Clinical Investigations

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A Risk Score for No Reflow in Patients With ST-Segment Elevation Myocardial Infarction After Primary Percutaneous Coronary Intervention

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ABSTRACT

Background: Many factors are associated with no-reflow (NRF) phenomenon in ST-segment elevation myocardial infarction (STEMI), including plasma glucose, age, and pre–percutaneous coronary intervention (PCI) thrombus score. Initial clinical assessment would benefit from accurate NRF prediction. This study aimed to develop a simple scoring system to predict the risk of NRF in patients undergoing primary PCI with STEMI.

Methods: Baseline clinical and procedural variables were used for risk score development (the training dataset, n = 912) and validation (the test dataset, n = 864). Independent predictors of NRF from the multivariable model were assigned integer weights based on their coefficients and incorporated into a risk score. The discriminant ability of the score was tested by receiver operating characteristic analysis using the test dataset.

Results: The final model included 7 significant variables, which were age, pain-to-PCI time, neutrophil count, admission plasma glucose level, pre-PCI thrombus score, collateral circulation, and Killip class. All these variables were then used to build a risk score in terms of the prediction of NRF. Receiver operating characteristic analysis demonstrated good risk prediction with a c statistic of 0.800 (95% confidence interval: 0.772-0.826) in the test dataset.

Conclusions: In patients with STEMI treated by primary PCI, incidence of NRF phenomenon may be predicted with an acceptable accuracy based on a 7-item simplified risk score.

Introduction

Primary percutaneous coronary intervention (PCI) has been shown to be the most effective reperfusion strategy in the treatment of acute myocardial infarction (AMI).[1] Brisk Thrombolysis In Myocardial Infarction (TIMI) grade-3 flow immediately after PCI in AMI is related to improved clinical outcomes.[2] However, a sizable number of patients fail to restore optimal myocardial reperfusion, mostly because of no-reflow (NRF) phenomenon. No-reflow phenomenon is defined as suboptimal myocardial reperfusion through a part of coronary circulation without angiographic evidence of mechanical vessel obstruction.[3] This phenomenon has been documented in >30% of AMI patients after thrombolysis or primary mechanical intervention.[4] Also, in patients with ST-segment elevation myocardial infarction (STEMI) treated by primary PCI, the NRF phenomenon is a strong predictor of both short-term and long-term mortality.[5] Compared with those with adequate reflow, patients with NRF phenomenon tend to have higher incidences of death, myocardial infarction, and heart failure.[6,7] The etiology of NRF is not yet fully understood, but it is assumed to be of multifactorial origin. Previous studies have identified several factors associated with NRF phenomenon, including plasma glucose, age, and pre-PCI thrombus score.[8–11] However, there is no screening tool to predict individual risk of developing NRF and to help health professionals make a decision on further intervention and select eligible patients into protocols focusing on

mechanism and therapy of NRF. Therefore, we developed a score based on weighted clinical and angiographic characteristics to predict risk of NRF in patients with STEMI.

Methods

Study Population

We prospectively recruited patients age >18 years who had a STEMI of <15 hours' duration from onset of symptoms until arrival at the department of cardiology in 3 participating institutions. Those who had ≥1 of the following factors were excluded from this study: (1) patients undergoing coronary artery bypass grafting; (2) patients with mechanical complications (ventricular free wall rupture, ventricular septal rupture, and papillary muscle rupture with severe mitral regurgitation); and (3) patients undergoing thrombolysis. All patients signed the written informed consent. The study was approved by the University Human Ethics Committee.

Clinical Data Collection

Blood samples, including plasma glucose, white blood cell count, creatine kinase (CK), and cardiac troponins, were required to be obtained on admission. Detailed clinical data were obtained, including age, sex, Killip class on hospital admission, time to hospital admission, and medication before AMI. A 12-lead electrocardiogram was acquired at the time of presentation.

