Article

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Systemic Inflammatory Burden Combined With CMR-Defined Microvascular Injury Phenotypes for Risk Stratification of Major Adverse Cardiovascular Events in Patients With ST-Segment Elevation Myocardial Infarction

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Background: Systemic inflammation and microvascular injury both contribute to adverse remodeling and unfavorable prognosis after ST-segment elevation myocardial infarction (STEMI). We examined whether a simple inflammatory burden score based on routine laboratory markers could provide complementary risk stratification information when considered together with cardiovascular magnetic resonance (CMR)-defined microvascular injury phenotypes.

Methods: This single-center retrospective study consecutively enrolled patients with STEMI treated at The Affiliated Hospital of Xuzhou Medical University between January 2019 and December 2021. Patients were eligible if STEMI was diagnosed according to guideline criteria, primary percutaneous coronary intervention (PCI) was performed, and CMR was completed within 1 week after PCI with analyzable angiographic and CMR images. A total of 454 patients with definite outcome status were included, of whom 93 experienced major adverse cardiovascular events (MACEs). Systemic inflammatory burden was scored using admission neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP). For exploratory stratification within the present cohort, the NLR and CRP cutoffs were determined by single-variable receiver operating characteristic (ROC) analysis using the Youden index, yielding thresholds of 5.66 and 3.30 mg/L, respectively. One point was assigned for high NLR and one point for high CRP. Although prior studies support the prognostic relevance of NLR and CRP, the exact cut points reported in the literature are not uniform; these values should therefore be interpreted as cohort-derived exploratory thresholds. CMR phenotypes were classified as no microvascular obstruction (MVO)/intramyocardial hemorrhage (IMH), MVO alone, and MVO with IMH. Multivariable logistic regression was used to evaluate the independent associations of inflammatory burden and CMR phenotypes with MACEs and to explore their combined risk stratification performance. Sensitivity analyses included an expanded logistic model and Cox regression in patients with analyzable follow-up time.

Results: MACEs occurred in 93 of 454 patients (20.48%). The highest event rate was observed in patients with both MVO and IMH and an inflammatory burden score of 2 (55.93%). In the fully adjusted model, post-PCI Thrombolysis in Myocardial Infarction (TIMI) flow grade <3 (odds ratio [OR] 4.182, 95% confidence interval [CI] 1.106–15.808, $p = 0.035$), MVO with IMH (OR 16.302, 95% CI: 8.196–32.425, $p < 0.001$), and an inflammatory burden score of 2 (OR 4.517, 95% CI: 1.505–13.560, $p = 0.007$) were independently associated with MACEs. The area under the receiver operating characteristic curve (AUC) increased from 0.608 for the clinical model to 0.830 after adding CMR phenotype, and to 0.841 after further adding inflammatory burden. In an expanded sensitivity analysis including left ventricular ejection fraction (LVEF), N-terminal pro-B-type natriuretic peptide (NT-proBNP), and late gadolinium enhancement (LGE) extent, the AUC increased from 0.892 to 0.912 after addition of CMR phenotype, whereas further addition of inflammatory burden yielded only a small increase to 0.915.

Conclusions: CMR-defined microvascular injury phenotypes provided the main risk stratification information for MACEs in patients with STEMI and remained robust in expanded logistic and Cox sensitivity analyses. The incremental contribution of inflammatory burden was modest, although patients with both MVO and IMH together with high inflammatory burden had the highest observed risk.

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Keywords: STEMI; systemic inflammatory burden; NLR; CRP; MVO; IMH; CMR; MACEs

Introduction

ST-segment elevation myocardial infarction remains one of the most severe forms of acute coronary syndrome despite substantial advances in timely reperfusion therapy [1]. Even after timely primary percutaneous coronary intervention (PCI), a considerable proportion of patients develop microvascular injury, reperfusion-related tissue damage, adverse left ventricular remodeling, heart failure, recurrent ischemic events, or death [1,2,3,4]. Early and accurate identification of patients at high risk for adverse outcomes therefore remains a central challenge in ST-segment elevation myocardial infarction (STEMI) management. Cardiovascular magnetic resonance (CMR) provides comprehensive tissue characterization after STEMI and is particularly useful for identifying microvascular obstruction (MVO) and intramyocardial hemorrhage (IMH), two major imaging phenotypes of severe reperfusion injury [2,3,4,5]. These phenotypes have been associated with adverse remodeling and worse clinical outcomes [5,6,7,8,9]. Systemic inflammation is involved throughout the continuum of STEMI, from plaque destabilization and acute necrosis to reperfusion injury and late remodeling. Among routinely available laboratory biomarkers, neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein (CRP) have shown reproducible associations with mortality and major adverse cardiovascular events (MACEs) after acute myocardial infarction [10,11,12,13,14]. However, these biomarkers mainly reflect systemic inflammatory activation and do not fully capture the local severity of myocardial tissue injury.

Existing studies have typically evaluated inflammatory biomarkers or CMR markers separately rather than within a unified prognostic framework. We therefore aimed to determine whether systemic inflammatory burden, defined using admission NLR and CRP, could provide complementary risk stratification information when evaluated together with CMR-defined microvascular injury phenotypes in patients with STEMI.

Patients and Methods

Study Design and Population

This was a single-center retrospective observational study. Consecutive patients with STEMI who were hospitalized at The Affiliated Hospital of Xuzhou Medical University between January 2019 and December 2021 were screened. STEMI was diagnosed according to contemporary guideline criteria [1]. Patients were included if: (1) STEMI was diagnosed according to guideline standards; (2) primary PCI was performed; and (3) CMR was completed within 1 week after PCI with analyzable CMR and coronary angiographic images. Patients were excluded if: (1) key clinical data, outcome data, or imaging data were missing; (2) coronary angiography was incomplete or of insufficient quality; or (3) CMR sequences were incomplete or of insufficient quality to assess MVO, IMH, and core imaging parameters.

Among all screened patients, 454 had complete outcome status and were included in the primary analysis. Of these, 93 developed MACEs and 361 did not.

Data Collection

Baseline demographic, clinical, procedural, laboratory, and imaging variables were extracted from the electronic medical and imaging records. Source verification against the original study workbook confirmed that patient-level hospital number and date fields were retained, together with procedural, imaging, outcome (status and outcome name), and follow-up duration overall survival (OS) variables. Baseline variables included age, sex, body mass index, smoking status, diabetes mellitus, hypertension, Killip class, number of diseased vessels, and post-PCI TIMI flow grade. Laboratory markers included admission NLR and CRP, together with white blood cell count, cardiac troponin T, creatine kinase-MB, and NT-proBNP. When serial measurements were available for laboratory biomarkers other than admission NLR and CRP, peak values during the acute STEMI hospitalization were recorded. CMR-derived variables included left ventricular ejection fraction (LVEF), MVO, IMH, MVO extent, IMH extent, late gadolinium enhancement (LGE) extent, edema ratio, and myocardial salvage index (MSI) [2,3,4,5,15,16,17,18].

Definition of Inflammatory Burden

Systemic inflammatory burden was defined using admission NLR and CRP. In this exploratory cohort-based score, high NLR was defined as NLR of at least 5.66 and high CRP as CRP of at least 3.30. Although prior studies support the prognostic relevance of NLR and CRP, exact cutoff values are not uniform across the literature; accordingly, these thresholds were treated as cohort-derived exploratory cutoffs rather than universally established clinical thresholds. One point was assigned to each abnormal marker, yielding a total score ranging from 0 to 2.

