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ORIGINAL RESEARCH

Nomogram to Predict Outcomes After Staged Revascularization in ST-Segment Elevation Myocardial Infarction and Multivessel Coronary Artery Disease

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Objective: Approximately 50% of ST-segment elevation myocardial infarction (STEMI) patients have multivessel coronary artery disease (MVD). The management strategy for these patients remains controversial. This study aimed to develop predictive models and nomogram of outcomes in STEMI patients with MVD for better identification and classification.

Methods: The least absolute shrinkage and selection operator (LASSO) method was used to select the features most significantly associated with the outcomes. A Cox regression model was built using the selected variables. One nomogram was computed from each model, and individual risk scores were obtained by applying the nomograms to the cohort. After regrouping patients based on nomogram risk scores into low- and high-risk groups, we used the Kaplan–Meier method to perform survival analysis.

Results: The C-index of the major adverse cardiovascular event (MACE)-free survival model was 0·68 (95% CI 0·62–0·74) and 0·65 [0·62–0·68]) at internal validation, and that of the overall survival model was 0·75 (95% CI 0·66–0·84) and (0·73 [0·65–0·81]). The predictions of both models correlated with the observed outcomes. Low-risk patients had significantly lower probabilities of 1-year or 3-year MACEs (4% versus 11%, $P= 0.003$; 7% versus 15%, $P=0.01$, respectively) and 1-year or 3-year all-cause death (1% versus 3%, $P=0.048$; 2% versus 7%, respectively, $P=0.001$) than high-risk patients.

Conclusion: Our nomograms can be used to predict STEMI and MVD outcomes in a simple and practical way for patients who undergo primary PCI for culprit vessels and staged PCI for non-culprit vessels.

Keywords: ST-segment elevation myocardial infarction, multivessel coronary artery disease, percutaneous coronary intervention, major adverse cardiovascular events, all-cause death

Introduction

Acute coronary syndrome (ACS) is a common critical cardiovascular disease and a leading cause of death worldwide.[1,2] ST-segment elevation myocardial infarction (STEMI) accounts for ~36% of ACS cases.[3] STEMI is defined as a combination of persistent ST-segment elevation on electrocardiogram and the subsequent release of biomarkers of myocardial necrosis.[4] Previous studies have shown that approximately half of STEMI patients have multivessel coronary artery disease (MVD). MVD increases the risk of recurrence and short-term death after percutaneous coronary intervention (PCI) and is an important cause of poor prognosis in STEMI patients.[5,6]

The first-line treatment for STEMI patients is timely primary PCI (PPCI) for culprit vessels.[4] However, the presence of non-culprit vessels makes the treatment more complicated for patients with MVD. The management strategy and its impact on patient prognosis for non-culprit vessels are still controversial. The COMPLETE trial confirmed that complete revascularization was superior to culprit-lesion-only PCI in patients with STEMI and MVD.[7] However, intervention strategies for non-culprit vessels, such as the optimal timing of intervention, are not very consistent. Previous

retrospective studies reported inconsistent results due to the enrollment of different populations and different sample sizes.[8–10] This suggests that this population is highly heterogeneous, and further assessment and classification are needed.

Therefore, this study aimed to develop predictive models of major adverse cardiovascular events (MACEs) and all-cause mortality in patients with STEMI combined with MVD to better identify and classify these patients.

Methods

Study Design and Participants

We conducted a retrospective investigation. Nomograms were developed to predict outcomes after staged revascularization (SR) in acute STEMI and MVD patients using data from the First Affiliated Hospital of Xi'an Jiaotong University. All patients met the diagnostic criteria for acute STEMI. They all underwent PPCI for culprit vessels and staged PCI for non-culprit vessels. The exclusion criteria were as follows: (1) STEMI without PPCI or staged PCI and (2) acute non-STEMI or unstable angina. This study complies with the Declaration of Helsinki and was approved by the Ethics Committee of First Affiliated Hospital of Xi'an Jiaotong University. The informed consent was gained from the patients and their families.

