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ORIGINAL ARTICLE

D-Dimer Level Predicts Angiographic No-Reflow Phenomenon After Percutaneous Coronary Intervention Within 2–7 Days of Symptom Onset in Patients with ST-Segment Elevation Myocardial Infarction

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Abstract

It remains uncertain whether plasma D-dimer level can predict no-reflow in patients with STEMI who had pPCI after 48 h of symptom onset. This study retrospectively enrolled 229 consecutive patients who had pPCI for acute STEMI within 2–7 days of symptom onset between January 2008 and December 2018. Patients were divided into no-reflow group (TIMI flow grade 0–2) and reflow group (TIMI flow grade 3). Predictors of no-reflow were assessed by univariate and multivariate binary logistic regression analyses. Plasma D-dimer level can independently predict no-reflow in patients with STEMI who had pPCI within 2–7 days of symptom onset (OR 2.52 per 1 mg/L increase, 95% CI 1.16–5.47, $p = 0.019$). This finding indicated that pPCI may be safe and feasible for STEMI patients within 2–7 days of symptom onset with low D-dimer level.

Keywords D-dimer · No-reflow · ST-segment elevation myocardial infarction · Primary percutaneous coronary intervention

Abbreviations

cTnT	Cardiac troponin T
ECG	Electrocardiogram
eGFR	Estimated glomerular filtration rate
hs-CRP	High-sensitivity C-reactive protein
IRA	Infarct-related artery
MACE	Major cardiovascular adverse events
MI	Myocardial infarction
NT-pro BNP	N-terminal pro-B-type natriuretic peptide
pPCI	Primary percutaneous coronary intervention
PTCA	Percutaneous transluminal coronary angioplasty
STEMI	ST-segment elevation myocardial infarction
TIMI	Thrombolysis in myocardial infarction

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Introduction

Primary percutaneous coronary intervention (pPCI) is the most effective reperfusion strategy for patients with acute ST-segment elevation myocardial infarction (STEMI) [1], especially when performed within 12 h of symptom onset and, according to the 2017 European Society of Cardiology (ESC) guidelines, up to 48 h [2]. However, approximately one-third of eligible patients do not receive early reperfusion therapy because of late presentation [3], for which optimal strategy remains uncertain [4]. Serious complications especially no-reflow phenomenon occur more likely when PCI was performed at 2–7 days, leading to higher early and late morbidity and mortality [5, 6]. The high incidence of immediate no-reflow after stenting has discouraged PCI during said period [7].

No-reflow is commonly secondary to heavy intra-coronary thrombus burden [8, 9] and impaired microvascular function [10]. An increase in the level of D-dimer, the simplest degradation product of fibrin, reflects ongoing or recent thrombosis [11]. D-dimer level can independently predict no-reflow and major cardiovascular adverse events (MACE) after PCI in early STEMI [12–14]; however, it remains to be determined if this also applies to the 2–7-day interval. We hypothesized that, as an indirect estimate of thrombus burden, plasma D-dimer level can also predict no-reflow phenomenon when PCI was performed at 2–7 days of symptom onset.

Methods

Study Population and Design

We retrospectively screened 240 consecutive patients who had pPCI for acute STEMI from 48 h to 7 days after the onset of symptoms between January 2008 and December 2018. Of them, 229 patients whose D-dimer levels were measured on admission were included in this study. The diagnosis of acute STEMI was based on the specific electrocardiography (ECG) criteria laid down in the European Society of Cardiology, American College of Cardiology Foundation, American Heart Association, and World Heart Federation (ESC/ACCF/AHA/WHF) committee [15]. Coronary blood flow was analyzed according to thrombolysis in myocardial infarction (TIMI) flow grade [16]. Angiographic no-reflow was defined as postinterventional TIMI flow grade < 3 without clear evidence of dissection, stenosis, or vasospasm [17]. Patients were divided into no-reflow group (TIMI flow grade 0–2) and reflow group (TIMI flow grade 3). Patients with culprit lesion in the left main coronary artery; left main coronary artery stenosis > 50%; previous coronary artery bypass surgery; major surgeries or severe injuries in the past 6 months; cardiogenic shock; pain to balloon time < 48 h; thrombolysis failure and rescue PCI; active infectious or inflammatory diseases; presence of any chronic inflammatory-autoimmune disease including rheumatologic disorders, hematologic diseases, class IV heart failure, severe respiratory, renal, or hepatic dysfunction or failure; and history of thromboembolic disease, treated cancer, inflammatory process, or pregnancy were excluded from the current study. The study protocol was reviewed and approved by the Ethics Committee of Zhongshan Hospital, Fudan University.

