Evaluation of related factors, prediction and treatment drugs of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction after direct PCI

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Abstract. This study determined the related factors of no-reflow phenomenon in patients with acute ST-segment elevation myocardial infarction (STEMI) after direct percutaneous coronary intervention (PCI), and evaluated related factor scores in predicting the occurrence of no-reflow phenomenon and drug treatments. A total of 203 patients with acute STEMI receiving PCI who were admitted to the Department of Cardiovascularology, Xiangyang No. 1 People's Hospital, Hubei University of Medicine (Xiangyang, China) from January 2015 to December 2016 were selected. The clinical and image data were analyzed to determine the related factors of no-reflow phenomenon after operation, and related factor scores were quantified to predict the occurrence of no-reflow phenomenon. Three drugs (diltiazem, nitroglycerin and tirofiban needles) were continuously injected in coronary arteries of patients with no-reflow phenomenon, and the effects of these drugs were analyzed. There were 38 patients (18.7%) with no-reflow phenomenon. The correlation analysis showed that 10 factors were associated with no-reflow phenomenon, in which five factors were identified as risk factors, including IRA open-up time ≥8 h, SBP <100 mmHg, Hs-CRP >18 mg/l, thrombus loads, length of the culprit vessel ≥20 mm. The score analysis of related factors of 38 patients with no-reflow phenomenon was conducted. Three points were set for five risk factors each, and 1 point was set for the other five factors each. It was found that the score was approximately normally distributed. The average was 11.5±1.57 points and the lower limit of 95% confidence interval was >8.93 points. The effective rates of three drugs were different (P<0.05), and the pairwise comparison showed their effective rates were not fully identical (P<0.05). The results showed that: i) There are 10 related factors, including five risk factors; ii) related factors with the score ≥9 points can be used for clinical prediction of STEMI after direct PCI; and iii) it is obviously effective to use diltiazem needle and tirofiban needle to treat no-reflow phenomenon, but this conclusion lacks statistical support.

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Introduction

The key of acute ST-segment elevation myocardial infarction (STEMI) treatment is to restore myocardial perfusion as soon as possible. Direct percutaneous coronary intervention (PCI), as the most effective means of treatment, it can open up the infarct-related artery (IRA) as early as possible (1), which significantly improves the quality of life of patients and prevent further necrosis of the myocardium. It is minimally invasive and rapid, thus significantly reducing the mortality rate of acute myocardial infarction. The latest evidence-based guide recommended it as the preferred treatment of STEMI (2). However, in some cases, myocardial reperfusion cannot restore the myocardium to the optimal level, which is known as the 'no-reflow' phenomenon.

Risks of left ventricular dysfunction and progressive myocardial damage of patients with no-reflow phenomenon are increased. A study showed that no-reflow phenomenon of STEMI patients after direct PCI is an independent predictive factor for the mortality rate of STEMI patients at more than 5 years after acute events (3). Thus, the clinical priority is to predict the occurrence of the no-reflow phenomenon as early as possible to select effective treatments.

In this study, a number of possible clinical and image factors associated with the no-reflow phenomenon were collected to determine the related factors, and the score allocation was quantified to predict the occurrence of no-reflow phenomenon, and the drug treatment of no-reflow phenomenon was analyzed and evaluated.

Patients and methods

Patients. In total, 203 patients with acute STEMI receiving PCI who were admitted to Xiangyang No. 1 People's Hospital,

Hubei University of Medicine (Xiangyang, China) from January 2015 to December 2016 were selected.

Inclusion and exclusion criteria. Inclusion criteria for the study were: i) Electrocardiogram: Patients with at least two adjacent leads, one in the limb with the ST-segment elevated >0.1 mv, the other in the chest with the ST-segment elevated >0.2 mv, or patients with left bundle branch block and ii) patients who signed the informed consent or the form was signed by their family members. This study was approved by the Ethics Committee of Xiangyang No. 1 People's Hospital, Hubei University of Medicine. Patients who successfully received direct PCI within 12 h in the event of symptoms, and who had sustained chest pains at >12 h after the occurrence or successfully received direct PCI within 24 h. Exclusion criteria for the study were: i) Patients with coronary spasm; ii) patients whose culprit coronary stenosis diameter was ≤50%, and coronary blood flow (CBF) was normal; and iii) patients whose severe left main coronary artery or multiple-vessel lesions needed emergency vascular revascularization (4).

Judgment criteria and methods

Thrombolysis in myocardial infarction (TIMI), coronary angiography, direct PCI and the intervention in no-reflow phenomenon with drugs. TIMI flow classification (5) clinically evaluates the criteria for coronary artery reperfusion using coronary angiography and is divided into TIMI grade 0 flow (no perfusion): There is no filling of antegrade flow (contrast agent) on the coronary occlusion and the distal coronary bed; TIMI grade 1 flow (penetration without perfusion; microfusion): The antegrade coronary flow partly passes through the coronary occlusion, but cannot fill the distal coronary bed at any time; TIMI grade 2 flow (partial reperfusion): The antegrade flow passes through the coronary occlusion with the filling of the distal coronary bed, but the filling speed is significantly slowed down compared with that of normal blood vessels; TIMI grade 3 flow (complete perfusion): The antegrade flow fills the distal coronary bed quickly and completely.

