A Scoring System to Predict No-Reflow Phenomenon in Elective Percutaneous Coronary Intervention: The RECOVER Score

Han Xu, MD[1], Chenxi Song, MD[1], Bo Xu, MBBS, Dong Yin, MD*, Chenggang Zhu, MD, Lei Feng, MD, Dong Zhang, MD, Guofeng Gao, MD, Weihua Song, MD, Shubin Qiao, MD, Yang Wang, MSc, Sidong Li, MSc, Yuejin Yang, MD, and Kefei Dou, MD*

From the Fuwai Hospital Chinese Academy of Medical Sciences, National Center for Cardiovascular Diseases, Xicheng District, Beijing, China.

Abstract: The RECOVER score system aimed to stratify the risk of no-reflow phenomenon in patients undergoing elective percutaneous coronary intervention. A total of 3967 patients with 5340 lesions were used for the construction and validating of the risk model and score system. In multivariable analyses, 3 variables were independently associated with the risk of no-reflow phenomenon (model C-statistic=0.746 (95% confidence interval [CI]: 0.690 to 0.803) with good calibration). No-reflow phenomenon rates in both construction and validation cohort increased significantly across different risk groups. The RECOVER score can help identify patients at risk for phenomenon during percutaneous coronary intervention. (Curr Probl Cardiol 2021;46:100676.)

[1] The first two authors (HX and CS) contributed equally to this work.
Conflicts of interest: All of the authors have no relevant disclosures related to this manuscript.
Curr Probl Cardiol 2021;46:100676
0146-2806/$ – see front matter
https://doi.org/10.1016/j.cpcardiol.2020.100676

Introduction

Percutaneous coronary intervention (PCI) procedure is one of the most common procedures in the cardiovascular field. Millions of patients underwent PCI every year.[1] No-reflow phenomenon is defined as inadequate myocardial perfusion through a given segment of the coronary circulation without angiographic evidence of mechanical vessel obstruction.[2] No-reflow phenomenon during PCI could develop periprocedural myocardial infarction (MI) and in-hospital major adverse cardiac events (MACE), and they may present with progressive left ventricular dilatation and congestive heart failure after PCI. Depending on the diagnostic criteria used and target population, no-reflow phenomenon occurred in 0.6%-25% patients who underwent PCI.[3-6]

Previous researches have been focusing on the acute MI patients who are more likely to develop no-reflow phenomenon than stable angina patients.[7,8] No-reflow during elective PCI was thought to be hardly predictable.[9] Despite the rate of no-reflow phenomenon is relatively low, it still affects a large number of patients since millions of PCI procedure is performed every year. In the past decades, although PCI has been associated with improved clinical outcomes, no-reflow phenomenon has remained a considerable problem. Identifying predictors of no-reflow risk may help cardiologists and interventionalists adopt preventive measure to lower no-reflow rate and improve long-term outcome. Accordingly, this study was designed to investigate the predictors and generate a novel risk prediction score system, *the RECOVER (no-REflow of COranary risk eValuation in Elective inteRvention)* score system to predict the risk of no-reflow during elective PCI.

Methods

Study Population

From January 2013 to April 2013, a cohort of 3302 consecutive patients underwent PCI at Fuwai hospital in Beijing, China. In addition, 1320 consecutive patients who had underwent PCI at Fuwai hospital between January 2017 and February 2017 were included as the external validation cohort of the scoring system. For this study, the inclusion criteria were as follows[1]: patients who underwent successful PCI without angiographic evidence of mechanical vessel occlusion[2] myocardial blush grade could be assessed in the core laboratory. Patients who underwent emergency PCI were excluded from this study. A total of 2647 patients

(3497 elective lesions) who met all the inclusion criteria and had no exclusion criteria were included as the derivation group and a total of 1320 patients (1843 elective lesions) as the validation group in this single-center retrospective analysis (Fig 1).

The study complied with the Declaration of Helsinki. The study protocol was approved by the ethics committee of Fuwai hospital at each site. All patients provided written informed consent.

Procedure and Periprocedural Medications

In all cases, the interventional strategy and instrumentation used were at the discretion of the interventional cardiologists. Coronary angioplasty was performed in the conventional manner, and coronary stents or other procedures/devices were used only when required. The administration of periprocedural antiplatelet and antithrombotic medications was based on the operator's discretion and current guidelines. For patients who have taken clopidogrel and aspirin within 7 days, administration of 300 mg clopidogrel and 300 mg aspirin as loading doses within 24 hours and before the procedure was mandatory. Lifelong aspirin (100 mg/day) was prescribed to all patients. At least 12 months of clopidogrel (75 mg/day) was recommended to all patients.

Data collection and definition

Clinical data were obtained through a review of the medical records. All baseline and procedural cineangiograms were reviewed and analyzed by an independent core laboratory. Blood samples were routinely obtained from all of the patients before and after the procedure. Echocardiographic images were recorded before PCI, and then ejection fraction was calculated using the Teichholtz method. Coronary angiography findings including lesion location, baseline thrombolysis in myocardial infarction (TIMI) flow grade, SYNTAX score, the diameter and length of the target lesion were recorded. Uncomplete PCI was defined as residual stenosis distal to the target vessels>80%. Anterograde coronary flow in the target vessel was graded according to the TIMI scale.[10] The effectiveness of myocardial perfusion was estimated by myocardial blush grade (MBG).[11] No-reflow phenomenon was defined as TIMI flow grade <3 or MBG <2 without angiographic evidence of mechanical vessel obstruction.[4] The SCAI-defined periprocedural MI criteria is used as the diagnostic criteria in this study: A biomarker elevation of CK-MB to $\geq 10 \times$ ULN or cTn (I or T) to $\geq 70 \times$ ULN or by CK-MB to $\geq 5 \times$ ULN or cTn to