Data Collection

General data (age, sex, body mass index (BMI), and smoking), medical history (including coronary heart disease, history of hypertension, type 2 diabetes mellitus, myocardial infarction, and coronary intervention), vital signs at admission (body temperature, pulse, respiratory rate, blood pressure), auxiliary examinations (white blood cell count, neutrophil count, red blood cell count, hemoglobin, platelet count, serum creatinine, uric acid, cholesterol, triglycerides (TG), low-density lipoprotein (LDL-C), high-density lipoprotein (HDL-C), creatine kinase (CK) and creatine kinase MB (CK-MB) peak, N-terminal pro b-type natriuretic peptide (NT-proBNP), left ventricular end-diastolic diameter (LDVd) and left ventricular ejection fraction (LVEF)), and estimated glomerular filtration rate (eGFR) calculated using the Modification of Diet in Renal Disease (MDRD) formula were recorded. Chest pain data, interventions (culprit vessels, location, diameter, length, number of vessels with lesions, treatment of non-culprit vessels or not, preoperative Thrombolysis in Myocardial Infarction (TIMI) flow, grading of postoperative TIMI flow, and intra-aortic balloon pump (IABP)), stents (most of the stents used in this study were drug-coated stents), medications (β-blocker, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), aldosterone, diuretic, calcium channel blocker or no medication during the three months before admission), and administration of the above medications after admission were also collected from the medical charts.

Definitions

In-hospital mortality was defined as all-cause mortality during hospitalization. Chest pain data included symptom-to-door time and first medical contact time. The time of chest pain onset was obtained by asking the patient and consulting the family accompanying the patient. After admission, ECG and blood sampling were performed within 10 minutes. The self-reported chest pain onset time was validated according to the presence or absence of a Q wave, the dynamic evolution of ST-T, and whether blood myoglobin and CK-MB levels were elevated. MACEs were defined as cardiac death, recurrent myocardial infarction, revascularization or stroke.[11]

Statistical Analysis

The sample size was derived based on the available data, and no power calculation for sample size was performed upfront. Descriptive statistics are reported as frequencies and proportions for categorical variables and as medians (IQRs) or means (SDs) for continuous variables.

The least absolute shrinkage and selection operator (LASSO) method was used to select the features that were most significantly associated with the outcomes (MACEs and all-cause mortality). Then, Cox regression models were built using the selected variables.[12,13] Cox regression analyses were applied to estimate the hazard ratios (HRs) or odds ratios and their 95% CIs or *P* values. The prediction accuracy of overall survival and MACE-free survival models was

evaluated using two methods. First, discrimination was measured by Harrell's concordance index (C-index) and its 95% CI. Second, model calibration was evaluated by calibration plots predicting the survival probability at 1 and 3 years versus the observed probability. One nomogram was computed from each model, and individual risk scores were obtained by applying the nomograms to the cohort. Then, the median of the nomogram-computed individual risk scores was taken as the cutoff point to stratify patients into low-risk or high-risk groups. Differences in overall survival and MACE-free survival between the low-risk and high-risk cohorts were determined using the Log rank test. The Kaplan–Meier (K-M) method was used for survival analysis. The distribution of putative variables between the low-risk and high-risk cohorts was compared using the Wilcoxon Mann–Whitney test (for continuous variables) or Fisher's exact test (for categorical variables).

Internal validation of the model was performed using a bootstrap resampling process to provide an unbiased estimate of model performance (validate.cph package in R) as the C-index and its 95% CI. All statistical analyses were performed using R version 4.1.1(Vienna, Austria).

