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Development and Validation of Risk Nomogram Model Predicting Coronary Microvascular Obstruction in Patients with ST-Segment Elevation Myocardial Infarction (STEMI) Undergoing Primary Percutaneous Catheterization

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Background: Coronary microvascular functional and structural obstruction (CMVO) remains a major complication in patients with ST-segment elevation myocardial infarction (STEMI). This study was designed to develop and validate a nomogram model to predict CMVO risk during primary percutaneous catheterization procedure.

Material/Methods: Starting January 2014 to December 2016, a cohort of eligible candidates were enrolled and divided into a training or a validation database. Each database was divided into MO or NMO subgroups based on TIMI myocardial perfusion grade results after recanalization. Independent factors were identified by multivariate logistic regression, from which the nomogram was plotted. The echocardiography measurement of the left ventricular ejection fraction (LVEF) was arranged within 7 days after the procedure.

Results: A nomogram was built for CMVO risk prediction for the first time. There were 446 participants in the training database with 319 cases in the NMO subgroup and 127 participants in the MO subgroup. The validation database included 99 participants with 25 cases in the NMO subgroup and 74 in the MO subgroup. The risk model was developed by 6 independently significant factors: age, symptom onset to balloon time, Killip classification, admission activated clotting time, neutrophil/lymphocyte ratio, and glucose value. Internal receiver operating characteristic displayed favorable performance with concordance index of 0.925, while external validation area under curve was 0.939. There were significant differences in LVEF values during hospitalization between the subgroups of each database (both $P<0.001$).

Conclusions: The nomogram model consisting of 6 factors could predict CMVO risk accurately for STEMI patients undergoing primary percutaneous catheterization.

MeSH Keywords: **Microvessels • Models, Cardiovascular • Myocardial Infarction • Nomograms • Percutaneous Coronary Intervention**

Abbreviations: **ACT** – activated clotting time; **AUC** – area under curve; **BMI** – body mass index; **BNP** – brain natriuretic peptide; **CI** – confidence interval; **C-index** – concordance index; **CK-MB** – creatine kinase MB isozyme; **CMVO** – coronary microvascular functional and structural obstruction; **cTFC** – corrected TIMI frame count; **cTn** – cardiac troponin; **FMC** – B first medical contact to balloon; **hs-CRP** – high sensitive C-reactive protein; **LVEF** – left ventricular ejection fraction; **NLR** – neutrophil/lymphocyte ratio; **NRF** – no-reflow phenomenon; **PCI** – percutaneous coronary intervention; **PTCA** – percutaneous transluminal coronary angioplasty; **ROC** – receiver operating characteristic; **SO-B** – symptom onset to balloon; **STEMI** – ST-segment elevation myocardial infarction; **TIMI** – thrombolysis in myocardial infarction; **TMPG** – TIMI myocardial perfusion grade; **UFH** – unfractionated heparin

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Background

ST-segment elevation myocardial infarction (STEMI), a typical symptom mostly generated from acute intracoronary thrombus formation and coronary blood flow cessation, remains a dominating threat to public health throughout the world. In patients presenting with acute STEMI, the main target of the reperfusion strategy is to promptly implement the intervention on the culprit artery. Regardless of epicardial repatency after revascularization, a considerable number of patients suffer from inadequate perfusion at the myocardial tissue level, resulting from coronary microvascular functional and structural obstruction (CMVO) during the perioperative period [1]. CMVO, previously identified and understood as "no-reflow phenomenon" (NRF), would add to the intervention strategy the incidence of adverse complications and events, thus affecting patients' short and long-period prognosis [2,3]. Therefore, attempts to decrease microvascular obstruction risk via mechanical and pharmaceutical pretreatments in the early stage of catheterization have been proposed and achieved promising results [4,5]. Nevertheless, for patients developing subsequent microvascular impairment, no specific or definitive therapeutic approaches for attenuation have proven to be valid from large scale tests, highlighting the urgent need to address timely recognition of this condition.

In recent years, many trials have been carried out to analyze and investigate the possible related indicators of CMVO or NRF [6]. However, due to the differences in study protocols, sample size, and auxiliary measurements, there have been no consistent conclusions so far. In addition, limited by the testing costs and time, some clinical or laboratory indexes are still not suitable or available in present practice. Among the current existing findings, time from chest pain symptom onset to balloon (SO-B) has been confirmed as one of the most acknowledged predictors of microvascular perfusion, which intensifies the significance of early reperfusion in the setting of STEMI [7,8]. Nevertheless, on the basis of animal experiments and earlier clinical trials, an assumption has been put forward that multiple process, including ischemia-reperfusion injury, distal embolization, and individual susceptibility are involved in CMVO development, and in an integrated manner contribute to deteriorating microvascular perfusion [9,10]. Accordingly, one single indicator may not be valid enough to evaluate the perfusion state of microvasculature. In order to determine CMVO probability in primary percutaneous coronary catheterization and thus rendering early and rapid identification of high-risk patients, we systematically screened the possible clinical and angiographic information retrospectively, with an attempt to construct and validate a predictive nomogram model for the first time.

Material and Methods

Population

Starting January 2014 to December 2016, the participants hospitalized to the Cardiology Division of the Second Hospital of Hebei Medical University were recruited in this retrospective analysis. The qualified candidates were enrolled based on the following criteria: 1) diagnosis of STEMI was based on the current guideline [11]; 2) the duration lasted less than 24 hours from the symptom onset till balloon inflation; 3) patients and their direct relatives agreed to undergo the emergent intervention in the Chest Pain Unit of our Institute. Meanwhile, our exclusion criteria included: 1) Killip IV grade; 2) intravenous or intracoronary fibrinolytic pharmaceutic treatment; 3) history of myocardial infarction; 4) rejecting the angiographic examination or preparing an elective intervention; 5) multiple lesions not advisable for stenting; 6) immunological or rheumatic diseases, end-stage hepato-renal failure, and cancer; 7) serious mechanical or operative complications; and 8) contraindication for the anticoagulant or antiplatelet agents. According to the Helsinki Declaration, the design and protocol has been approved by the Institutional Ethics Committee (Approval Letter No. 2018-P044). Each recruited member has agreed to take part in this study and signed the informed consent.