Coronary Angiography and Percutaneous Coronary Intervention

All patients received a 300 mg chewable aspirin and a 300-mg loading dose of clopidogrel or a 180-mg loading dose of ticagrelor on admission, and 100 U/kg intravenous standard heparin during the procedure. Coronary angiography and pPCI were performed by experienced interventional cardiologists. At least one drug-eluting stent was implanted in the culprit lesion of infarct-related artery (IRA). The technical aspects of the procedure, duration and pressure of inflation, and thrombus aspiration or not were at the discretion of individual operators. After the intervention, all patients were prescribed clopidogrel (75 mg once daily for 12 months) or ticagrelor (90 mg twice daily for 12 months) and aspirin (100 mg indefinitely).

Visual assessments for lesion characteristics, thrombus burden, and pre- and post-interventional TIMI flow grade were performed by two interventional cardiologists blinded to patients' clinical data. TIMI thrombus score was used to evaluate thrombus burden in all patients, and TIMI thrombus score ≥ 4 was defined as high-grade angiographic thrombus burden [18]. TIMI flow grade 3 was defined as complete coronary flow within three cardiac cycles, whereas TIMI flow grade < 3 denoted incomplete perfusion or complete perfusion over three cardiac cycles.

Data Collection

All clinical and sociodemographic characteristics of the patients were extracted from hospital files and computer records. Peripheral venous blood samples for the determination of baseline biochemical parameters including D-dimer, N-terminal pro-B-type natriuretic peptide (NT-pro BNP), cardiac troponin T (cTnT), high-sensitivity C-reactive protein (hs-CRP), creatine kinase, complete blood count, and renal function were obtained on admission in the emergency department and all measurements were performed 15 min after blood collection. Estimated glomerular filtration rate (eGFR) on admission was calculated according to modification of diet in renal disease formula. Blood sampling for D-dimer measurement was made using a commercial D-dimer assay (MDA immunoturbidimetric assay; Sysmex, CA7000). Postprocedural transthoracic echocardiography was performed on all patients during the in-hospital period as recommended [19]. MACEs were defined as in-stent thrombosis, nonfatal myocardial infarction (MI), and in-hospital mortality during the in-hospital follow-up period. In-stent thrombosis was defined as angiographically documented total occlusion. Non-fatal MI was defined as recurrent chest pain and/or development of new ECG changes accompanied by a new increase ≥ 20% in levels of cardiac biomarkers measured after the recurrent event. In-hospital mortality had to be verified as death from MI, cardiac arrest, or other cardiac causes.

Statistical Analysis

Continuous data were expressed as mean (standard deviation) and compared using independent samples *t* test, while

categorical variables were expressed as number (percentage) and were compared using the chi-square tests. A p value of < 0.05 was regarded as statistically significant. Independent predictors of angiographic no-reflow were determined by binary logistic regression analysis with stepwise selection. Odds ratios (ORs), 95% confidence intervals (CIs), and p values were calculated using the IBM SPSS Statistics 19.0 software package (SPSS, Inc., Chicago, IL). To assess the predictive value of D-dimer, receiver operating characteristics (ROC) analysis was conducted with calculations of the area under the ROC curve (AUC), sensitivity, and specificity.

Results

The study population consisted of 229 patients (mean age 63.7 (12.1); 83.0% male) who underwent pPCI for acute STEMI 2–7 days after symptom onset. Postinterventional TIMI flow grade 3 was achieved in most patients ($n = 201$, 87.8%) and the incidence of angiographic no-reflow was 12.2% ($n = 28$).