Results

Baseline Clinical Characteristics of the Two Groups

Between January 1, 2015, and December 31, 2020, 3256 patients were retrospectively screened, and 496 (15%) of them met the eligibility criteria. A total of 2760 (85%) patients were excluded: 1189 (37%) did not undergo primary PCI, 692 (21%) had single-vessel disease, 795 (29%) did not undergo staged revascularization for non-culprit vessels within 30 days after PPCI, 21 (0.6%) died during hospitalization or had cancer, and 42 (1.3%) were lost to follow-up (Figure 1).
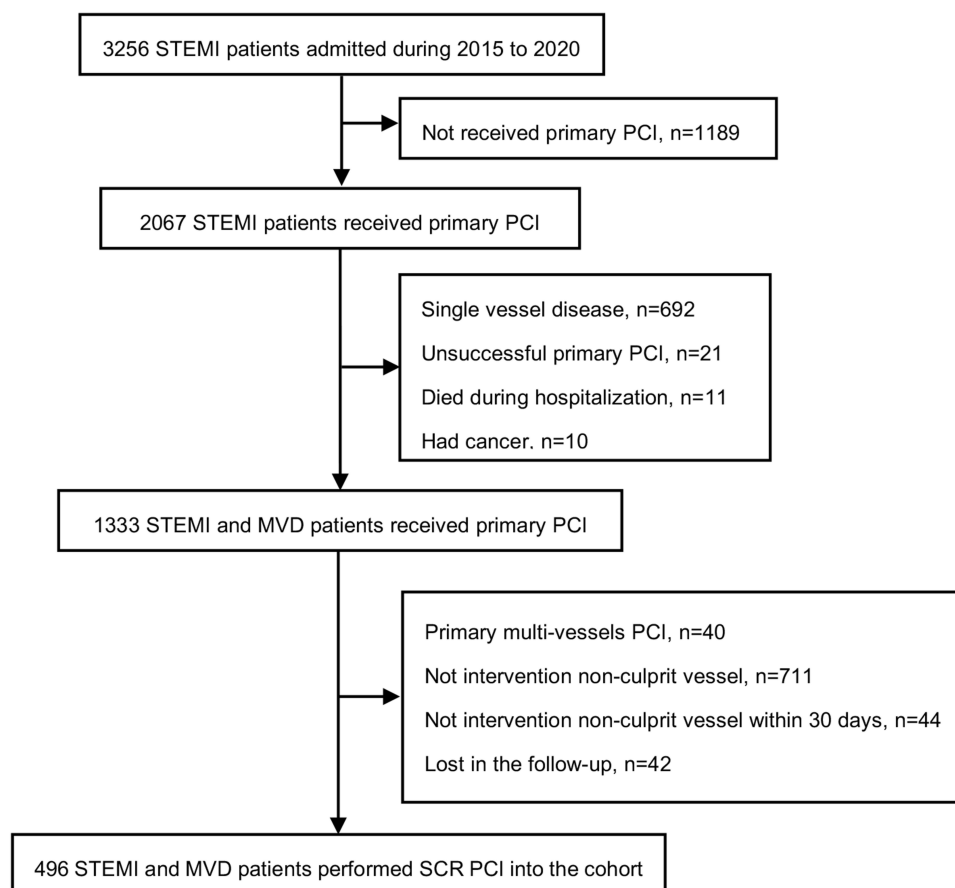
Figure 1 Study population flow chart.
Abbreviations: STEMI, ST-segment elevation myocardial infarction; MVD, multivessel coronary artery disease; PCI, percutaneous coronary intervention; SCR, staged complete revascularization.

Table 1 Baseline Characteristics of the Study Cohort

Risk factors	Total (n=496)	Low risk (n=248)	High risk (n=248)	*P* value
Male	422 (85.1)	229 (92.3)	193 (77.8)	**<0.001**
Age (years)	58.53 (9.96)	55.42 (9.58)	61.64 (9.36)	**<0.001**
BMI (kg/m^2)	24.48 (2.83)	24.98 (2.91)	23.97 (2.66)	**<0.001**
Diabetes (%)	108 (21.8)	54 (21.8)	54 (21.8)	**1**
Smoking (%)	304 (61.3)	165 (66.5)	139 (56.0)	**0.021**
Hypertension (%)	254 (51.2)	79 (31.9)	175 (70.6)	**<0.001**
Dyslipidemia (%)	320 (64.5)	163 (65.7)	157 (63.3)	**0.639**
Three vessels (%)	63 (12.7)	30 (12.1)	33 (13.3)	**0.788**
Culprit vessel (%)				**0.366**
LM	12 (2.4)	7 (2.8)	5 (2.0)	
LAD	172 (34.7)	91 (36.7)	81 (32.7)	
LCX	59 (11.9)	33 (13.3)	26 (10.5)	
RCA	253 (51.0)	117 (47.2)	136 (54.8)	
Total length of stent (mm)	40.10 (18.15)	39.33 (17.59)	40.86 (18.69)	**0.349**
Non-culprit vessel				
LM (%)	35 (7.1)	16 (6.5)	19 (7.7)	**0.726**
LAD (%)	328 (66.1)	161 (64.9)	167 (67.3)	**0.635**
LCX (%)	334 (67.3)	153 (61.7)	181 (73.0)	**0.01**
RCA (%)	187 (37.7)	99 (39.9)	88 (35.5)	**0.354**
Total length of stent (mm)	41.41 (23.18)	40.14 (22.16)	42.68 (24.14)	**0.222**
SR-time (%)				**<0.001**
1~3 d	187 (37.7)	132 (53.2)	55 (22.2)	
4~6 d	163 (32.9)	97 (39.1)	66 (26.6)	
>6 d	146 (29.4)	19 (7.7)	127 (51.2)	
LVEF	51.95 (9.36)	51.55 (9.26)	52.35 (9.46)	**0.34**
NT-proBNP	229.10 [87.50, 590.25]	216.15 [77.42, 435.52]	244.65 [106.72, 706.58]	**0.017**
eGFR	109.39 (29.81)	127.59 (23.66)	91.19 (23.58)	**<0.001**