Primary PCI and Angiographic Variables

Primary PCI and routine medical treatment were performed according to contemporary guideline-based practice by experienced interventional cardiologists. Coronary angiograms were retrospectively reviewed by 2 experienced interventional cardiologists who were blinded to the

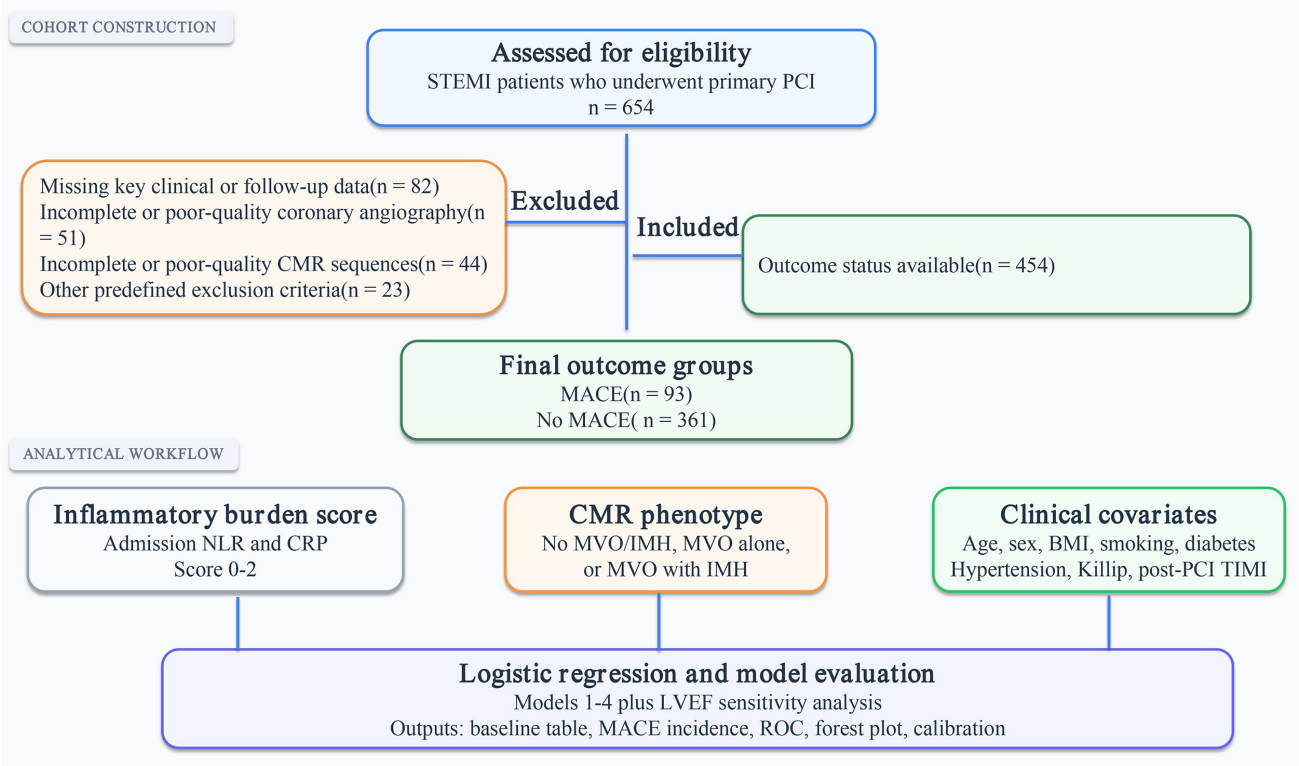


Fig. 1. Study design and statistical analysis workflow. Among 654 patients with ST-segment elevation myocardial infarction who underwent primary percutaneous coronary intervention, 454 eligible patients were included in the final analysis. The analytical framework integrated the inflammatory burden score, cardiac magnetic resonance-defined microvascular injury phenotypes, and clinical covariates for logistic regression and model performance evaluation. STEMI, ST-segment elevation myocardial infarction; PCI, percutaneous coronary intervention; NLR, neutrophil-to-lymphocyte ratio; CRP, C-reactive protein; CMR, cardiac magnetic resonance; MVO, microvascular obstruction; IMH, intramyocardial hemorrhage; MACE, major adverse cardiovascular event; LVEF, left ventricular ejection fraction; ROC, receiver operating characteristic. The figure was created using Microsoft PowerPoint for Mac (version 16.112; Microsoft Corporation, Redmond, WA, USA).

CMR findings. Infarct-related artery identification, post-PCI TIMI flow grade, and the number of diseased vessels were determined from standard angiographic projections and procedural records. Disagreements in angiographic classification were resolved by consensus.

CMR Acquisition and Image Analysis

All patients underwent CMR within 1 week after PCI. MR was performed on Ingenia 3.0-T systems (Philips Medical Systems Nederland B.V., Best, the Netherlands). A digital-stream (dS) phased-array surface coil was used in combination with an integrated dS posterior spinal matrix coil. All images were acquired with electrocardiographic gating during breath-holding. A gadolinium contrast agent gadopentetate dimeglumine (Magnevist; Bayer AG, Berlin, Germany) was administered at a dose of 0.15 mmol/kg and a flow rate of 3 mL/s, followed by acquisition of a stack of short-axis cine images covering the left ventricle. After 15 min, LGE images were obtained at the same image positions. The imaging parameters included a field of view of 350 × 350 mm, a repetition time/echo time of 2.6/1.3 ms, and a slice thickness of 8 mm. For T2* mapping, T2 and T2* spin-echo images were acquired during breath-holding before contrast administration. The high-signal edema area and the low-signal IMH core enclosed by the high-signal area were quantified on short-axis images of the infarcted myocardium. Myocardial edema ratio was calculated as the percentage of LV mass occupied by the edema area, and MSI was calculated as (myocardial edema ratio – LGE extent) / myocardial edema ratio. All CMR datasets were analyzed offline using CVI42 software (version 42, Circle Cardiovascular Imaging Inc., Calgary, Alberta, Canada) by Xiaohua Liu and Shuguang Han, two radiologists with more than 10 years of CMR experience. Image analysis was performed with the readers blinded to follow-up outcomes, and discrepant contouring or categorical classifications were resolved by consensus after joint review.

Definition of CMR Phenotypes

The infarcted myocardium was defined on LGE images as myocardium with signal intensity greater than 5 standard deviations above that of remote myocardium.

Table 1. Baseline characteristics stratified by long-term MACE status.