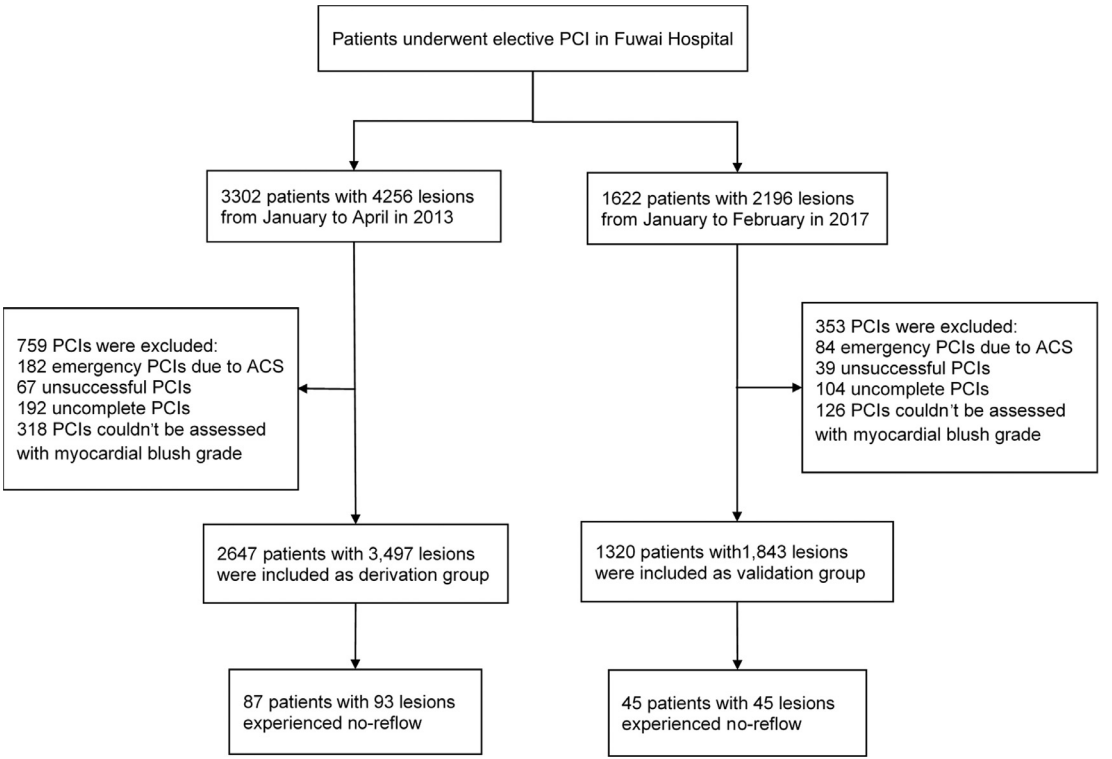

FIG. 1. Trial profile. From January 2013 to April 2013, a total of 2647 eligible patients with 3497 lesions were included in this study as derivation group. In addition, a cohort of 1320 patients with 1843 lesions from January 2017 to February 2017 were included as validation group. No-reflow occurred in 87 (3.29%) in derivation patients and in 45 (3.41%) in validation patients. Patients were divided into normal reflow group and no-reflow group.

≥35 × ULN plus the development of new pathologic Q-waves in ≥2 contiguous leads or new persistent LBBB.[12]

Follow-up

Follow up data at 24 months were obtained during outpatient clinic visit or by phone. We compared the rates of MACE (including all-cause death, MI, and target vessel revascularization) at 2 years in patients with and without no-reflow. All end points were defined according to the Academic Research Consortium (ARC) definitions.[13]

Statistical Methods and Score Determination

The data analysis was conducted using SAS 9.4 system (SAS Institute, Cary, NC, USA). Data are presented as median (interquartile range), mean ± SD, or n (%). The distribution of the data was analyzed with one-sample Kolmogorov-Smirnov test. Continuous data were compared with Kruskal-Wallis rank sum test or 2-tailed unpaired *t* test. Categorical variables were compared using Chi-square or Fisher's exact tests and summarized as percentages. In consideration of vessels from the same individuals are correlated, general estimated equation analysis was performed to identify independent predictor of no-reflow. Kaplan-Meier's curves for MACE were compared using log-rank testing. All *P* values were 2-tailed, and a *P* value of <0.05 was considered statistically significant.

The multivariable risk score was named the RECOVER score. The RECOVER score was created by fitting clinical, angiographic, and procedural variables into a general estimated equation analysis for prediction of no-reflow risk. To avoid excluding variables potentially correlated with the outcome, univariate selection was performed with the entry criteria set at $P < 0.1$. The multivariable model was then built by stepwise variable selection with an entry and exit criterion of 0.05.

Eight potential covariates were initially considered for inclusion in the generalized estimated equation multivariable model, including current smoker, baseline creatinine, ejection fraction, systolic pressure, location of target vessel, TIMI flow grade, SYNTAX score, the length of the lesion. The score was then derived by attributing integer numbers to the variables retained in the multivariable model. The variable with the smallest estimated coefficient was given 1 point and was considered the reference variable which is a 10% decrease in EF. The scores of the other variables were determined by dividing their estimated coefficients by the

coefficient of the reference variable.[14] Multicollinearity between variables was assessed using the variance inflation factor.Discrimination and calibration were determined by the C-statistic and the Hosmer-Lemeshow (HL) goodness-of-fit test, respectively.[15,16] The scoring system was then used to define two risk groups (low-risk and high-risk groups). The discrimination and calibration ability of the RECOVER score were tested in an independent cohort.