Baseline Characteristics

As summarized in Table 1, baseline and clinical characteristics were balanced between study groups except for higher proportions of smokers, Killip class ≥ 2, TIMI flow grades, and total ischemic time in no-reflow group compared with reflow group.

Laboratory Test Results

As shown in Table 2, angiographic no-reflow group had higher levels of D-dimer (Fig. 1a), log (NT-pro BNP), hs-CRP, white blood cell, and neutrophil counts compared with reflow group.

Table 1 Baseline characteristics by study group

Characteristic	No-reflow ($n = 28$)	Reflow ($n = 201$)	p
Age (years)	66.8 (14.8)	63.3 (11.7)	NS
Female gender	8 (28.6%)	31 (15.4%)	NS
BMI (kg/m^2)	23.8 (2.9)	22.9 (2.7)	NS
Previous CAD	2 (7.1%)	10 (5.0%)	NS
Diabetes	8 (28.6%)	60 (29.9%)	NS
Hypertension	18 (64.3%)	113 (56.2%)	NS
Hyperlipidemia	0	2 (1.0%)	NS
Smoker	16 (64.3%)	20 (10.0%)	< 0.01
Family history of CAD	0	0	NS
TT (h)	104.6 (36.5)	132.7 (35.8)	< 0.01
Killip class ≥ 2	8 (28.6%)	10 (5.0%)	< 0.01
TIMI flow grade ≤ 2	28 (100%)	131 (65%)	< 0.01

Data are presented as n (%) or mean (SD). *BMI*, body mass index; *CAD*, coronary artery disease; *TT*, total ischemic time; *NS*, not significant

Angiographic and Echocardiographic Findings

The proportion of patients with TIMI thrombus score ≥ 3 and thrombus aspiration in no-reflow group was significantly higher than that in reflow group. Multivessel disease proportion and postprocedural LVEF were similar between the two groups; however, the proportion of pericardial effusion in the no-reflow group was higher than that in the reflow group ($p < 0.05$; Table 3).

Independent Predictive Value of D-Dimer for Angiographic No-Reflow

D-dimer level was higher in patients with TIMI thrombus score ≥ 3 compared with those with TIMI thrombus score < 3 (1.9 (1.6) vs. 0.6 (0.6), $p < 0.01$) (Fig.1b). As shown in Table 4, besides TIMI thrombus score, plasma D-dimer level can independently predict the no-reflow phenomenon after PCI (OR 2.52 per 1 mg/L increase, 95% CI 1.16–5.47, $p = 0.019$).

Prognostic Value of D-Dimer Level on No-Reflow Phenomenon

In ROC analysis (Fig. 2), a D-dimer value of 0.53 (mg/L) was identified as an effective cut-off point in prediction of postprocedural no-reflow phenomenon, with 85.7% of sensitivity and 67.7% of specificity (AUC = 0.78; 95% CI, 0.69–0.88, $p = 0.049$).

In-Hospital Outcomes

There is no significance between the two groups in the in-stent thrombosis or non-fatal MI. The no-reflow group had a higher in-hospital mortality rate than the reflow group ($p = 0.014$; Table 5).

Discussion

This study, to our knowledge, is the first to demonstrate that plasma D-dimer level on admission can independently predict no-reflow in patients who had pPCI for acute STEMI 2–7 days after symptom onset.

PPCI is not recommended by the guidelines in patients with STEMI if the onset of symptoms came on over 48 h, because it provides little benefit after longstanding myocardial necrosis and is associated with complications, such as myocardial hemorrhage, microembolism, and no-reflow. However, Horie et al. [20] showed that even with late

Table 2 Laboratory findings on admission by study group

	No-reflow ($n = 28$)	Reflow ($n = 201$)	p
Baseline eGFR < 60 mL/min/1.73 m^2	4 (14.3%)	30 (14.9%)	NS
Log (NT-proBNP)	3.4 [0.3]	3.1 [0.5]	< 0.05
D-dimer (mg/L)	1.6 [1.4]	0.5 [0.6]	< 0.01
Troponin T (μmol/L)	2.0 [1.5]	1.5 [1.4]	NS
WBC count (*10^9/L)	11.0 [2.6]	9.6 [3.3]	< 0.05
Neu (%)	75.5 [5.2]	71.2 [9.5]	< 0.05
Monocyte count (*10^9/L)	6.7 [1.6]	7.2 [2.3]	NS
RDWsd (fl)	41.2 [2.7]	41.5 [2.7]	NS
Platelet count (*10^9/L)	196.2 [42.1]	203.7 [58.2]	NS
hs-CRP	75.8 [81.7]	43.3 [45.9]	< 0.01