Definitions

ST-segment elevation myocardial infarction was defined as chest pain suggestive of myocardial ischemia for ≥30 minutes within the previous 15 hours, accompanied by >1-mm (0.1-mV) ST-segment elevation in ≥2 contiguous leads and later confirmed by CK and CK-MB increases and/or troponin increase. Cardiac symptoms lasting >30 minutes that occurred within 48 hours before the onset of infarction were defined as preinfarction angina. Severity of heart failure was assessed according to the Killip classification. Anterograde coronary flow in the infarct-related artery (IRA) was graded based on the TIMI grading system.[12] Thrombus score was graded as previously described by the TIMI Study Group.[13] Myocardial blush grade was assigned as described by van 't Hof et al.[14] Angiographic NRF can be defined as a TIMI flow grade <3 or 3 plus a myocardial blush grade 0–1.[15]

Primary Percutanous Coronary Intervention Procedure and Angiographic Analysis

Patients were pretreated with oral 300 mg aspirin, oral 300 mg clopidogrel, and intravenous (IV) 5000 IU unfractionated heparin. Use of a glycoprotein IIb/IIIa inhibitor (tirofiban, 10 μg/kg bolus followed by 0.15 μg/kg/min IV infusion) was left to the discretion of the primary operator. Primary PCI, including balloon predilatation and stent implantation, was performed only for IRA with TIMI flow grade ≤2. Intracoronary stents were implanted as a final treatment option when the anatomy was suitable. Low-molecular-weight heparin was injected subcutaneously in

the subsequent 72 hours. The quantitative angiographic assessment was done by 2 independent observers on a validated quantitative coronary angiographic system, CMS 4.0 (Medis, Leiden, the Netherlands). Clinical investigators did not participate in the angiographic assessment.

Statistical Analysis

The dataset was randomly divided into 2 datasets using a computer-generated random number: the training dataset for model development and the test dataset for validation of the developed NRF risk score.

In the training dataset, associations between each variable and NRF were first tested using univariate analysis. Clinical variables considered for entry into the multivariate predictive model included age, sex, and smoking status; presence/absence of diabetes mellitus, hypertension, preinfarction angina, and/or prior PCI; systolic blood pressure, diastolic blood pressure, heart rate, admission plasma glucose, CK-MB, admission neutrophil counts, and B-type natriuretic peptide; and time interval from pain to PCI, medication before AMI (aspirin, angiotensin-converting enzyme inhibitors, statins, calcium channel blockers, and β-blockers), and Killip classes. Also, the following angiographic variables were involved: IRA, initial TIMI flow grade, number of narrowed coronary arteries, stent diameter, total stent length, administration of tirofiban, use of aspiration thrombectomy, pre-PCI thrombus score, collateral circulation grade, maximal inflation pressure, and the type of intervention. Receiver operating characteristic (ROC) curves were employed to identify the best cutoff point of each continuous variable in terms of the capability of prediction of the future incidence of NRF. The variables tested included age, time interval from pain to PCI, concentration of glucose, high-sensitivity C-reactive protein, neutrophil counts, and B-type natriuretic peptide, each of which was then transformed into a binomial categorical variable based on the cutoff point identified.

Multiple backward stepwise logistic regression was performed to identify the significant predictors with regard to NRF after primary PCI. Variables with a significant association ($P < 0.1$) with NRF based on univariate analyses were entered into a multivariate model. All the significant variables were then used to establish a clinical score system. The individual score for each variable was calculated based on its regression coefficient in the final step of the multiple logistic regression model. Each individual score was yielded via a linear transformation of the corresponding β regression coefficient, which was divided by 0.439 (the lowest β value, corresponding to collateral circulation grade ≤1), multiplied by a constant (2), and then rounded to the nearest integer. The overall score of a patient was the sum of all individual scores.

Validation of the risk score was performed using the test dataset. The discriminating properties of the NRF prediction model were investigated by calculating the area under a ROC curve. The ROC curve reflects the relationship between the sensitivity and the 1-specificity. The area under the curve (AUC) shows that to what extent this model could distinguish the patients with NRF from those with normal blood flow. The larger AUC means the better ability of