Results

Patient, Lesion, and Procedural Characteristics

No-reflow phenomenon was observed in 87(3.29%) of 2647 patients (93 lesions) in the derivation group and in 45 (3.41%) of 1320 patients (45 lesions) in the validation group. The overall patient characteristics are shown in Table 1. All baseline characteristics except current smoker, creatinine before PCI and basic left ventricular ejection fraction (LVEF) were balanced between the 2 groups.

Lesion and procedural characteristics are presented in Table 2. Among lesion and procedural characteristics, the location of the target vessel, TIMI flow grade, SYNTAX score, the length of lesion differed significantly between the 2 study groups.

Predictors of No-reflow

Some significant parameters in the univariate analysis remained significant in the generalized estimated equation multivariable model (shown in Table 3). These independent predictors included the location of the target lesion (LM or left anterior descending artery [LAD] disease; odds ratio [OR] = 2.291, 95% confidence interval [CI]: 1.155-4.545, $P = 0.018$, RCA disease; OR = 2.580, 95% CI: 1.254-5.310, $P = 0.010$), EF (1% increase; [OR] = 0.948, 95% CI: 0.925-0.971, $P < 0.001$), baseline TIMI flow (TIMI flow grade ≤ 2; [OR] = 4.691, 95% confidence interval [CI]: 3.055-7.203,$P < 0.001$). These independent predictors were then used to establish a clinical scoring system for estimating no-reflow risk.

No significant correlation or multicollinearity between the variables in the scoring model was detected, as shown by the variance inflation factor. The C-statistic for the multivariate model was 0.746 (95% CI: 0.690-0.803; Fig 2), and excellent calibration was observed (HL, $P = 0.15$).

Scores were attributed to each variable according to their estimated coefficients from derivation dataset (shown in Table 3). The risks of no-

TABLE 1. Baseline characteristics

	Derivation group			Validation group		
	Normal flow (n = 2560)	No reflow (n = 87)	*P*	Normal flow n = (1275)	No reflow n = (45)	*P*
Age, yrs	59.1 ± 9.9	59.97 ± 10.3	0.43	58.8 ± 10.1	57.62 ± 8.8	0.44
Male	78.3%	83.9%	0.19	76.5%	75.6%	0.88
Weight, kg	74.0 ± 11.1	75.0 ± 9.9	0.40	78.2 ± 9.1	77.1 ± 8.8	0.42
BMI, kg/㎡	26.0 ± 3.1	26.1 ± 3.0	0.63	27.5 ± 2.6	26.1 ± 3.0	0.54
Hypertension	68.2%	71.3%	0.54	62.6%	60.0%	0.59
Diabetes mellitus	32.1%	40.2%	0.12	32.6%	33.3%	0.66
Hyperlipidemia	74.4%	70.1%	0.37	75.6%	88.9%	0.07
Current smoker	56.3%	66.7%	0.08	33.6%	35.6%	0.06
Previous CABG	7.8%	9.2%	0.64	0.9%	0%	1.00
Previous PCI	48.8%	43.7%	0.35	27.0%	24.4%	0.60
Previous peripheral vascular disease	9.3%	9.2%	0.96	6.4%	2.2%	0.52
Previous stroke	11.0%	10.3%	0.85	12.5%	26.7%	0.01
Creatinine, μmol/L	75.3 ± 15.4	79.6 ± 18.1	0.03	79.8 ± 17.0	78.2 ± 14.6	0.53
GFR, ml/min	98.1 ± 27.4	95.2 ± 27.8	0.34	94.1 ± 28.9	96.0 ± 21.8	0.56
LVEF, %	63.6 ± 6.8	59.7 ± 9.1	<0.001	62.22 ± 5.5	53.07 ± 7.4	<0.001
SBP, mmHg	127.2 ± 17.0	123.9 ± 19.8	0.26	131.5 ± 17.8	125.2 ± 20.3	0.05
DBP, mmHg	77.31 ± 11.3	75.12 ± 13.1	0.10	79.72 ± 11.6	82.00 ± 14.1	0.29
ESR, mm/h	6 (3-12)	6 (3-11)	0.42	7 (3-13)	7 (3-10)	0.97

(*continued on next page*)

TABLE 1. (*continued*)

	Derivation group			Validation group		
	Normal flow (n = 2560)	No reflow (n = 87)	*P*	Normal flow n = (1275)	No reflow n = (45)	*P*
Hemoglobin, mg/dL	143.3 ± 14.9	142.9 ± 15.7	0.78	142.3 ± 13.7	144.3 ± 14.2	0.69
Blood platelet counts, mmol/L	198.5 ± 53.6	197.9 ± 45.2	0.90	233.7 ± 64.5	248.2 ± 54.7	0.14
Platelet distribution width, %	12.5 ± 2.0	12.7 ± 2.1	0.46	12.4 ± 2.1	11.9 ± 1.9	0.12
White blood count, 10^9/L	6.6 ± 1.6	6.9 ± 1.5	0.10	6.80 ± 1.9	7.47 ± 2.5	0.08
Glycated hemoglobin, %	6.7 ± 1.2	6.9 ± 1.5	0.23	6.39 ± 1.2	6.2 ± 0.9	0.13
hs-CRP, mg/L	1.5 (0.8-3.0)	1.8 (0.8-4.1)	0.12	1.7 (0.8-4.4)	1.4 (0.9-3.7)	0.44
Total cholesterol, mmol/L	4.2 ± 1.1	4.3 ± 1.1	0.18	4.0 ± 1.0	4.2 ± 1.1	0.23
LDL-C, mmol/L	2.4 ± 0.9	2.6 ± 1.0	0.17	2.46 ± 0.9	2.7 ± 0.9	0.15
CK-MB, IU/L	10 (8;13)	12(9;13)	0.17	11 (9;14)	10 (8;13)	0.05

Abbreviations: BMI, Body mass index; CABG, coronary artery bypass grafting; DBP, diastolic blood pressure; ESR, erythrocyte sedimentation rate; GFR, glomerular filtration rate; hs-CRP, hypersensitive c-reactive protein; LDL-C, low-density lipoprotein cholesterol; LVEF, left ventricular ejection fraction; SBP, systolic blood pressure.

