ± 2.1	9.4 ± 3.0	13.5 ± 5.3	< 0.001
FBG, mmol/L	8.4 ± 4.1	7.4 ± 3.2	7.5 ± 2.9	8.6 ± 4.7	10.1 ± 4.7	< 0.001
SHR	1.2 ± 0.4	0.8 ± 0.1	1.0 ± 0.1	1.2 ± 0.1	1.7 ± 0.5	< 0.001
Medication history						
Aspirin	3339 (99.1%)	828 (98.7%)	836 (99.1%)	835 (99.2%)	840 (99.5%)	0.333
Clopidogrel	2263 (67.2%)	550 (65.6%)	551 (65.3%)	568 (67.5%)	594 (70.4%)	0.097
Ticagrelor	1097 (32.6%)	287 (34.2%)	293 (34.7%)	272 (32.3%)	245 (29%)	0.054
Statins	3359 (99.8%)	837 (99.8%)	844 (99.9%)	841 (99.8%)	837 (99.6%)	0.709
Beta-blockers	2264 (67.2%)	542 (64.6%)	566 (67.0%)	598 (70.9%)	558 (66.4%)	0.043
Angiotensin-converting enzyme inhibitors/Angiotensin II receptor blockers	1977 (58.7%)	464 (55.3%)	495 (58.6%)	514 (61.0%)	504 (60.0%)	0.095
Mineralocorticoid receptor antagonists	324 (9.6%)	54 (6.4%)	72 (8.5%)	83 (9.8%)	115 (13.6%)	< 0.001

Data are presented as means ± SD or *n* (%). *Presented as median (interquartile range). FBG: fasting blood glucose; HbA1c: glycated hemoglobin A1c; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; NSTEMI: non-ST-segment elevation myocardial infarction; PCI: percutaneous coronary intervention; SHR: stress hyperglycemia ratio; STEMI: ST-segment elevation myocardial infarction.

Table 2 Angiographic and procedural characteristics stratified by SHR quartiles.

Variables	Total (n = 3384)	SHR				P-value
		Q1 (< 0.93) (n = 846)	Q2 (0.93–1.11) (n = 846)	Q3 (1.11–1.34) (n = 846)	Q4 (≥ 1.34) (n = 846)	
Culprit lesions						
Left anterior descending artery	1593 (47.1%)	427 (50.5%)	386 (45.6%)	397 (46.9%)	383 (45.3%)	0.125
Left circumflex artery	564 (16.7%)	155 (18.3%)	147 (17.4%)	129 (15.2%)	133 (15.7%)	0.290
Right coronary artery	1197 (35.4%)	258 (30.5%)	302 (35.7%)	318 (37.6%)	319 (37.7%)	0.005
Left main	22 (0.7%)	6 (0.7%)	5 (0.6%)	2 (0.2%)	9 (1.1%)	0.206
TIMI flow						
TIMI 0	1676 (49.5%)	304 (35.9%)	435 (51.4%)	447 (52.8%)	490 (57.9%)	< 0.001
TIMI ≥ 1	1699 (50.2%)	542 (64.1%)	405 (47.9%)	399 (47.2%)	353 (41.7%)	< 0.001
Number of diseased vessels						
Single-vessel disease	947 (28.0%)	234 (27.7%)	235 (27.8%)	237 (28.0%)	241 (28.5%)	0.982
Multivessel disease	2437 (72.0%)	612 (72.3%)	611 (72.2%)	609 (72.0%)	605 (71.5%)	0.982
Stent implantation						
Any stent implantation	2522 (74.7%)	632 (74.7%)	611 (72.7%)	632 (74.7%)	647 (76.7%)	0.331
Stent ≥ 2	986 (29.1%)	268 (31.7%)	235 (27.8%)	237 (28.0%)	246 (29.1%)	0.270

Data are presented as *n* (%). SHR: stress hyperglycemia ratio; TIMI: Thrombolysis in Myocardial Infarction.

Clinical Outcomes

Kaplan-Meier survival curves (Figure 2) demonstrated

a clear separation of event-free survival among the SHR quartiles (all log-rank $P < 0.001$). Patients in Q4 consistently had the worst outcomes, with 3-year cumulative in-



cidences of 8.2% for cardiovascular death, 10.3% for all-cause death, and 18.9% for MACE. By contrast, patients in Q1 had the most favorable outcomes, with corresponding rates of 3.9% for cardiovascular death, 5.4% for all-cause death, and 12.3% for MACE. Patients in Q3 exhibited intermediate risks, whereas those in Q2 represented a relatively stable group with outcomes between the extremes. These findings highlight the graded relation between SHR and long-term prognosis.