Variable	Overall (n = 454)	No MACEs (n = 361)	MACEs (n = 93)	Statistic ($Z/t/\chi^2$)	*p* value
Age (mean ± SD), years	57.45 ± 11.96	57.78 ± 11.76	56.19 ± 12.71	1.140	0.255
Female sex (%)	68 (14.98)	60 (16.62)	8 (8.60)	3.734	0.053
BMI (mean ± SD), kg/m^2	25.82 ± 3.43	25.70 ± 3.37	26.28 ± 3.65	–1.467	0.143
Current smoking (%)	253 (55.73)	201 (55.68)	52 (55.91)	0.002	0.968
Diabetes mellitus (%)	93 (20.48)	70 (19.39)	23 (24.73)	1.295	0.255
Hypertension (%)	195 (42.95)	153 (42.38)	42 (45.16)	0.233	0.629
Killip class ≥2 (%)	40 (8.81)	33 (9.14)	7 (7.53)	0.240	0.624
Post-PCI TIMI flow <3 (%)	15 (3.30)	7 (1.94)	8 (8.60)	8.297	0.004
Multivessel disease (≥2 vessels) (%)	323 (71.15)	259 (71.75)	64 (68.82)	0.309	0.578
NLR (median [IQR])	6.74 [4.42, 10.09]	6.20 [4.17, 9.34]	8.87 [5.87, 11.62]	4.425	<0.001
CRP (median [IQR]), mg/L	3.30 [1.00, 7.90]	3.00 [0.80, 7.60]	3.50 [1.87, 8.10]	1.645	0.100
WBC (mean ± SD), ×10^9/L	10.54 ± 3.03	10.27 ± 2.92	11.59 ± 3.21	–3.809	<0.001
cTnT (median [IQR]), ng/L	3613.50 [1656.75, 6588.50]	3058.00 [1356.00, 5016.00]	7366.00 [5156.00, 10000.00]	9.170	<0.001
CK-MB (median [IQR]), U/L	146.35 [71.54, 281.25]	122.74 [54.40, 228.00]	284.00 [192.00, 300.00]	7.625	<0.001
NT-proBNP (median [IQR]), pg/mL	1478.00 [855.50, 2355.50]	1348.00 [735.00, 2198.00]	1954.00 [1369.00, 2941.00]	4.775	<0.001
MVO presence (%)	191 (42.07)	110 (30.47)	81 (87.10)	97.294	<0.001
IMH presence (%)	167 (36.78)	90 (24.93)	77 (82.80)	106.483	<0.001
MVO extent (median [IQR]), % of LV mass	0.00 [0.00, 1.42]	0.00 [0.00, 0.37]	3.81 [1.05, 6.53]	12.251	<0.001
IMH extent (median [IQR]), % of LV mass	0.00 [0.00, 1.17]	0.00 [0.00, 0.03]	4.09 [1.01, 7.23]	12.376	<0.001
LGE extent (median [IQR]), % of LV mass	24.79 [16.14, 35.41]	22.08 [14.20, 29.53]	44.38 [32.05, 51.36]	10.483	<0.001
Myocardial edema ratio (median [IQR]), % of LV mass	46.49 [34.10, 57.33]	44.28 [31.50, 54.28]	59.18 [50.55, 64.69]	7.441	<0.001
Myocardial salvage index (median [IQR])	0.44 [0.25, 0.61]	0.47 [0.31, 0.63]	0.28 [0.17, 0.39]	–6.544	<0.001
Microvascular injury phenotype (%)				108.461	<0.001
No MVO/IMH	263 (57.93)	251 (69.53)	12 (12.90)		
MVO alone	24 (5.29)	20 (5.54)	4 (4.30)		
MVO with IMH	167 (36.78)	90 (24.93)	77 (82.80)		
Inflammatory burden score* (%)				19.014	<0.001
Score 0	83 (18.32)	78 (21.61)	5 (5.43)		
Score 1	247 (54.53)	198 (54.85)	49 (53.26)		
Score 2	123 (27.15)	85 (23.55)	38 (41.30)		

Note: Microvascular injury phenotype available in 454 patients. *Inflammatory burden score available in 453 patients because 1 patient had missing CRP. MACE, major adverse cardiovascular event; SD, standard deviation; BMI, body mass index; PCI, percutaneous coronary intervention; TIMI, Thrombolysis in Myocardial Infarction; NLR, neutrophil-to-lymphocyte ratio; IQR, interquartile range; CRP, C-reactive protein; WBC, white blood cell count; cTnT, cardiac troponin T; CK-MB, creatine kinase–myocardial band; NT-proBNP, N-terminal pro-B-type natriuretic peptide; MVO, microvascular obstruction; IMH, intramyocardial hemorrhage; LGE, late gadolinium enhancement; LV, left ventricle.

MVO was defined as a low- or no-signal-intensity core within the hyperenhanced infarct zone on LGE images. IMH was identified on T2* images as an area with a mean signal intensity 2 standard deviations lower than that of remote myocardium, and a T2* value <20 ms was considered indicative of IMH. IMH volume and the T2* value of the IMH area were measured. For descriptive reporting, MVO extent, IMH extent, LGE extent, and edema burden were harmonized and expressed as percentages of LV mass. Based on the presence or absence of MVO and IMH on CMR, patients were categorized into three microvascular injury phenotypes: no MVO/IMH, MVO alone, and MVO with IMH. Because isolated IMH was extremely uncommon in this cohort, it was not analyzed as a separate category in the primary analysis.

