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Integrated Metabolic-Inflammatory Risk Assessment: HbA1c/HDL-c and hsCRP-to-Albumin Ratios Synergistically Predict Major Adverse Cardiovascular Events in Post-PCI STEMI Patients

Jinyong Huang^{a#}, Junyi Zhang^{b#}, Zhonghui Xie^a, Linjie Li^a, Meiyan Chen^c, Yongle Li^a, Xiangdong Yu^a, Shaozhuang Dong^a, Qing Wang^a, Jun Chen^a, Qing Yang^{a*}, Shaopeng Xu^{a*}

^aDepartment of Cardiology, Tianjin Medical University General Hospital, Tianjin, China

^bDepartment of Cardiology, Tianjin Chest Hospital, Tianjin, China

^cDepartment of Emergency, Qilu Hospital of Shandong University, Shandong, China

(#Each author made an equal contribution to this piece of writing.)

***Corresponding author:** Shaopeng Xu, Qing Yang

¹²Department of Cardiology, Tianjin Medical University General Hospital

No. 154, Anshan Road, Heping District, Tianjin 300052, China

Phone: +86-13332093191

Fax: +86-22-60362779

E-mail: tjzyyxsp@163.com (Shaopeng Xu)

E-mail: cardio-yq@outlook.com (Qing Yang)

Abstract

Background: This study looked into how predictive in ¹⁸ST-segment elevation myocardial infarction (STEMI) is the high-sensitivity C-reactive protein-to-albumin ratio (hsCAR) as well as ²glycated hemoglobin to high-density lipoprotein cholesterol (HbA1c/HDL-c) ratio.

Methods: This retrospective cohort research was carried out on 1,177 patients having STEMI who were given ²⁸percutaneous coronary intervention (PCI). For major adverse cardiovascular events (MACE), the independent and combined predictive values ²of the HbA1c/HDL-c ratio (threshold ≥ 6.61) and hsCAR (threshold ≥ 0.18) were assessed. MACE was an amalgamation of death from all causes, ischemia-induced revascularization, myocardial infarction not leading to death, heart failure hospitalization, and cerebrovascular events. The team used Cox regression models, causal mediation examination, and receiver operating characteristic curves to assess prognostic performance and mechanistic pathways, and compared them ⁸with the Global Registry of Acute Coronary Events (GRACE) risk score.

Results: The interquartile range for follow-up was 79 to 672 days, with 461 median days. A raised HbA1c/HDL-c ratio (≥ 6.61) and hsCAR (≥ 0.18) independently predicted MACEs, with 1.51 ¹(95% confidence interval [CI]: 1.26–1.81; $P < 0.001$) as well as 1.84 (95% CI: 1.53–2.21; $P = 0.005$) hazard ratios (HRs), respectively. Combined use enhanced risk stratification, with the high HbA1c/HDL-c–high hsCAR group showing the highest risk ²⁴(adjusted HR 2.19, 95% CI: 1.67–2.87; $P < 0.001$). Causal mediation examination revealed that coronary lesion complexity partially mediated these associations; ³the SYnergy between PCI with TAXUS and Cardiac Surgery (SYNTAX) and the residual SYNTAX scores were responsible for accounting for 24.2%/17.7% of the hsCAR effect and 16.8%/25.2% of the HbA1c/HDL-c

ratio effect, respectively. Compared with the individual markers or the GRACE risk score, the combined biomarker model demonstrated superior discriminatory capacity (area under the curve⁶=0.63, 95% CI=0.60–0.66; $P<0.001$), with significant improvement in integrated discrimination.

Conclusion: The integration of HbA1c/HDL-c and hsCAR can significantly improve risk stratification in patients with STEMI, outperforming traditional scoring systems and assisting in the precise management of individuals at risk.

Keywords: ST-elevation myocardial infarction; HbA1c/HDL-c ratio; High-sensitivity C-reactive protein-to-albumin ratio; Risk stratification; Major adverse cardiovascular events

51 Introduction

52 One ³⁵of the main reasons of morbidity and death throughout the world today is
53 coronary heart disease. Even after advancements in interventional techniques as well as
54 pharmacological therapies that have substantially improved early survival rates in ⁴⁷ST-
55 segment elevation myocardial infarction (STEMI), these individuals face considerable risk of
56 long-term cardiovascular problems after percutaneous coronary intervention (PCI) [1].
57 Consequently, identifying more precise risk assessment tools, particularly biomarker
58 combinations that integrate multiple pathophysiological mechanisms, holds significant
59 clinical importance for improving outcomes in patients with STEMI.

60 STEMI pathogenesis covers a complex interplay between disruptions in the body's
61 normal metabolic processes and inflammatory processes, which are intimately interconnected
62 and mutually reinforcing [2-3]. In the acute phase of myocardial infarction, metabolic
63 perturbations, including insulin resistance, hyperglycemia, and dyslipidemia, create a
64 proatherogenic environment that accelerates plaque instability and promotes thrombosis [4-
65 5]. Simultaneously, the inflammatory cascade triggered by myocardial necrosis leads to
66 systemic inflammatory activation, which not only exacerbates tissue damage but also
67 influences long-term cardiovascular risk through effects on endothelial function, plaque
68 vulnerability, and coronary microcirculation [2, 6]. While individual biomarkers provide
69 valuable insights into specific pathophysiological pathways, emerging evidence suggests that
70 composite markers integrating multiple parameters may offer superior predictive capacity.
71 This integrated approach better captures the multifaceted nature of cardiovascular disease
72 progression, potentially enabling more precise risk stratification and personalized therapeutic

73 strategies.

74 In 2021, Hu et al. proposed² the glycated hemoglobin to high-density lipoprotein
75 cholesterol (HbA1c/HDL-c) ratio, which has since become a likely metabolic composite
76 marker [7]. This ratio uniquely integrates two crucial aspects of cardiometabolic health: long-
77 term glycemic control (via HbA1c, showing the mean glucose levels during 2 to 3 months)
78 and lipid metabolism functionality (via HDL-c, reflecting cholesterol reverse transport and
79 anti-inflammatory capacity). By simultaneously capturing these complementary dimensions,
80² the HbA1c/HDL-c ratio provides a more comprehensive assessment of metabolic
81 dysregulation than either parameter alone.

82 Since its introduction,² the HbA1c/HDL-c ratio shows clinical utility across multiple
83 conditions, including carotid atherosclerosis [7] and stroke risk estimation [8]. These
84 investigations indicate that this ratio not only reflects insulin resistance states but also
85 captures the composite risk arising from prolonged hyperglycemia-induced vascular
86 endothelial damage coupled with diminished HDL-c protective function.
87 Nevertheless, no research has thoroughly examined the link between major adverse
88 cardiovascular event (MACE) risk and the HbA1c/HDL-c ratio in STEMI after PCI, despite
89 these encouraging uses.

90 Complementing metabolic assessments, inflammatory responses govern
91 atherosclerosis as well as myocardial infarction. A¹ high-sensitivity C-reactive protein
92 (hsCRP)-to-albumin ratio (hsCAR) represents an inflammatory indicator that has
93 demonstrated prognostic value in various cardiovascular scenarios [9-13]. By combining a
94 proinflammatory marker (hsCRP) with a parameter reflecting nutritional status and anti-

inflammatory capacity (albumin), this ratio offers additional insights into systemic inflammatory status that may complement metabolic risk assessment.

One method that shows promise for risk stratification in STEMI is the combination of metabolic and inflammatory biomarkers, given the well-established interaction between these systems during acute myocardial infarction [14-15]. Metabolic dysfunction promotes inflammation through advanced glycation, oxidative stress, and dyslipidemia [16], whereas inflammation can worsen metabolic disturbances via cytokine-induced insulin resistance and stress hyperglycemia [17-18]. This two-way interaction may amplify cardiovascular risk beyond the contribution of either factor alone.