SHR and Adverse Prognosis in Patients with AMI Undergoing PCI

Multivariate Cox regression analysis confirmed that SHR was an independent predictor of adverse outcomes (Table 3). In the fully adjusted model (Model 3), patients in Q4 had significantly higher risks of cardiovascular death (HR = 1.56, 95% CI: 1.02–2.39, $P=0.042$), all-cause death (HR = 1.48, 95% CI: 1.03–2.13, $P=0.036$), and MACE (HR = 1.34, 95%

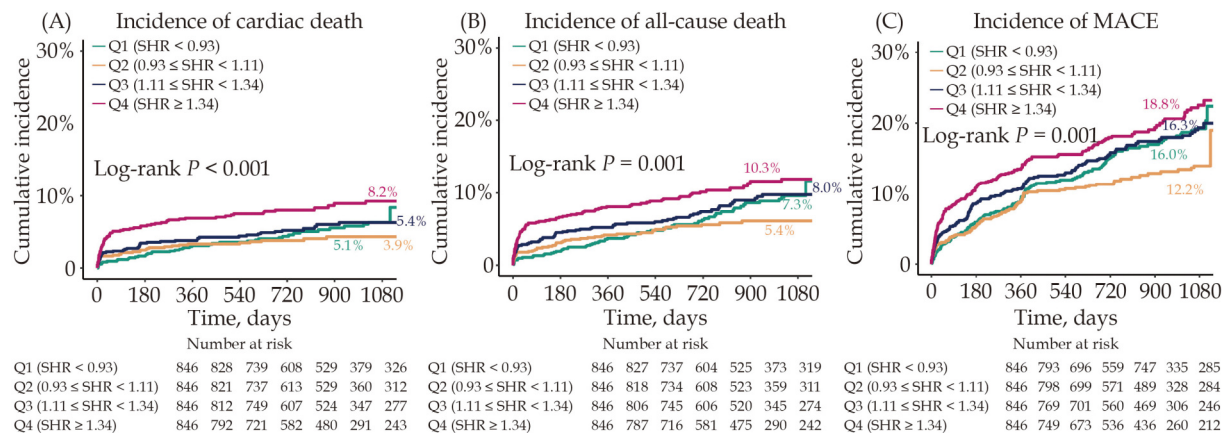


Figure 2 Kaplan-Meier survival curves for clinical outcomes stratified by SHR quartiles. (A): Cardiac death; (B): all-cause death; and (C): MACE. Survival curves are stratified by SHR quartiles. Numbers at risk are presented at baseline and follow-up intervals. Group differences were compared with the log-rank test. MACE: major adverse cardiovascular event; SHR: stress hyperglycemia ratio.

Table 3 Multivariable Cox regression analysis of SHR for clinical outcomes.

Outcome	Model 1		Model 2		Model 3	
	HR (95% CI)	P-value	HR (95% CI)	P-value	HR (95% CI)	P-value
Cardiac death						
Q1 (< 0.93)	1.26 (0.80–1.99)	0.314	1.23 (0.78–1.94)	0.380	1.20 (0.76–1.90)	0.433
Q2 (0.93–1.11)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q3 (1.11–1.34)	1.29 (0.82–2.02)	0.268	1.2 (0.77–1.89)	0.424	1.24 (0.79–1.95)	0.350
Q4 (≥ 1.34)	1.93 (1.27–2.93)	0.002	1.75 (1.15–2.68)	0.009	1.56 (1.02–2.39)	0.042
All-cause death						
Q1 (< 0.93)	1.3 (0.89–1.91)	0.176	1.26 (0.86–1.85)	0.244	1.24 (0.84–1.83)	0.273
Q2 (0.93–1.11)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q3 (1.11–1.34)	1.37 (0.94–1.99)	0.101	1.30 (0.89–1.89)	0.178	1.34 (0.92–1.96)	0.125
Q4 (≥ 1.34)	1.74 (1.22–2.50)	0.002	1.61 (1.12–2.32)	0.010	1.48 (1.03–2.13)	0.036
MACE						
Q1 (< 0.93)	1.28 (0.99–1.66)	0.056	1.25 (0.96–1.62)	0.092	1.25 (0.96–1.62)	0.093
Q2 (0.93–1.11)	1.00 (Reference)		1.00 (Reference)		1.00 (Reference)	
Q3 (1.11–1.34)	1.30 (1.01–1.68)	0.043	1.24 (0.95–1.60)	0.108	1.27 (0.98–1.64)	0.072
Q4 (≥ 1.34)	1.52 (1.19–1.95)	0.001	1.41 (1.09–1.82)	0.008	1.34 (1.04–1.73)	0.023