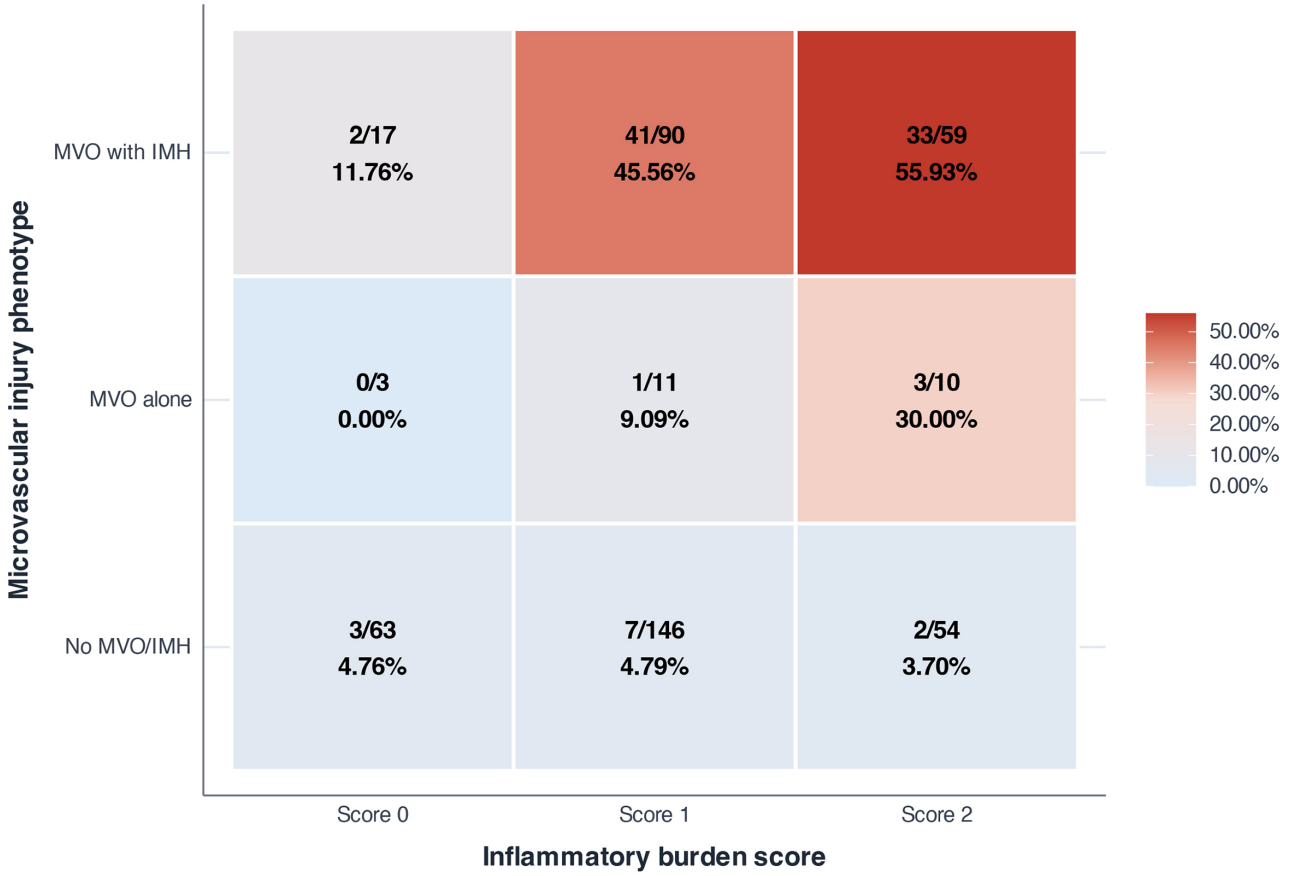


Fig. 2. Heatmap of MACE rates across inflammatory burden scores and microvascular injury phenotypes. The heatmap presents the number of MACE events divided by the number of patients and the corresponding event rate within each combination of inflammatory burden score and microvascular injury phenotype. The analysis included 453 patients with available inflammatory burden data. MACE, major adverse cardiovascular event; MVO, microvascular obstruction; IMH, intramyocardial hemorrhage.

Table 2. Distribution of inflammatory burden and microvascular injury phenotypes in 453 patients with complete inflammatory burden data.

Microvascular phenotype	Inflammatory burden score	n	Events	MACE rate (%)
No MVO/IMH	Score 0	63	3	4.76
No MVO/IMH	Score 1	146	7	4.79
No MVO/IMH	Score 2	54	2	3.70
MVO alone	Score 0	3	0	0.00
MVO alone	Score 1	11	1	9.09
MVO alone	Score 2	10	3	30.00
MVO with IMH	Score 0	17	2	11.76
MVO with IMH	Score 1	90	41	45.56
MVO with IMH	Score 2	59	33	55.93

Note: 1 patient with MVO and IMH was excluded because CRP was missing.

Outcome Definition

The primary endpoint was long-term MACEs, defined as a composite of all-cause death, nonfatal recurrent myocardial infarction, stroke, repeat revascularization, or heart failure hospitalization. All-cause death referred to death from any cause during index hospitalization or follow-up. Recurrent myocardial infarction, stroke, repeat revascularization, and heart failure hospitalization were identified from discharge diagnoses, procedure records, or follow-up documentation in the medical record. Because this was a retrospective study, no formal blinded independent clinical event adjudication committee was established; endpoints were classified by the study investigators on the basis of source-document review. Follow-up was calculated from the date of primary PCI. Available follow-up information was ascertained through hospital records and telephone contact, and repeated events were counted once at the patient level based on the first recorded major event during follow-up. Case-level review confirmed that no patient experienced MACEs before completion of CMR acquisition. Survival time was calculated from the index PCI date to the first recorded MACE or the last known follow-up. A follow-up duration variable (OS) was available for 306 of 454 patients, with a median duration of 545.0 days (interquartile range 361.25–795.50 days; range 7–1084 days); analyzable time information was unavailable

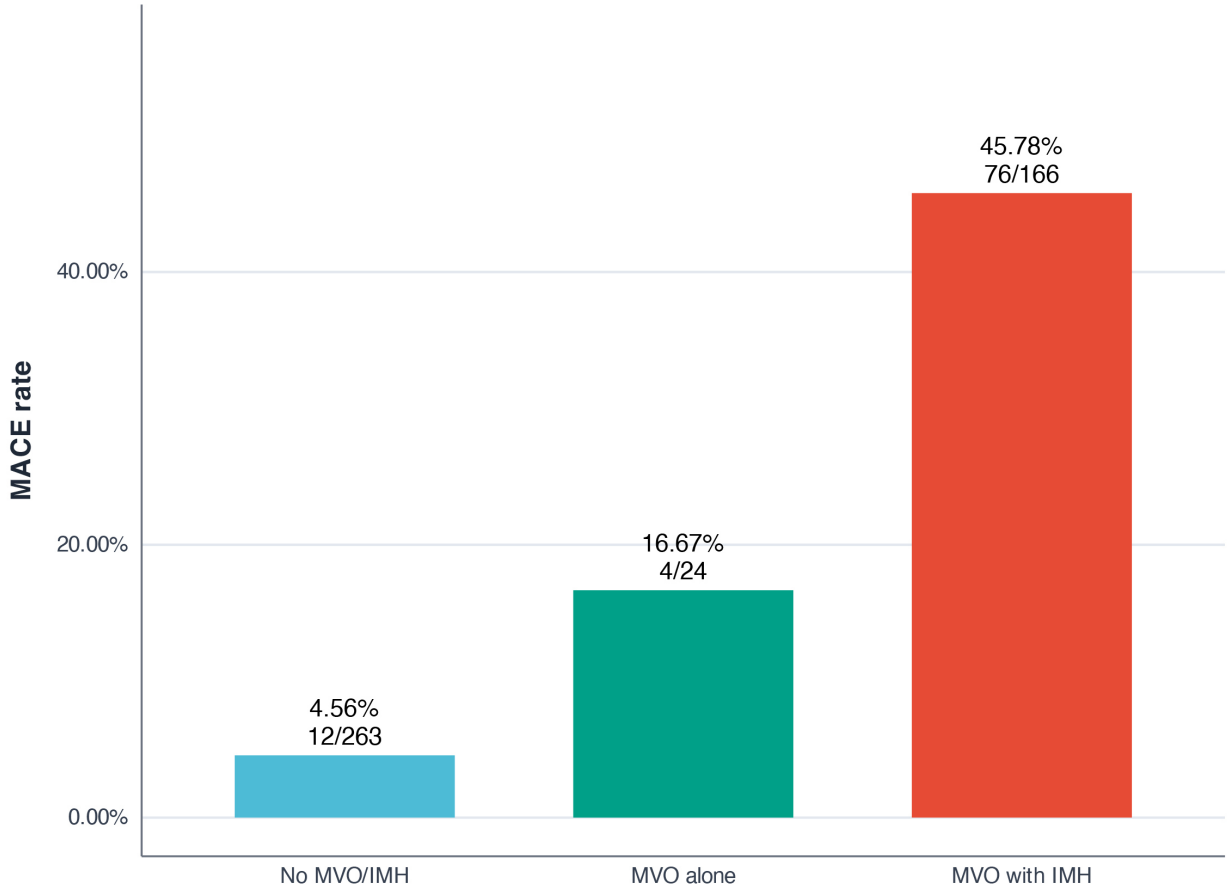


Fig. 3. MACE rates across microvascular injury phenotypes in the 453 patients with complete inflammatory burden data. The bars show the proportions and numbers of patients who experienced MACE in the no MVO/IMH, MVO-alone, and MVO-with-IMH groups. MACE, major adverse cardiovascular event; MVO, microvascular obstruction; IMH, intramyocardial hemorrhage; CMR, cardiac magnetic resonance.

in the exported source records for the remaining 148 patients. Therefore, MACEs were analyzed as a binary outcome in the primary analysis using the final status variable, and Cox regression was performed as a sensitivity analysis in the subset with available follow-up time.

