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The Value of Pre-Infarction Angina and Plasma D-Dimer in Predicting No-Reflow After Primary Percutaneous Coronary Intervention in ST-Segment Elevation Acute Myocardial Infarction Patients

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Statistical Analysis C
Data Interpretation D
Manuscript Preparation E
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Background: Primary percutaneous coronary intervention (PCI) has improved outcomes greatly in patients with ST-elevation myocardial acute infarction (STEMI). However, the no-reflow phenomenon significantly reduces its efficacy.

Material/Methods: In this study, we investigated the value of combining plasma D-dimer level on admission and pre-infarction angina (PIA) in predicting no-reflow phenomenon in STEMI patients after primary PCI. A total of 926 STEMI patients who underwent primary PCI were included.

Results: The average age was 52.6 years, 617 (66.6%) of them had experienced a PIA, and 435 (47.9%) showed no-reflow phenomenon after primary PCI. Both PIA and plasma D-dimer on admission were independent predictors of no-reflow, with a risk of 0.516 (95% CI: 0.380 to 0.701) and 2.563 (95% CI: 1.910 to 3.439), respectively. Plasma D-dimer level had an area under curve (AUC) of 0.604 (95% CI: 0.568~0.641) in predicting no-reflow phenomenon, and PIA had an AUC of 0.574 (95% CI: 0.537 to 0.611). Importantly, the new signature combining D-dimer level on admission and PIA showed an increased AUC (0.637, 95%CI: 0.601 to 0.673) in predicting the no-reflow phenomenon. Moreover, the patients with high D-dimer level on admission but without PIA had significantly increased ratio of no-reflow phenomenon and in-hospital mortality compared to the other patients (P<0.001 and P=0.041, respectively).

Conclusions: Based on these solid results, we conclude that combining plasma D-dimer level on admission and PIA might create a good signature for use in predicting the no-reflow phenomenon after primary PCI in STEMI patients.

MeSH Keywords: Angina, Stable • Coronary Thrombosis • Myocardial Infarction • No-Reflow Phenomenon • Percutaneous Coronary Intervention

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Background

Primary percutaneous coronary intervention (PCI) has substantially enhanced outcomes in patients with ST-elevation myocardial acute infarction (STEMI) and has become the favored reperfusion strategy in patients with STEMI [1–3]. However, the no-reflow phenomenon significantly reduces the efficacy of PCI treatment for STEMI [4,5]. "No-reflow phenomenon" is the term used to describe inadequate myocardial reperfusion of a given coronary segment after an obstruction or conduit vessel spasm in an epicardial vessel has been removed [4,5]. No-reflow phenomenon is clinically important because of its independent association with higher incidences of in-hospital mortality, malignant arrhythmias, and cardiac failure [6,7]. In addition, the no-reflow phenomenon is associated with poor long-term prognosis due to post-procedural myocardial infarction [8]. Although some potential predictors of no-reflow phenomenon have been reported, such as the platelet/lymphocyte ratio and monocyte count [9, 10], more predictors are still urgently needed.

Pre-infarction angina (PIA) occurring shortly before the onset of acute myocardial infarction (AMI) has a cardioprotective effect [11]. PIA has been shown to preserve microvascular function after reperfusion in STEMI patients [11]. Mechanistically, the protective roles are through the ischemic preconditioning mechanism, i.e., the phenomenon by which brief episodes of ischemia induce the tolerance of the myocardial cells to a subsequent major ischemic attack [12]. Clinically, PIA predicts thrombus burden in patients admitted for STEMI [13]. However, the association between PIA and no-reflow phenomenon has received little research attention.

During thrombus formation, fibrinogen is converted to fibrin monomers. Cross-linking of the fibrin monomers then takes place in the region termed the "D-domain." Adjacent D-domains are covalently linked and form a fibrin-specific feature of a thrombus. Fibrin polymers can be degraded by plasmin during the fibrinolytic process. One of the terminal products of the fibrinolytic process is the covalently linked D-Domain called the D-dimer. Thus, the D-dimer level emerged as a useful marker of procoagulant activity and ongoing fibrinolysis [14]. D-dimer tests are widely used as a non-invasive triage biomarker in patients with acute thoracic pain [15]. In STEMI patients, high D-dimer level is associated with increased in-hospital cardiovascular mortality and 6-month all-cause mortality in patients after primary PCI [16]. Another study showed a correlation between D-dimer level and no-reflow phenomenon [17]. However, the predictive value of a single biomarker is usually limited. In the present study, we combined the PIA and D-dimer level as a predictive signature, aiming to enhance the accuracy of no-reflow prediction.