Values are mean ± SD or (%) or median (interquartile range).

TABLE 2. Lesion and procedural characteristics

	Derivation group no. (%)			Validation group no. (%)		
	Normal reflow (n = 3404)	No-reflow (n = 93)	*P*	Normal reflow (n = 1798)	No-reflow (n = 45)	*P*
Target vessel			<0.001			0.02
LM&LAD	42.5%	44.1%		46.5%	68.9%	
LCX	23.8%	9.7%		20.4%	8.9%	
RCA	32.5%	43.0%		33.0%	22.2%	
SVG	1.1%	3.2%		0.1%	0%	
Baseline TIMI flow grade ≤2	24.2%	62.4%	<0.001	18.4%	55.6%	<0.001
Initial SYNTAX score	9.0 (5-14.5)	11.0 (6.0-19.5)	.02	11.5 (7-18)	10.0 (7-16)	0.77
Reference diameter, mm	3.0 (2.70-3.50)	3.0 (2.70-3.50)	0.50	3.0 (2.5-3.5)	3.5 (3-4)	0.03
Target lesion length, mm	20(14-31)	26(17-39)	0.01	23.0(15-34)	26(20-41)	0.35
Ostial lesion	14.5%	18.2%	0.30	11.5%	4.4%	0.10
Bifurcation lesion	36.5%	33.3%	0.58	37.0%	53.3%	0.03
Transfemoral route PCI	10.9%	16.1%	0.13	5.1%	6.7%	0.59
Pretreatment of target lesion	91.8%	92.5%	0.81	90.9%	88.9%	0.60

Abbreviations: LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; RCA, right coronary artery; TIMI, thrombolysis in myocardial infarction.

Values are mean ± SD or (%) or median (interquartile range).

TABLE 3. Independent predictors and scoring system

Risk factor	OR	95% CI	*P*	Score
Ejection fraction (%)	0.948	0.924-0.971	<0.001	
<40				4
40-49				3
≥50				0
Location of target vessel				
LAD&LM	2.291	1.155-4.545	0.018	2
RCA	2.580	1.253-5.310	0.01	2
Saphenous vein bypass graft	3.520	0.929-13.329	0.064	2
LCX				0
Initial TIMI flow ≤2	4.691	3.055-7.203	<0.001	

Abbreviations: CI, confidence interval; OR, odds ratio.

reflow associated with each point are presented in the Table 4. The C-statistic for the risk score was 0.726 (95% CI: 0.673-0.780) which was only slightly worse than that of the original model. There is no significant difference in the C-statistic between the model and the RECOVER score (0.726 vs 0.746, $P = 0.07$).

The RECOVER score ranges from 0 to 9. The interquartile range and the frequency distribution are shown in Table 5. As shown in the table, no-reflow rates in the cohort across the quartiles of RECOVER score were as follows: 0.96% in quartile I (RECOVER score: 0), 1.32% in quartile II (RECOVER score: 2), 1.58% in quartile III (RECOVER score: 3-4), 7.54% in quartile IV (RECOVER score: 5-9; $P < 0.001$). The odds of no-reflow phenomenon were 1.348 (95%CI: 0.568-3.224, $P = 0.502$) for quartile II vs quartile I, 1.710 (95%CI: 0.465-6.283, $P = 0.419$) for quartile III vs quartile I, 8.166 (95%CI: 3.603-18.509, $P < 0.001$) for quartile IV vs quartile I. No-reflow rates were not significant different between quartile I, quartile II, and quartile III. Therefore, quartile I,II, and III were defined as the low-risk group and quartile IV was defined as the high-risk group patients were divided into high-risk group(score: ≥5) and low-risk group(score: 0-4) according to the quartile of the score (Table 5). The Youden index also revealed that the optimal threshold score for predicting no-reflow was ≥5, with a 63.4% sensitivity and 78.8% specificity. The no-reflow rate was significantly higher in the high-risk group than low-risk group (7.54% vs 1.25%, $P < 0.001$).

For the 1843 lesions included in the external validation cohort, RECOVER score also showed a good prognostic accuracy with a C-statistic of 0.732 (95% CI: 0.657-0.807; Fig 3), the HL $P = 0.143$. The no-