Statistical Analysis

All statistical analyses were performed using R 4.3.2. Distributional characteristics of continuous variables were assessed using the Shapiro-Wilk test. Normally distributed continuous variables are presented as mean ± SD, and non-normally distributed variables as median (interquartile range). Categorical variables are presented as counts (percentages). Between-group comparisons were performed using the independent-samples *t*-test or Wilcoxon rank-sum test for continuous variables and the Pearson chi-square test, Yates' continuity-corrected chi-square or Fisher exact test for categorical variables.

For descriptive analyses of the derived inflammatory burden score and the joint phenotype-score distribution, available-case data were used; one patient with missing CRP in the source dataset could not be assigned an inflammatory burden score. For multivariable modeling, missing covariate data were handled using a simple prespecified imputation strategy in the analytic dataset: continuous variables were imputed with the cohort median and categorical variables with the mode; the outcome variable was not imputed. To evaluate the prognostic contribution of inflammatory burden and CMR phenotype, five logistic regression models were developed: Model 1 included clinical variables only; Model 2 additionally incorporated CMR phenotype; Model 3 additionally incorporated inflammatory burden score; Model 4 incorporated both CMR phenotype and inflammatory burden score; and Model 5 further adjusted the joint model for LVEF. LVEF was not included in the primary model because it may represent a downstream functional consequence of myocardial injury. As a supplementary expanded-base sensitivity analysis, we also evaluated a broader model incorporating LVEF, NT-proBNP, and LGE extent, and then tested the incremental value of CMR phenotype and inflammatory burden within that framework. We also performed Cox proportional haz-

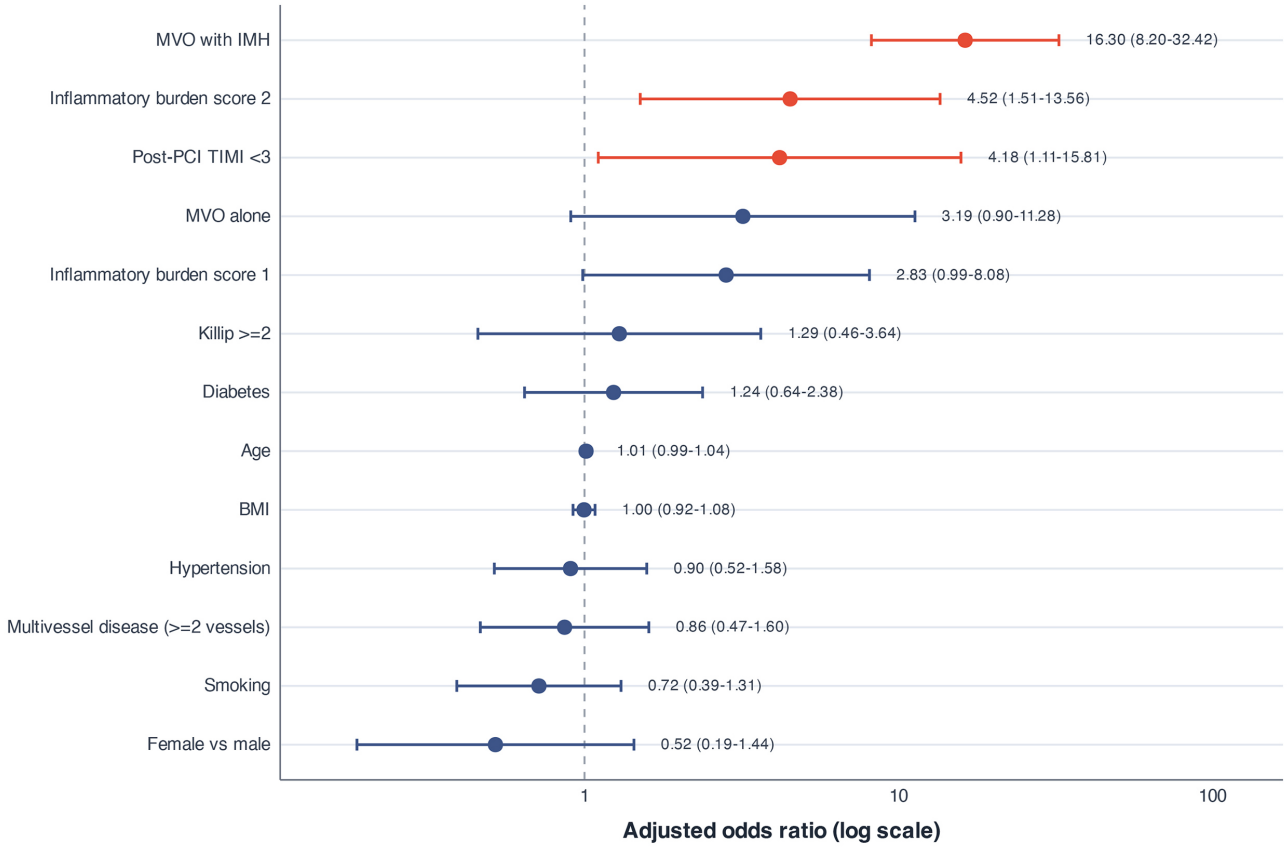


Fig. 4. Forest plot of the joint model. Points represent adjusted odds ratios, and horizontal lines represent 95% confidence intervals. The vertical dashed line indicates an odds ratio of 1. Variables shown in red were statistically significant at $p < 0.05$. MACE, major adverse cardiovascular event; OR, odds ratio; CI, confidence interval; MVO, microvascular obstruction; IMH, intramyocardial hemorrhage; PCI, percutaneous coronary intervention; TIMI, thrombolysis in myocardial infarction; BMI, body mass index.

ards regression in complete-case patients with analyzable follow-up time. Because the inflammatory burden score was based on within-cohort ROC/Youden-derived thresholds, and because exact cutoff values vary across prior studies, its incremental performance was interpreted as exploratory. Odds ratios and hazard ratios are presented with 95% confidence intervals. Model performance was assessed using the area under the receiver operating characteristic curve (AUC) with 95% confidence intervals, Akaike information criterion, Bayesian information criterion, the Hosmer-Lemeshow goodness-of-fit test, a bootstrap bias-corrected calibration curve based on 1000 resamples, and the C-index for Cox sensitivity models. AUC confidence intervals were estimated using the DeLong method. The study design and analytical workflow are summarized in Fig. 1. All tests were two-sided, and $p < 0.05$ was considered statistically significant.

Results

Baseline Characteristics

Among the 454 included patients, 93 experienced MACEs, corresponding to an event rate of 20.48%. Baseline characteristics are summarized in Table 1. Compared with the non-MACE group, patients with MACEs had a higher proportion of post-PCI TIMI flow grade <3 (8.60% vs. 1.94%, $p = 0.004$), higher white blood cell count, and higher median NLR, cardiac troponin T (cTnT), creatine kinase–myocardial band (CK-MB), and NT-proBNP levels, together with substantially more severe CMR-defined injury, including higher frequencies and greater extents of MVO and IMH, larger LGE burden, and a higher edema ratio. Extent variables were expressed as percentages of LV mass using a harmonized scale.