Hazard ratio (HR) with 95% CI was estimated using Cox proportional hazards regression. Model 1: adjusted for age, sex, and body mass index. Model 2: adjusted for variables in Model 1 plus the smoking, DM, hypertension, prior myocardial infarction, and clinical presentation. Model 3: adjusted for variables in Model 2 plus the LVEF, multivessel disease, ≥ 2 stents, statin, LDL-C, stent implantation, and cardiac troponin I. DM: diabetes mellitus; LDL-C: low-density lipoprotein cholesterol; LVEF: left ventricular ejection fraction; MACE: major adverse cardiovascular event; SHR: stress hyperglycemia ratio.



CI: 1.04–1.73, $P = 0.023$) compared with those in the reference group (Q2). Patients in Q3 also had a modestly increased risk, particularly for all-cause death and MACE, although these associations were attenuated after full adjustment. No significant differences were observed between Q1 and Q2. These results underscore the prognostic relevance of elevated SHR beyond traditional risk factors.

Restricted cubic spline regression was used to examine the continuous relation between SHR and clinical outcomes. As shown in Figure 3, SHR exhibited a significant non-linear J-shaped association with cardiovascular death, all-cause death, and MACE (all $P_{\text{non-linearity}} < 0.01$). The nadir of risk occurred at an SHR of approximately 1.0. Both low (< 0.8) and high (> 1.0) values were associated with progressively

greater risks, indicating that inadequate and excessive SHG may be detrimental. These findings suggest that SHR provides prognostic information not only as a categorical variable but also as a continuous measure, with an optimal threshold near 1.0 for risk stratification.

Subgroup and Sensitivity Analyses

To assess the robustness of the results, subgroup analyses were conducted and are illustrated in forest plots (Figure 4). Subgroups were defined by age, sex, DM, hypertension, clinical presentation (STEMI vs. NSTEMI), and presence of multivessel disease. The adverse prognostic effect of elevated SHR was consistent across all subgroups, with no significant interactions observed (all $P_{\text{interaction}} > 0.05$).

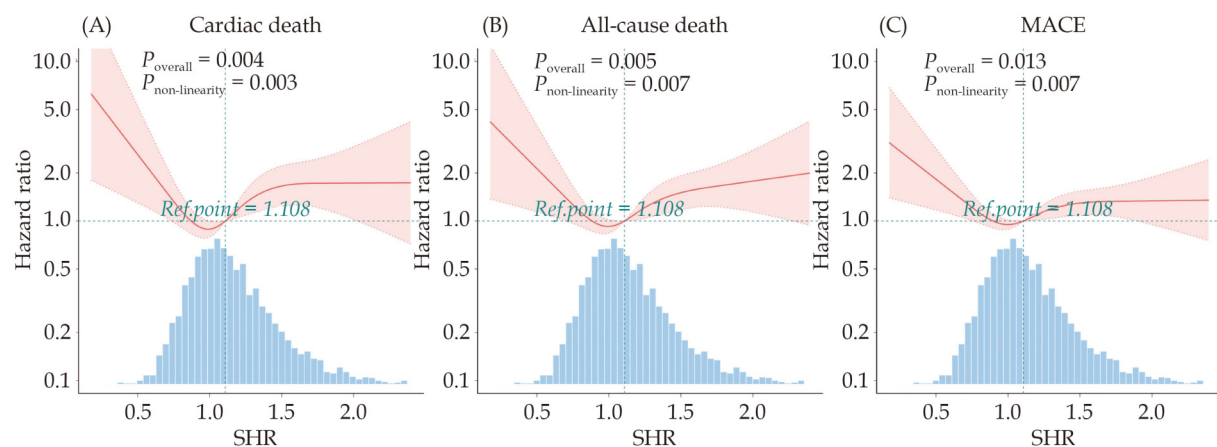


Figure 3 Restricted cubic spline curves for the association between SHR and adverse outcomes. It shows adjusted hazard ratio (HR) with 95% CI of the SHR for cardiac death (A), all-cause death (B), and MACE (C). Red lines indicate adjusted HR, shaded areas 95% CI, and blue histograms the distribution of SHR values. Models were adjusted for covariates as described in Methods. P -value for overall association and non-linearity are shown. MACE: major adverse cardiovascular event; SHR: stress hyperglycemia ratio.