Data are presented as n (%) or mean [SD]. *eGFR*, estimated glomerular filtration rate; *hs-CRP*, high-sensitivity C-reactive protein; *NT-proBNP*, N-terminal pro B-type natriuretic peptide; *RDW*, red blood cell distribution width; *WBC*, white blood cell; *Neu*, neutrophil count; *NS*, not significant

reperfusion, percutaneous transluminal coronary angioplasty (PTCA) had beneficial effects on cardiac events' occurrence over a 5-year period after MI. Both DECOPI [21] and OAT [22] trials demonstrated no difference in clinical outcomes between patients randomized to PCI versus optimal medical therapy alone with an occluded IRA over 48 h post-MI (25% of PCI was performed within 5 days). The results are consistent with the safety documented in the present study and may be related to thrombus aspiration and extensive use of glycoprotein IIb/IIIa antagonists. However, the incidence of no-reflow in DECOPI, OAT, and the present study is 17.8%, 18%, and 12.23%, respectively, which is higher than that for PCI within 12 h of symptom onset. No-reflow remained a powerful independent predictor of death or myocardial infarction, patients with no-reflow presented more frequently with congestive heart failure and pericardial effusion than patients with normal flow [23], most of which was confirmed in our study. Therefore, it is necessary to assess risk for no-reflow before pPCI for this subpopulation to further improve the safety of intervention.

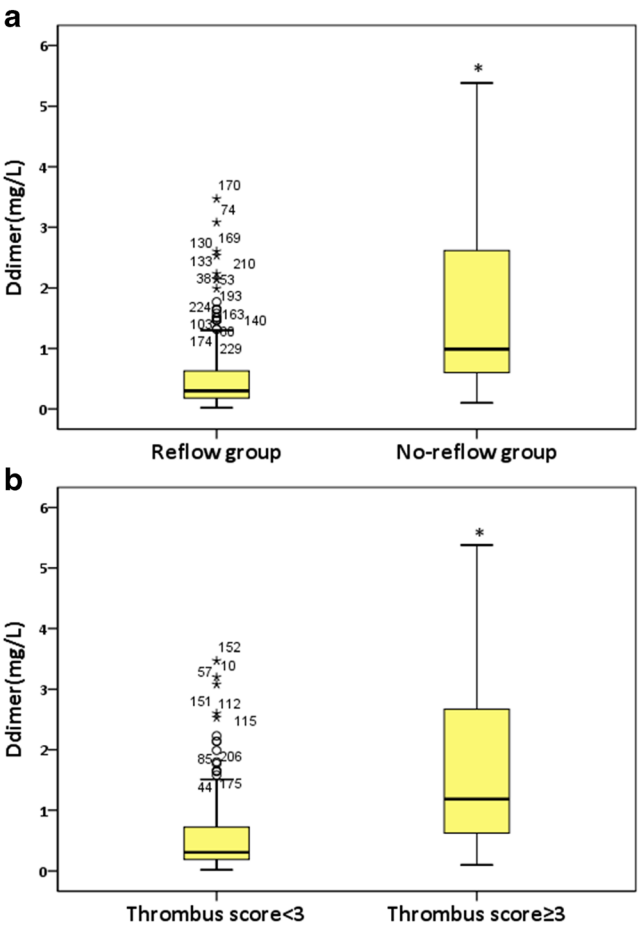

Fig. 1 Box diagram for comparison of D-dimer level in different groups. **a** Mean D-dimer level was significantly higher in no-reflow group than that in reflow group (*p value < 0.05). **b** Mean D-dimer level was significantly higher in patients with TIMI thrombus score ≥ 3 compared with those with TIMI thrombus score < 3 (*p value < 0.01)