Distribution of Inflammatory Burden and CMR Phenotypes

The joint distribution of inflammatory burden and microvascular injury phenotypes is shown in Table 2 and Fig. 2. Among 453 patients with available inflammatory burden data, 263 (58.06%) had no MVO/IMH, 24 (5.30%) had MVO alone, and 166 (36.64%) had both MVO and IMH. Inflammatory burden scores of 0, 1, and 2 were observed in 83 (18.32%), 247 (54.53%), and 123 (27.15%) patients, respectively. One patient in the MVO with IMH group had missing inflammatory burden data and was therefore not in-

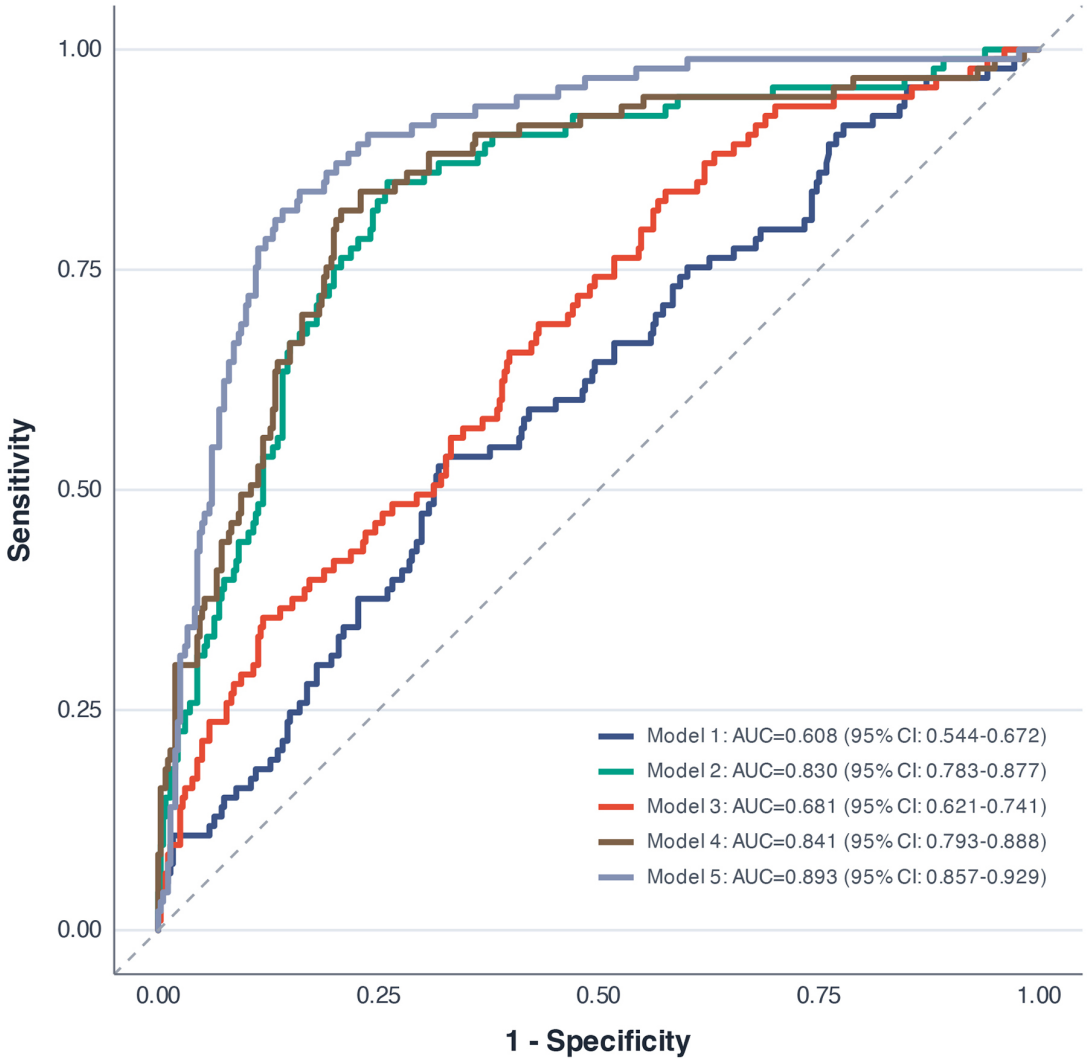


Fig. 5. Receiver operating characteristic curves of different prediction models. Model 1 was the clinical model; Model 2 added the CMR-defined microvascular injury phenotype; Model 3 added the inflammatory burden score to the clinical model; Model 4 included both the microvascular injury phenotype and inflammatory burden score; and Model 5 additionally adjusted Model 4 for LVEF. The diagonal line represents discrimination equivalent to chance. MACE, major adverse cardiovascular event; AUC, area under the receiver operating characteristic curve; CI, confidence interval; CMR, cardiac magnetic resonance; LVEF, left ventricular ejection fraction.

cluded in this joint-distribution analysis. Accordingly, the phenotype subsection in Table 1 reflects the full CMR cohort (n = 454), whereas the joint phenotype-score distribution shown here is restricted to the 453 patients with available inflammatory burden data.

Combined stratification suggested that risk heterogeneity was primarily evident in patients with MVO and IMH. In patients without MVO/IMH, MACE rates remained low across inflammatory burden categories (4.76%, 4.79%, and 3.70% for scores 0, 1, and 2, respectively). In patients with MVO alone, the MACE rate was 9.09% for a score of 1 and 30.00% for a score of 2. In patients with both MVO and IMH, MACE rates were 11.76%, 45.56%, and 55.93% for inflammatory burden scores of 0, 1, and 2, respectively. Because several strata were small, these subgroup findings were interpreted descriptively; however, the observed pattern suggests that higher inflammatory burden may further increase risk within the most severe microvascular injury phenotype, as also illustrated in Fig. 3.

Multivariable Logistic Regression

Multivariable logistic regression results are summarized in Table 3 and visualized in Fig. 4. In the fully adjusted joint model, post-PCI TIMI flow grade <3, MVO with IMH, and an inflammatory burden score of 2 remained independently associated with MACEs. Specifically, post-PCI TIMI flow grade <3 was associated with an OR of 4.182 (95% CI: 1.106–15.808; $p = 0.035$), MVO with IMH with an OR of 16.302 (95% CI: 8.196–32.425; $p < 0.001$), and an inflammatory burden score of 2 with an OR of 4.517