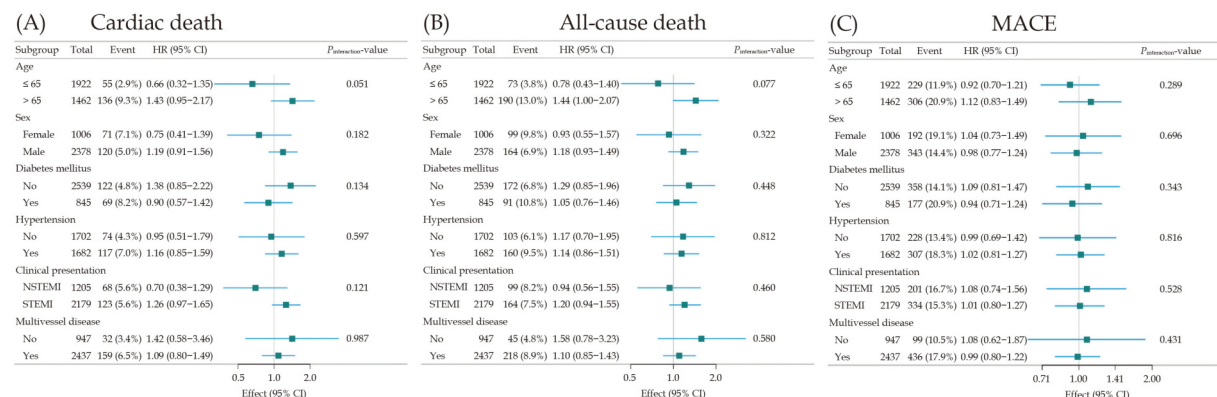


Figure 4 Subgroup analyses of SHR and clinical outcomes. Subgroup analyses for the association of SHR with cardiac death (A), all-cause death (B), and MACE (C). Hazard ratio (HR) with 95% CI was estimated using multivariable Cox regression analysis. HR is indicated by squares, with size proportional to the number of events in each subgroup; horizontal lines indicate 95% CI, and the vertical dashed line marks HR = 1.0. The P -values for the interaction effect were calculated using likelihood ratio tests to assess heterogeneity across subgroups. MACE: major adverse cardiovascular event; NSTEMI: non-ST-segment elevation myocardial infarction; SHR: stress hyperglycemia ratio; STEMI: ST-segment elevation myocardial infarction.



Although stronger associations were noted in older patients and in those with STEMI, these differences were not statistically significant. Collectively, these findings support the stability of the main results and underscore the broad applicability of SHR as a prognostic marker in heterogeneous AMI populations.

Comparative Prognostic Value of FBG and SHR

As shown in supplemental material, Table 2S and supplemental material, Figures 1S & 2S, higher FBG quartiles were associated with increased risks of cardiac death, all-cause death, and MACE ($P_{\text{trend}} < 0.05$). Restricted cubic spline curves demonstrated a linear relationship between FBG and adverse outcomes, with risk slightly increasing above 7.1 mmol/L (supplemental material, Figure 2S). Time-dependent receiver operating characteristic analyses indicated that SHR had comparable or slightly higher AUCs than FBG for predicting cardiac and all-cause mortality, with greater temporal stability across follow-up periods (supplemental material, Figure 1S). Although FBG showed marginally higher AUCs for MACE at 2 years and 3 years ($\Delta\text{AUC} < 0.05$), these differences were small and clinically insignificant. Together, these results suggest that SHR provides more robust and physiologically meaningful prognostic information compared with FBG.