Both processes influence important post-STEMI outcomes, including coronary complexity, microvascular function, ventricular remodeling, and thrombosis risk [19]. However, the combined prognostic value of the HbA1c/HDL-c ratio (showing a chronic metabolic condition) and inflammatory markers remains underexplored in PCI-treated patients with STEMI. This gap is important to address, given patient heterogeneity in metabolic and inflammatory status, which may affect long-term outcomes.

Based on this background, this study looked into the independent and combined predictive power of the hsCAR alongside the HbA1c/HDL-c ratio after PCI for MACE in STEMI. The hypothesis is that the HbA1c/HDL-c ratio provides noteworthy prognostic factors beyond conventional risk factors, and integrating metabolic and inflammatory assessments further enhances risk stratification by capturing the synergistic effects of these interconnected pathophysiological pathways, potentially informing tailored management strategies for this high-risk population.

117

118 **Methods**

119 ³⁸ *Study design and participants*

120 A comprehensive retrospective analysis was carried out on consecutive people having
121 STEMI enrolled at the Tianjin Medical University General Hospital's Cardiovascular Disease
122 Registry³ from August 2018 to December 2023. Tianjin Medical University General
123 Hospital's Ethics Committee approved the protocol (approval number: IRB2023-YX-301-
124 01/2023), which matched the philosophies mentioned¹³ in the Declaration of Helsinki (1975)
125 and its subsequent revisions. Taking into account the retrospective data analysis based on
126 standard clinical records, written informed consent was not needed.

127 The research team selected people aged ≥ 18 years who had the following conditions
128 for a definitive STEMI diagnosis [20]: (i) characteristic ischemic symptoms lasting¹⁹ ≥ 30
129 minutes; (ii) = ST-segment rise ≥ 1 mm in electrocardiography by a new left bundle branch¹⁹
130 block or minimum two adjoining leads; and (iii) increased cardiac troponin exceeding the
131 99th reference percentile. Researchers eliminated 303 of the 1,480 consecutive patients based
132 on these predefined criteria: (1) no coronary angiography or angiography without treatment
133 (n=33); (2) liver impairment (aspartate aminotransferase or alanine aminotransferase >thrice
134 the upper normal limit), advanced renal damage (<30 ²⁹ mL/min/1.73 m² estimated glomerular
135 filtration rate), or simultaneous active infection (n=23); (3)³³ PCI, coronary artery bypass
136 grafting (CABG), or myocardial infarction (n=140), which aims to reduce confounding from
137 chronic disease status and prior interventions, thereby allowing a more accurate assessment
138 of baseline biomarker associations with post-PCI outcomes; (4) insufficient clinical or

laboratory data pertinent to glycemic parameters or lipid profiles (n=31); and (5) inability to complete the follow-up protocol (n=76). The final analytical cohort comprised 1,177 patients who underwent a standardized evaluation and treatment protocol (Supplementary Fig. S1).

Baseline demographic and clinical characteristics were systematically recorded at admission. Current smoking status was defined as the consumption of ≥ 1 cigarette daily within 30 days preceding hospital admission [21]. Diabetes mellitus was defined by either an established prehospitalization diagnosis or documented use of glucose-lowering agents. One of these events meant hypertension: (1) previous clinical diagnosis, (2) antihypertensive medication use prior to admission, or (3) new diagnosis during the index hospitalization based on repetitive blood pressure records beyond 140/90 mmHg.

Sample size

Researchers calculated the study sample based on Cox proportional hazards model assumptions to detect a 1.5 hazard ratio with 80% statistical power at a two-sided 0.05 value showing significance. Drawing upon previously published data on cardiovascular event rates among patients with STEMI [22-23], a 15% cumulative incidence of MACE was estimated over 2 years of follow-up. These parameters yielded the required sample size of 637 participants. After applying a 10% adjustment factor for potential losses to follow-up, the minimum required enrollment was established at 708 patients. The final cohort of 1,177 participants substantially exceeded this requirement, ensuring robust statistical power for both primary analyses and prespecified subgroup investigations.

Comprehensive data collection and laboratory assessment

Researchers used electronic medical records alongside a standardized data collection protocol to extract comprehensive information. Demographic figures included sex, anthropometric measurements (height and weight, which helped us compute the body mass index [BMI]), age, smoking pattern, and vital parameters (heart rate and blood pressure). The medical history included diagnoses of diabetes mellitus, hypertension, and cerebrovascular events.

Blood samples were collected immediately upon admission before administration of antiplatelet agents or anticoagulants. Certified laboratory technicians, unaware of the clinical data, carried out laboratory assessments using standardized assays on automated platforms. Hematological parameters included complete blood counts with differential, comprehensive metabolic panels, and specialized cardiovascular biomarkers. Specifically, platelet count, hemoglobin concentration, serum albumin, renal function parameters (serum creatinine + eGFR obtained via the Modification of Diet in Renal Disease formula), cardiac biomarkers (B-type natriuretic peptide [BNP]), glycemic indices (HbA1c as well as fasting blood glucose [FBG]), and lipid profile (triglycerides [TG], total cholesterol [TC], HDL-c, and low-density lipoprotein cholesterol [LDL-c]) were quantified.

The team used Beckman Coulter, Inc.'s latex-enhanced immunoturbidimetric test to find HsCRP, with a 0.02 mg/L detection limit alongside inter- and intra-test coefficients of variation <5%. Researchers found HbA1c using Tosoh G8 high-performance liquid chromatography (Tosoh Bioscience, Inc.) with standardization according to the National Glycohemoglobin Standardization Program. HDL-c was quantified using a direct enzymatic

colorimetric assay following selective precipitation of apolipoprotein B-containing lipoproteins. See Supplementary Table S1 for details.

From these laboratory parameters, two composite indices were calculated:

- HbA1c/HDL-c ratio : HbA1c percentage $\div$ HDL-cholesterol concentration (mmol/L).
- hsCAR : hsCRP (mg/L) $\div$ serum albumin concentration (g/L).

Cardiac function was assessed via transthoracic echocardiography performed within a day of admission by veteran cardiologists by means of standardized protocols. The Biplane Simpson's process helped us measure the left ventricular ejection fraction (LVEF).

Coronary intervention procedure and angiographic assessment

All patients were given PCI after coronary angiography per current technical guidelines [24]. A loading dose containing 300 mg acetylsalicylic acid and either 180 mg ticagrelor or 300 mg clopidogrel were given before the procedure, based on clinical signs and bleeding risk test. Unless otherwise mentioned, antiplatelet therapy after the procedure involved taking 100 mg acetylsalicylic acid every day alongside either 90 mg ticagrelor two times a day or 75 mg clopidogrel regularly for at least a year.

Two skilled interventional cardiologists who were unaware of clinical information used the SYNergy between PCI with TAXUS and the Cardiac Surgery (SYNTAX) scoring system to systematically assess the complexity of coronary lesions. When scores differed, a third cardiologist made a decision to reach an agreement. After PCI, the team calculated the untreated coronary disease burden via the residual SYNTAX score (rSS). Both the initial

SYNTAX score and the rSS have demonstrated prognostic utility in previous investigations [25].

All patients were given standard evidence-based pharmacotherapy, consisting of statins, beta-blockers, angiotensin receptor blockers [ARBs], renin-angiotensin-aldosterone system inhibitors (angiotensin-converting enzyme inhibitors [ACEIs], or angiotensin receptor-neprilysin inhibitors [ARNIs]). Additionally, researchers prescribed proprotein convertase subtilisin/kexin type 9 inhibitors (PCSK9is) as well as sodium-glucose cotransporter 2 inhibitors (SGLT2is) per specific clinical indications, glycemic parameters, cardiac function assessment, and lipid profiles in accordance with contemporary guidelines.