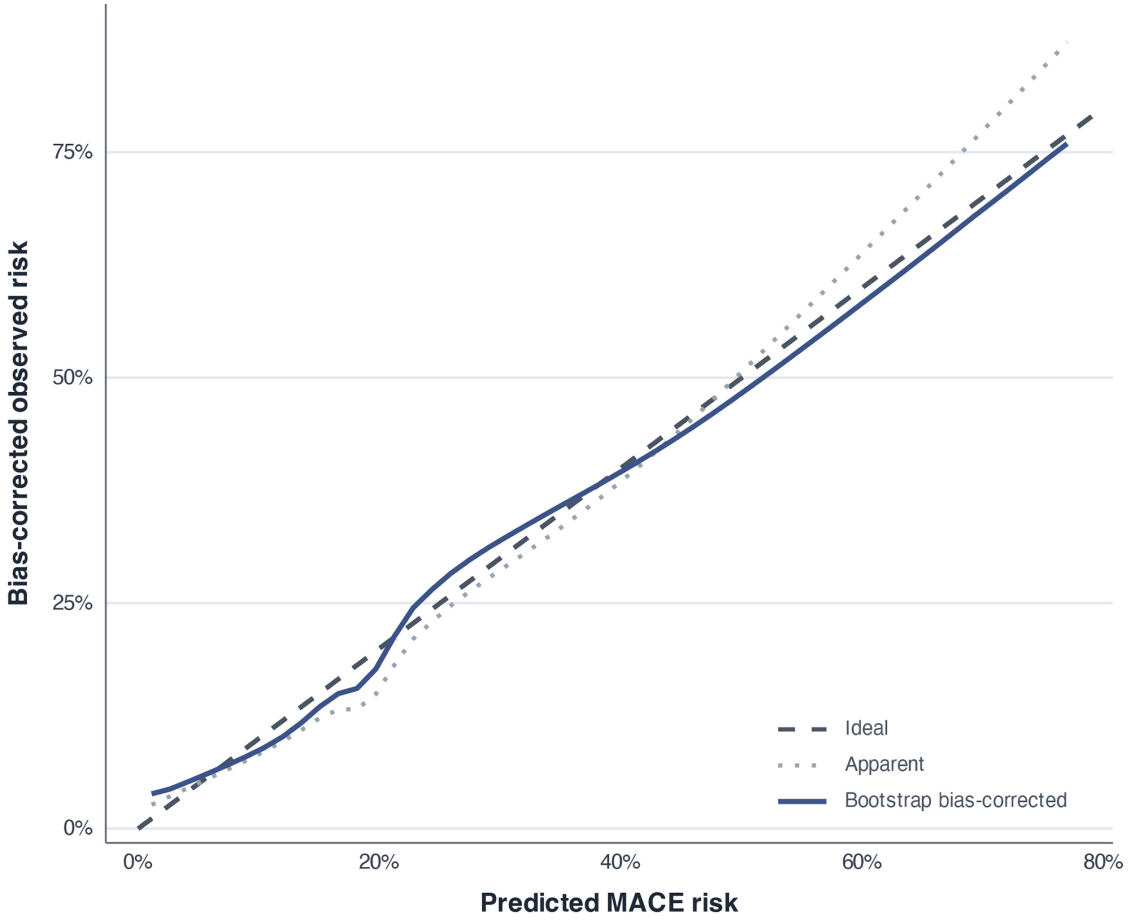


Fig. 6. Bootstrap bias-corrected calibration curve of the joint model. The calibration plot compares predicted MACE risk with observed risk. The dashed line represents ideal calibration, the dotted line represents the apparent model performance, and the solid line represents the bias-corrected calibration derived from 1000 bootstrap resamples. MACE, major adverse cardiovascular event.

(95% CI: 1.505–13.560; $p = 0.007$). MVO alone showed a non-significant trend toward higher risk (OR = 3.194, 95% CI: 0.904–11.282; $p = 0.071$), and an inflammatory burden score of 1 showed borderline significance (OR = 2.825, 95% CI: 0.988–8.082; $p = 0.053$).

Model Performance

Model performance is summarized in Table 4, with receiver operating characteristic curves shown in Fig. 5 and the bootstrap bias-corrected calibration curve in Fig. 6. The clinical model showed limited discrimination for MACEs (AUC = 0.608, 95% CI: 0.544–0.672). Adding CMR phenotype increased the AUC to 0.830 (95% CI: 0.783–0.877), and adding inflammatory burden further increased it to 0.841 (95% CI: 0.793–0.888). The Hosmer-Lemeshow test indicated acceptable calibration of the joint model ($p = 0.127$), and bootstrap internal validation showed good agreement between predicted risk and bias-corrected observed risk. In an expanded sensitivity analysis restricted to 452 patients with complete LVEF, NT-proBNP, and LGE extent data, the expanded base model achieved an AUC of 0.892 (95% CI: 0.856–0.928). Adding CMR phenotype increased the AUC to 0.912 (95% CI: 0.878–0.945; DeLong $p = 0.034$), whereas further addition of inflammatory burden produced only a small, non-significant increase to 0.915 (95% CI: 0.881–0.948; DeLong $p = 0.314$) (**Supplementary Tables 1–3**). In a Cox sensitivity analysis restricted to 304 complete-case patients with 73 events, adding CMR phenotype improved the C-index from 0.648 to 0.815, whereas further addition of inflammatory burden yielded only a minimal increase to 0.817 (**Supplementary Tables 4,5**).

Discussion

The present study showed that adding CMR-defined microvascular injury phenotypes to a conventional clinical model improved discrimination for long-term MACEs after STEMI, whereas adding a simple inflammatory burden score based on NLR and CRP provided only modest incremental prognostic information. Both MVO with IMH and a higher inflammatory burden score were independently associated with adverse outcomes. Together, these findings

Table 3. Logistic regression models for predicting MACEs.

Model	Variable	OR (95% CI)	*p* value
Model 1	Age	0.996 (0.975–1.017)	0.688
	Female vs male	0.422 (0.181–0.983)	0.046
	BMI	1.029 (0.958–1.104)	0.437
	Smoking	0.789 (0.475–1.313)	0.362
	Diabetes	1.313 (0.752–2.292)	0.338
	Hypertension	1.044 (0.642–1.696)	0.862
	Killip ≥2	0.897 (0.374–2.154)	0.808
	Post-PCI TIMI <3	4.843 (1.636–14.339)	0.004
	Multivessel disease (≥2 vessels)	0.962 (0.565–1.640)	0.888
Model 2	Age	1.009 (0.983–1.035)	0.497
	Female vs male	0.620 (0.232–1.659)	0.341
	BMI	1.008 (0.931–1.091)	0.844
	Smoking	0.683 (0.376–1.240)	0.210
	Diabetes	1.073 (0.566–2.033)	0.829
	Hypertension	0.963 (0.557–1.667)	0.894
	Killip ≥2	1.461 (0.517–4.130)	0.474
	Post-PCI TIMI <3	4.208 (1.150–15.395)	0.030
	Multivessel disease (≥2 vessels)	0.843 (0.459–1.551)	0.584
	MVO alone vs no MVO/IMH	3.731 (1.074–12.961)	0.038
	MVO with IMH vs no MVO/IMH	18.446 (9.326–36.486)	<0.001
Model 3	Age	0.999 (0.978–1.021)	0.960
	Female vs male	0.390 (0.164–0.926)	0.033
	BMI	1.012 (0.941–1.088)	0.750
	Smoking	0.851 (0.507–1.430)	0.543
	Diabetes	1.447 (0.816–2.568)	0.206
	Hypertension	0.960 (0.583–1.581)	0.873
	Killip ≥2	0.751 (0.310–1.819)	0.525
	Post-PCI TIMI <3	4.839 (1.596–14.668)	0.005
	Multivessel disease (≥2 vessels)	0.971 (0.562–1.677)	0.915
	Inflammatory burden score 1 vs 0	3.925 (1.491–10.336)	0.006
	Inflammatory burden score 2 vs 0	7.281 (2.671–19.852)	<0.001
Model 4	Age	1.012 (0.986–1.038)	0.384
	Female vs male	0.520 (0.188–1.437)	0.208
	BMI	0.997 (0.919–1.080)	0.934
	Smoking	0.716 (0.392–1.307)	0.277
	Diabetes	1.238 (0.644–2.377)	0.522
	Hypertension	0.903 (0.516–1.579)	0.719
	Killip ≥2	1.291 (0.458–3.643)	0.629
	Post-PCI TIMI <3	4.182 (1.106–15.808)	0.035
	Multivessel disease (≥2 vessels)	0.864 (0.466–1.603)	0.643
	MVO alone vs no MVO/IMH	3.194 (0.904–11.282)	0.071
	MVO with IMH vs no MVO/IMH	16.302 (8.196–32.425)	<0.001
	Inflammatory burden score 1 vs 0	2.825 (0.988–8.082)	0.053
	Inflammatory burden score 2 vs 0	4.517 (1.505–13.560)	0.007
Model 5	Age	1.010 (0.982–1.038)	0.486
	Female vs male	0.500 (0.166–1.506)	0.218
	BMI	0.998 (0.916–1.087)	0.957
	Smoking	0.652 (0.341–1.244)	0.194
	Diabetes	1.285 (0.643–2.570)	0.478
	Hypertension	0.836 (0.456–1.532)	0.563
	Killip ≥2	1.065 (0.364–3.112)	0.909
	Post-PCI TIMI <3	2.873 (0.622–13.278)	0.177
	Multivessel disease (≥2 vessels)	1.165 (0.596–2.279)	0.655
	MVO alone vs no MVO/IMH	2.084 (0.552–7.866)	0.279
	MVO with IMH vs no MVO/IMH	13.487 (6.525–27.876)	<0.001
	Inflammatory burden score 1 vs 0	2.254 (0.745–6.820)	0.150
	Inflammatory burden score 2 vs 0	3.565 (1.122–11.331)	0.031
	LVEF (per 1%)	0.921 (0.896–0.947)	<0.001