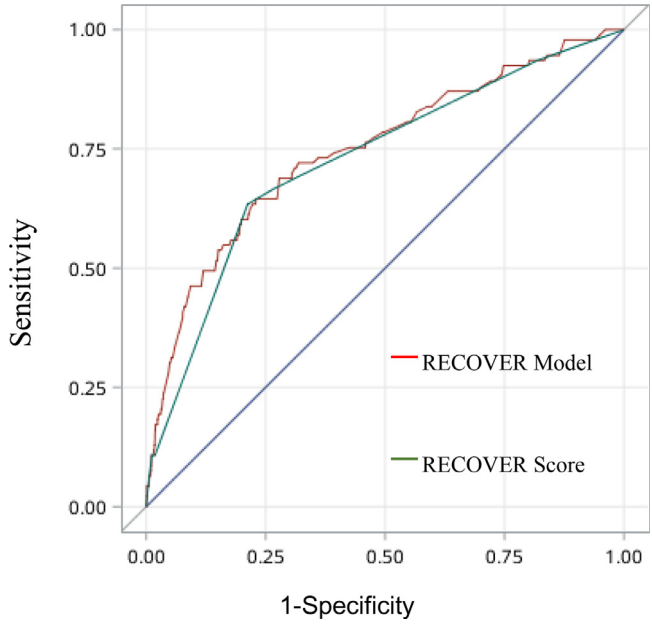

FIG 2. ROC curve of GEE model and RECOVER score. The area under the curve (AUC) of the GEE model: 0.746 (95% CI: 0.690-0.803). The area under the curve (AUC) of the RECOVER score: 0.726 (95% CI: 0.673-0.780). There is no significant difference in the AUC between the GEE model and the RECOVER score ($P = 0.07$).

reflow rate was significantly higher in the high-risk group than the low-risk group. (7.93% vs 1.25%, $P < 0.001$).

Periprocedural Results and MACE During Follow-up

The periprocedural results which includes TIMI flow after PCI, MBG after PCI and periprocedural myocardial infarction (PMI) are shown in

Table 4. Risks associated with points

Point	Estimate of risk
0	0.00643
2	0.01601
3	0.02516
4	0.03933
5	0.06097
6	0.09338
7	0.14042
8	0.20579
9	0.29128

TABLE 5. Incidence of no-reflow across quartiles

	Quartile I	Quartile II	Quartile III	Quartile IV	*P*
Score range	0	2	3-4	5-9	
No-reflow rate in Derivation dataset (n = 3497)	6/624 (0.96%)	25/1901 (1.32%)	3/190 (1.58%)	59/782 (7.54%)	<0.001
No-reflow rate in Validation dataset (n = 1843)	2/307 (0.65%)	16/1148 (1.39%)	1/60 (1.67%)	26/328 (7.93%)	<0.001

Table 6. Trend analysis revealed no-reflow group have a lower classification of TIMI flow grade, a lower MBG and a higher rate of periprocedural MI compared with normal-flow group. Kaplan-Meier analysis showed that the rates of all-cause death, MI, target vessel revascularization, MACE were higher in no-reflow group compared with normal-reflow group (Fig 4).

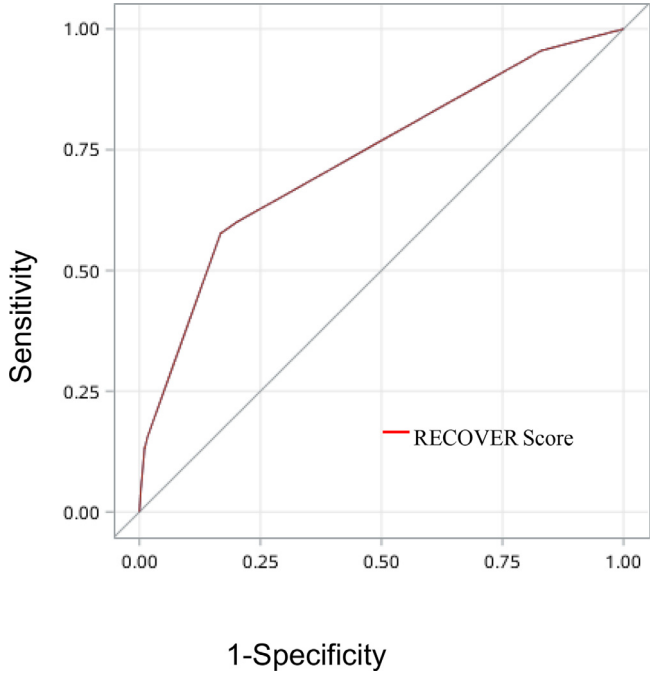

FIG 3. ROC curve of RECOVER score in validation population. The area under the curve (AUC) of the RECOVER score: 0.732 (95% CI: 0.657-0.807).

TABLE 6. TIMI flow, MBG. and PMI after procedure

		Normal flow (N = 3404)	No-reflow (N = 93)	*P*
TIMI flow after procedure				<0.001
	3	3404 (100%)	32 (34.4%)	
	2	0 (0%)	44 (47.3%)	
	0/1	0 (0%)	17 (18.3)	
MBG after procedure				<0.001
	3	2972 (87.3%)	0 (0%)	
	2	432 (12.7%)	4 (4.3%)	
0/1	0 (0%)	89 (95.7%)		
PMI	84 (2.5%)	18 (19.3%)		<0.001

Abbreviations: MBG, myocardial blush grade; PMI, periprocedural myocardial infarction; TIMI, thrombolysis in myocardial infarction.

Discussion

Major Findings

The major findings of this study are as follows[1]: TIMI flow before PCI, location of the target lesion, EF were independent predictors of no-reflow phenomenon during elective PCI[2]; a novel no-reflow risk stratification score system (the RECOVER score) for elective PCI was developed: based on RECOVER score, patients in high-risk group had a more than 6-time higher risk of no-reflow than patients in low-risk group.