Material and Methods

Patient's selection

This study had a prospective design. Patient admission started in March 2008 and ended in September 2015. A balanced number of reflow (531 cases) and no-reflow (530 cases) STEMI patients were randomly selected from the reflow patient population and the no-reflow patient population, respectively. We further selected patients based on the following exclusion criteria: 1) primary PCI was performed after 12 h of admission to hospital or no stent was implanted during the PCI; 2) age >75 years; 3) major surgeries or severe injuries in the past 6 months; 4) high risk of bleeding (patients who underwent anticoagulant therapy within 12 months before admission, had history of bleeding disorder, vascular abnormality, a count of platelet <100 000/mm^3, or severe chronic liver disease); 5) bypass grafting or stenting treatment due to previous myocardial infarction; 6) thrombolysis failure and rescue PCI; 7) class IV heart failure; 8) severe respiratory, renal, or hepatic dysfunction or failure; 9) history of thromboembolic disease, treated cancer, imflammatory process, and pregnancy. All patients signed the inform consent. This study was approved by the local ethics committee of Tianjin Baodi Hospital.

PCI procedure and angiographic analysis

We performed the PCI procedure by a femoral approach with a 6F guiding catheter. A bolus of heparin (5000 IU) was administered before the procedure. After routine wire crossing, we performed balloon pre-dilatation, followed by stenting implantation whenever possible. After vessel recanalization, intracoronary nitrates were administered. Before and after vessel recanalization, we collected the following angiographic data: 1) coronary TIMI flow grading; 2) corrected TIMI frame count (CTFC); 3) TIMI score. To prevent bias, 2 independent angiographers who were blind to the aim of this study did the assessment; their final consistency was 92%. Any disagreements were resolved by consensus. The no-reflow phenomenon was defined as a coronary TIMI flow grade less than 3 after vessel reopening by PCI. Presence of PIA was determined by asking the patient to recall symptoms of angina that presented within 72 h before admission. The symptoms include chest pain (may be described as pressure or discomfort), pain in shoulders (or in back, arms, or neck), dizziness, weakness, nausea, fatigue, and shortness of breath.

Key laboratory assays

We collected venous blood from a branchial vein using EDTA tubes and non-anticoagulant tubes before the PCI procedure on the day of patient admission to the hospital. Blood samples were then centrifuged for 10 min at 10 000 rpm. The aliquots

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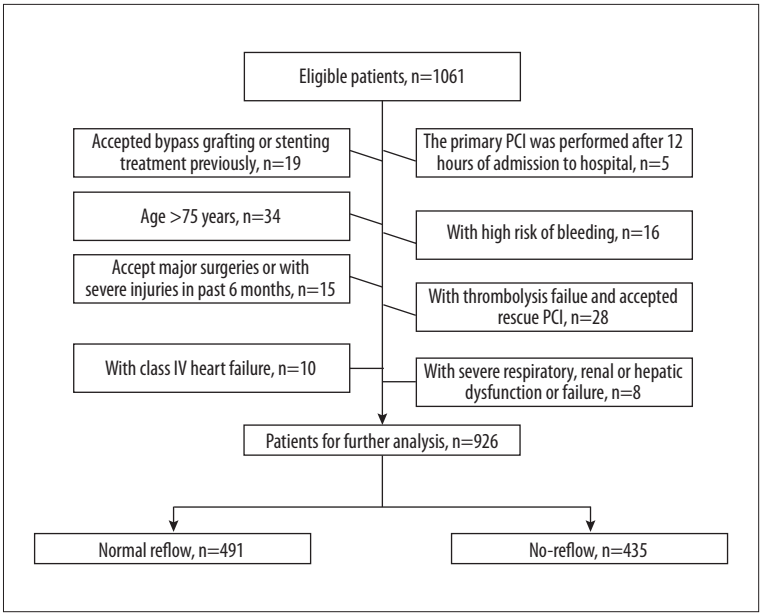