There are ample evidences for using D-dimer to assess thrombus burden. The coagulation system plays a major role in the development of thrombosis in the setting of AMI [24]. Over 60% of thrombus is fibrin fibers, with the proportion increasing with ischemic time [25], while platelets, erythrocytes, cholesterol crystals, and leukocytes together comprise the remaining 40% [25]. D-dimer is a final product of the specific degradation of fibrin monomer crosslinked by activating factor XIII and hydrolyzed by plasmin. The plasma level of D-dimer increases in subjects with ongoing or recent thrombosis [11], reflecting activation of the fibrinolysis and coagulation systems [26], and serves as an indirect estimation of the size of the thrombotic mass available for fibrinolysis and the severity of the hypercoagulable state [27]. It has been suggested that high D-dimer levels reflect a systemic prothrombotic state and focal vessel wall-related fibrin formation with unstable atherosclerotic plaque activity [6]. Plasma D-dimer levels have been correlated with thrombus burden in cases of acute pulmonary embolism and lower extremity

Table 3 Angiographic and echocardiographic characteristics by study group

	No-reflow ($n = 28$)	Reflow ($n = 201$)	p
TIMI thrombus score			< 0.01
0	4	140	
1	4	42	
2	4	19	
3	11	2	
4	1	0	
5	4	0	
Thrombus aspiration	18 (64.29%)	20 (9.95%)	< 0.01
Multivessel disease	20 (71.43%)	127 (63.18%)	NS
Postprocedural LVEF (%)	49.4 [9.5]	51.7 [8.2]	NS
Pericardial effusion	10 (35.71%)	29 (14.43%)	< 0.05

Data are presented as *n*, *n* (%) and mean [SD]. *LVEF*, left ventricular ejection fraction; *NS*, not significant

venous thrombosis [28–31] and acute myocardial infarction [14, 32]. D-dimer levels are significantly higher in patients treated within 12 h of symptom onset and with TIMI thrombus score > 4 vs. ≤ 4 [12].

Thrombus age has impact on D-dimer level [14]. Thrombosis activity and thrombus burden are important contributors to magnitude of D-dimer level increase, with D-dimer level positively correlating with "fresh" thrombus burden. In theory, old thrombosis no longer leads to D-dimer production, and continuously, negative D-dimer would suggest resolution or chronic organization of acute thrombosis [33–36]. However, in our study, D-dimer level correlated with thrombus burden in STEMI patients with 2–7 days of symptom onset. Patients with TIMI thrombus score ≥ 3 vs. < 3 had significantly higher D-dimer levels, indicating that heavy thrombus burden beyond the initial 2 days window for PCI also increases the risk of distal embolization and no-reflow. Studies in the setting of pulmonary embolism also documented that plasma D-dimer levels reflect thrombus burden over a long period [30, 31, 37]. The finding that D-dimer level predicts no-reflow is consistent with thrombus burden being an important underlying factor of no-reflow [8, 9, 26, 38], which might allow risk assessment of pPCI procedure for the patients who had pPCI within 2–7 days of symptom onset, a thus far controversial PCI time window [39, 40] and not recommended in guidelines. This finding implies

Table 4 Univariate and multivariate analysis of risk factors for angiographic no-reflow status

	Univariate analysis		Multivariate analysis	
	OR	95%CI	OR	95%CI
BMI (kg/m^2)	1.12	0.98–1.29	–	–
Age (years)	1.03	0.99–1.06	–	–
Female gender	2.19	0.89–5.42	–	–
Smoke (yes vs. no)	12.07	5.01–29.08#	0.83	0.11–6.59
Killip	7.64	2.71–21.56#	0.69	0.08–6.22
Pre TIMI	14.43	1.92–108.42#	8.90	0.56–140.82
Thrombus score	132.67	27.29–644.88#	55.26	4.18–730.03#
Thrombus aspiration	13.99	5,76–33.99#	3.84	0.61–23.96
TT	0.98	0.97–0.99#	1.0	0.98–1.03
D-dimer	3.16	2.0–5.0#	2.52	1.16–5.47*
WBC	1.12	1.0–1.24*	1.03	0.85–1.25
Neutrophil	1.06	1.01–1.12*	1.03	0.94–1.13
hs-CRP	1.01	1.0–1.01#	1.0	0.99–1.01
LogNT-proBNP	3.75	1.44–9.78#	0.79	0.17–3.61
cTnT	1.25	0.99–1.57	–	–