Strength of the Current Study

Compared with previous studies,[6,7,11,17-22] the strengths of our study are the following[1]: previous studies have focused on the no-reflow phenomenon in emergency PCI patients. To the best of our knowledge, it is the first large-scale study regarding no-reflow phenomenon in the context of elective PCI.[2] Currently, angiography is the most common and valuable method for detecting no-reflow. TIMI flow grade after the procedure is traditionally used to diagnose no-reflow. However, TIMI flow grade only reflects the velocity of the blood flow, but not the information regarding myocardium reperfusion. In the present study, we defined no-reflow using the TIMI flow grade combined with MBG grade, which is an effective and clinically feasible approach for assessing myocardial reperfusion after PCI.[3] We have established the RECOVER score system as a risk stratification tool for no-reflow during elective PCI. Patients in the high-risk group had a more than six times higher risk of no-reflow than that of the low-risk group. The no reflow score was able to

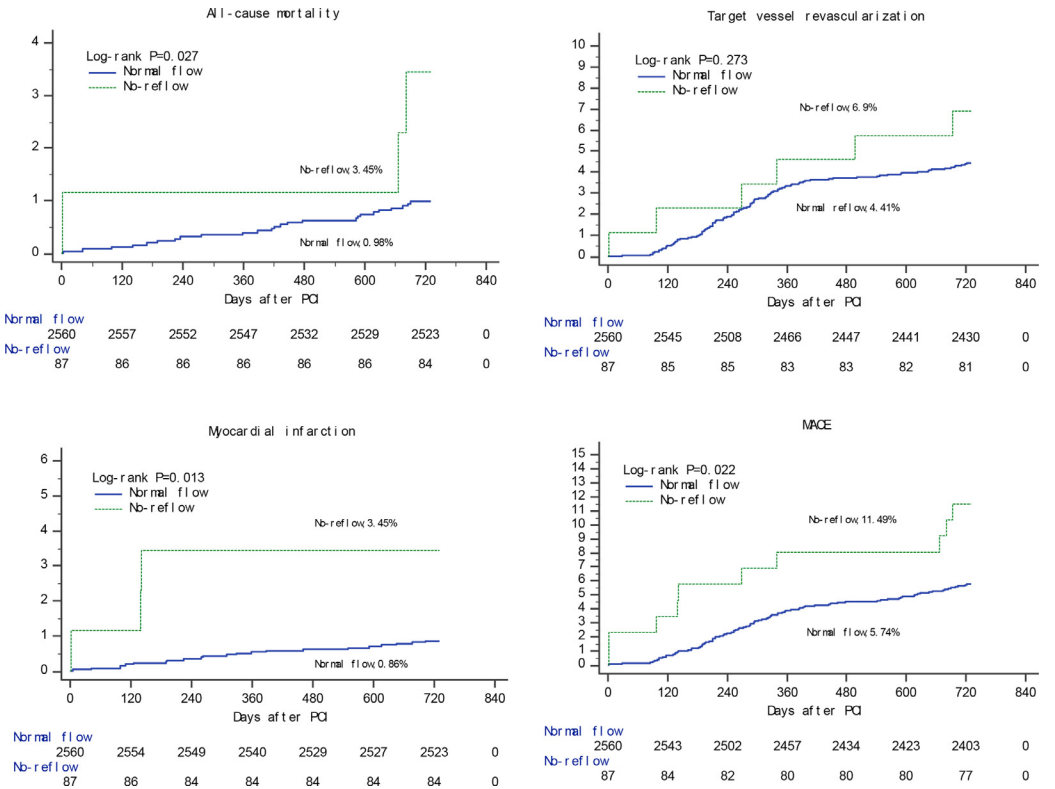

Fig 4. Probability of end points at 2 yrs. Kaplan-Meier's survival curves show the rates of all-cause death, myocardial infarction, target vessel revascularization and MACE in patients with and without no-reflow. *P* values were calculated by the log-rank test.

accurately predict the risk of no reflow in patients undergoing coronary intervention with good discrimination and calibration in both derivation and validation datasets.[4] The RECOVER score system contains only 3 variables and is easy to calculate.

Predictors and Mechanisms of No-reflow

No-flow occurs in 1 of 30 patients undergoing elective PCI, which is even higher in the high-risk group according to the present study. The no-reflow phenomenon is more common in patients with acute coronary syndrome compared with those with stable angina, however, the harm caused by the phenomenon in patients undergoing elective PCI could not be ignored in consideration of the large number of elective PCI procedures. Results of the most previous studies revealed that the pathophysiology of no-reflow consisted of ischemic injury, reperfusion injury, endothelial injury, infarct size, and distal embolization. The emergency PCI is more likely to be associated with reperfusion injury, thrombus burden and inflammation response compared with elective PCI.

In the present study, three parameters were found to predict the development of no-reflow in patients undergoing elective PCI. Consistent with previous studies,[7,17,18,20,22] low EF and TIMI flow $\leq$2 before PCI have been identified as risk factor for no-reflow in this study. The pathogenesis of no reflow is complex and multifactorial. The major mechanisms underlying this phenomenon is the distal coronary embolization of plaque components. Mechanical obstruction of microvasculature may be accompanied by the inflammatory vascular response that leads to vascular spasm.[4,23] Two putative mechanisms have been proposed to explain more no-reflow happened in patients with TIMI flow less than 3 before PCI than those with TIMI flow grade of 3. First, the degree of plaque burden is closely related to TIMI flow grade before PCI. It is confirmed that the lipid content from plaques as assessed by the intravascular image techniques are directly associated with no-reflow phenomenon after PCI. The presence of pathologically vulnerable plaques was reported to be related to low preprocedural TIMI flow grade. Large lipid-rich plaque is more likely to rupture and produce more microthrombus during angioplasty.[19,24,25] Second, TIMI flow grade less than 3 before procedure indicates the preexisting microvascular circulation damage and dysfunction before PCI. At the endothelial level the microcirculation is obstructed by the ischemic injury. A proportion of our study patients suffered from chronic total occlusion of the coronary artery. The long-existed ischemia may cause endothelial cell necrosis which leads to the loss of vascular integrity, vascular compression and the

obstruction in the microvessel lumen. Although the final coronary blood flow is restored by the PCI, the myocardium perfusion may not be adequate in these patients.[26,27]