Figure 1. Patient selection flow-chart for this study.

of plasma and serum were stored at –80°C until assayed. We measured the D-dimer using the human D-dimer ELISA kit (EHDDIMER, Thermo Fisher Scientific, Waltham, MA, USA) with a sensitivity of 0.08 pg/mL. Serum creatine kinase (CK) and CK-MB fraction were evaluated at admission, every 4 h during the first day, and every 24 h in the following 5 days, using routine methods. Left ventricular ejection fraction (LVEF) at admission and within 2 h after PCI was measured by a 2D echocardiography (Simpson method). Other clinical information and laboratory tests were obtained through routine clinical tests.

Statistical analysis

All the statistical analysis and data visualization were performed using SPSS software 14.0 (SPSS Inc., Chicago, IL, USA) and Prism GraphPad software (San Diego, CA, USA). Data are presented as means with standard deviation (SD) or frequencies (n) and percentages. Comparisons between 2 groups were conducted using the *t* test. Relationships between nominal or ordinal variables were analyzed by chi-squared test. Univariant and multivariant logistic regression were performed to analyze the value of variables in predicting the no-reflow phenomenon. Receiver operating characteristic (ROC) curves were made to analyze the sensitivity and specificity of predicting the no-reflow phenomenon by using PIA and plasma D-dimer level. To evaluate the significance of combining PIA and plasma D-dimmer level in predicting no-reflow phenomenon, patients were graded based on the 2 potential risk factors (no-PIA and high plasma D-dimer at admission): 0 for double-negative patients (with PIA and low D-dimer), 1 for single-positive patients (no-PIA or high D-dimer), and 2 for double-positive patients (no-PIA and high D-dimer. High D-dimer was defined as more than the mean value of all the patients (383.1 ng/ml). A two-tail P value less than 0.05 was defined as statistical significance.

Table 1. Basic clinical features of the STEAMI patients.

Baseline features	Data
Age (year)	52.6±7.81
Male, n (%)	429 (46.3)
BMI (kg/m^2)	25.9±5.1
Smoker, n (%)	356 (38.4)
Hypertension, n (%)	415 (55.2)
History of ischemic heart disease, n (%)	231 (24.9)
Diabetes, n (%)	366 (39.5)
Hyperlipemia, n (%)	415 (55.2)
Angina, n (%)	617 (66.6)
D-dimer (ng/ml)	383.1±264.2
No-reflow, n (%)	435 (47.0)

Result

Characteristics of included patients

To explore the value of PIA and D-dimer level on admission in predicting no-reflow phenomenon after primary PCI, we included a total of 926 STEMI patients (Figure 1). The basic clinical characteristics of these patients are summarized in Table 1. Briefly, the average age of these patients was 52.6 years with

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Table 2. Potential predictors of the no-reflow after PCI.

Features	Normal reflow (n=491)	No-reflow (n=435)	P value
Age (>53 year)	269 (54.8)	238 (54.7)	0.982
Male, n (%)	225 (45.8)	204 (46.9)	0.744
BMI (kg/m^2)	25.6±5.0	26.2±5.0	0.105
Hypertension, n (%)	240 (48.9)	271 (62.3)	<0.001
Smoke, n (%)	172 (35.0)	184 (42.3)	0.023
History of ischemic heart disease, n (%)	106 (21.6)	125 (28.7)	0.012
Diabetes, n (%)	152 (31.0)	214 (49.2)	<0.001
Hyperlipemia, n (%)	200 (40.7)	215 (49.4)	0.008
TIMI grade at admission <3, n (%)	296 (60.3)	332 (76.3)	**<0.001**
CTFC before recanalization	35.3±6.7	38.6±8.1	**<0.001**
TIMI score	3.81±0.44	4.31±0.67	**<0.001**
Total serum bilirubin (μmol/L)	11.5±6.3	12.3±7.4	**0.076**
Pre-infarction angina, n (%)	198 (40.3)	111 (25.5)	<0.001
Angina time	15.1±22.5	11.5±21.6	**0.013**
Time before PCI (hour)*	5.8±2.6	6.3±2.3	**0.001**
CK-MB on admission (mmol/L)	212.2±168.9	247.1±202.4	**0.004**
LVEF, n (%)**	205 (41.8)	223 (51.3)	**0.004**
D-dimer (ng/ml)	272.0±218.9	508.5±254.7	<0.001