Follow-up protocol and endpoint definitions

In this retrospective study, follow-up data were systematically obtained after checking electronic medical records from both outpatient visits and subsequent hospitalizations. To ensure the complete ascertainment of events, trained research personnel conducted structured telephone interviews using standardized questionnaires for patients with incomplete documentation in the electronic health record system. The combination of nonfatal myocardial infarction (per the Fourth Universal Definition [20]), death from all causes, ischemia-caused repeat revascularization, cerebrovascular complications (transient ischemic attack or ischemic stroke established by imaging alongside neurological tests), or heart failure hospitalization (needing inotropes, intravenous diuretics, or vasodilators) comprised MACE, which was the primary endpoint. To maintain rigor in this retrospective analysis, standardized criteria were applied consistently across all event evaluations, with particular attention to

distinguishing between index hospitalization complications and true post-discharge events. Researchers computed the time-to-event from the index PCI date to the first established MACE date, with censoring at the date of the last documented follow-up or study conclusion for event-free patients.

Statistical analysis methodology

After analyzing for normality, researchers use the means $\pm$ standard deviations to show continuous variables, or, if appropriate, medians with interquartile ranges. The team uses percentages and frequencies to show categorical variables. For continuous variables, researchers carried out the ⁴⁰t-test / Mann-Whitney U test to find between-group variances; for categorical variables, they carried out Fisher's exact/chi-square tests. The team created a directed acyclic plot to show the associations among hsCAR, MACE, ²and the HbA1c/HDL-c ratio (Supplementary Fig. S2).

Researchers found associations among MACE, hsCAR, ²and the HbA1c/HDL-c ratio by creating multivariable Cox proportional hazards models. Nonlinear associations were assessed using restricted cubic spline (RCS) functions. Cutoff values for HbA1c/HDL-c and hsCAR were determined based on optimal thresholds identified from log-rank statistics and spline inflection points, respectively.

Based on the established threshold values, the team stratified patients as: (1) lowHbA1c/HDL-c ratio with low hsCAR; (2) low HbA1c/HDL-c ratio with high hsCAR; (3) ²high HbA1c/HDL-c ratio with low hsCAR; and (4) ²high HbA1c/HDL-c ratio with high hsCAR. The Kaplan-Meier technique helped us create cumulative incidence curves, and the

log-rank test helped us find variances between groups.

To evaluate HbA1c/HDL-c ratio's and hsCAR's prognostic value (together as well as alone), a series of hierarchical Cox proportional hazards models were developed via progressive modification for confounding variables: Model 1: not adjusted; Model 2: for demographic factors (sex, BMI, and age); Model 3: Model 2 alongside clinical indices (blood pressure, heart rate, smoking pattern, diabetes, and stroke) and LVEF; Model 4: Model 3 alongside pharmacotherapy (antiplatelet regimen, ARBs/ARNIs/ACEIs, and beta-blockers) and laboratory parameters (platelet count, hemoglobin, eGFR, LDL-c); and Model 5: application of bootstrapping techniques with 1,000 resampling iterations to enhance the robustness of effect estimates. Researchers affirmed the proportional hazards assumption via log(-log) survival plots as well as scaled Schoenfeld residuals. Values less than three were deemed allowable when checking multicollinearity through variance inflation factors.

To elucidate potential mechanistic pathways linking the HbA1c/HDL-c ratio and hsCAR to MACEs, formal causal mediation analyses were carried out using the approach defined by Baron and Kenny, which was extended with bootstrapping procedures [26]. This methodology allows for decomposition of the total effect of each biomarker into direct effects and indirect effects mediated through coronary lesion burden (assessed via the SYNTAX score and rSS). Researchers carried out a causal mediation test to evaluate if the coronary lesion burden governs HbA1c/HDL-c's and hsCAR's prognostic effects.

Subgroup analyses explored potential differences in treatment effects according to age, sex, SYNTAX score category, diabetes status, and SGLT2i/PCSK9i therapy. Researchers modified Cox models to add interaction terms and test for treatment effect heterogeneity

across subgroups. Hazard ratios with interaction P values alongside 95% confidence intervals (CIs) are shown in forest plots.

The team calculated the area under the curve (AUC) with a 95% CI was computed using the receiver operating characteristic (ROC) curve, to find the HbA1c/HDL-c ratio's and hsCAR's incremental prognostic value. Improvements in risk discrimination and reclassification over existing models (e.g., the Global Registry of Acute Coronary Events [GRACE] and modified GRACE risk scores) were quantified using category-free net reclassification improvement (NRI) as well as integrated discrimination improvement (IDI) [27]. Likelihood ratio tests helped us find improvements in model fit.

Considering the established link between the MACE and triglyceride glucose (TyG) index, researchers carried out a supplemental test to evaluate the TyG index's effect on MACEs and the predictive capability of the TyG index along with the hsCAR.

To assess whether these losses were random or systematic, they compared the starting point features of all patients, and using inverse probability weighting, the team carried out a sensitivity analysis to evaluate how potential bias affected the results.

R 4.3.0 (R Foundation for Statistical Computing, Vienna, Austria) helped us with all tests. Significant results were described as two-sided P values less than 0.05. The Benjamini-Hochberg technique helped us regulate the false discovery rate during multiple comparisons.

Results

Study population and baseline characteristics

Between August 2018 and December 2023, researchers carried out this retrospective

3

study at Tianjin Medical University General Hospital, and initially, 1,480 patients with STEMI were identified. Because they were unable to finish the follow-up owing to the loss of contact (e.g., invalid contact information or relocation), they excluded 76 patients. Finally, 1,177 patients were enrolled. During 461 days of median follow-up (interquartile range: 79–672 days), 483 patients (41.0%) experienced MACEs.

When the team compared the starting point features of patients with and without MACE, they found a number of noteworthy variances (Supplementary Table S2). Patients who developed MACEs were characterized by advanced age, more complex coronary artery disease (elevated SYNTAX scores and rSS), and more diabetes and hypertension. The MACE group also demonstrated compromised renal function (reduced eGFR), enhanced systemic inflammation (elevated hs-CRP and hsCAR), and adverse metabolic profiles (increased HbA1c, FBG, and HbA1c/HDL-c ratio). Additionally, these patients more frequently required multiple stent implantation and exhibited reduced LVEF.

2

Prognostic value of the hsCAR and HbA1c/HDL-c ratio for MACEs

39

The HbA1c/HDL-c ratio and hsCAR frequencies are illustrated in Supplementary Fig. S3. Multivariable RCS analysis revealed different relationship patterns between these biomarkers and MACE risk (Fig. 1A-B). The HbA1c/HDL-c ratio was linearly related to MACE risk, with maximally selected rank statistics identifying an optimal cutoff value of 6.61. In contrast, hsCAR exhibited a nonlinear relationship with MACE risk, with a significance threshold of $hsCAR \geq 0.18$, beyond which the hazard ratio increased substantially.

Kaplan-Meier curves with conforming log-rank test outcomes (Fig. 1C-D) illustrated the differential MACE risk stratified by these biomarkers according to their respective cutoff points. Individuals with an elevated HbA1c/HDL-c ratio (≥ 6.61) presented a greater risk of MACEs (< 6.61) (hazard ratio [HR] 1.51, 95% CI: 1.26–1.81; $P < 0.001$). Similarly, the high-hsCAR group (≥ 0.18) demonstrated a more pronounced risk of MACEs (HR 1.84, 95% CI: 1.53–2.21; $P < 0.001$) than those with lower hsCAR values, suggesting that compared with the HbA1c/HDL-c ratio, hsCAR might be a more potent indicator of adversative cardiovascular consequences.