Notes: Data are expressed as the median (IQR) or n (%) unless otherwise stated. The patient characteristics were analyzed using the Wilcoxon Mann–Whitney test or Fisher's exact test, depending on whether the variable was continuous or categorical.
Abbreviations: BMI, body mass index; LM, left main coronary artery; LAD, left anterior descending coronary artery; LCX, left circumflex coronary artery; RCA, right coronary artery; SR, staged revascularization; LVEF, left ventricular ejection fraction; NT-proBNP, N-terminal pro b-type natriuretic peptide; eGFR, estimated glomerular filtration rate.

The median follow-up time was 39 (IQR 21, 59) months. Baseline characteristic data were well balanced between the two groups except for sex, age, BMI, history of smoking and hypertension, SR time, NT-proBNP and eGFR (Table 1). During the follow-up, MACEs occurred in 68 (14%) patients, and 34 (7%) patients died in the total study cohort. Postdischarge medication use was similar between the high-risk and low-risk groups (Table 2).

Table 2 Medication After Discharge

Risk factors	Total (n=496)	Low risk (n=248)	High risk (n=248)	*P* value
Medicine				
Aspirin (%)	496 (100.0)	248 (100.0)	248 (100.0)	–
DAPT (%)				0.015
Clopidogrel	228 (46.0)	100 (40.3)	128 (51.6)	
Ticagrelor	268 (54.0)	148 (59.7)	120 (48.4)	
Statin (%)	494 (99.6)	248 (100.0)	246 (99.2)	0.499
ACEI/ARB (%)	393 (79.2)	191 (77.0)	202 (81.5)	0.268
β-blockers (%)	437 (88.1)	225 (90.7)	212 (85.5)	0.095
Diuretic (%)	142 (28.6)	64 (25.8)	78 (31.5)	0.196

Notes: *P* values are from a comparison of patient medication after discharge using Fisher's exact test.
Abbreviations: DAPT, dual antiplatelet therapy; ACEI, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blocker; β-blockers, beta-adrenergic blocking agents.

Cox Regression Analysis of MACEs and All-Cause Death

Based on the LASSO analysis, eGFR, age, history of hypertension and SR time were selected as predictors for the MACE risk prediction model (Table 3). eGFR, age and chronic total occlusion (CTO) were selected as predictors for the MACE risk prediction model (Table 4).

Development and Validation of Nomograms for Predicting MACE Risk and All-Cause Death Risk

The C-index of the MACE-free survival model was 0·68 (95% CI 0·62–0·74) and 0·65 [0·62–0·68] at internal validation. The nomogram was built based on the MACE-free survival model (Figure 2C). On the calibration plots, the model's predicted probabilities were close to the observed probabilities (Figure 2A and B).

The C-index of the overall survival model was 0·75 (95% CI 0·66–0·84). Similar C-index was achieved at internal validation (0·73 [0·65–0·81]). The nomogram was built based on the overall survival model (Figure 3C). On the calibration plots, the model's predicted probabilities were close to the observed probabilities (Figure 3A and B).

K-M Analysis

In the first model, the MACEs probability in the low-risk group was lower than that in the high-risk group (P<0.001). The 1-year MACEs probability for low-risk patients versus high-risk patients was 4% versus 11% (P= 0.003), and the 3-year MACEs probability was 6% versus 15% (P=0.01) (Figure 4A).

In the second model, the all-cause death probability in the low-risk group was also lower than that in the high-risk group (P=0.009). The 1-year all-cause mortality for low-risk patients versus high-risk patients was 1% versus 3% (P=0.048), and the 3-year death probability was 2% versus 7% (P=0.001) (Figure 4B).