* Time before PCI was defined as the interval between occurrence of infarction symptoms and execution of PCI procedures. ** n (%) indicated the number and percentage of patients with LVEF less than 45%.

a standard deviation of 7.81 years. There were 429 (46.3%) males and 497 (53.7%) females and 617 (66.6%) of them had experienced angina before they were admitted to the hospital due to STEMI. No-reflow phenomenon after primary PCI was found in 435 (47.9%) and 491 (53.0%) showed a normal reflow after PCI.

Relationship between the no-reflow phenomenon and other clinical features of STEMI patients

To explore the potential factors related to the no-reflow phenomenon of STEMI patients after primary PCI, we analyzed the relationship between no-reflow and many important clinical features. As shown in Table 2, we found that there was a significantly higher ratio of hypertension, smoking, history of ischemic heart disease, diabetes, hyperlipemia, low TIMI grade (<3) at admission, and longer delay before primary PCI, higher CTFC before recanalizaiton, TIMI score, and CK-MB levels among the patients with the no-reflow phenomenon (P: <0.001, 0.023, 0.012, <0.001, 0.008, <0.001, 0.001, <0.001, <0.001, and 0.004, respectively). Importantly, the patients with no-reflow phenomenon had significantly lower ratio of PIA than the patients with normal reflow (n=111 [25.5%] *vs.* n=198 [40.3%], P<0.001). No-reflow patients had significantly higher plasma D-dimer level than patients with normal reflow after primary PCI (P<0.001).

PIA and plasma D-dimer level on admission are independent predictors of no-reflow phenomenon

Because our results indicated multiple potential clinical factors associated with the no-reflow phenomenon of STEMI patients, we performed logistic regression analysis to find the independent predictors of no-reflow. As shown in Table 3, in the univariant analysis, hypertension, smoke, history of ischemic heart disease, diabetes, hyperlipidemia, TIMI grade on admission, PIA, time before primary PCI, CK-MB level, LVEF, and D-dimer level on admission were potential predictors of no-reflow phenomenon. In the multivariant analysis, most of these potential predictors maintained their significance in predicting no-reflow phenomenon. Importantly, PIA was an independent protective predictor of no-reflow, with a risk of 0.516 (95% CI:

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Table 3. Logistic regression analysis of predictors of no-reflow in T2DM patients after PCI.

Features	Univariant analysis				Multi-variant analysis			
	P value	Risk	95% CI		P value	Risk	95% CI	
			Lower bound	Upper bound			Lower bound	Upper bound
Age (>53 *vs.* ≤53 years)	0.982	1.003	0.774	1.300	0.818	0.967	0.724	1.290
Male (yes *vs.* no)	0.744	0.958	0.739	1.241	0.991	1.002	0.735	1.366
BMI (kg/m^2)	0.105	1.022	0.996	1.048	0.117	0.977	0.950	1.006
Hypertension (yes *vs.* no)	**<0.001**	1.727	1.330	2.247	**<0.001**	1.783	1.332	2.388
Smoke (yes *vs.* no)	**0.023**	1.359	1.043	1.773	0.078	1.330	0.969	1.825
History of ischemic heart disease (yes *vs.* no)	**0.012**	1.464	1.086	1.976	**0.011**	1.545	1.107	2.156
Diabetes (yes *vs.* no)	**<0.001**	2.160	1.653	2.825	**<0.001**	2.233	1.643	3.035
Hyperlipemia (yes *vs.* no)	**0.008**	1.422	1.096	1.845	0.438	1.126	0.834	1.521
TIMI grade at admission (<3 *vs.* =3)	**<0.001**	2.123	1.595	2.825	**<0.001**	2.182	1.598	2.980
Pre-infarction angina (yes *vs.* no)	**<0.001**	0.507	0.383	0.671	**<0.001**	0.516	0.380	0.701
Time before PCI (hour)	**0.001**	1.088	1.033	1.146	**0.003**	1.093	1.031	1.159
CK-MB peak (mmol/L)	**0.005**	1.001	1.002	1.000	**0.015**	1.001	1.000	1.002
LVEF (%)	**0.004**	1.468	1.131	1.905	**0.007**	1.486	1.114	1.984
D-dimer (ng/ml)	**<0.001**	2.387	1.828	3.115	**<0.001**	2.563	1.910	3.439