Combined prognostic value of the hsCAR and HbA1c/HDL-c ratio

Based on the established cutoff points, researchers divided the population into: (1) low HbA1c/HDL-c ratio (< 6.61) with low hsCAR (< 0.18); (2) low HbA1c/HDL-c ratio with high hsCAR (≥ 0.18); (3) high HbA1c/HDL-c ratio (≥ 6.61) having low hsCAR; and (4) high HbA1c/HDL-c ratio with high hsCAR. Table 1 shows their features at the starting point.

People in the low HbA1c/HDL-c ratio -low hsCAR group showed a lower diabetes prevalence than those in groups with minimum one raised biomarker. Additionally, these patients exhibited progressively elevated SYNTAX scores and rSSs, increased indices of glucose metabolism and inflammatory markers, and a greater proportion received SGLT2i therapy following hospitalization.

Table 2 and Fig. 2 demonstrate the synergistic effect of the combined HbA1c/HDL-c ratio and hsCAR on MACE incidence. The MACE risk was significantly higher in the three groups with minimum one raised biomarker in the Model 1 than the low HbA1c/HDL-c ratio

-low hsCAR group. Following sequential adjustments for demographic characteristics, clinical parameters, and angiographic variables, the elevated risk persisted in both the high hsCAR -low HbA1c/HDL-c ratio group (HR 1.88, 95% CI=1.45–2.44) and the high hsCAR -high HbA1c/HDL-c ratio group (HR 2.19, 95% CI=1.67–2.87) in the fully adjusted model (Model 4). The robustness of these findings was further validated through bootstrap analysis with 1,000 replicates, with the associations maintaining statistical significance across iterations.

Causal mediation analysis

Researchers carried out a mediation analysis in light of the possibility that coronary artery lesions might govern the biomarker–MACE relationship (Fig. 3) Regarding the HbA1c/HDL-c ratio, mediation analysis revealed that both the SYNTAX score and the rSS partially mediated its effect on MACEs. The HbA1c/HDL-c ratio showed a significant effect on MACEs. The proportion mediated by the SYNTAX score was 16.8% (95% CI: 1.95% to 38.0%), whereas the rSS mediated a greater proportion (25.2%, 95% CI: 12.0% to 52.0%), indicating that while both measures of coronary lesion complexity had a role in mediating the effect of the ratio on MACEs, the HbA1c/HDL-c ratio's direct effect persisted.

In hsCAR, a similar pattern emerged. The total effect of hsCAR on MACEs was significant. The SYNTAX score mediated 24.2% (95% CI: 15.5% to 37.0%) of this effect, whereas the rSS mediated 17.7% (95% CI: 8.61% to 29.0%). These findings suggest that while coronary lesion complexity contributed to the relationship between systemic inflammation and MACEs, the majority of hsCAR's effect remained direct, indicating an

independent risk factor influencing cardiovascular risk.

Sensitivity analyses demonstrated that the estimated mediation effects were robust to moderate levels of unmeasured confounding (ρ ranging from approximately -0.3 to +0.3) in all tested pathways. The results remained statistically significant across a broad range of ρ values, particularly for models involving the SYNTAX score and hsCAR, suggesting strong internal validity of the identified indirect effects. (Supplementary Fig. S4-5)

Subgroup analysis

Subgroup analysis (Fig. 4) revealed that both an elevated HbA1c/HDL-c ratio (≥ 6.61) and hsCAR (≥ 0.18) were independent risk factors with differential impacts across patient populations. Risk stratification was most pronounced in nondiabetic patients, normotensive individuals, and patients having raised SYNTAX scores. The prognostic significance of these biomarkers varied according to antiplatelet and lipid-lowering treatment regimens, indicating therapy-specific risk modifications.

Notably, elevated hsCAR (≥ 0.18) consistently predicted adverse outcomes regardless of SGLT2i therapy ($P < 0.001$); however, the degree of risk was considerably greater among nonusers (odds ratio [OR]=2.61) than among users (OR=1.62), suggesting that SGLT2i may attenuate inflammation-mediated cardiovascular events.

ROC analysis and reclassification metrics

To gauge the incremental prognostic value of biomarker integration, ROC analysis was conducted to compare the combined HbA1c/HDL-c ratio + hsCAR model against

individual biomarkers and the traditional GRACE score. The integrated model demonstrated superior discriminatory capacity (AUC: 0.63, 95% CI: 0.60–0.66; $P<0.001$) (Fig. 5), significantly outperforming the GRACE risk scores (AUC: 0.56, 95% CI: 0.53–0.58; $P<0.001$) alongside individual biomarkers when assessed separately. Notably, the combination yielded a significant integrated discrimination improvement (IDI: 0.02, 95% CI: 0.01–0.03; $P<0.01$) (Table 3), reinforcing multimarker strategies' clinical relevance in cardiovascular risk assessment for patients with STEMI following PCI. Similarly, there is a consistent result compared with that of the modified GRACE score (Supplementary Fig. S6 and Table S3).

⁴⁹ *Prognostic value of the TyG index*

Multivariable RCS test showed that the TyG index was nonlinearly related to MACE risk, with a threshold of 7.2, above which elevated TyG was significantly related to raised MACE risk (HR 1.58, 95% CI: 1.27–1.97; $P<0.001$) (Supplementary Fig. S7). Additionally, combining the TyG index with hsCAR yielded a predictive model with a 0.64 AUC (95% CI: 0.61–0.67), similar to a 0.63 AUC (95% CI: 0.60–0.66) for the HbA1c/HDL-c ratio combined with hsCAR (Supplementary Fig. S8).

Sensitivity analysis of select bias

At the starting point, features of patients who completed follow-up, as well as those who were lost to follow-up, are shown in Supplementary Table S4. The distribution of sexes and ages was similar, but the group lost-to-follow-up had a lower rSS

403 and SYNTAX score, a higher BMI, and fewer comorbidities (such as diabetes and
404 hypertension). Moreover, these patients were less likely to get key drugs, such as
405 ACEIs/ARBs/ARNIs, PCSK9is, and SGLT2is. Then, the team conducted an inverse
406 probability weighting sensitivity analysis (Supplementary Table S5). The HbA1c/HDL-c
407 ratio, hsCAR, and their combination's weighted effects on MACEs were consistent with the
408 primary analysis.

Discussion

Here, researchers offer fresh perspectives on the predictive value of integrating inflammatory as well as metabolic biomarkers for STEMI risk stratification after PCI. By simultaneously evaluating the HbA1c/HDL-c ratio and hsCAR, a synergistic approach was demonstrated to significantly enhance the prediction of MACEs. The identification of clinically relevant thresholds (HbA1c/HDL-c ratio ≥ 6.61 ; hsCAR ≥ 0.18) further enables practical implementation of these findings in clinical settings. This thorough examination, which takes causal mediation into account, shows how intricately systemic inflammation, metabolic dysfunction, cardiovascular outcomes, and coronary lesion complexity interact, offering new perspectives on pathophysiological mechanisms and potential therapeutic targets.

Integration of Metabolic and Inflammatory Biomarkers

The HbA1c/HDL-c ratio reflects both long-term glycemic control and dyslipidemia. Since its introduction by Hu et al. in 2021 [7], it has shown prognostic value in conditions such as carotid atherosclerosis and stroke. This study extends its relevance to patients with STEMI undergoing PCI, a previously unstudied high-risk group.

Complementing this metabolic marker, hsCAR combines hsCRP and albumin to capture systemic inflammation. It has been validated in various cardiovascular settings, including chronic total occlusion and post-CABG atrial fibrillation [28-29]. In STEMI cases, the hsCAR outperforms individual inflammatory markers [13, 30], and the findings further support that it strongly indicates complications after PCI.