Table 3 The Characteristics of the Variables in the MACE Prediction Model

| Variables	Univar			Multivar		
	OR	95% CI	P value	OR	95% CI	P value
eGFR	0.98	0.97–0.99	<0.001	0.98	0.97–0.99	0.004
Age	1.03	1–1.05	0.0291	1.01	0.98–1.04	0.325
Hypertension	0.584	0.357–0.957	0.033	1.4	0.84–2.32	0.193
SR-Time	-	-	0.011		-	0.037
1–3 d	0.433	0.241–0.777	0.005	0.48	0.27–0.87	0.015
4–6 d	0.549	0.312–0.967	0.038	0.61	0.34–1.07	0.085
>6 d	reference	-	-	-	-	-

Abbreviations: OR, odds ratio; CI, confidence interval; SR, staged revascularization; eGFR, estimated glomerular filtration rate.

Table 4 The Characteristics of the Variables in the All-Death Prediction Model

Variables	Univar			Multivar		
	OR	95% CI	P value	OR	95% CI	P value
eGFR	0.97	0.96–0.98	<0.001	0.97	0.96–0.98	<0.001
Age	1.07	1.03–1.11	<0.001	1.04	1.01–1.09	0.013
CTO	3.12	1.09–8.93	0.0338	2.98	1.04–8.55	0.042