0.516~0.380). Plasma D-dimer level on admission was an adverse predictor of the no-reflow phenomenon, with a risk of 2.563 (95% CI: 1.910~3.439).

Combining PIA and plasma D-dimer on admission showed better prediction of the no-reflow phenomenon

We plotted ROC curves to evaluate the accuracy of predicting the no-reflow phenomenon of PIA and plasma D-dimer level on admission. A high D-dimer level was defined as a D-dimer level more than the mean value of all patients included in this study (>383.1 ng/ml). As shown in Figure 2A, PIA had an area under the curve (AUC) of 0.574 (95% CI: 0.537~0.611), a sensitivity of 0.745, and a specificity of 0.403 in predicting no-reflow phenomenon, while the plasma D-dimer level on admission had an AUC of 0.604 (95% CI: 0.568~0.641, Figure 2B), with a sensitivity of 0.526 and a specificity of 0.682. Then, we combined the plasma D-dimer level on admission and the PIA to form a new signature. Using this new signature to predict no-reflow, the AUC was increased to 0.637 (95%CI: 0.601, 0.673) with the best sensitivity of 0.871 and the best specificity of 0.819 (Figure 2C). These data suggest that combining PIA and plasma D-dimer on admission would be a sound signature for use in predicting the no-reflow phenomenon for STEMI patients.

Plasma D-dimer level on admission and PIA are associated with mortality of STEMI patients

All the patients were divided into 3 groups according to their plasma D-dimer level on admission and PIA: patients with high-D-dimer and without PIA, patients with either high D-dimer or no-PIA group, and patients with low D-dimer and PIA. The ratio of the no-reflow phenomenon and in-hospital all-cause mortality of these patients were compared. As shown in Figure 3A, the percentage of the no-reflow phenomenon among the patients with high D-dimer and without PIA was the highest among these 3 groups (P value <0.001). In addition, these patients had the highest all-cause in-hospital mortality (P value=0.041, Figure 3B).

Discussion

The no-reflow phenomenon has been investigated extensively in clinical settings and basic science laboratories. No-reflow phenomenon, which develops mostly within the first 2 h after reperfusion, is mainly the consequence of ischemic endothelial cell injury obstructing the capillary lumen [18,19]. The incidence of no-reflow phenomenon is around 20% in all AMI

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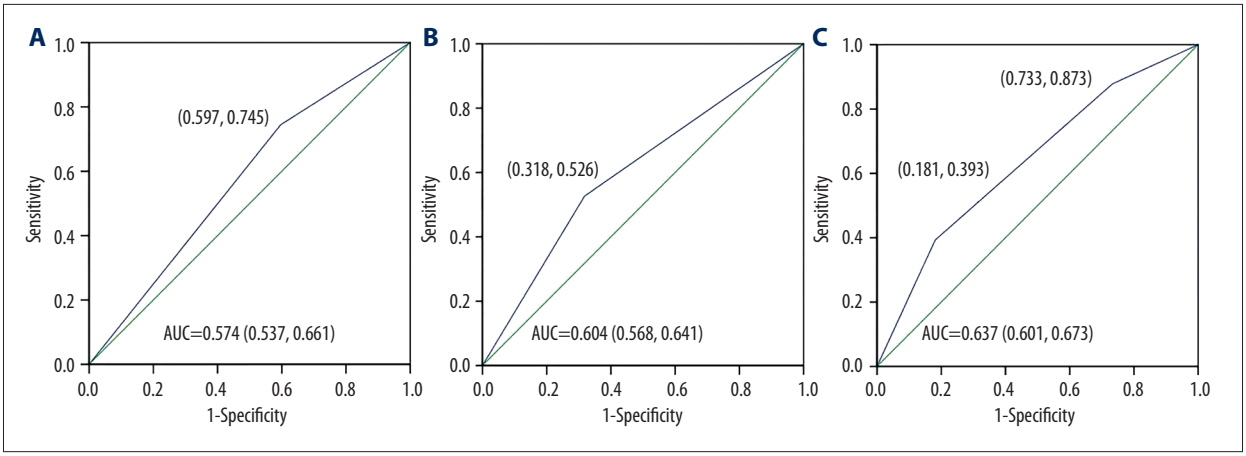