The significant incremental prognostic value achieved by combining these biomarkers

represents a key finding of the study. Compared with either the marker alone or the established GRACE risk score, the integrated model demonstrated superior discriminatory capacity (AUC: 0.63, 95% CI: 0.60-0.66; $P<0.001$). This enhanced performance suggests that simultaneously capturing metabolic dysfunction and inflammatory activation offers a more all-inclusive information of the basic pathophysiology than conventional risk stratification approaches. Although the AUC of 0.63 for the combined biomarker model reflects moderate discrimination, this efficacy exceeds that of both the GRACE score (AUC: 0.56) and the individual markers. Moreover, in high-risk STEMI cases, even modest improvements in risk stratification based on easily obtainable biomarkers can inform early clinical decision making. The significant improvement in integrated discrimination (IDI: 0.02, 95% CI: 0.01–0.03; $P<0.01$) further validates the clinical relevance of this multimarker strategy.

The homeostasis model assessment of insulin resistance, along with the hyperinsulinemia-euglycemic clamp, shows strong link with the TyG index, which suggests insulin resistance. Researchers calculated it as $\ln[\text{fasting triglycerides (mg/dL)} \times \text{fasting plasma glucose (mg/dL)}]/2$ [31]. The TyG index's relationship with cardiovascular events has been well established [32]. Similar to the TyG index, the HbA1c/HDL-c ratio reflects long-term glycemic control and HDL-mediated cholesterol transport. These findings indicate that both markers exhibit comparable predictive capabilities for MACEs.

Mechanistic Insights from Causal Mediation Analysis

The causal mediation analysis revealed important insights into the pathways linking these biomarkers to cardiovascular outcomes. Both biomarkers demonstrated significant direct effects on MACEs, with coronary lesion complexity (SYNTAX score and rSS) serving

as partial mediators. These findings suggest a dual impact of both biomarkers on cardiovascular risk: first, through direct pathophysiological mechanisms, and second, through their influence on coronary lesion burden. The stronger mediation of HbA1c/HDL-c's impact through the rSS suggests that metabolic dysfunction may particularly affect incomplete revascularization outcomes, whereas inflammation (as reflected by hsCAR) may more strongly influence baseline coronary complexity. Importantly, the effects of the majority of both biomarkers remained direct, indicating that additional pathways beyond coronary anatomy contribute to adverse outcomes.

Pathophysiological Framework

The combined prognostic value of the hsCAR alongside the HbA1c/HDL-c ratio likely reflects the interplay of metabolic dysfunction with systemic inflammation in cardiovascular disease. Elevated HbA1c indicates chronic hyperglycemia, which promotes oxidative stress, endothelial dysfunction, and glycation [33], whereas low HDL-c impairs reverse cholesterol transport and antioxidant defenses [34], together accelerating atherogenesis and thrombosis [35-36]. The hsCAR captures the inflammatory burden by combining hsCRP and albumin. High hsCRP reflects proinflammatory activity, and low albumin indicates diminished anti-inflammatory and nutritional reserves. Inflammation enhances endothelial activation, plaque vulnerability, platelet reactivity, and thrombogenicity, thereby increasing post-PCI risk [37-40].

This bidirectional relationship forms a vicious cycle: hyperglycemia drives inflammation via advanced glycation end-products (AGE-RAGE) signaling and oxidative stress, whereas inflammation worsens metabolic dysfunction through insulin resistance and

lipid dysregulation [41-42]. By capturing both processes, the combined biomarker model offers a more integrated assessment of residual risk than either marker alone.

Clinical Implications

The HbA1c/HDL-c ratio and hsCAR capture complementary pathophysiological pathways—namely, metabolic dysfunction and systemic inflammation—that are not fully addressed by traditional risk scores. Improving existing risk stratification by integrating these markers is clinically meaningful. A key strength of this approach lies in its practicality: HbA1c, hsCRP, HDL-c, and albumin are routinely measured in standard clinical settings, requiring no additional laboratory infrastructure. Therefore, the derived ratios can be readily incorporated into electronic health record (EHR) systems as automated calculation tools, enabling real-time identification of high-risk individuals.

This strategy aligns well with the principles of stratified medicine, where low-cost, easily accessible biomarkers can support tailored decision-making in acute coronary syndrome care pathways [43]. Notably, such integration could help prioritize early or complete revascularization in STEMI cases, a critical determinant of prognosis [44]. Furthermore, given that microvascular obstruction (MVO) contributes to complications even after successful epicardial reperfusion, the inflammatory and metabolic milieu reflected by these ratios may offer insight into individual susceptibility to MVO [45].

In addition to predicting MACEs, assessing bleeding risk is critical for comprehensive post-PCI management, as bleeding complications significantly impact patient outcomes [46-49]. The PRECISE-HBR score combines the Academic Research Consortium for High Bleeding Risk (ARC-HBR) criteria with the Predicting Bleeding Complications in Patients

Undergoing Stent Implantation and Subsequent Dual Antiplatelet Therapy (PRECISE-DAPT) score. It is one example of a recent development in risk stratification that offers useful tools to find people susceptible to bleeding complications after PCI [50]. Integrating these bleeding risk models with the proposed metabolic-inflammatory biomarker approach (HbA1c/HDL-c ratio and hsCAR) could further enhance personalized treatment strategies, balancing ischemic and bleeding risks to optimize the duration and intensity of dual antiplatelet therapy.

Strengths and Limitations

This study has more than a few strengths, namely its substantial sample size, comprehensive clinical characterization, systematic evaluation of coronary anatomy, and formal causal mediation analysis. The identification of specific biomarker thresholds enhances clinical applicability, whereas extensive adjustment for potential confounders strengthens the validity of the findings.

This study is limited in a number of ways. First, the team might have caused selection bias because of the single-center, retrospective design, which would have limited how broadly the findings could be applied. The multivariable adjustments and large, well-defined cohort did not rule out the possibility. Second, all biomarkers were measured at a single time point during the acute STEMI phase, which may not fully reflect the patients' chronic metabolic or inflammatory status. Acute-phase physiological stress and early treatment may influence biomarker levels, potentially introducing variability and limiting the interpretation of causal relationships [51-52]. Third, other emerging biomarkers (e.g., N-terminal pro B-type natriuretic peptide, interleukin-6, and troponin dynamics) and detailed imaging parameters (such as infarct size or microvascular obstruction on cardiac magnetic resonance

519 imaging) were not available in this dataset. As such, researchers could not explore their
520 additive or mediating roles in conjunction with the hsCAR as well as HbA1c/HDL-c ratio.

521 **Conclusions**

522 When researchers combined the ³high-sensitivity C-reactive protein-to-albumin ratio
523 and the HbA1c/HDL-c ratio, risk stratification in STEMI greatly improved following PCI by
524 capturing complementary metabolic and inflammatory pathways, providing actionable
525 biomarker thresholds that enable personalized therapeutic strategies and precision medicine
526 applications in contemporary cardiovascular practice. Future prospective validation studies in
527 diverse populations and randomized trials evaluating biomarker-guided therapeutic
528 interventions are essential to confirm their clinical utility and establish whether enhanced risk
529 stratification translates into improved patient outcomes.