Study design and procedures

Patients' demographic data (gender, age, body mass index, Killip grade), previous history (hypertension, diabetes mellitus, dyslipidemia and smoking) and present illness description were recorded in medical files while hospitalized. Electrocardiogram and conventional laboratory examinations [complete blood cell, myocardial damage indicators, biochemical indices, glycosylated hemoglobin A1c (HbA1c), serum brain natriuretic peptide (BNP), and activated clotting time (ACT)] for STEMI patients were performed on admission. ACT assay test was detected by the double-channel mechanical plunger (ACT plus, Medtronic Inc., Minneapolis, MN, USA) on reaction temperature of 37°C.

Patients received 300 mg aspirin, 600 mg clopidogrel or 180 mg ticagrelor, and unfractionated heparin (UFH) 70–100 U/kg as pretreatment prior to the procedure. The coronary angiographic examination was conducted in keeping with the technical principle via radial, ulnar, or femoral access. Angiographic review and analysis were accomplished by no less than 2 skillful interventional cardiologists in different working teams. ACT levels were kept 250–300 seconds under the application of UFH conventionally, while Bivalirudin (initial bolus of 0.75 mg/kg, then intravenous infusion with 1.75 mg/kg/hour for 3–4 hours after procedure) served as an alternative for patients at high hemorrhage risk. Percutaneous coronary intervention (PCI) would be preferred when the stenosis degree of infarct related

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artery (IRA) was beyond 75%. When the lesions were not suitable or the patients refused stenting, transluminal coronary angioplasty (PTCA) would be adopted. Reperfusion therapy delay [for instance, SO-B and first medical contact to balloon (FMC-B) time] would be calculated when the balloon was inflated. The choice of interventional device, procedure (numbers and pressure of predilation and postdilation, thrombus aspiration, and temporary pacemaker implantation) and adjuvant medication (tirofiban, anisodamine, etc.) were left to the operators' decisions. Some invasive indices were also assessed and listed as previously introduced, such as thrombolysis in myocardial infarction (TIMI) grade [12], Gibson's intracoronary thrombus scores [13], TIMI myocardial perfusion grade (TMPG) [14], and corrected TIMI frame count (cTFC). Culprit artery cTFC was counted at the rate of 15 frames per second in accordance with Gibson's method [15]. After the procedure, all the participants were administered with anticoagulant and antithrombotic therapy, β-receptor blocker, statins, nitrates, and angiotensin-converting enzyme inhibitors or angiotensin receptor blocker as stated in the guideline. The echocardiography measurement of left ventricular ejection fraction (LVEF) was arranged in 7 days after the emergent catheterization.

Among all eligible participants, ID numbers were given according to the admission time. The candidates administered from January 2014 to June 2016 were scheduled to create a training database, while the patients enrolled from July 2016 to December 2016 were planned to validate the established model. Each database was divided into subgroups based on TMPG results after the recanalization, namely MO subgroup with 0–2 grade and NMO subgroup with 3 grade.

Statistical analysis

Kolmogorov-Smirnov's test was utilized to evaluate those continuous data's normality. If the data were distributed normally, they would be indicated as mean ± standard deviation (SD), or else they would be reported as median (25^{th} quartile, 75^{th} quartile). For categorical data, they would be presented as numbers and proportions. The statistical difference between continuous data were compared by Student's *t*-test for normally distributed values and Mann-Whitney U test for those non- normally distributed. Proportions were assessed by chi-square test or Fisher's exact test if the expected frequency was <5. Binary multivariate logistic regression was used to recognize the independent elements that influence myocardial perfusion by a backward step-down process in the training database. The multicollinearity among all potential factors was estimated. Then, those risk factors were put into use for development of nomogram. Statistical calculations and analysis were conducted by SPSS Software (Version 23.0, SPSS Inc., Chicago, IL, USA). A 2-tailed *P* value less than 0.05 was considered statistical significance.

Generated from multivariate logistic regression analysis of the training database, a nomogram was established with R Software (Version 3.4.4 for Windows, *http://www.r-project.org/*) and RStudio (*https://www.rstudio.com/*). The construction of nomogram was performed by running the programming codes and a series of R packages (Hmisc, grid, lattice, Formula, ggplot2, rms, haven, pROC, etc.), which were downloaded and installed from R Software online platform. The nomogram's discriminant performance was assessed and analyzed by concordance index (C-index), and illustrated as receiver operating characteristic (ROC) and area under curve (AUC) [16]. Calibration curve was derived to test calibration ability. Five-fold cross-validation method was used for further internal validation afterwards, while external validation was carried out by substituting the validation data in the developed model.

Results

Group enrollment

Since January 2014 to June 2016, a total of 446 eligible STEMI participants formed the training database. Among those cases, 127 patients developed CMVO with an incidence of 28.48%. Beginning July 2016 to December 2016, a total of 99 eligible patients were enrolled to construct the validation database. Amongst these patients, 25 cases were diagnosed with CMVO with an incidence of 25.25%.

Baseline clinical characteristics between both subgroups in the training database

The demographic characteristic, baseline information, and clinical laboratory indices of the candidates in the NMO and the MO subgroups of the training database, and the relevant details of comparisons are described in Table 1. No evident difference was noticed between the 2 subgroups on gender, body mass index, previous history, life signs, red blood cell count, platelet count, electrolyte, lipid values, and HbA1c (all $P>0.05$). The average age of the MO subgroup participants was higher than that of the NMO subgroup (62.06±13.95 versus 57.68±12.29, $P=0.019$). Patients in the MO subgroup shared a higher proportion of Killip 3 grade and a lower proportion of Killip 1 grade upon admission (44.88% versus 10.34%, $P<0.001$; 10.34% versus 58.31%, $P<0.001$). Besides, GRACE, as well as CRUSADE scores of the MO subgroup were significantly higher [135.14±26.42 versus 151.28±32.41, $P<0.001$; 20 (13, 30) versus 27 (15, 44), $P<0.001$]. The following laboratory items were also distinctly different between the 2 subgroups, including white blood count, neutrophil count, lymphocyte count, neutrophil/lymphocyte ratio (NLR), high sensitive C-reactive protein (hs-CRP), cardiac troponin I (cTnI), creatine kinase-MB isozyme (CK-MB), ACT, serum creatinine, evaluated glomerular filtration rate (eGFR), glucose, D-dimer, and BNP (all $P<0.05$).