Previous studies indicated that the incidence of no-reflow was higher in patients with poor cardiac function.[7,17,20,28] Ejection fraction before the procedure reflects the cardiac function which is an independent predictor in the development of no-reflow. The microvascular perfusion of the patients with decreased LVEF could be damaged before PCI and may not recover after the procedure. Although the blood flow is restored after the PCI, the microcirculation may not be recovered. This may explain part of the patients with normal blood velocity have inadequate myocardial perfusion after PCI. Patients with lower ejection infarction have increased left ventricular end-diastolic pressure, and decreased coronary perfusion pressure, leading to suboptimal coronary flow.[7,17,20,28] The patients with heart failure may have different levels of endothelial dysfunction. Reduced bioavailability of NO plays an important role in endothelial dysfunction and may lead to inadequate blood flow despite the patency of the target vessel. In our study, the risk of no-reflow increased significantly with the decrease of LVEF value.

Some researchers have proposed that the length and diameter of the lesions are predictors of no-reflow. In the univariate analysis of the current study, the average lesion length in no-reflow patients is greater than that in the normal-flow patients in the derivation cohort and the average lesion diameter in the no-reflow cohort is larger than that in the normal-flow patients in the validation cohort. The length and diameter of the lesion as well as the initial TIMI flow could reflect the plaque burden. More precise imaging modalities such as quantitative coronary angiography (QCA) and intravenous ultrasound (IVUS) should be used in the future to assess plaque burden which may play the key role in the no-reflow phenomenon.

Previous studies have shown the trend that the incidence of no-reflow is lower in left circumflex coronary artery (LCX) PCI,[18,21] but no statistical significance has been found between different target vessels. In the present study, no-reflow phenomenon was less likely to occur in LCX lesions compared with LAD or RCA lesions. We found that the average lesion length and the lesion diameter is smaller in LCX than those in LAD or RCA. In the present study, the patients are mostly right coronary dominance, lesion characteristics varies between target vessels, and LCX lesions are less complicated than those in LAD or RCA. As previously mentioned, the diameter together with the length of the lesions may represent the plaque burden. The reason that no-reflow phenomenon is less

likely to occur in LCX still needs to be explored. In future we may analyze the anatomical and hemodynamic characteristics of LCX lesions by QCA and fractional flow reserve (FFR).

Compared with previous studies, the current study focused on the patients undergoing elective PCIs. As described above, the mechanisms of no-reflow are not exactly the same between the emergency and elective PCI, but some similar predictors of no-reflow phenomenon such as low initial coronary flow and cardiac function are observed in our study and the previous studies. Possible explanation may be that a proportion of no-reflow patients in our study were in the stage prior to ACS sharing similar characteristics with the ACS patients. Current explanations about no-reflow phenomenon were mostly derived from emergency PCI studies with inconsistent results. The mechanisms and predictors of no-reflow phenomenon remains to be examined in future studies.

Implications for Clinical Practice

As described earlier, the high-risk group in our score system had a significant higher incidence of no-reflow phenomenon, even within the high-risk group, the incidence of no-reflow phenomenon increased notably for every rise of one point in RECOVER score. The interventional strategy is made by cardiologists and interventionalists according to the baseline angiography, in addition to this, the risk of no-reflow could be evaluated by using the RECOVER score and may help clinicians estimate the risk of no-reflow phenomenon more precisely and take necessary measures before PCI. For example, preprocedural intracoronary administration of nicorandil or sodium nitroprusside may improve the microcirculation before PCI. The deployment of an embolic protection device and the administration of glycoprotein IIb/IIIa inhibitors to patients may reduce the risk of distal embolism.[29,30] The RECOVER score could help cardiologists to adopt optimal preoperative preparation rapidly which may minimize the possible damage of no-reflow phenomenon.

Study Limitations

There are several limitations of our study. First, although the discrimination and calibration ability of the RECOVER score was validated in an external cohort, its predictive accuracy should be further validated in different study datasets. Second, the main procedure characteristics such as the length and diameter of the target lesion were acquired by

visual inspection, which provides a less objective assessment of the coronary artery disease than QCA does. Finally, IVUS and OCT may provide a more meaningful assessment of plaque. However, the variables in our score system are easy to obtain in routine clinical practice.

Conclusions

Location of target lesion, ejection fraction and TIMI flow grade before PCI are predictive factors of no-reflow phenomenon. The RECOVER score could help identify patients at high-risk of no-reflow after PCI. Further validation of its performance in other patient populations is warranted.

Funding

This research was supported by National Key Research and Development Project of China (no. 2018YFC1315602) &Chinese Academy of Medical Sciences Innovation Fund for Medical Sciences (CIFMS) (no. 2016-I2M-1-009).