DISCUSSION

In this large cohort of patients with AMI undergoing PCI,

we demonstrated that SHR, which integrates admission glucose with HbA1c, is a strong and independent predictor of long-term outcomes. Elevated SHR was associated with significantly high risks of cardiovascular death, all-cause mortality, and MACE. Importantly, the relation between SHR and adverse outcomes followed a J-shaped curve, with the lowest risk observed at approximately 1.0. These findings highlight SHR as a clinically practical biomarker that bridges the gap between metabolic disturbances and cardiovascular prognosis (Figure 5).

Our results are consistent with those of previous studies demonstrating the adverse prognostic impact of SHG. Earlier investigations based solely on admission glucose suggested that elevated glucose at presentation was associated with worse mortality and morbidity.^[11,13–15] However, admission glucose does not distinguish between chronic hyperglycemia and acute stress response, particularly in patients with poorly controlled DM.^[6] To overcome this limitation, Roberts, *et al.*^[4] introduced SHR in 2015, and subsequent studies confirmed its superiority over absolute glucose values in predicting outcomes across acute coronary syndromes (ACS).^[3,10] Our findings extend this knowledge specifically to PCI-treated patients with AMI, thereby establishing SHR as a robust prognostic marker in this high-risk setting.

We found that patients in the highest SHR quartile (Q4) had markedly increased risks of cardiovascular death, all-cause death, and MACE compared with the reference gr-

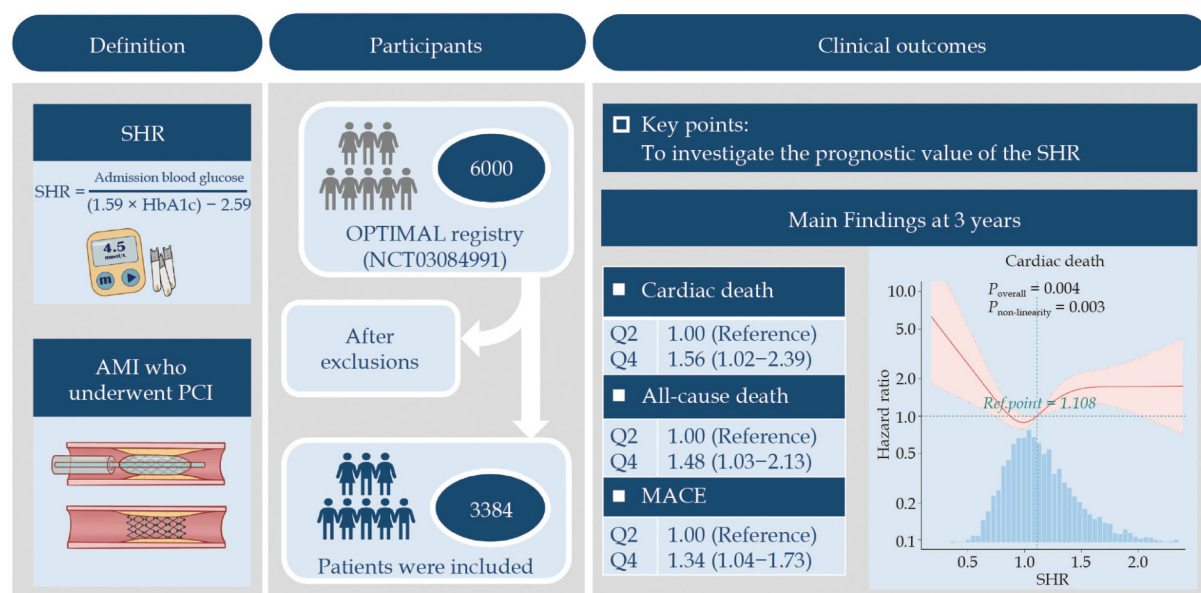


Figure 5 J-shaped association between SHR and long-term outcomes after AMI. AMI: acute myocardial infarction; HbA1c: glycated hemoglobin A1c; MACE: major adverse cardiovascular event; PCI: percutaneous coronary intervention; SHR: stress hyperglycemia ratio.



oup. These results are consistent with those of a recent large-scale study. For example, a registry analysis^[17] showed that SHR provided incremental prognostic information beyond admission glucose, whereas another multicenter cohort^[18] demonstrated that adding SHR to existing risk scores significantly improved predictive performance. Our data corroborate these findings and confirm that SHR has strong prognostic value in contemporary PCI-treated AMI populations. Although FBG was positively associated with long-term outcomes, SHR demonstrated stronger discrimination and pathophysiological relevance by adjusting acute glucose for chronic glycemic background. This finding reinforces SHR as a superior and clinically meaningful biomarker for stress-induced metabolic disturbance in AMI patients undergoing PCI.