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Table 1. Baseline clinical characteristics between the 2 subgroups in the training database.

Variables	NMO group (n=319)		MO group (n=127)		*P* value
Age (years)	57.68±12.29		62.06±13.95		0.019
Male, n (%)	271	(84.95)	100	(78.74)	0.124
BMI (kg/m^2)	25.59±3.15		26.06±3.68		0.274
SBP (mmHg)	133.15±26.78		128.93±23.95		0.123
DBP (mmHg)	77.29±16.85		78.47±15.30		0.494
Heart rate (bpm)	76.31±16.44		79.05±18.71		0.128
Killip grade					
Grade I, n (%)	186	(58.31)	21	(16.54)	<0.001
Grade II, n (%)	100	(31.35)	49	(38.58)	0.144
Grade III, n (%)	33	(10.34)	57	(44.88)	<0.001
History of CAD, n (%)	177	(55.49)	64	(50.39)	0.347
Hypertension, n (%)	204	(63.95)	74	(58.27)	0.264
Diabetes mellitus, n (%)	85	(26.65)	44	(35.43)	0.065
Hyperlipidemia, n (%)	137	(42.95)	50	(39.37)	0.490
Smoking, n (%)	122	(38.24)	60	(47.24)	0.081
Laboratory test on admission					
WBC count (10^9/L)	8.50	(10.20, 12.40)	10.12	(12.00, 14.55)	<0.001
Neutrophil count (10^9/L)	8.00	(6.50, 9.80)	10.30	(8.55, 12.50)	<0.001
Lymphocyte count (10^9/L)	1.5	(1.20, 2.00)	1.06	(0.80, 1.35)	<0.001
N/L ratio	5.30	(3.94, 7.00)	9.73	(7.81, 12.69)	<0.001
Erythrocyte count (10^{12}/L)	4.45±0.87		4.33±0.92		0.197
Platelet count (10^{12}/L)	205.37±63.55		209.79±55.03		0.549
High sensitive CRP (mg/L)	3.20	(1.60, 5.70)	4.40	(2.05, 8.40)	0.016
ACT (s)	160	(141, 182)	124	(98, 138)	<0.001
CK-MB (U/L)	107	(33, 280)	154	(61, 308)	0.075
Cardiac troponin I (ng/mL)	4.5	(2.7, 10.4)	11.4	(5.5, 29.5)	<0.001
Serum creatinine (μmol/L)	72	(61.2, 82.7)	75	(68.9, 96.0)	0.046
eGFR (mL/min/1.73 m^2)	99.6	(84.40, 120.00)	91.76	(63.24, 111.86)	0.011
Serum potassium (mmol/L)	4.02	(3.76, 4.31)	3.94	(3.69, 4.40)	0.845
Triglyceride (mmol/L)	1.29	(0.87, 1.85)	1.26	(0.81, 1.64)	0.547
Total cholesterol (mmol/L)	4.22	(3.59, 4.91)	4.05	(3.58, 5.46)	0.908
LDL cholesterol (mmol/L)	2.81	(2.20, 3.39)	2.70	(2.23, 3.40)	0.905
HDL cholesterol (mmol/L)	1.02	(0.88, 1.26)	1.10	(0.95, 1.30)	0.061
HbA1c (%)	6.30±1.23		6.53±1.32		0.085
Glucose (mmol/L)	9.61	(7.30, 10.85)	12.74	(10.23, 14.42)	<0.001

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Table 1 continued. Baseline clinical characteristics between the 2 subgroups in the training database.

Variables	NMO group (n=319)		MO group (n=127)		*P* value
D-dimer (μg/mL)	0.11	(0.08, 0.20)	0.19	(0.12, 0.37)	<0.001
BNP (pg/mL)	58.5	(30,108)	95	(35,177.5)	0.025
Preprocedural medication					
DAPT, n (%)	304	(95.30)	118	(92.91)	0.314
Statins, n (%)	131	(41.07)	43	(33.86)	0.159
Beta-blocker, n (%)	24	(7.52)	8	(6.30)	0.665
GRACE score	135.14±26.42		151.28±32.41		<0.001
CRUSADE score	20	(13, 30)	27	(15, 44)	<0.001

Normally distributed continuous data are indicated as mean ± standard deviation; or else they would be reported as median (25th quartile, 75th quartile). Categorical data are shown as numbers and proportions (%). MO and NMO subgroups based on TIMI myocardial perfusion grade results after recanalization. MO subgroup with 0–2 grade and NMO subgroup with 3 grade. ACT – activated clotting time; BMI – body mass index; BNP – brain natriuretic peptide; CAD – coronary artery disease; CK-MB – creatine kinase-MB isozyme; CRP – C-reactive protein; DAPT – dual antiplatelet therapy; DBP – diastolic blood pressure; eGFR – evaluated glomerular filtration rate; HbA1c – Glycosylated hemoglobin A1c; HDL – high density lipoprotein; LDL – low density lipoprotein; SBP – systolic pressure; WBC – white blood cell.

Table 2. Procedural and angiographic features between the 2 subgroups in the training database.