REFERENCES

1. Benjamin EJ, Virani SS, Callaway CW, et al. Heart disease and stroke statistics-2018 update: a report from the American Heart Association. *Circulation* 2018;137:558.
2. Rezkalla SH, Kloner RA. Coronary no-reflow phenomenon: from the experimental laboratory to the cardiac catheterization laboratory. *Catheterization Cardiovas Interventions Off J Soc Cardiac Angiograph Interventions* 2010;72:950–7.
3. Reffelmann T, Kloner RA. The "no-reflow" phenomenon: basic science and clinical correlates. *Heart (Br Cardiac Soc)* 2002;87:162.
4. Eeckhout E, Kern MJ. The coronary no-reflow phenomenon: a review of mechanisms and therapies. *Eur Heart J* 2001;22:729–39.
5. Ito H, Maruyama A, Iwakura K, et al. Clinical implications of the 'no reflow' phenomenon a predictor of complications and left ventricular remodeling in reperfused anterior wall myocardial infarction. *Circulation* 1996;93:223.
6. Piana RN, Paik GY, Moscucci M, et al. Incidence and treatment of 'no-reflow' after percutaneous coronary intervention. *Circulation* 1994;89:2514–8.
7. Iwakura K, Ito H, Kawano S, et al. Predictive factors for development of the no-reflow phenomenon in patients with reperfused anterior wall acute myocardial infarction. *J Am Coll Cardiol* 2001;38:472–7.
8. Burzotta F, Crea F. Thrombus-aspiration: a victory in the war against no reflow. *Lancet* 2008;371:1889–90.
9. Ronen J, Thierry C, Geoffrey P, Alexander D, Strauss BH. Microvascular obstruction and the no-reflow phenomenon after percutaneous coronary intervention. *Circulation* 2008;117:3152–6.

10. Gibson CM, Lemos JAD, Murphy SA, et al. Combination therapy with abciximab reduces angiographically evident thrombus in acute myocardial infarction: a TIMI 14 substudy. *Circulation* 2001;103:2550–4.
11. Hof AWVT, Liem A, Suryapranata H, Hoorntje JC, Boer MJD, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. *Zwolle Myocard Infarct Study Group Circulation* 1998;97:2302–6.
12. Moussa ID, Klein LW, Shah B, et al. Consideration of a new definition of clinically relevant myocardial infarction after coronary revascularization: an expert consensus document from the Society for Cardiovascular Angiography and Interventions (SCAI). *Catheter Cardiovasc Interv* 2014;83:27–36.
13. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. *Circulation* 2007;115:2344–51.
14. Sullivan LM, Massaro JM, Sr. DR. Presentation of multivariate data for clinical use: The Framingham Study risk score functions. *Stat Med* 2004;23:1631–60.
15. Hosmer DW, Hosmer T, Cessie SL, Lemeshow S. A comparison of goodness-of-fit tests for the logistic regression model. *Statist Med* 2015;16:965–80.
16. Cook NR. Use and misuse of the receiver operating characteristic curve in risk prediction. *Circulation* 2007;115:928–35.
17. Ndrepepa G, Tiroch K, Fusaro M, et al. 5-year prognostic value of no-reflow phenomenon after percutaneous coronary intervention in patients with acute myocardial infarction. *J Am Coll Cardiol* 2010;55:2383–9.
18. Kim MC, Cho JY, Jeong HC, et al. Long-term clinical outcomes of transient and persistent no reflow phenomena following percutaneous coronary intervention in patients with acute myocardial infarction. *Korean Circ J* 2016;46:490–8.
19. Tanaka A, Kawarabayashi T, Nishibori Y, et al. No-reflow phenomenon and lesion morphology in patients with acute myocardial infarction. *Circulation* 2002;105: 2148–52.
20. Bayramoğlu A, Taşolar H, Kaya A, et al. Prediction of no-reflow and major adverse cardiovascular events with a new scoring system in STEMI patients. *J Intervent Cardiol* 2018;31:144–9.
21. Harigaya H, Motoyama S, Sarai M, et al. Prediction of the no-reflow phenomenon during percutaneous coronary intervention using coronary computed tomography angiography. *Heart Vessels* 2011;26:363–9.
22. Ndrepepa G, Tiroch K, Keta D, et al. Predictive factors and impact of no reflow after primary percutaneous coronary intervention in patients with acute myocardial infarction clinical perspective. *Circ Cardiovasc Interv* 2010;3:27–33.
23. Abbo KM, Dooris M, Glazier S, et al. Features and outcome of no-reflow after percutaneous coronary intervention. *Am J Cardiol* 1995;75:778–82.
24. Suda A, Namiuchi S, Kawaguchi T, et al. A simple and rapid method for identification of lesions at high risk for the no-reflow phenomenon immediately before elective coronary stent implantation. *Heart Vessels* 2016;31:1904–14.

25. Tanaka A, Imanishi T, Kitabata H, et al. Lipid-rich plaque and myocardial perfusion after successful stenting in patients with non-ST-segment elevation acute coronary syndrome: an optical coherence tomography study. *Eur Heart J* 2009;30:1348–55.
26. Wang L, Lu MJ, Feng L, et al. Relationship of myocardial hibernation, scar, and angiographic collateral flow in ischemic cardiomyopathy with coronary chronic total occlusion. *J Nucl Cardiol* 2018.
27. Durante A, Camici PG. Novel insights into an "old" phenomenon: the no reflow. *Int J Cardiol* 2015;187:273–80.
28. Jeong YH, Kim WJ, Park DW, et al. Serum B-type natriuretic peptide on admission can predict the 'no-reflow' phenomenon after primary drug-eluting stent implantation for ST-segment elevation myocardial infarction. *Int J Cardiol* 2010;141:175–81.
29. Blankenship JC, Tasissa G, O'Shea JC, et al. Effect of glycoprotein IIb/IIIa receptor inhibition on angiographic complications during percutaneous coronary intervention in the ESPRIT trial. *J Am Coll Cardiol* 2001;38:653–8.
30. Baim DS, Wahr D, George B. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. *Circulation* 2002;11:70–1.