Table 1. Clinical Characteristics of Patients in the Training and Test Datasets

Characteristics	Training Dataset, n = 912	Test Dataset, n = 864	Total, N = 1776
Age, y	62.3 ± 11.8	59.6 ± 12.1	61.1 ± 12.1
Age ≥55 years	572 (62.7)	566 (65.5)	1138 (64.1)
Male sex	682 (74.8)	720 (83.3)	1402 (78.9)
Hypertension	485 (53.2)	475 (54.9)	960 (54.1)
DM	221 (24.2)	231 (26.7)	452 (25.5)
Smoking status			
Current smoker	378 (41.4)	191 (22.1)	569 (32.0)
Ex-smoker	79 (8.7)	45 (5.2)	124 (7.0)
Never smoked	455 (49.9)	628 (72.7)	1083 (61.0)
Prior PCI	63 (6.9)	56 (6.5)	119 (6.7)
Preinfarction angina	468 (51.3)	505 (58.4)	973 (54.8)
Medication before MI			
ASA	158 (17.3)	70 (8.1)	228 (12.8)
ACEI	56 (6.1)	106 (12.3)	162 (9.1)
β-Blocker	151 (16.6)	96 (11.1)	247 (13.9)
CCB	257 (28.2)	237 (27.4)	494 (27.8)
Statin	43 (4.7)	40 (4.6)	83 (4.7)
Pain-to-PCI time, h	7.4 ± 6.4	7.1 ± 6.0	7.2 ± 6.3
Pain-to-PCI time ≥4 h	415 (45.5)	324 (37.5)	739 (41.6)
Physical findings on admission			
SBP, mm Hg	118 ± 25	121 ± 23	119 ± 24
DBP, mm Hg	69 ± 15	73 ± 14	71 ± 16
Heart rate, bpm	76 ± 18	76 ± 17	76 ± 18
Plasma glucose, mmol/L	10.3 ± 4.8	9.4 ± 4.2	9.9 ± 4.6
Plasma glucose ≥12.0, mmol/L	119 (13.0)	112 (12.9)	231 (13.0)
BNP, mmol/L	576.2 ± 1.8	537.8 ± 1.7	567.8 ± 1.7
BNP ≥250, mmol/L	769 (84.3)	706 (81.7)	1475 (83.1)
Neutrophil count, 10^9/counts/L	9.56 ± 3.18	9.45 ± 2.89	9.50 ± 3.02
Neutrophil count ≥8.81, 10^9/counts/L	328 (36.0)	291 (33.7)	619 (34.9)
CK-MB, U/L	95 ± 113	87 ± 107	92 ± 109
Killip class			
1	422 (46.3)	446 (51.6)	868 (48.9)
2	380 (41.7)	396 (45.8)	776 (43.7)
3	32 (3.5)	31 (3.6)	63 (3.5)
4	36 (3.9)	33 (3.8)	69 (3.9)

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ASA, aspirin; BNP, B-type natriuretic peptide; CCB, calcium channel blocker; CK-MB, creatine kinase-MB; DBP, diastolic blood pressure; DM, diabetes mellitus; MI, myocardial infarction; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; SD, standard deviation.
Data are presented as mean ± SD or n (%).

Table 2. Angiographic and PCI Characteristics of Patients in the Training and Test Datasets

Characteristics	Training Dataset, n = 912	Test Dataset, n = 864	Total, n = 1776
NRF	203 (22.3)	164 (19.0)	367 (20.7)
IRA			
LM	9 (1.0)	6 (0.7)	15 (0.8)
LAD	410 (45.0)	407 (47.1)	817 (46.0)
LCX	124 (13.6)	153 (17.7)	277 (15.6)
RCA	362 (39.7)	305 (35.3)	667 (37.6)
No. of narrowed coronary arteries			
1	186 (20.4)	282 (32.6)	468 (26.4)
2	236 (25.9)	327 (37.8)	563 (31.7)
3	489 (53.6)	256 (29.6)	745 (41.9)
Initial TIMI flow			
0	599 (65.7)	524 (60.6)	1123 (63.2)
1	23 (2.5)	42 (4.9)	65 (3.7)
2	57 (6.3)	55 (6.4)	112 (6.3)
3	231 (25.3)	245 (28.4)	476 (26.8)
Pre-PCI thrombus score			
0–1	190 (20.8)	209 (24.2)	399 (22.5)
2	30 (3.3)	83 (9.6)	113 (6.4)
3	38 (4.2)	303 (35.1)	341 (19.2)
4	41 (4.5)	72 (8.3)	113 (6.4)
5	611 (67.0)	199 (23.0)	810 (45.6)
Collateral circulation			
0–1	757 (83.0)	671 (77.7)	1428 (80.4)
2	124 (13.6)	156 (18.1)	280 (15.8)
3	29 (3.2)	39 (4.5)	68 (3.8)
Type of intervention			
Stenting	870 (95.4)	826 (95.6)	1696 (95.5)
Balloon angioplasty	42 (4.6)	38 (4.4)	80 (4.5)
Maximal inflation pressure, atm	15.7 ± 3.4	15.9 ± 3.3	15.8 ± 3.3
Stent diameter, mm	3.02 ± 0.71	3.09 ± 0.76	3.08 ± 0.72
Total stent length, mm	24.7 ± 6.3	24.8 ± 6.4	24.6 ± 6.4
Tirofiban usage (only tirofiban in China)	301 (33.0)	252 (29.2)	553 (31.1)
Aspiration thrombectomy	496 (54.4)	387 (44.8)	883 (49.7)