Variables	NMO group (n=319)		MO group (n=127)		*P* value
Onset to balloon (hours)	4.5	(3.5, 6.0)	7.0	(5.0, 9.1)	<0.001
FMC to balloon (hours)	2.0	(1.2, 3.0)	2.5	(1.5, 4.8)	0.007
Myocardial wall, n (%)					
Anterior wall	150	(47.02)	68	(53.54)	0.214
Others	169	(52.98)	59	(46.46)	0.214
Stenosed artery number, n (%)					
1	70	(21.94)	21	(16.54)	0.201
2	107	(33.54)	46	(36.22)	0.591
3	142	(44.52)	60	(47.24)	0.601
Intervention pattern, n (%)					
PCI	279	(87.46)	110	(86.61)	0.809
PTCA	40	(12.54)	17	(13.39)	0.809
Initial TIMI flow, n (%)					
0	172	(53.92)	114	(89.76)	<0.001
1	45	(14.10)	11	(8.66)	0.117
2	51	(15.99)	2	(1.58)	<0.001
3	51	(15.99)	0	(0.00)	<0.001
Initial thrombus score, n (%)					
0–1	10	(3.13)	0	(0.00)	0.044
2	34	(10.66)	1	(0.79)	<0.001

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Table 2 continued. Procedural and angiographic features between the 2 subgroups in the training database.

Variables	NMO group (n=319)		MO group (n=127)		*P* value
3	70	(21.94)	3	(2.36)	<0.001
4	33	(10.34)	9	(7.09)	0.288
5	172	(53.93)	114	(89.76)	<0.001
Final TIMI flow, n (%)					
0	0	(0.00)	0	(0.00)	—
1	0	(0.00)	2	(1.58)	0.025
2	0	(0.00)	61	(48.03)	<0.001
3	319	(100)	64	(50.39)	<0.001
IRA-cTFC	22	(18, 29)	46	(34, 57)	<0.001
Stent number per patient, n (%)					
1	242	(86.74)	91	(82.73)	0.310
≥2	37	(13.26)	19	(17.27)	0.310
Stent length (mm)	23	(18, 29)	24	(18, 29)	0.143
Stent diameter (mm)	3.0	(2.60, 3.50)	2.75	(2.50, 3.00)	0.204
Predilation pressure (atm)	14	(12, 16)	14	(12, 16)	0.193
Predilation numbers	2	(1, 3)	2	(1, 3)	0.348
Stent expansion pressure (atm)	14	(15, 16)	14	(14, 16)	0.509
Postdilation pressure (atm)	14	(12, 16)	14	(11, 16)	0.467
Postdilation numbers	1	(0, 2)	1	(0, 2)	0.960
Thrombus aspiration, n (%)	38	(11.91)	9	(7.09)	0.134
Temporary pacemaker, n (%)	7	(2.19)	5	(3.94)	0.305
Collateral circulation, n (%)	72	(22.57)	35	(27.56)	0.266
Contrast media volume (mL)	160	(130, 180)	160	(145, 195)	0.181
Procedural medication, n (%)					
Tirofiban	275	(86.21)	101	(79.53)	0.085
Bivalirudin	60	(18.81)	32	(25.20)	0.154
Anisodamine	70	(21.94)	28	(22.05)	0.981

Normally distributed continuous data are indicated as mean ± standard deviation; or else they would be reported as median (25^{th} quartile, 75^{th} quartile). Categorical data are shown as numbers and proportions (%). cTFC – corrected TIMI frame count; FMC – first medical contact; IRA – infarct related artery; PCI – percutaneous coronary intervention; PTCA – percutaneous transluminal coronary angioplasty; TIMI – thrombolysis in myocardial infarction.

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Table 3. Baseline clinical characteristics between the 2 subgroups in the validation database.

Variables	NMO group (n=74)	MO group (n=25)	*P* value
Age (years)	60.20±1.57	68.36±11.41	0.003
Male, n (%)	62 (83.78)	18 (74.00)	0.242
BMI (kg/m^2)	24.84±2.41	25.74±3.06	0.136
SBP (mmHg)	138.58±24.61	133.0±29.96	0.374
DBP (mmHg)	81.27±15.91	78.20±17.93	0.421
Heart rate (bpm)	74.32±16.71	79.52±20.57	0.209
Killip grade			
Grade I, n (%)	46 (62.16)	5 (20.00)	<0.001
Grade II, n (%)	21 (28.38)	9 (36.00)	0.473
Grade III, n (%)6	7 (9.46)	11 (44.00)	<0.001
History of CAD, n (%)	38 (51.35)	10 (40.00)	0.326
Hypertension, n (%)	40 (54.05)	12 (48.00)	0.600
Diabetes mellitus, n (%)	17 (22.97)	10 (40.00)	0.098
Hyperlipidemia, n (%)	30 (40.54)	11 (44.00)	0.655
Smoking, n (%)	31 (41.89)	14 (56.00)	0.221
Laboratory test on admission			
WBC count (10^9/L)	10.19 (8.71, 12.46)	11.90 (9.80, 14.50)	0.034
Neutrophil count (10^9/L)	8.17 (6.34, 9.75)	10.31 (8.10, 12.60)	0.003
Lymphocyte count (10^9/L)	1.52 (1.29, 1.85)	1.00 (0.90, 1.30)	<0.001
N/L ratio	5.25 (4.11, 6.87)	9.69 (7.97, 11.70)	<0.001
Erythrocyte count (10^{12}/L)	4.33±0.84	4.36±0.51	0.915
Platelet count (10^{12}/L)	211 (179, 254)	213 (184, 244)	0.894
High sensitive CRP (mg/L)	3.50 (1.50,10.85)	5.5 (3.50, 11.00)	0.087
ACT (s)	166 (140, 182)	108 (95, 122)	<0.001
CK-MB (U/L)	82 (37, 174)	177 (43, 383)	0.004
Cardiac troponin I (ng/mL)	5.35 (2.1, 16.0)	11.4 (6.5, 30.5)	<0.001
Serum creatinine (μmol/L)	85.84±19.92	77.33±15.35	0.054
eGFR (mL/min/1.73 m^2)	95.56 (86.42, 117.95)	80.00 (69.04, 97.85)	0.011
Serum potassium (mmol/L)	3.90 (3.60, 4.10)	3.85 (3.50, 4.25)	0.762
Triglyceride (mmol/L)	1.34 (0.89, 2.14)	1.24 (0.85, 1.85)	0.784
Total cholesterol (mmol/L)	4.46±1.04	4.30±0.73	0.498
LDL cholesterol (mmol/L)	2.91 (2.59, 3.35)	2.78 (2.38, 3.21)	0.192
HDL cholesterol (mmol/L)	1.03±0.19	1.07±0.25	0.437
HbA1c (%)	6.26±1.30	6.49±1.07	0.458
Glucose (mmol/L)	9.16 (7.52, 11.14)	12.39 (10.56, 16.33)	0.005

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Table 3 continued. Baseline clinical characteristics between the 2 subgroups in the validation database.