530 **List of Abbreviations**

531 **Cardiovascular Conditions and Outcomes**⁴⁵

532 MACE: Major adverse cardiovascular events

533 ¹¹ CAD: Coronary artery disease

534 ACS: Acute coronary syndrome

535 CVD: Cardiovascular disease

536 STEMI: ST-elevation myocardial infarction

537 **Clinical Parameters and Biomarkers**

538 BMI: Body mass index

539 ¹ DBP: Diastolic blood pressure

540 BNP: B-type natriuretic peptide

541 ³⁷ HbA1c: Glycated hemoglobin A1c

542 FBG: Fasting blood glucose

543 ⁴ HDL-C: High-density lipoprotein cholesterol

544 hsCRP: High-sensitivity C-reactive protein

545 LVEF: Left ventricular ejection fraction

546 LDL-C: Low-density lipoprotein cholesterol

547 ¹⁰ SBP: Systolic blood pressure

548 TG: Triglyceride

549 Scr: Serum creatinine

550 TC: Total cholesterol

551 TNT: Troponin T

552 **Interventional Procedures and Scoring Systems**

553 ⁹ SYNTAX score: SYNergy between PCI with TAXUS and the cardiac surgery score

554 rSS: Residual SYNTAX score

555 PCI: Percutaneous coronary intervention

556 **Therapeutic Agents**

557 ³¹ ARB: Angiotensin receptor blocker

558 ACEI: Angiotensin-converting enzyme inhibitor

559 ¹⁷ GLP1-RA: Glucagon-like peptide-1 receptor agonist

560 ARNI: Angiotensin receptor and neprilysin inhibitor

561 PCSK9i: Proprotein convertase subtilisin/kexin type 9 inhibitor

562 ¹ SGLT2i: Sodium-glucose cotransporter 2 inhibitor

563 MRA: Mineralocorticoid receptor antagonist

564 **Statistical method**

565 ROC: Receiver operating characteristic

566 ⁴² CI: confidence interval

567 RCS: restricted cubic splines

568 ²¹ HR: hazard ratio

569 OR: odds ratio

570

571 **Declarations**

572 ***Ethics Approval and Consent to Participate***

573 ¹ Tianjin Medical University General Hospital's Ethics Committee gave its clearance for ⁵ this
574 study, which was carried out in compliance with the Declaration of Helsinki (approval
575 number: IRB2023-YX-301-01/2023). ¹ The institutional review board exempted the need for
576 each person's written informed permission because this research was retrospective and used
577 deidentified medical information.

578 ***Consent for Publication***

579 Not relevant because there is no personally identifying information in the paper.

580 ***Availability of Data and Materials***

581 Due to institutional norms and privacy laws, the information sets created and examined
582 during this study are not accessible to everyone. However, they can be obtained from the
583 corresponding author upon a fair inquiry, provided that the institutional ethics committee has
584 given its consent.

585 ***Competing Interests***

586 The writers of this paper state that they have no conflicting financial or nonfinancial interests
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593 *Authors Contributions*

594 **SX and QY:** Ideation, methodology, finance acquisition, and project management. **JH:**
595 Methodology, gathering data, presentation, statistical tests, writing—creation of the first
596 draft. **JZ:** Gathering data, formal test, presentation, and statistical validation. **ZX and LL:**
597 Formal analysis, statistical validation, data interpretation. **MC, YL, XY, SD, QW, and JC:**
598 Patient enrollment, data collection, clinical assessment, and follow-up coordination. SX and
599 QY³⁰ contributed equally as corresponding authors. JH and JZ contributed equally as first
600 authors. The final draft of the paper has been read, edited, and cleared by all authors, who
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References

1. Thrane PG, Olesen KKW, Thim T, Christiansen EH, Kaltoft A, Maeng M, et al. 10-Year Mortality After ST-Segment Elevation Myocardial Infarction Compared to the General Population. *J Am Coll Cardiol*. 2024;83(25):2615-25.
2. Matter MA, Paneni F, Libby P, Frantz S, Stähli BE, Templin C, et al. Inflammation in acute myocardial infarction: the good, the bad and the ugly. *Eur Heart J*. 2024;45(2):89-103.
3. Fahed G, Aoun L, Bou Zerdan M, Allam S, Bou Zerdan M, Bouferraa Y, et al. Metabolic Syndrome: Updates on Pathophysiology and Management in 2021. *Int J Mol Sci*. 2022;23(2):786.
4. Smit JW, Romijn JA. Acute insulin resistance in myocardial ischemia: causes and consequences. *Semin Cardiothorac Vasc Anesth*. 2006;10(3):215-9.
5. Karrowni W, Li Y, Jones PG, Cresci S, Abdallah MS, Lanfear DE, et al. Insulin resistance is associated with significant clinical atherosclerosis in nondiabetic patients with acute myocardial infarction. *Arterioscler Thromb Vasc Biol*. 2013;33(9):2245-51.
6. Sagris M, Theofilis P, Antonopoulos AS, Oikonomou E, Paschalioti C, Galiatsatos N, et al. Inflammation in Coronary Microvascular Dysfunction. *Int J Mol Sci*. 2021;22(24):13471.
7. Hu X, Li W, Wang C, Yang X, Qi W, Chen J, et al. Association between the Plasma-Glycosylated Hemoglobin A1c/High-Density Lipoprotein Cholesterol Ratio and Carotid Atherosclerosis: A Retrospective Study. *J Diabetes Res*. 2021;2021:9238566.

- 629 8. Huang C, You H, Zhang Y, Wang L, Yang H, Wang Z, et al. Association between the
630 hemoglobin A1c/High-density lipoprotein cholesterol ratio and stroke incidence: a
631 prospective nationwide cohort study in China. *Lipids Health Dis.* 2025;24(1):1-10.
- 632 9. Kayapinar O, Ozde C, Kaya A. Relationship Between the Reciprocal Change in
633 Inflammation-Related Biomarkers (Fibrinogen-to-Albumin and hsCRP-to-Albumin
634 Ratios) and the Presence and Severity of Coronary Slow Flow. *Clin Appl Thromb*
635 *Hemost.* 2019;25:1076029619835383.
- 636 10. Yang J, Li C, Zheng Y, Fu Y, Liu Z, Xu L, et al. The association between high-sensitivity
637 C-reactive protein/albumin ratio and cardiovascular prognosis in patients undergoing
638 percutaneous coronary intervention. *Angiology.* 2022;73(9):818-26.
- 639 11. Akkaya S, Cakmak U. Association between C-Reactive Protein to Albumin Ratio and
640 Multi-Vessel Coronary Artery Disease in Patients with Stable Coronary Artery Disease. *J*
641 *Pers Med.* 2024;14(1):1-10.
- 642 12. Katkat F, Kalyoncuoglu M, Ozcan S, Eren YE, Korkmaz FS, Dogan AR, et al. C-reactive
643 protein to albumin ratio as a novel inflammatory-based marker for 30-day mortality in
644 patients undergoing transcatheter aortic valve replacement. *Braz J Cardiovasc Surg.*
645 2022;37(2):292-300.
- 646 13. Söğüt Ö, Akdemir T, Can MM. Prognostic value of the C-reactive protein to albumin
647 ratio in patients undergoing primary percutaneous coronary intervention for ST-segment
648 elevation myocardial infarction. *Turk J Med Sci.* 2021;51(3):1281-8.

- 649 14. Liu J, Huang L, Shi X, Gu C, Xu H, Liu S. Clinical Parameters and Metabolomic
650 Biomarkers That Predict Inhospital Outcomes in Patients With ST-Segment Elevated
651 Myocardial Infarctions. *Front Physiol.* 2022;12:820240.
- 652 15. Björkenheim A, Sunnefeldt E, Finke K, Smith DR, Fröbert O, Brasier N. Biomarkers of
653 inflammation in sweat after myocardial infarction. *Sci Rep.* 2025;15(1):5564.
- 654 16. Mengstie MA, Chekol Abebe E, Behaile Teklemariam A, Tilahun Mulu A, Agidew MM,
655 Teshome Azezew M, et al. Endogenous advanced glycation end products in the
656 pathogenesis of chronic diabetic complications. *Front Mol Biosci.* 2022;9:1002710.
- 657 17. Rehman K, Akash MS. Mechanisms of inflammatory responses and development of
658 insulin resistance: how are they interlinked? *J Biomed Sci.* 2016;23(1):87.
- 659 18. Nian M, Lee P, Khaper N, Liu P. Inflammatory cytokines and postmyocardial infarction
660 remodeling. *Circ Res.* 2004;94(12):1543-53.
- 661 19. Ong SB, Hernández-Reséndiz S, Crespo-Avilan GE, Mukhametshina RT, Kwek XY,
662 Cabrera-Fuentes HA, et al. Inflammation following acute myocardial infarction: Multiple
663 players, dynamic roles, and novel therapeutic opportunities. *Pharmacol Ther.*
664 2018;186:73-87.
- 665 20. Ibañez B, James S, Agewall S, Antunes MJ, Bucciarelli-Ducci C, Bueno H, et al. 2017
666 ESC guidelines for the management of acute myocardial infarction in patients presenting
667 with ST-segment elevation. *Eur Heart J.* 2018;39(2):119-77.
- 668 21. Figtree GA, Vernon ST, Hadziosmanovic N, Sundström J, Alfredsson J, Arnott C, et al.
669 Mortality in STEMI patients without standard modifiable risk factors: a sex-

disaggregated analysis of SWEDEHEART registry data. *Lancet*. 2021;397(10276):1085-94.