Figure 2. ROC curve of predicting the no-reflow phenomenon after primary PCI of STEMI patients. ROC curves were plotted using the plasma D-dimer level on admission and PIA to predict the no-reflow phenomenon. (**A**) Predicting no-reflow phenomenon using PIA had an AUC of 0.574 (95% CI: 0.537 to 0.661), with a sensitivity of 0.745 and a specificity of 0.403. (**B**) The AUC of using D-dimer to predict no-reflow phenomenon was 0.604 (95% CI: 0.568 to 0.641), with a sensitivity of 0.526 and a specificity of 0.682. (**C**) Combining plasma D-dimer level on admission and PIA to predict the no-reflow phenomenon showed an increased AUC of 0.637 (95%CI: 0.601 to 0.673).

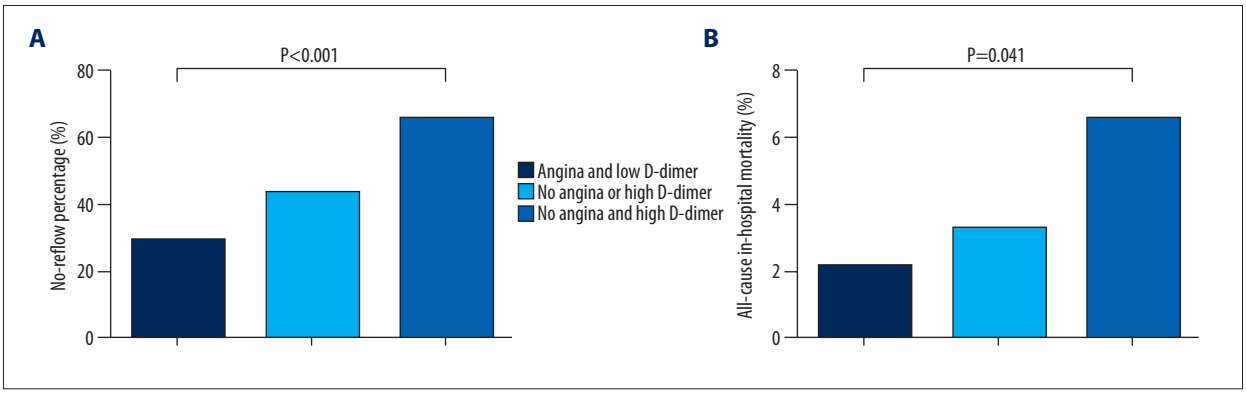

Figure 3. No-reflow rate and all-cause in-hospital mortality of STEMI patients after primary PCI. (**A**) The percentage of no-reflow was highest among STEMI patients with high D-dimer level on admission and without PIA compared with other patients (P<0.001). (**B**) All-cause in-hospital mortality of the STEMI patients with high D-dimer level on admission and without PIA was higher compared with other patients (P=0.041).

patients after primary PCI and is the major cause of primary PCI failure [20]. However, it is still a challenge to predict no-reflow in STEMI patients in clinical practice.