Variables	NMO group (n=74)		MO group (n=25)		*P* value
D-dimer (μg/mL)	0.10	(0.07, 0.20)	0.24	(0.11, 0.57)	<0.001
BNP (pg/mL)	70	(30,158)	100	(60,277.5)	0.004
Preprocedural medication					
DAPT, n (%)	69	(93.24)	23	(92.00)	1.000
Statins, n (%)	33	(44.59)	9	(36.00)	0.545
Beta-blocker, n (%)	4	(5.41)	2	(8.00)	0.641
GRACE score	136	(120, 159)	156	(144, 184)	0.001
CRUSADE score	20	(11, 27)	32	(20, 43)	<0.001

Normally distributed continuous data are indicated as mean ± standard deviation; or else they would be reported as median (25^{th} quartile, 75^{th} quartile). Categorical data are shown as numbers and proportions (%). MO and NMO subgroups based on TIMI myocardial perfusion grade results after recanalization. MO subgroup with 0–2 grade and NMO subgroup with 3 grade. ACT – activated clotting time; BMI – body mass index; BNP – brain natriuretic peptide; CAD – coronary artery disease; CK-MB – creatine kinase-MB isozyme; CRP – C-reactive protein; DAPT – dual antiplatelet therapy; DBP – diastolic blood pressure; eGFR – evaluated glomerular filtration rate; HbA1c – Glycosylated hemoglobin A1c; HDL – high density lipoprotein; LDL – low density lipoprotein; SBP – systolic pressure; WBC – white blood cell.

Table 4. Procedural and angiographic features between the 2 subgroups in the validation database.

Variables	NMO group (n=74)		MO group (n=25)		*P* value
Onset to balloon (hours)	3.5	(2.5, 5.0)	6.5	(4.0, 9.3)	0.001
FMC to balloon (hours)	1.5	(1.0, 2.5)	2.0	(1.0, 3.5)	0.108
Myocardial wall, n (%)					
Anterior wall	28	(37.83)	12	(48.00)	0.371
Others	46	(62.17)	13	(52.00)	0.371
Stenosed artery number, n (%)					
1	23	(31.08)	6	(24.00)	0.501
2	25	(33.78)	8	(32.00)	0.870
3	26	(35.14)	11	(44.00)	0.428
Intervention pattern, n (%)					
PCI	66	(89.18)	22	(88.00)	1.000
PTCA	8	(10.81)	3	(12.00)	1.000
Initial TIMI flow, n (%)					
0	42	(56.76)	22	(88.00)	0.005
1	21	(28.38)	3	(12.0)	0.099
2	6	(8.11)	0	(0.00)	0.333
3	5	(6.75)	0	(0.00)	0.326
Initial thrombus score, n (%)					
0–1	4	(5.41)	0	(0.00)	0.569
2	9	(12.16)	0	(0.00)	0.107

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Table 4 continued. Procedural and angiographic features between the 2 subgroups in the validation database.

Variables	NMO group (n=74)		MO group (n=25)		*P* value
3	12	(16.22)	2	(8.00)	0.508
4	14	(18.92)	3	(12.00)	0.549
5	35	(47.29)	20	(80.00)	0.004
Final TIMI flow, n (%)					
0	0	(0.00)	3	(12.00)	0.015
1	0	(0.00)	2	(8.00)	0.062
2	0	(0.00)	11	(44.00)	<0.001
3	74	(100.00)	9	(36.00)	<0.001
IRA-cTFC	26	(22, 28)	40	(33, 60)	<0.001
Stent number per patient, n (%)					
1	59	(88.06)	17	(77.27)	0.165
≥2	8	(11.94)	5	(22.73)	0.165
Stent length (mm)	24	(18, 33)	24	(16, 31)	0.937
Stent diameter (mm)	3.0	(2.75, 3.00)	2.75	(2.50, 3.00)	0.911
Predilation pressure (atm)	14	(12, 16)	14	(12, 16)	0.378
Predilation numbers	2	(1, 3)	2	(1, 3)	0.272
Stent expansion pressure (atm)	14	(14, 16)	14	(12, 16)	0.379
Postdilation pressure (atm)	16	(14, 18)	14	(12, 16)	0.502
Postdilation numbers	0	(0, 2)	1	(0, 2)	0.134
Thrombus aspiration, n (%)	25	(33.78)	7	(28.00)	0.593
Temporary pacemaker, n (%)	0	(0.00)	1	(4.00)	0.253
Collateral circulation, n (%)	13	(18.92)	5	(20.00)	0.771
Contrast media volume (mL)	150	(130, 180)	160	(150, 190)	0.233
Procedural medication, n (%)					
Tirofiban	63	(85.14)	20	(80.00)	0.542
Bivalirudin	15	(20.27)	9	(36.00)	0.113
Anisodamine	14	(18.92)	6	(24.00)	0.584

Normally distributed continuous data are indicated as mean ± standard deviation; or else they would be reported as median (25^{th} quartile, 75^{th} quartile). Categorical data are shown as numbers and proportions (%). MO and NMO subgroups based on TIMI myocardial perfusion grade results after recanalization. MO subgroup with 0–2 grade and NMO subgroup with 3 grade. cTFC – corrected TIMI frame count; FMC – first medical contact; IRA – infarct related artery; PCI – percutaneous coronary intervention; PTCA – percutaneous transluminal coronary angioplasty; TIMI – thrombolysis in myocardial infarction.

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Table 5. Predictors of CMVO by binary logistic regression analysis in the training database.