Abbreviations: IRA, infarct-related artery; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main artery; NRF, no reflow; PCI, percutaneous coronary intervention; RCA, right coronary artery; SD, standard deviation; TIMI, Thrombolysis In Myocardial Infarction grade.
Data are presented as mean ± SD or n (%).

prediction regarding the risk of NRF incidence. Based on the ROC curve, the following values were calculated: the sensitivity, specificity, positive predictive value, and negative predictive value. The selection of the optimal cutpoint was based on the Youden index, the maximum sum of sensitivity and specificity.

Statistical analyses were performed using SPSS 18 (SPSS Inc., Chicago, IL) and/or MedCalc 9 (MedCalc Software,

Table 3. Multivariate Analysis for NRF and Scoring System[a]

Variables[b]	OR (95% CI)	P Value	β-Coefficient	Risk Score[c]
Age ≥55 years				
Yes	3.15 (2.23-4.44)	<0.001	1.147	5
No				0
Pain-to-PCI time ≥4 h				
Yes	1.69 (1.25-2.28)	0.001	0.522	2
No				0
Admission plasma glucose ≥12.0 mmol/L				
Yes	2.03 (1.38-3.02)	<0.001	0.712	4
No				0
Neutrophil count ≥8.81 10^9/counts/L				
Yes	6.36 (4.66-8.69)	<0.001	1.851	8
No				0
Killip class 4				
Yes	1.87 (1.30-2.69)	0.001	0.626	3
No				0
Pre-PCI thrombus score ≥2				
Yes	3.23 (2.06-5.06)	<0.001	1.173	5
No				0
Collateral circulation grade ≤1				
Yes	1.55 (1.03-2.34)	0.037	0.439	2
No				0

Abbreviations: BNP, B-type natriuretic peptide; CI, confidence interval; DBP, diastolic blood pressure; hsCRP, high-sensitivity C-reactive protein; IRA, infarct-related artery; NRF, no reflow; OR, odds ratio; PCI, percutaneous coronary intervention; SBP, systolic blood pressure; TIMI, Thrombolysis In Myocardial Infarction grade.
[a]The backward stepwise multiple logistic regression was used. [b]Only the variables entering the last step of stepwise logistic regression were shown in the table. Basically, variables entering the multiple logistic regression model included sex, age, smoking status, preinfarction angina, pain-to-PCI time, SBP, DBP, hsCRP, BNP, fasting plasma glucose, neutrophil count, IRA, β-blocker usage, maximal inflation pressure, initial TIMI flow, pre-PCI thrombus score, collateral circulation grade, tirofiban usage, and aspiration thrombectomy. [c]Assignment of scores to risk factors was based on a linear transformation of the corresponding β regression coefficient. The coefficient of each variable was divided by 0.439 (the lowest β value, corresponding to collateral circulation grade ≤1), multiplied by a constant (2), and rounded to the nearest integer.

Mariakerke, Belgium). All P values reported are 2-tailed, and $P < 0.05$ was considered to be statistically significant.

Results

Between January 2007 and January 2011, 2017 patients with STEMI were admitted and assessed with regard to the eligibility of primary PCI. Among them, 241 were not eligible for the study protocol. After the primary PCI procedure, 367 of 1776 patients (20.7%) suffered from a TIMI flow grade ≤2 (NRF group). The training dataset and the test dataset contained 912 (NRF 22.3%) and 864 (NRF 19.0%) patients, respectively. Admission clinical characteristics and angiographic and PCI characteristics of the 2 sets are detailed in Table 1 and Table 2.