Abbreviations: OR, odds ratio; CI, confidence interval; eGFR, estimated glomerular filtration rate; CTO, chronic total occlusion.
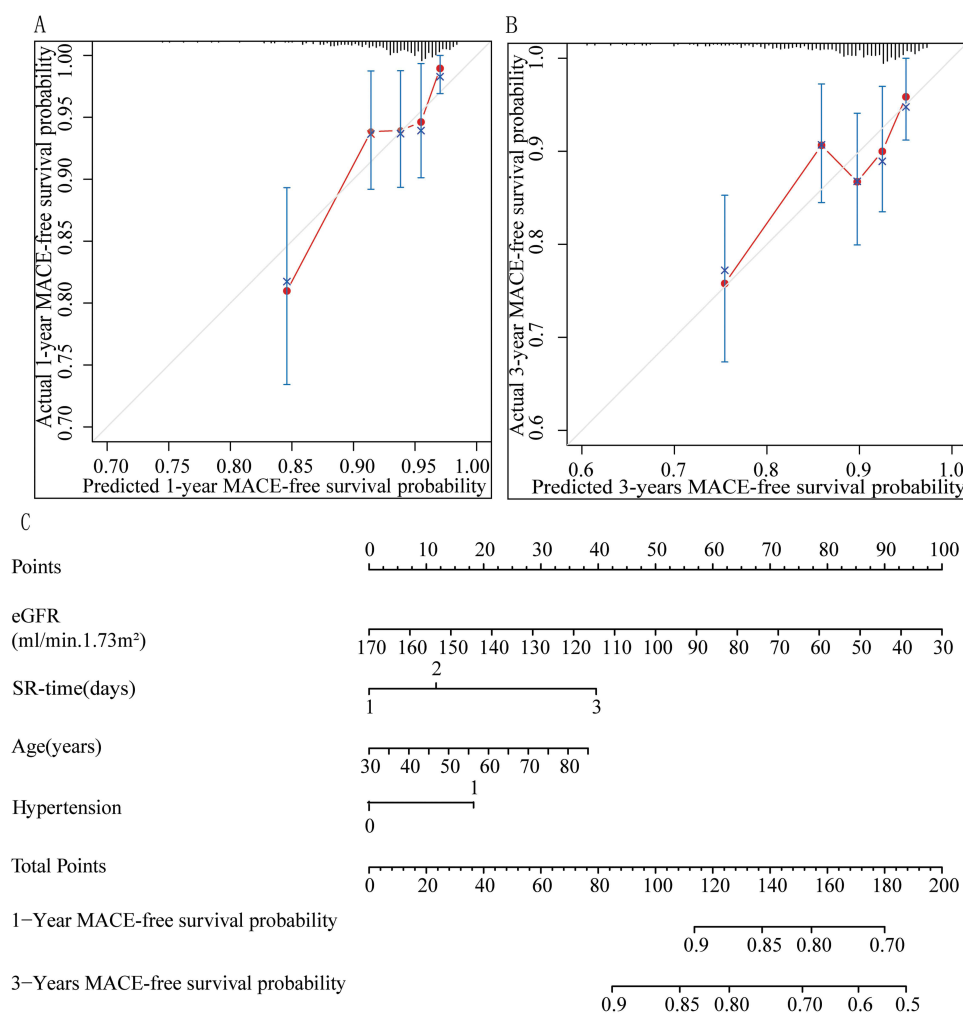
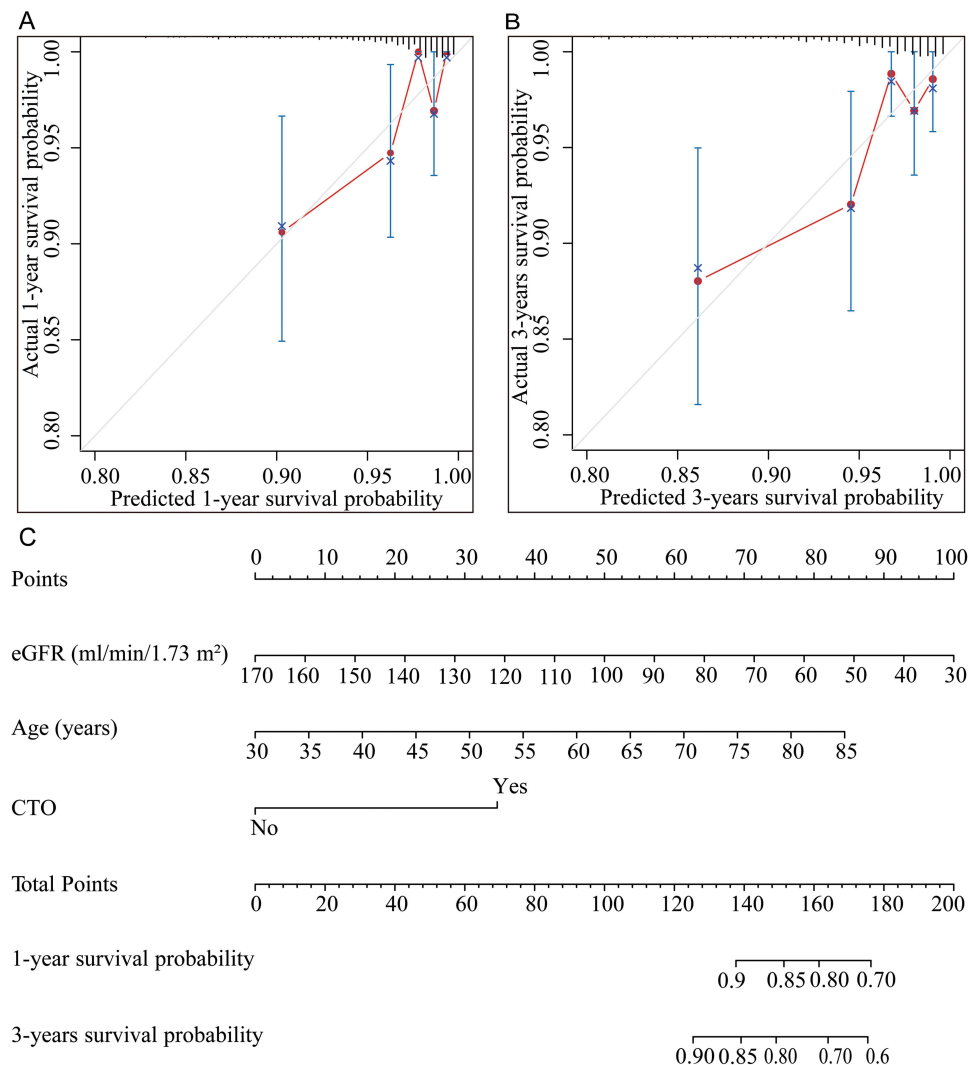**Figure 2** MACE-free survival probabilities. Calibration plots of MACE-free survival probabilities at 1 year (**A**) and 3 years (**B**). Nomogram-predicted MACE-free survival is plotted on the x-axis, with observed MACE-free survival on the y-axis. Dashed lines along the diagonal line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (**C**) Nomogram for predicting the probability of MACE-free survival at 1 year and 3 years. The presence or absence of each clinical characteristic indicates a certain number of points. The number of points for each clinical characteristic is in the top row. For each characteristic, absence is assigned 0 points. The presence of characteristics is associated with a number of points generated using the nomogram function rms package in R based on the results of LASSO analysis. The points for each characteristic are summed to generate a total-points score. The total points correspond to the respective 1-year and 3-year MACE-free survival probabilities.
Abbreviations: MACE, major adverse cardiovascular event; eGFR, estimated glomerular filtration rate; SR, staged revascularization.