One novel contribution of our study is the identification of a J-shaped association. Patients with excessively low and high SHR values had worse outcomes than those with values around 1.0. This observation parallels the work of Yang, *et al.*^[9] who reported that both low and high SHR quintiles were linked to an increased 2-year risk of major adverse cardiovascular and cerebrovascular events in ACS. Wei, *et al.*^[19] further demonstrated similar findings in PCI-treated patients with ACS during long-term follow-up. Our J-shaped finding aligns with that of a recent meta-analysis,^[21] highlighting the dual risk of both low and high SHR levels across ACS populations. However, it differs from another cohort study,^[21] that suggested a linear relation between SHR and mortality. These discrepancies may reflect differences in patient selection, follow-up duration, and adjustment strategies, underscoring the need for further multicenter validation.

Mechanistically, this dual risk is plausible. Moderate SHG levels may be adaptive, enhance cellular survival pathways, and protect against ischemic injury.^[22,23] Conversely, excessive hyperglycemia exacerbates inflammation, oxidative stress, endothelial dysfunction, and thrombosis, worsening reperfusion injury.^[24,25] An abnormally low SHR may instead reflect an insufficient metabolic response or overtreatment with glucose-lowering therapy, impairing myocardial energy supply. This hypothesis is supported by recent mechanistic studies: experimental data^[26,27] showed that acute hyperglycemia induces oxidative stress and platelet activation, aggravating ischemia-reperfusion injury, while excessively aggressive glucose control compromises cardiomyocyte survival. These findings provide biological plausibility for the J-shaped association observed in our clinical data.

Our subgroup analyses provide additional insights. We observed that the prognostic value of SHR was consistent across age, sex, hypertension, and DM status, with no significant interactions. This finding challenges the traditional view that SHG is predominantly harmful to patients without DM.^[28] For instance, in a large STEMI cohort of 6287 patients, SHR was predictive of long-term outcomes regardless of diabetic status.^[29] Similarly, a Chinese AMI cohort showed no SHR-diabetes interaction in predicting all-cause mortality. Our results reinforce these findings and are in line with recent reports,^[30,31] showing that SHR predicts adverse outcomes independently of diabetic status. These consistent results suggest that SHR reflects the acute metabolic stress response rather than preexisting glycemic background, supporting its universal applicability as a prognostic marker.

LIMITATIONS

Despite these strengths, several limitations must be acknowledged. Firstly, this was a retrospective, single-center analysis, and selection bias could not be fully excluded. Secondly, SHR was calculated only at admission, and we lacked data on glycemic variability or in-hospital glucose management, which may further influence prognosis.^[32] Thirdly, residual confounding by unmeasured variables such as inflammatory biomarkers, insulin resistance, and medication adherence remains possible. Fourthly, although SHR is predictive of outcomes, causality cannot be inferred, and interventional trials are needed to determine whether modifying SHR improves survival. Last but not least, the follow-up duration was limited to 3 years, potentially underestimating long-term risks.

These findings have several clinical and scientific implications. SHR is derived from routine laboratory tests and is readily available at no additional cost, making it feasible for real-world practice. The J-shaped relation highlights the need for balanced glycemic management, and clinicians should avoid both insufficient and excessive hyperglycemia in the acute settings. Future research should validate SHR in multicenter, ethnically diverse cohorts and test SHR-guided glucose management strategies in randomized controlled trials. Mechanistic investigations incorporating inflammatory, oxidative, and endothelial biomarkers will further clarify the biological pathways linking SHR to adverse outcomes.

In summary, our study demonstrated that SHR is independently associated with long-term cardiovascular death,



all-cause mortality, and MACE in patients with PCI-treated AMI, with a distinctive J-shaped association. By integrating acute and chronic glycemia, SHR provides a more precise reflection of metabolic stress than glucose alone. These findings underscore the clinical value of SHR as a simple and widely applicable biomarker for risk stratification and bridge the gap between metabolic derangement and adverse cardiovascular outcomes.

CONCLUSIONS

SHR is an independent predictor of cardiovascular death, all-cause death, and MACE in patients with AMI treated with PCI. A J-shaped relationship was observed, with the lowest risk near 1.0, supporting SHR as a simple biomarker for early risk stratification.

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