Variables	CMVO					
	Coefficient	SE	Wald	OR	95% CI	*P* value
Age (years) >65	1.055	0.301	12.286	2.871	1.592–5.179	0.000
Symptom onset to balloon (hours)	0.278	0.048	33.609	1.320	1.202–1.450	0.000
Killip grade	1.461	0.213	47.228	4.312	2.842–6.541	0.000
Admission ACT (seconds)	–0.037	0.007	29.712	0.964	0.951–0.977	0.000
NLR >7.0	1.423	0.315	20.441	4.148	2.239–7.687	0.000
Admission glucose (mmol/L) >12.0	0.893	0.304	8.643	2.441	1.346–4.426	0.003
Constant Term	–6.113	1.215	25.307	0.002		0.000

ACT – activated clotting time; CI – confidence interval; CMVO – coronary microvascular functional and structural obstruction; NLR – neutrophil/lymphocyte ratio; OR – odds ratio; SE – standard error.

Procedural and angiographic features between both subgroups in the training database

The angiographic features in the training database are listed in Table 2. SO-B and FMC-B time of the MO subgroup were apparently delayed compared with that in the NMO subgroup [7.0 (5.0, 9.1) versus 4.5 (3.5, 6.0), $P<0.001$; 2.5 (1.5, 4.8) versus 2.0 (1.2, 3.0), $P=0.007$]. Likewise, initial TIMI blood flow and thrombus score of IRA were different between the 2 subgroups. After the intervention, obvious differences were displayed regarding blood flow perfusion indicators, including TIMI 3 grade proportion (50.39% versus 100%, $P<0.001$) and cTFC [22 (18, 29) versus 36 (37,53), $P<0.001$]. Other angiographic and procedural details, like IRA distribution, intervention type, stent information, medication, and supplementary treatment were comparable for the subgroups (all $P>0.05$).

Baseline clinical and procedural characteristics between both subgroups in the validation database

The statistical analysis of the validation database shared similar conclusions with the training database. The correlative results of baseline information and interventional data are listed in Tables 3 and 4. Compared to their counterparts, members in the MO subgroup were of elderly age (68.36±11.41 years versus 60.20±1.57 years, $P=0.003$), poorer heart function with higher Killip 3 classification proportion (44.00% versus 20.00%, $P<0.001$), elevated risk score and corresponding test indexes (all $P<0.05$). In respect to the angiographic and procedural features, the perfusion intervals (SO-B and FMC-B time) were significantly shorter in the NMO subgroup [6.5 (4.0, 9.3) versus 3.5 (2.5, 5.0), $P=0.001$; 2.0 (1.0, 3.5) versus 1.5 (1.0, 2.5), $P=0.108$]. Moreover, post-procedural TIMI 3 grade percentage and cTFC in the NMO subgroup were superior to those of the MO subgroup [40.00% versus 100%, $P<0.001$; 26 (22, 28) versus 40 (33, 60), $P<0.001$].

Cardiac function

All patients accepted cardiac ultrasound evaluation after the procedure in hospital. In the training database, LVEF of the NMO subgroup was higher than that of the MO subgroup (57.94±4.46 versus 48.33±6.67, $P<0.001$). Similarly, the LVEF value of the NMO subgroup in the validation database was also elevated (57.20±4.70 versus 48.04±9.37, $P<0.001$).

Logistic regression analysis of CMVO

Binary logistic regression analysis was conducted to recognize the CMVO independent risk factors in STEMI patients undergoing a primary catheterization. In accordance with the regression model, the following indicators were highly associated with the occurrence of CMVO: age >65 years (X1), admission Killip classification (X2), SO-B time (X3), baseline ACT level (X4), baseline NLR >7.0 (X5) and glucose value >12.0 mmol/L (X6). Regression formula was established as follows: Logit $P=-7.580+1.055\times X1+1.461\times X2+0.278\times X3-0.734\times X4+1.423\times X5+0.893\times X6$. The predictive rate of the model was calculated to be 86.3%. The result of logistic regression analysis is described in Table 5. Nomogram was plotted on the regression results with R software and relevant packages (Figure 1).

Validation of nomogram model

The C-index of nomogram model built by the training database was 0.925. AUC value, identical to C-index level, was 0.925 [95% confidence interval (CI): 0.900–0.949] as well. After 5-fold cross internal validation, the corresponding AUC values were 0.945, 0.943, 0.898, 0.914, and 0.901 respectively, with the mean AUC value of 0.902. The calibration curve is shown in Figure 2. In the training database, the mean absolute error

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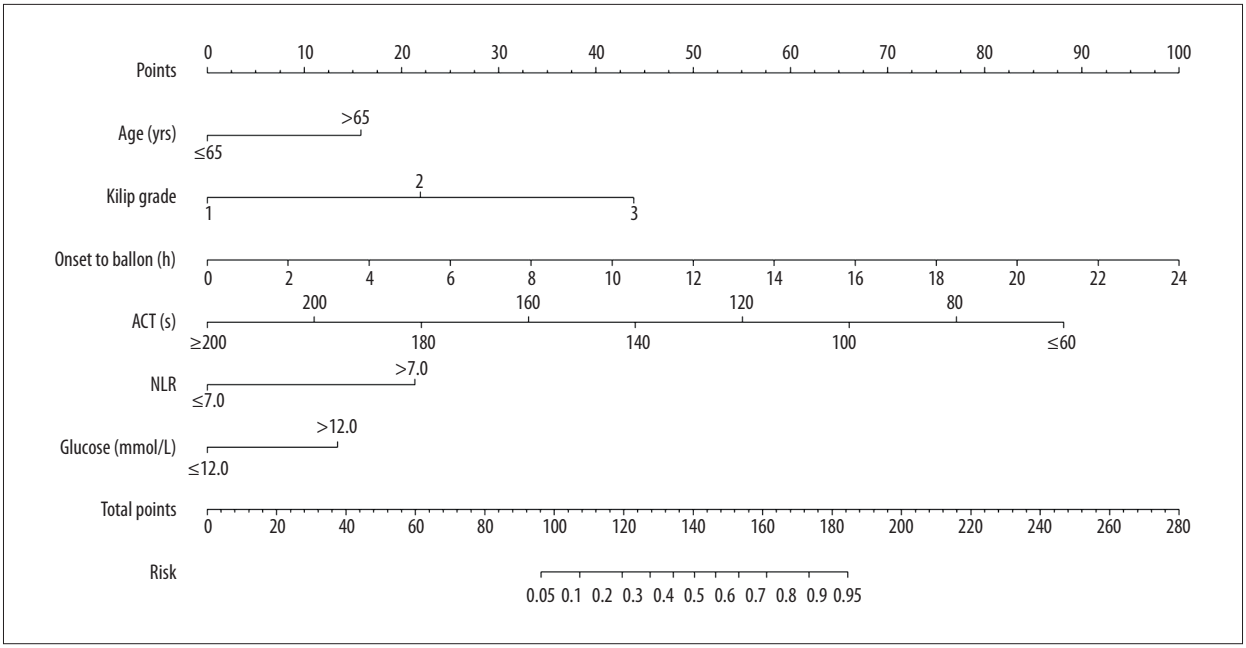