PIA is the angina episode preceding the onset of definite AMI. Previous studies have shown that patients with PIA tend to have reduced infarct size and increased ejection fraction compared with patients without PIA [21,22]. Therefore, PIA was identified as a favorable prognosticator in patients with STEMI [23]. Mechanisms underlying this association are likely related to activation of ischemic preconditioning (IP) by PIA [24]. In animal models, IP can reduce infarct size by half [25]. In addition to infarct size reduction, the microcirculation may also be protected by IP after reperfusion, as previously shown in animal models [26]. This effect may be related to endothelial function improvement and prevention of neutrophil activation caused by ischemic reperfusion. The severe cell injury caused by ischemia is one of the major causes of no-reflow phenomenon[27]. Considering the mechanistic connections between the IP by PIA and no-reflow phenomenon, we expected that the absence of PIA could serve as a predictor of the no-reflow phenomenon. To this end, we designed a prospective study to evaluate the association between PIA and no-reflow in STEMI patients. In the no-reflow cohort, the proportion of patients with PIA was significantly lower than in the normal reflow cohort. The multivariate analysis indicated that the presence of PIA could significantly reduce the odds of having no-reflow phenomenon (OR=0.516, 95%CI=0.380, 0.701). This observation is in line with a previous study reporting that absence of PIA is associated with higher risk of no-reflow in STEMI patients [28].

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D-dimer is the final product of fibrin degradation by plasmin, the plasma concentrations of which are increased in ongoing or recent thrombosis. Earlier studies have already shown that plasma D-dimer levels were higher in patients with AMI than in patients with stable angina or in healthy individuals, meaning that the D-dimer level reflects the ongoing thrombotic disease [29]. Plasma D-dimer levels on admission were shown to be significantly associated with thrombus burden in AMI patients [30]. These facts highly suggest that the plasma D-dimer level on admission is a potential biomarker of no-reflow, which is positively influenced by the thrombus burden. In our study, plasma D-dimer level on admission was significantly higher in patients with no-reflow phenomenon than in those patients without no-reflow phenomenon. In the multivariate analysis, the plasma D-dimer level on admission was an independent predictor of no-reflow. This observation is in agreement with a previous publication by Ayhan et al. [17].

Our study also revealed several other independent predictors of no-reflow phenomenon after the primary PCI, such as hypertension, history of ischemic heart disease, and CK-MB peak level. These results suggest that no-reflow phenomenon is a multiple-factor-driven outcome. Some other potential risk factors of the no-reflow phenomenon of STEMI patients after PCI have also been reported by previous studies, such as the number of infarct-related Q-waves in the ECG precordial leads before the primary PCI, primary platelet/lymphocyte ratio, C-reactive protein level, and monocyte count on admission [9,10,31]. Many of these reported potential risk factors of the no-reflow phenomenon are related to the inflammation response after myocardial infarction, which is currently recognized as one of the most important pathogenesis mechanism of no-reflow [32]. These observations indicate the complicated nature of the no-reflow mechanism, as well as the difficulty of no-reflow prediction.

Although the protective effect of PIA and the clinical value of plasma D-dimer level were previously investigated, our study expanded these earlier observations by showing that combining PIA and plasma D-dimer level had stronger prediction value of the no-reflow phenomenon than using each parameter alone. This combination provides a potential novel clinical feature for treatment selection in STEMI patients. Further studies are warranted to investigate whether STEMI patients with high D-dimer levels and absence of PIA on admission might be selected for more aggressive complementary treatment strategies to enhance microvascular perfusion after primary PCI and even long-term prognosis. However, there are several limitations to the present study. First, assessment of PIA depends on correct symptom recognition by the patients. Therefore, our study could not exclude the influence of recall bias for PIA. Second, although we have tried to include relevant clinical parameters as extensively as possible to minimize the influence of the differences in baseline characteristics, unmeasured factors, such as cardiac troponin, could influence the time course of ongoing myocardial necrosis. Third, in the present study, we only combined PIA and plasma D-dimer level to predict the no-reflow phenomenon. To further improve the predictive value, it is important to include more parameters to form a comprehensive model. Overall, our findings indicate the needs for concomitant assessment of the clinical value of PIA, plasma D-dimer level, and more clinical parameters in well-defined or controlled patient populations.

Conclusions

Based on these solid results, we conclude that combining plasma D-dimer level on admission and PIA might be a useful signature for use in predicting the no-reflow phenomenon after primary PCI in STEMI patients. It may help to screen STEMI patients with relatively high risk of no-reflow on admission and help the physicians select the best treatment.

Conflict of interest

None.

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