Note: Model 1, Clinical; Model 2, Clinical + phenotype; Model 3, Clinical + inflammatory burden; Model 4, Joint model; Model 5, Joint model with additional LVEF adjustment. LVEF, left ventricular ejection fraction; OR, odds ratio; CI, confidence interval.

suggest that CMR-defined injury and systemic inflammatory activation capture related, but not identical, dimensions of post-infarction risk.

This pattern is consistent with current understanding of reperfusion injury after STEMI. Restoration of epicardial coronary flow does not fully prevent downstream microvascular dysfunction and tissue injury [2,3,4]. MVO is closely linked to ischemia-reperfusion injury, infarct expansion, and adverse remodeling, whereas IMH generally reflects more severe microvascular damage [2,4,8,9]. In our cohort, the MVO with IMH phenotype was associated with the highest risk. Recent cohort studies and meta-analyses have likewise shown adverse prognostic implications of persistent MVO [19,20,21]. Other studies have linked IMH to larger infarct size, lower LVEF, more pronounced remodeling, worse clinical outcomes, and heightened inflammatory activation [22,23,24,25]. Related work has also identified clinical predictors of this phenotype after reperfused STEMI [26].

The inflammatory component also warrants consideration. Systemic inflammation has been implicated in post-infarction injury and ventricular remodeling [27,28]. NLR and CRP are readily available biomarkers and have been repeatedly associated with mortality and MACEs after STEMI [10,11,12]. More recent reviews and longitudinal data further support the prognostic relevance of CRP in acute myocardial infarction [13,14]. At the same time, reported cutoff values vary across cohorts and clinical settings, and no universally accepted thresholds are available

Table 4. Model performance comparison.

Model	AUC (95% CI)	AIC	BIC	H-L chi-square	H-L *p* value
Model 1	0.608 (0.544–0.672)	464.444	505.625	5.781	0.672
Model 2	0.830 (0.783–0.877)	365.597	415.014	4.091	0.849
Model 3	0.681 (0.621–0.741)	447.682	497.100	5.192	0.737
Model 4	0.841 (0.793–0.888)	360.851	418.505	12.593	0.127
Model 5	0.893 (0.857–0.929)	323.508	385.280	8.859	0.354

Note: Model 1, Clinical; Model 2, Clinical + phenotype; Model 3, Clinical + inflammatory burden; Model 4, Joint model; Model 5, Joint model with additional LVEF adjustment. AIC, Akaike Information Criterion; BIC, Bayesian Information Criterion; H-L, Hosmer-Lemeshow; AUC, area under the receiver operating characteristic curve.

for the present application [29,30]. In the present study, inflammatory burden alone showed limited prognostic utility, but model performance improved slightly after its addition to the CMR phenotypes. This pattern suggests that systemic inflammation and local tissue injury are not fully redundant and may provide prognostic information at different levels of the disease process.

The combined stratification analysis provides additional context. Patients without MVO/IMH had consistently low event rates across inflammatory burden categories, whereas differences in event rates across inflammatory burden categories were most apparent among patients with both MVO and IMH. These observations suggest that the CMR phenotype reflects the structural severity of reperfusion injury, whereas inflammatory burden may further characterize the intensity of the post-infarction response.

This study has several limitations. First, it was a retrospective single-center study and is therefore susceptible to selection bias. Second, the primary analysis used a binary MACE endpoint because exact event dates and censoring times were incompletely captured in the retrospective follow-up records, precluding a sufficiently robust time-to-event analysis in the full cohort. The Cox sensitivity analysis showed a directionally consistent pattern, with CMR phenotype contributing most of the prognostic information and inflammatory burden providing only limited incremental value. Third, the NLR and CRP cutoffs were derived from the present cohort and require external validation; accordingly, the exploratory inflammatory burden score should not yet be interpreted as a stand-alone clinical decision tool. Fourth, missing covariates were handled using simple single imputation, which may have influenced effect estimates. Finally, external validation is needed before this combined framework can be broadly generalized.

Conclusions

CMR-defined microvascular injury phenotypes improved risk stratification for MACEs in patients with STEMI and retained incremental value in expanded sensitivity analyses that include LVEF, NT-proBNP, and LGE extent. Patients with both MVO and IMH and a high inflammatory burden score represented a particularly high-risk subgroup, whereas the additional contribution of inflammatory burden to discrimination was modest.

Availability of Data and Materials

The data used or analyzed in this study are available on request from the corresponding authors.

Author Contributions

KX was the guarantor of the integrity of the entire study. All authors participated in the conception and design of the study, data collection, statistical analysis, and result interpretation. XHL drafted the original manuscript. XHL and WD completed the literature retrieval. XHL and HSZ performed the statistical analyses, and HSZ provided statistical methodological support and critically revised the manuscript for important intellectual content. XHL and SGH jointly collected and processed the imaging data, and SGH critically reviewed and revised the manuscript for important intellectual content. WD and YJZ participated in manuscript writing, critically revised the manuscript for important intellectual content, and contributed to the interpretation of the clinical findings. SQC coordinated cardiology data collection, provided guidance on manuscript drafting, and critically reviewed and revised the manuscript for important intellectual content. XHL, CFH, and KX critically revised the manuscript for important intellectual content and polished the manuscript. All authors have read and agreed to the final version of the manuscript. All authors have participated sufficiently in the work to take public responsibility for appropriate portions of the content and agreed to be accountable for all aspects of the work in ensuring that questions related to its accuracy or integrity.

Ethics Approval and Consent to Participate

This study was conducted in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Clinical Investigation of The Affiliated Hospital of Xuzhou Medical University (ethics approval num-

ber: XYFY2023-KL171-02). The requirement of written informed consent was waived by the committee due to the retrospective nature of the study.

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Conflict of Interest

The authors declare no conflict of interest.

Supplementary Material

Supplementary material associated with this article can be found, in the online version, at https://doi.org/10.24976/Discov.Med.202638214.281.

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