The results of multiple stepwise logistic regression analysis showed that 7 major predictors highly significantly correlated with the incidence of NRF: age (≥55 years; odds ratio [OR]: 3.15, 95% confidence interval [CI]: 2.23-4.44, $P < 0.001$), prolonged pain-to-PCI time (≥4 hours; OR: 1.69, 95% CI: 1.25-2.28, $P = 0.001$), high neutrophil count (≥8.81 × 109/L; OR: 6.36, 95% CI: 4.66-8.69, $P < 0.001$), high admission plasma glucose level (≥12 mmol/L; OR: 2.03, 95% CI: 1.38-3.02, $P < 0.001$), high thrombus burden (a pre-PCI thrombus score of ≥2; OR: 3.23, 95% CI: 2.06-5.06, $P < 0.001$), low grading of collateral circulation (≤1; OR: 1.55, 95% CI: 1.03-2.34, $P = 0.037$), and high Killip class (4; OR: 1.87, 95% CI: 1.30-2.69, $P = 0.001$). These identified predictors were then used to build a clinical score system regarding the prediction of postprocedural NRF. The overall score for a patient ranged from 0 to 29 (Table 3).

The validity of the NRF score was then tested in the other half of the study population (n = 864). The optimal

Table 4. Sensitivity and Specificity of Each Cutoff Value for the Risk Score for NRF in the Test Dataset

Cutoff Value	No. (%)[a]	Sensitivity	Specificity	PPV	NPV
10	7 (8.1)	88.32	50.3	34.6	97.5
11	1 (14.3)	87.31	52.11	35.3	93.2
12	20 (16.0)	77.16	67.92	41.8	90.9
13	1 (7.7)	76.65	69.73	43.1	90.9
14[b]	1 (12.5)	76.14	70.78	43.8	90.8
15	34 (8.9)	58.88	84.19	52.7	87.3
16	4 (13.3)	56.85	88.1	58.8	87.3
17	1 (33.3)	56.85	88.55	60.5	87.4
18	12 (57.1)	50.76	89.91	60.3	85.9
19	11 (61.1)	45.18	90.96	60.0	84.8
20	49 (50.0)	20.81	98.34	78.5	80.6
21	3 (100)	19.29	98.34	77.2	80.3
22	2 (100)	19.29	98.64	80.5	80.4
23	14 (82.4)	12.18	99.1	80.2	79.0
24	15 (75)	5.08	99.85	88.4	77.8
25	1 (100)	5.08	100	100	77.9

Abbreviations: NPV, negative predictive value; NRF, no reflow; PPV, positive predictive value.
[a] Incidence of NRF for each level of the score. [b] Optimal cutoff point.

Figure 1. ROC curve for the NRF risk model in the test dataset. Abbreviations: NRF, no reflow; ROC, receiver operating characteristic.

cutoff score was ≥14 (sensitivity 76.14%, specificity 70.78%; Table 4). The positive predictive value and negative predictive value for the cutoff score of ≥14 were 43.8% and 90.8%, respectively. The ROC curve for the weighted score showed good discriminant power with a c statistic of 0.800 (95% CI: 0.772-0.826; Figure 1).

Discussion

No-reflow phenomenon is by far an important issue in the treatment of AMI patients using PCI techniques. In this study, based on multiple logistic regression, 7 significant indicators were located and were then used to build a clinical score system that could be used to identify patients at high risk of NRF. Based on the score system, clinical staff would be able to readily and rapidly identify those who might require further care, such as using thrombus aspiration techniques and implanting embolic protection devices, all of which are either expensive or unnecessary for low-risk patients in the clinical practice but would be beneficial to those identified. We also tested the accuracy of this newly built score system in STEMI patients and found that, with clinical and procedural variables, its efficacy is good in predicting postprocedural NRF (AUC = 0.800).