Figure 1. Nomogram of microvascular obstruction risk in patients with ST-segment elevation myocardial infarction (STEMI) undergoing primary percutaneous catheterization. The present nomogram indicates the possible risk prediction of coronary microvascular functional and structural obstruction (CMVO) in patients with STEMI undergoing primary percutaneous catheterization. For clinical use, draw a straight line from the corresponding value of each variable to the top point axis repeatedly. Add the points together, obtaining the total points and the risk probability according to the bottom axis.

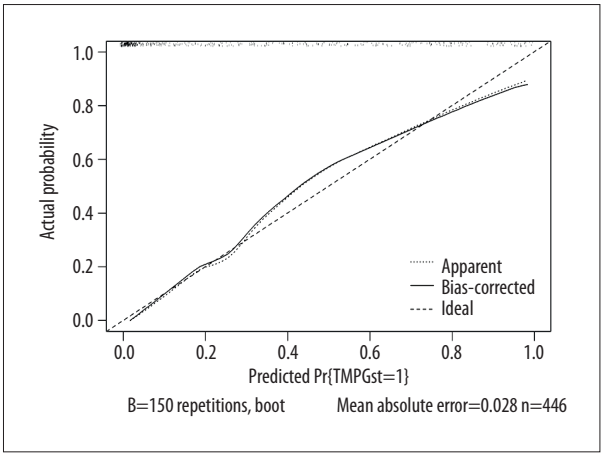

Figure 2. Calibration curve for the coronary microvascular functional and structural obstruction (CMVO) risk model in the training database.

(MAE) between the actual and evaluated possibilities was 0.026. External validation was carried out with validation database information. The correlated AUC was 0.939 (95% CI: 0.894–0.984), sharing the sensitivity of 0.811 and specificity of 0.960.

Discussion

STEMI has become a major public health issue and is among the primary causes of cerebro-cardiovascular deaths worldwide. As for STEMI patients, rapid reperfusion is of great significance in restoring epicardial coronary flow, salvaging jeopardized myocardium, limiting infarction extension and ventricular remodeling. Although considerable advancements have been achieved in therapeutic strategies, there remains room for further exploration and enhancement. Despite IRA repatency, a portion of patients fail to benefit due to insufficient perfusion of the microvasculature, which is termed as CMVO or NRF. As from accumulated literature, impaired myocardial perfusion is closely associated with poorer cardiac function, increasing mortality and worsening prognosis [17,18]. Similarly, in our study, distinct differences in LVEFs during hospitalization were observed between the study subgroups, emphasizing the importance of timely evaluation and recognition of patients at high risk in the early setting.

Note that multiple mechanisms contribute to microvascular obstruction development together, a single element may not be convincing enough in risk prediction and stratification. Therefore, risk scores or models, consisting of various indicators are favored for accurate detection and diagnosis. In this study, potential factors chosen from earlier hypothesis and practical experience have been tested for their possible

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correlations with CMVO from the institute database system. The logistic regression results showed that age, Killip classification, symptom onset to balloon time, initial ACT level, NLR, and admission glucose value were independently responsible for microcirculatory injury in STEMI patients undergoing emergent catheterization.

Among all these factors, CMVO development is most likely driven by prolonged reperfusion time, known as symptom onset to balloon time. Consequently, prompt diagnosis and revascularization are of remarkable importance in preventing vasculature damage, improving prognosis and decreasing the incidence of cardiac events.

With the development of angiographic techniques and device, advanced age is no longer an absolute contraindication for coronary intervention. It is not rare for elderly STEMI patients receiving primary catheterization, particularly when they share the contradiction of thrombolysis, renal failure, or high bleeding risk. However, earlier evidence has proven the hypothesis with the similar conclusion of this study that, CMVO incidence would increase if the patient's age was over 65 years [19,20], possibly owing to preexisting pathophysiological basis, such as severe and diffuse coronary lesions, serious calcification, and endothelial dysfunction [21].

As for myocardial infarction patients, Killip classification acts as a simple and fundamental assessment for myocardial ischemic injury and hemodynamics. Higher Killip grade is recognized as poorer functional capacity and extensively damaged myocardium as well as microvasculature. As De Luca et al. reported, Killip 3 grade is an independent indicator of myocardial perfusion impairment after emergent PCI [22]. Jeong et al. has also suggested that baseline levels of serum BNP, which is commonly used parameter for left ventricular function, is linked to NFR [23]. Nevertheless, we failed to verify this assumption, considering that serum BNP level could not elevate in the early phase. Moreover, patients with Killip grade >4 were excluded, taking into account the fact that those cardiac shock candidates required additional rescue support and adjuvant treatment, leading to unbalanced comparisons between the subgroups.