BMI, body-mass index; *TT*, total ischemic time; *hs-CRP*, high-sensitivity C-reactive protein; *NT-pro BNP*, N-terminal pro B-type natriuretic peptide; *cTnT*, cardiac troponin T; *WBC*, white blood cell count; *p value < 0.05; #p value < 0.01

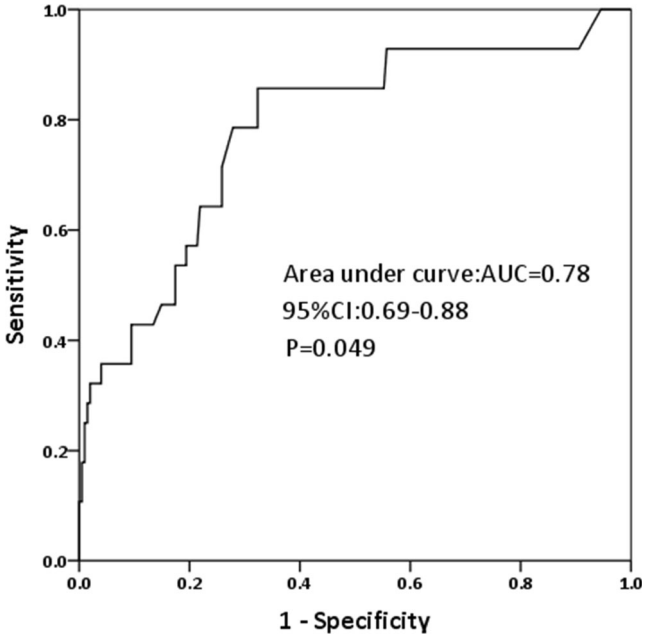

Fig. 2 Receiver operating curve analysis to obtain optimal cut-off for D-dimer to predict no-reflow phenomenon. The cut-off value of D-dimer was 0.53 (mg/L), with 85.7% of sensitivity and 67.7% of specificity (AUC = 0.78; 95% CI, 0.69–0.88, $p = 0.049$)

Table 5 In-hospital major adverse cardiac events by study group

	No-reflow ($n = 28$)	Reflow ($n = 201$)	p
In-hospital MACE:			
In-stent thrombosis	0	0	NS
Non-fatal MI	0	0	NS
Death	2	0	< 0.05

MACE, major adverse cardiac event; *MI*, myocardial infarction; *NS*, not significant

that pPCI may be safe and feasible for STEMI patients within 2–7 days with low D-dimer level, while PCI should be delayed for those with high D-dimer level. Large-scale multicenter studies are warranted to further assess the safety and long-term efficacy of pPCI performed within 2–7 days of symptom onset for STEMI and to explore other cardiac biomarkers that could be used to identify patients who would benefit most from pPCI.

Limitations

The study has the limitations inherent to its single center, retrospective design with a relatively small sample size which might introduce selection bias. The pathophysiological process of AMI is very complex, including endothelial integrity destruction, plaque rupture, thrombosis, mechanical effects, reperfusion, stress, and changes in blood composition, among other variables. Therefore, it might be simplistic to expect a single biochemical parameter related to thrombus burden to allow risk stratification of pPCI for STEMI. We only presented in-hospital events in our study; lack of follow-up data may be another limitation for our study.

Conclusion

Plasma D-dimer level on admission can independently predict no-reflow in patients with STEMI who had pPCI within 2–7 days of symptom onset; pPCI may be safe and feasible for these patients with low D-dimer level.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human Subjects/Informed Consent Statement No treatment was tested in patients by the authors for this article. Fudan University affiliated Zhongshan Hospital Ethics Committee had approved the work and received all the written informed consent.

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