In the present study, in terms of the significance in the predication, the order of the 7 indicators are level of neutrophil at admission, pre-PCI thrombus score, age, random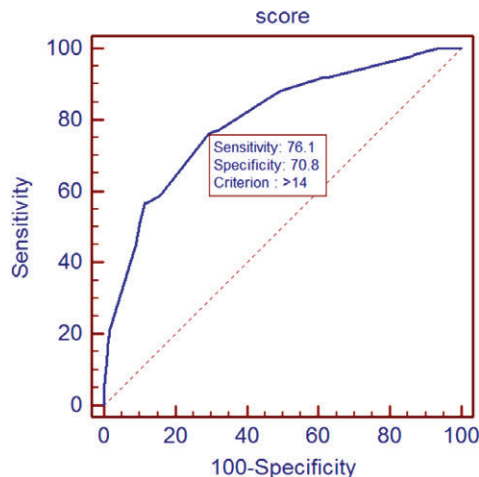 blood glucose levels, Killip class, pain-to-PCI time, and collateral circulation grade. In agreement with Takahashi et al, who reported association of neutrophil counts on admission with microvascular injury in AMI patients treated with PCI,[16] we found that neutrophil level had a strong independently predictive effect. Patients in the highest quartile of neutrophil count were nearly 3× more likely to experience post-PCI NRF than were those in the lowest quartile. Various mechanisms have been described to explain why, in patients with AMI, worse TIMI flow significantly correlates to elevated levels of neutrophils. Advances in basic science have now highlighted that ischemia-reperfusion injury is essential to the pathophysiology of NRF.[17,18] Neutrophils have been shown to play a causative role in reperfusion injury and are a major source of oxidants in hearts reperfused after prolonged ischemia.[19] In addition, neutrophil recruitment and activation at the site of endothelial damage is considered an initial event in thrombus formation. Neutrophil-derived tissue factors are associated with hypercoagulability and reduce probability of early successful reperfusion.[20,21] The benefits of clopidogrel in improving IRA patency following fibrinolysis is also shown to be attenuated in STEMI patients with an elevated baseline neutrophil count.[22] These findings lend further support for therapies targeting both platelets and leukocytes in STEMI.

Both collateral circulation and thrombus burden are important angiographic predisposing factors of the outcome of PCI. Yip et al found that presence of accumulated thrombus is an independent predictor of postprocedural NRF in patients undergoing PCI.[8] Results in our study support this finding. The coronary collateral circulation, as an alternative source of blood supply, has been shown to be beneficial with regard to several clinical endpoints in AMI patients.[23] Well-developed collaterals tend to have a protective effect on coronary microcirculation and may lead to less NRF in patients with STEMI. In this study, collateral circulation was also an independent angiographic predictor of the incidence of NRF. Therefore, attentive evaluation of collateral circulation and thrombus burden during PCI procedure, especially before intervention, is highly recommended.

In the present study, proportion of subjects with TIMI grade 3 flow (476, 26.8%) is higher than that in some previous studies, such as Primary Angioplasty in Myocardial Infarction (PAMI) trials, where TIMI-3 flow was present at initial angiography (spontaneous reperfusion) in 16% of patients.[24] No baseline demographic characteristics were confirmed as predictors in terms of spontaneous reperfusion. We note that, however, more patients received preprocedural clopidogrel in addition to aspirin and unfractionated heparin in the emergency department than the participants in PAMI did. This may partly explain the higher initial TIMI-3 rate.

Selection of an optimal cutoff point largely depends on the purpose of utilizing the risk score and needs to balance its sensitivity and specificity. When it comes to the prediction of post-PCI NRF, which is associated with mortality and great expense, our purpose is to identify more potentially risky patients and higher sensitivity is preferred. Therefore, a score ≥14 was used as the cutoff point, and the sensitivity and the specificity were 76.1% and 70.8%, respectively.

Study Limitations

Although this study is a carefully designed multicenter study with a large sample, it has some limitations. First, the predictive performance of the score was tested on the same population in which the risk score was developed. Its predictive efficacy needs to be further tested in a well-designed large-scale prospective study. Second, tirofiban was the only formulation of glycoprotein IIb/IIIa inhibitor approved by China's State Food and Drug Administration (SFDA). Bivalirudin was not administered in the present study, and this may have influenced the outcomes. Thirdly, intravascular ultrasound could be useful tool in the prediction of postprocedural NRF after primary PCI.[25] However, intravascular ultrasound has not been routinely adopted during PCI in patients with STEMI in China. This information would be added in our future studies.

Conclusion

We have developed a simple risk score for the prediction of NRF based on 7 variables: age, pain-to-PCI time, admission plasma glucose, neutrophil count, Killip class, pre-PCI thrombus grade, and collateral circulation grade. Given the high risk of mortality of NRF, a risk score with excellent performance would help clinicians to identify high-risk subjects requiring intensive treatment.

Acknowledgements

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