Intracoronary thrombus burden is directly related to microvascular perfusion in myocardial infarction patients. Apart from the thrombus burden score, the interactions of thrombotic or coagulant laboratory parameters with CMVO were worthy of consideration. Compared with activated partial thromboplastin time and D-dimer, ACT is the most frequently utilized point of care test in monitoring whole blood coagulation and anticoagulant effects of heparin during a coronary intervention procedure, sharing advantages of shorter testing time, smaller blood sample size, and less sample degradation [24]. Levels of initial ACT prior to primary catheterization were assessed to predict IRA patency and coronary coagulating effects in our center conventionally, but without definite reference cutoff values and supporting evidence. Additionally, the relationship of this bedside index with patients' prognosis is controversial. Tolleson et al. reported that for patients receiving contemporary intervention, an ACT of 200 seconds to 250 seconds was efficient to reduce ischemic events, while bleeding events increased with ACT levels [25]. Participants in the EASY trial were administered with abciximab and UFH to determine the relationship between the final ACT value in emergent PCI and outcomes, suggesting that with abciximab treatment, a higher final ACT value was beneficial in reducing post procedure myocardial injury without increasing bleeding [26]. The FUTURA/OASIS-8 trial conducted by Ducrocq et al. pointed out that peak ACT ≤300 seconds values of NSTE-ACS patients in PCI procedure are at high thrombotic risk with no clear hemorrhagic threat [27]. Rajpurohit et al. studied and reviewed 12 055 candidates who underwent conventional PCI, proposing that ACT values before intervention was not independently related to short- and long-period survival [28]. In consequence, for STEMI members, whether baseline ACT values are independently associated with ischemic, hemorrhagic risks and cardiac events, is worth further investigation. In this study, based on multivariate logistic regression result, we found that the initial ACT prior to the procedure had a close relationship with microvascular obstruction occurrence, with the possible cutoff values listed in the nomogram. Despite its advantages over other laboratory indexes, ACT value is influenced by various conditions (hypothermia, antiplatelet treatment, and hemodilution). Whereas this study was performed in a single center, the range of ACT values might be different in other centers due to different personnel and testing device.

Inflammatory activation plays an essential role during coronary atherosclerosis, along with microvascular dysfunction. With the growing understanding of the pathophysiological mechanisms, neutrophil-platelets are thought to be activated to exaggerate inflammatory cascade reaction by releasing mediators, radical oxygen, and to aggregate to block the coronary lumen, deteriorating microvascular perfusion after restoring the blood flow of the culprit vessel. Among all the routine blood indexes, NLR has been confirmed as the most significantly independent parameter of CMVO [29,30], which is consistent with the present study findings.

In a myocardial infarction setting, the glucose level rises as a result of sympathetic nerve activation and increase in plasma catecholamine. It has been implied that, regardless of diabetes history, admission with hyperglycemia has a close connection with mortality [31]. Yildiz et al. reported that glucose on admission was independent of high TFC, regardless of diabetes history [32]. Recently, a study revealed that hyperglycemia

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affects coronary thrombus burden and inflammatory status, resulting in worse prognosis in patients undergoing interventional treatment [33]. As seen in the present study, we obtained comparable results, supporting that hyperglycemia on admission directly correlated to CMVO among the STEMI patients undergoing primary recanalization.

Limited by sample size and evaluation conditions, there were some statistically different indicators between the 2 subgroups, including hs-CRP, eGFR, D-dimer, diabetes history, and collateral circulation, which were shown not to be responsible for CMVO independently. Additionally, some predictors with obvious significance were not entered into the regression analysis owing for several reasons. First, the scores that incorporated a series of clinical elements, like GRACE, CRUSADE, SYNTAX, and CHA2DS2-VASc scores, are presumably not suitable and practical in constructing new models, considering that they might influence the weight of risk variables, regardless of their correlation with NRF incidence [34,35]. Second, given the fact that cardiac biomarker values were strongly correlated with ischemic time and affected by a range of factors (infarct size, collateral circulation, and several other conditions) [10], initial CK-MB and cTnI were excluded. Furthermore, in spite of the confirmed independence of microvascular obstruction, initial coronary thrombus burden was eliminated due to its multicollinearity with ACT values in regression analysis.

In addition to the potential factors, previous models or estimating scores of NFR have been recently created. Dogan et al. reported that hyperglycemia, prolonged ischemic time, and low neutrophil count were attributed to the development of the risk model [36]. Bayramoglu et al. built a predictive model covering age, LVEF value, SYNTAX score, stent length, thrombus burden score, Killip classification and reperfusion time [37]. The retrospective study conducted by Wang et al. showed that age, pre-PCI thrombus score, pain to PCI time, Killip class, neutrophil level, admission glucose, and collateral circulation could be adopted to establish a no reflow model [38]. Regardless of those results, the existing models were usually displayed as counting scores.

To our knowledge, this is the first study to present a nomogram model as a novel and valid representation form to identify the possibility of CMVO. Unlike the former systems, nomogram is a specific and graphical tool that integrates quantified independent predictors with corresponding risk or prognosis possibility according to the individual condition [39,40]. Markedly, C-index or AUC value over 0.75 is recognized as a reliable validation. The present nomogram performed well in calculating the risk probability, and its validity was tested by internal and external validation and the calibration curve, highlighting the predictive accuracy of the established model and nomogram. The comprehensive nomogram might be reasonable and sensible in facilitating the physicians assessing the potential CMVO risk in the early stage of STEMI, offering therapeutic and mechanical guidance in clinical practice.

This study exhibits the following limitations: first, this retrospective trial was conducted from one single institutional dataset with a relatively small sample scale, hence C-index and AUC for internal as well as external validation might be higher. Therefore, multicenter prospective validations of this risk model are required to confirm this. Second, hyperglycemia impairs the microvascular integrity in complex mechanisms, and we did not investigate the possible correlations of glucose intolerance/insulin resistance indices and CMVO due to the lack of original data. In future studies, glucose tolerance test, glycosylated hemoglobin, free fatty acids, post prandial insulin concentrations, and other relative quantifications need to be addressed. Furthermore, the level of ACT is influenced by a series of factors, and the reference range in the present nomogram might be different depending on the testing equipment and surroundings.

Conclusions

In conclusion, the nomogram model based on 6 variables, including age, symptom onset to balloon time, Killip classification, admission ACT, neutrophil/lymphocyte ratio, and glucose value, could accurately predict coronary microvascular obstruction risk for STEMI patients undergoing primary percutaneous catheterization.

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Conflict of interest

None.

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