22. Jernberg T, Hasvold P, Henriksson M, Hjelm H, Thuresson M, Janzon M. Cardiovascular risk in post-myocardial infarction patients: nationwide real world data demonstrate the importance of a long-term perspective. *Eur Heart J*. 2019;40(19):1203-11.

23. Puymirat E, Simon T, Cayla G, Cottin Y, Elbaz M, Coste P, et al. Acute Myocardial Infarction: Changes in Patient Characteristics, Management, and 6-Month Outcomes Over a Period of 20 Years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction). *Circulation*. 2022;145(4):518-29.

24. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, et al. 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization: Executive Summary: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *J Am Coll Cardiol*. 2022;79(2):197-215.

25. Farooq V, Serruys PW, Bourantas CV, Zhang Y, Muramatsu T, Feldman T, et al. Quantification of incomplete revascularization and its association with five-year mortality in the synergy between percutaneous coronary intervention with taxus and cardiac surgery (SYNTAX) trial validation of the residual SYNTAX score. *Circulation*. 2013;128(2):141-51.

26. Baron RM, Kenny DA. The moderator-mediator variable distinction in social psychological research: conceptual, strategic, and statistical considerations. *J Pers Soc Psychol*. 1986;51(6):1173-82.

27. Georgiopoulos G, Kraler S, Mueller-Hennessen M, Delialis D, Mavraganis G, Sopova K, et al. Modification of the GRACE Risk Score for Risk Prediction in Patients With Acute Coronary Syndromes. *JAMA Cardiol.* 2023;8(10):946-56.
28. Cheng L, Meng Z, Wang Q, Jia Z, Han J, Zhang L, et al. The usefulness of C-reactive protein to albumin ratio in the prediction of adverse cardiovascular events in coronary chronic total occlusion undergoing percutaneous coronary intervention. *Front Cardiovasc Med.* 2021;8:731261.
29. Ma M, He L, Zhou L. Comment on "relationship between C-reactive protein/albumin ratio and new-onset atrial fibrillation after coronary artery bypass grafting". *Rev Assoc Med Bras.* 2022;68(6):742-3.
30. Acet H, Güzel T, Aslan B, Isik MA, Ertas F. Predictive value of C-reactive protein to albumin ratio in ST-segment elevation myocardial infarction patients treated with primary percutaneous coronary intervention. *Angiology.* 2021;72(3):244-51.
31. Guerrero-Romero F, Simental-Mendía LE, González-Ortiz M, Martínez-Abundis E, Ramos-Zavala MG, Hernández-González SO, et al. The product of triglycerides and glucose, a simple measure of insulin sensitivity. Comparison with the euglycemic-hyperinsulinemic clamp. *J Clin Endocrinol Metab.* 2010;95(7):3347-51.
32. Köktürk U, Önalın O, Somuncu MU, Akgül Ö, Uygur B, Püştüroğlu H. Impact of triglyceride-glucose index on intracoronary thrombus burden in ST-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention. *Nutr Metab Cardiovasc Dis.* 2024;34(4):860-7.

33. Pusuroglu H, Akgul O, Cakmak HA, Erturk M, Surgit O, Celik O, et al. Long-term prognostic value of admission haemoglobin A1c (HbA1c) levels in patients with ST-segment elevation myocardial infarction undergoing primary percutaneous coronary intervention. *Postepy Kardiol Interwencyjne*. 2014;10(3):168-73.
34. Park JS, Cha KS, Lee HW, Oh JH, Choi JH, Lee HC, et al. Predictive and protective role of high-density lipoprotein cholesterol in acute myocardial infarction. *Cardiol J*. 2018;26(2):123-30.
35. Angiolillo DJ, Ferreiro JL. Diabetes and antiplatelet therapy in acute coronary syndrome. *Circulation*. 2011;123(7):798-806.
36. Calabresi L, Gomaschi M, Franceschini G. Endothelial protection by high-density lipoproteins: from bench to bedside. *Arterioscler Thromb Vasc Biol*. 2003;23(10):1732-7.
37. Libby P, Ridker PM, Hansson GK. Inflammation in atherosclerosis: from pathophysiology to practice. *J Am Coll Cardiol*. 2009;54(21):2129-38.
38. Hansson GK. Inflammation, atherosclerosis, and coronary artery disease. *N Engl J Med*. 2005;352(16):1685-95.
39. Gurbel PA, Bliden KP, Kreutz RP, Dichiaro J, Antonino MJ, Tantry US. The link between heightened thrombogenicity and inflammation: pre-procedure characterization of the patient at high risk for recurrent events after stenting. *Platelets*. 2009;20(2):97-104.
40. Wang Y, Zeller M, Auffret V, Georgiopoulos G, Räber L, Roffi M, et al. Sex-specific prediction of cardiogenic shock after acute coronary syndromes: the SEX-SHOCK score. *Eur Heart J*. 2024;45(43):4564-78.

- 734 41. Bornfeldt KE, Tabas I. Insulin resistance, hyperglycemia, and atherosclerosis. *Cell*
735 *Metab.* 2011;14(5):575-85.
- 736 42. Chen L, Chen R, Wang H, Liang F. Mechanisms Linking Inflammation to Insulin
737 Resistance. *Int J Endocrinol.* 2015;2015:508409.
- 738 43. Montone RA, Ford TJ, Galli M, Rinaldi R, Bland A, Morrow A, et al. Stratified medicine
739 for acute and chronic coronary syndromes: A patient-tailored approach. *Prog Cardiovasc*
740 *Dis.* 2024;85:2-13.
- 741 44. Bujak K, Rinaldi R, Vidal-Cales P, Montone RA, Diletti R, Gąsior M, et al. Immediate
742 versus staged complete revascularization in acute coronary syndrome: A meta-analysis of
743 randomized controlled trials. *Int J Cardiol.* 2023;393:131397.
- 744 45. Benenati S, Montorfano M, Pica S, Crimi G, Ancona M, Montone RA, et al. Coronary
745 physiology thresholds associated with microvascular obstruction in myocardial
746 infarction. *Heart.* 2024;110(4):271-80.
- 747 46. Ye Z, Xu Y, Tang L, Wu M, Wu B, Zhu T, et al. Predicting long-term prognosis after
748 percutaneous coronary intervention in patients with new onset ST-elevation myocardial
749 infarction: development and external validation of a nomogram model. *Cardiovasc*
750 *Diabetol.* 2023;22(1):87.
- 751 47. Tang L, Wu M, Xu Y, Zhu T, Fang C, Ma K, et al. Multimodal data-driven prognostic
752 model for predicting new-onset ST-elevation myocardial infarction following emergency
753 percutaneous coronary intervention. *Inflamm Res.* 2023;72(9):1799-809.