Discussion

It is a widely accepted fact that STEMI patients with MVD are at high risk. Management strategies for these patients, especially regarding intervention time in non-culprit vessels, remain controversial.[14] We developed prediction models for MACEs and all-cause mortality based on several clinical indicators with promising accuracy (the C-index values were 0.68 and 0.75), allowing easier classification of such patients and identification of those at high risk.

Several previous studies have established nomograms for predicting different outcomes in patients with ACS undergoing PCI.[15–17] However, these models are relatively complex, and there is currently no prediction model specifically tailored for STEMI patients with MVD. Our nomograms for MACE-free and overall survival combine traditional clinical prognostic variables (ie, age, history of hypertension), laboratory test results, characteristics of coronary vascular disease (CTO) and treatment strategy (SR time). Both nomograms support previous studies and suggest that eGFR is an independent predictor of outcomes in STEMI patients with or without MVD treated with PCI.[18,19] Go AS et al found that the risk of all-cause mortality from cardiovascular adverse events (coronary heart disease, acute myocardial infarction, heart failure, and stroke) increased with the interval decrease in eGFR in a large-scale epidemiological

Figure 3 Total survival probabilities. Calibration plots of total survival probabilities at 1 year (**A**) and 3 years (**B**). Nomogram-predicted total survival is plotted on the x-axis, with observed total survival on the y-axis. Dashed lines along the diagonal line through the origin point represent the perfect calibration models in which the predicted probabilities are identical to the observed probabilities. (**C**) Nomogram for predicting the probability of total survival at 1 year and 3 years. The presence or absence of each clinical characteristic indicates a certain number of points. The number of points for each clinical characteristic is in the top row. For each characteristic, absence is assigned 0 points. The presence of characteristics is associated with a number of points generated using the nomogram function rms package in R based on the results of LASSO analysis. The points for each characteristic are summed to generate a total-points score. The total points correspond to the respective 1-year and 3-year total survival probabilities.
Abbreviations: eGFR, estimated glomerular filtration rate; CTO, chronic total occlusion.

study.[20] Most patients with STEMI and MVD require multiple PCI procedures with more contrast agents, implying a higher risk of contrast-induced nephropathy. Clinically, we should be more vigilant and closely monitor renal function.

Complete revascularization of non-culprit vessels can significantly improve the prognosis of STEMI in MVD patients,[7,21,22] although strategies for intervention in non-culprit vessels are still under investigation. Prior research indicates that utilizing fractional flow reserve (FFR) and intravascular imaging to guide interventions in non-culprit vessels may benefit such patients.[23–25] A randomized clinical study by Lee et al found that compared to the traditional strategy of PCI based on angiographic diameter stenosis, a selective PCI strategy guided by FFR decision-making reduced the risk of death, myocardial infarction, or repeat revascularization in patients with AMI and MVD.[25] In addition to preventive revascularization, comprehensive management approaches including adequate antiplatelet therapy, and the use of plaque-stabilizing medications (such as PCSK9 inhibitors and statins) are essential to further improve the prognosis of these patients.
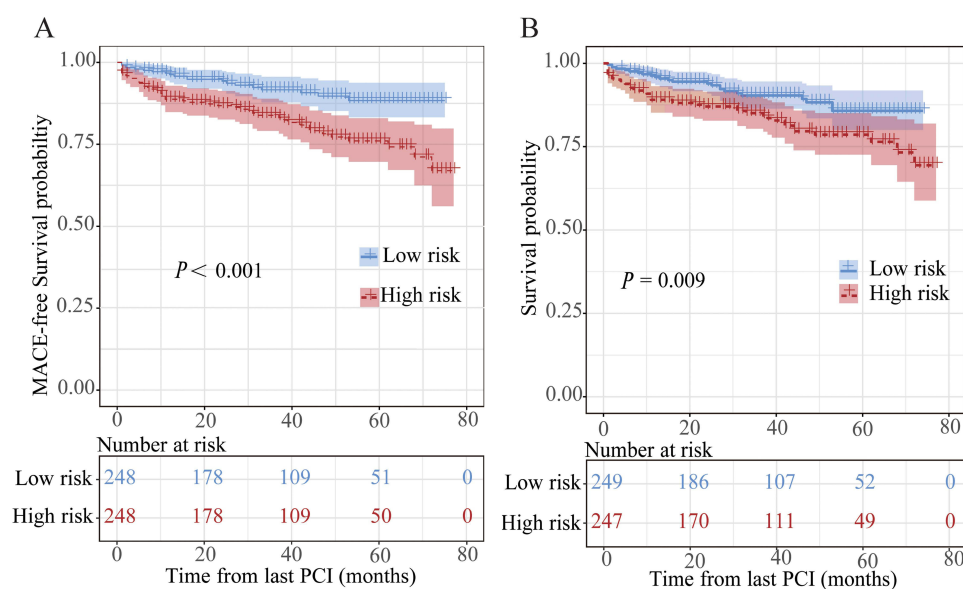
Figure 4 Survival curves by different risk groups. MACE-free survival curves (**A**) and overall survival curves (**B**), stratified into low-risk and high-risk groups by the median of the risk scores from the nomograms above.
Abbreviations: MACE, major adverse cardiovascular event; PCI, percutaneous coronary intervention.

The optimum timing of the revascularization strategy for non-culprit vessels in STEMI and MVD remains unclear. The results of previous studies investigating the optimum strategy for non-culprit vessels are also inconsistent due to differences in sample size, selection criteria, research methods, intervention timing, and intervention criteria. However, most of them suggest that early intervention (the best time point obtained by each study is different) of non-culprit vessels may benefit such patients' prognosis.[8,26] Our nomograms show that delayed intervention in non-culprit vessels may be detrimental to the prognosis of patients, but the optimal timing and strategy require further study in well-designed randomized controlled clinical trials. In patients with STEMI, the prevalence of CTO in a non–infarct-related artery (non-IRA) is 8% to 15%, with 2-fold greater morbidity and mortality than in those with single-vessel disease.[27,28] We also found that CTO was a predictor of all-cause mortality.

This study has important clinical implications. STEMI and MVD patients experienced more MACEs and higher mortality than STEMI patients with single-vessel lesions.[29,30] MVD is an essential factor in the poor prognosis of these patients and can significantly increase recurrence of myocardial infarction and short-term mortality after PCI.[6,31] The COMPLETE trial demonstrated that, on a background of optimal medical therapy, compared with a culprit lesion-only revascularization strategy, a complete revascularization strategy can significantly reduce the risk of cardiovascular death or myocardial infarction, as well as the risk of cardiovascular death, myocardial infarction, or ischemia-driven revascularization.[7] However, even complete revascularization has been performed, these patients still have a high rate of mortality and MACEs. This may be partly because most of these patients have comorbidities, such as advanced age, diabetes, hypertension and chronic kidney disease.[32] Early identification and classification of those at risk among them and individualized management may improve the prognosis of this group of patients, but there is a lack of rapid and straightforward clinical methods for identifying and classifying these patients. Our study provides a preliminary tool to help clinicians make decisions and manage these patients in their clinical work.

The major limitations of this study are the small size of the cohort and the absence of a prospective external validation of the models. Although the recommended number of at least ten events per predictor variable was followed,[33] validation of the models in larger patient populations is warranted. Second, this study was a single-center, retrospective, observational study with selection bias to adequately assess the impact of confounding factors on the study results. The prognostic discrimination (C-index: 0·68 for the MACE-free survival model and 0·75 for the overall survival model) was not ideal. The addition of other parameters to a larger patient population might increase the prognostic discrimination. Last, we did not adequately

assess the severity of patients' coronary lesions, such as applying the Gensini score or SYNTAX score to evaluate the severity of coronary artery lesions. The Gensini score and SYNTAX score are significantly associated with the prognosis of patients.

In summary, our study established two predictive nomograms based on four or three variables with promising discrimination to help clinicians predict the risk of MACEs and all-cause death in STEMI patients with MVD who underwent primary PCI for culprit vessels and staged PCI for non-culprit vessels. Use of the nomograms helps to manage these patients more precisely and personalize their treatment in the clinic.

Data Sharing Statement

The datasets analyzed during the current study are available from the corresponding author on reasonable request.

Author Contributions

All authors contributed to data analysis, drafting or revising the article, have agreed on the journal to which the article will be submitted, gave final approval of the version to be published, and agree to be accountable for all aspects of the work. We thank AJE language editing services for English language editing.

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Disclosure

The authors report no conflicts of interest in this work.

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