- 754 48. Yang Y, Wang J, Wai Si Ding AJGL, Xu Y, Jiang H, Ma K, et al. Serum total bilirubin
755 and long-term prognosis of patients with new-onset non-ST elevation myocardial
756 infarction: a cohort study. *BMC Cardiovasc Disord.* 2022;22(1):165.
- 757 49. Zhou B, Tan W, Duan S, Wang Y, Bian F, Zhao P, et al. Inflammation Biomarker-Driven
758 Vertical Visualization Model for Predicting Long-Term Prognosis in Unstable Angina
759 Pectoris Patients with Angiographically Intermediate Coronary Lesions. *J Inflamm Res.*
760 2024;17:10571-84.
- 761 50. Gragnano F, van Klaveren D, Heg D, Räber L, Krucoff MW, Raposeiras-Roubín S, et al.
762 Derivation and Validation of the PRECISE-HBR Score to Predict Bleeding After
763 Percutaneous Coronary Intervention. *Circulation.* 2025;151(6):343-355.
- 764 51. Marfella R, Siniscalchi M, Esposito K, Sellitto A, De Fanis U, Romano C, et al. Effects
765 of stress hyperglycemia on acute myocardial infarction: role of inflammatory immune
766 process in functional cardiac outcome. *Diabetes Care.* 2003;26(11):3129-35.
- 767 52. Barbu E, Mihaila A, Filippi A, Stoenescu A, Ciortan L, Butoi E, et al. Stress,
768 Hyperglycemia, and Insulin Resistance Correlate With Neutrophil Activity and Impact
769 Acute Myocardial Infarction Outcomes. *Cureus.* 2024;16(7):e63731.

Figure legends

Fig. 1. Relationship between metabolic-inflammatory biomarkers and MACE risk in patients with STEMI. (A) Multivariable restricted cubic spline test demonstrating the predominantly linear association of the HbA1c/HDL-c ratio with MACE (optimal cutoff: 6.61, determined by maximally selected rank statistics). (B) Multivariable restricted cubic spline test shows the nonlinear link of hsCAR with MACE risk (inflection point: 0.18). (C) Kaplan-Meier curves stratified by the HbA1c/HDL-c ratio (<6.61 vs. ≥ 6.61), showing significantly divergent survival rates without MACE (HR 1.51, 95% CI: 1.26–1.81; $P<0.001$). (D) Kaplan-Meier curves stratified by hsCAR (<0.18 vs. ≥ 0.18), illustrating substantial differences in survival without MACE (HR 1.84, 95% CI: 1.53–2.21; $P=0.005$). Shaded areas around the survival curves represent 95% confidence intervals.

Fig. 2. Synergistic effect of hsCAR stratification plus the HbA1c/HDL-c ratio on MACE incidence. K-M curves for four patient subgroups: low HbA1c/HDL-c-low hsCAR (reference), low HbA1c/HDL-c-high hsCAR (HR 1.62, 95% CI: 1.25–2.11), high HbA1c/HDL-c-low hsCAR (HR 1.38, 95% CI: 1.03–1.85), and high HbA1c/HDL-c-high hsCAR (HR 1.94, 95% CI: 1.48–2.55), demonstrating progressive MACE risk across metabolic-inflammatory phenotypes (log-rank $P<0.001$). The shaded areas around the survival curves represent 95% confidence intervals.

Fig. 3. Mechanistic pathways linking biomarkers to cardiovascular outcomes: causal mediation analysis. Schematic representation of direct and indirect effects through coronary lesion complexity. For the HbA1c/HDL-c ratio, the residual SYNTAX score (rSS) alongside the SYNTAX score mediated 25.2% and 16.8% of the total effect, respectively. For hsCAR,

the SYNTAX score and rSS mediated 24.2% and 17.7% of the total effect, respectively. The width of the arrows is proportional to the effect magnitude; percentages indicate proportion-mediated effects (bootstrap-derived 95% CIs provided in the main text).

Fig. 4. Subgroup test of the link of MACE risk with combined biomarker phenotypes. Forest plot showing HR and 95% CIs for MACEs in prespecified subgroups. Patients were stratified into four phenotypes based on HbA1c/HDL-c and hsCAR levels, with the dual-negative group (HbA1c/HDL-c < 6.61 and hsCAR < 0.18) used as the reference. Each panel compares one biomarker group with the reference group across all subgroups. *P* for trend tests the significance across the four biomarker groups; *P* for interaction (*P* for int) assesses the heterogeneity of biomarker-associated risk across subgroups.

Fig. 5. Discriminatory capacity of individual and combined biomarker models for MACE prediction. Receiver operating characteristic curves comparing the prognostic value of the hsCAR alone (AUC 0.60, 95% CI: 0.57–0.63), GRACE risk score (AUC 0.56, 95% CI: 0.53–0.58), HbA1c/HDL-c ratio alone (AUC 0.58, 95% CI: 0.55–0.61), the combined HbA1c/HDL-c+ hsCAR model (AUC 0.63, 95% CI: 0.60–0.66; *P*<0.001 for comparison with all other models). The integrated model demonstrated significant improvement in risk reclassification (IDI: 0.02, 95% CI: 0.01–0.03; *P*<0.01).

Fig. 6. Central illustration. Synergistic biomarker approach for enhanced MACE prediction after PCI in patients with STEMI: Combined HbA1c/HDL-c ratio and hsCAR risk stratification.

Table legends

Table 1. Comparison of baseline characteristics by HbA1c/HDL-c ratio and hsCAR

grouping.

Median (interquartile range) shows continuous variable data, and numbers (percentages)

show categorical variable data. Researchers stratified patients into four classes based on

HbA1c/HDL-c ratio (< 6.61 vs. ≥ 6.61) and hsCAR levels (< 0.18 vs. ≥ 0.18 mg/L).

Differences between continuous variable groups were found via the Kruskal-Wallis test, but

for categorical variable groups via Fisher's exact test/the chi-square test. P values represent

overall comparisons across all four groups.

Table 2. Impact of HbA1c/HDL-c ratio combined with hsCAR on MACE.

Hazard ratios (95% confidence intervals) are presented for MACE occurrence across the four

stratified groups; the low hsCAR group alongside low HbA1c/HDL-c ratio are as the

reference category. Model 1: not adjusted analysis. Model 2: demographic factors (age, sex,

BMI) + Model 1. Model 3: clinical parameters (blood pressure, heart rate, smoking pattern,

diabetes, stroke) and LVEF + Model 2. Model 4: building upon Model 3 with additional

adjustment for pharmacotherapy (beta-blockers, antiplatelet regimen, ARBs/ARNIs/ACEIs),

and laboratory parameters (platelet count, hemoglobin, LDL-c, and eGFR). Model 5:

application of bootstrapping techniques with 1,000 resampling iterations to enhance the

robustness of effect estimates. P for trend was calculated by treating the four groups as an

ordinal variable. Researchers used Cox proportional hazards regression. $*P < 0.05$, $**P <$

0.01 , $***P < 0.001$. Ref., reference.

Table 3. Reclassification metrics analysis.

834 Ninety-five percent confidence intervals show the area under the curve (AUC). Researchers
835 computed the Integrated Discrimination Improvement (IDI) as well as the Net
836 Reclassification Improvement (NRI) to find the incremental prognostic value of the hsCAR
837 and HbA1c/HDL-c ratio beyond the baseline GRACE risk scores. The GRACE score served
838 as the reference model. Researchers carried out a receiver operating characteristic curve test
839 using DeLong's method for AUC comparisons. NRI was calculated using a risk threshold of
840 10% for event probability. Bootstrap resampling (1000 iterations) was used to calculate
841 confidence intervals for NRI and IDI. $*P < 0.05$, $**P < 0.01$, $***P < 0.001$ vs. GRACE risk
842 score model.