All patients took orally 300 mg aspirin and 600 mg clopidogrel sulfate while receiving intravenous injection of 6,000-8,000 units of unfractionated heparin. The right radial artery or femoral artery of patients received PCI. Before and after operation, at least two coronary angiography images at the best position were obtained from each patient, and two senior cardiac experts conducted a series of evaluations on these images and reached a consensus. These parameters included IRA judgment, IRA TIMI flows before and after intervention, thrombus loads, the target vessel diameter, the number of implanted stents, the length of culprit vessels and whether there was a need for aspiration catheters. All patients were divided into two groups according to IRA postoperative TIMI flow grading: TIMI flow ≤ grade 2 (no-reflow) and TIMI grade 3 flow (reflow) group. After the IRA fully expanded, and the obstruction was relieved, if no perforation, spasm and distal vascular thrombosis emerged, IRA TIMI flow ≤ grade 2 represented that the no-reflow phenomenon occurred in patients (6).

For patients with no-reflow phenomenon, firstly, 200 μg diltiazem (Tianjin Tianbian Pharmaceutical Co., Ltd., Tianjin, China; National Medicine permission number: J20160015) was injected into the IRA through the guidance catheter, and re-angiography was conducted to check whether the TIMI flow was restored to grade 3. If not, 200 μg nitroglycerin (Henan Runhong Pharmaceutical Co., Ltd., Henan, China; National Medicine permission number: H20057216) was further injected into the coronary artery, and the coronary angiography was further performed to see whether the TIMI flow was restored to grade 3. If not, 500 μg tirofiban injection (Lunan Beite Pharmaceutical Co., Ltd., Shandong, China; National Medicine permission number: H20090328) was injected into the coronary artery to record whether the TIMI flow was restored to grade 3. If it was restored, the treatment was effective; if not, the treatment was not effective (after the drug treatment, patients whose TIMI flows were still not restored to grade 3 received other treatments).

Analyses of related factors. The clinical and image data of two groups of patients were collected, and the relevant statistical method was used to analyze whether the related factors of no-reflow were statistically significant. Then a multivariate logistic regression model was used to obtain the risk factors of no-reflow.

Score allocation analyses of related factors in no-reflow phenomenon. One point was allocated for the condition that the univariate analysis showed no statistically significance while the multivariate analysis revealed statistically significance in the no-reflow group. Three points were allocated for the condition that both the univariate analysis and multivariate analysis showed statistical significance (independent risk factors). The score of the no-reflow group was comprehensively analyzed.

Evaluations of no-reflow drug treatments. Three drug treatments are shown below: Group A (diltiazem needle), group B (diltiazem + nitroglycerin) and group C (dilthiazole + nitroglycerin + tirofiban needles). Pairwise comparisons of the effective rates of the three groups in the treatment of no-reflow phenomenon were conducted.

Statistical analysis. Continuous variables were expressed as mean ± standard deviation (SD), the Chi-square test was used to analyze categorical variables, and ANOVA test was used for comparison between groups and the post hoc test was SNK test. The univariate and multivariate analyses were conducted to determine the related factors of no-reflow phenomenon. SPSS 17.0 software (SPSS, Inc., Chicago, IL, USA) was used, and $P<0.05$ was considered to indicate a statistically significant difference.

Results

Analyses of related factors and risk factors. In total, 203 STEMI patients received direct PCI, in which no-reflow phenomenon occurred in 38 cases (18.7%). Table I shows the clinical and laboratory examination data of the two groups of patients. There were no significant differences between the reflow group and the no-flow group in sex, hypertension, diabetes history, smoking >10 years, preoperative diastolic blood pressure, preoperative heart rate, hyperlipidemia, myocardial infarction history, family history of coronary heart disease, creatine kinase-MB

Table I. Clinical and laboratory examination data of two groups of patients (mean ± SD).

Variable	Reflow (n=165)	No-reflow (n=38)	t/χ^2 test	P-value
Age (years)	61.2±10.1	65.6±11.2	2.376	0.019
Sex (M/F)	90/75	20/18	0.046	0.836
Hypertension	63 (38.2)	19 (50.0)	1.792	0.181
Diabetes history	40 (24.2)	10 (26.3)	0.072	0.789
Smoking (>10 years)	70 (42.4)	17 (44.8)	0.067	0.795
IRA open-up time			8.936	0.003
<8 h	116 (70.3)	17 (44.7)		
≥8 h	49 (29.7)	21 (55.3)		
(h)	5.9±1.9	8.1±2.4	3.757	<0.001
SBP (mmHg)	115.3±19.4	101.5±20.5	3.912	<0.001
Diastolic pressure (mmHg)	72.3±12.2	68.5±14.2	1.677	0.952
Preoperative heart rate (bpm)	75±19	74±18	0.672	0.51
Hyperlipidemia	75 (45.5)	20 (52.6)	0.639	0.424
Myocardial infarction history	7 (4.2)	2 (5.3)	0.076	0.783
Family history of coronary heart disease	31 (18.8)	8 (21.1)	0.102	0.749
Killip classification (≤2 classes)	138 (83.6)	8 (68.4)	4.607	0.032
Creatine kinase-MB peak value (U/l)	161±98	175±105	1.180	0.250
White blood cell count (/mm^3)	10751±2950	12941±3001	2.832	0.004
Hs-CRP (mg/l)	8.20±2.54	18.15±3.42	11.194	<0.001
Glomerular filtration rate (ml/min)	77.28±19.28	76.34±18.64	0.589	0.684
Preoperative blood glucose (mmol/l)	10.5±2.95	11.8±3.19	2.412	0.025
Elevation amplitude peak of ST-segment (mm)	2.95±0.87	3.50±1.11	2.840	0.004

(CK-MB) peak value and glomerular filtration rate (all the above factors, P<0.05). Compared with the reflow group, the patients were older, white blood cell count was higher, the level of preoperative blood glucose was higher, the ST-segment was elevated to a higher degree, infarct-related blood vessels were opened up at a later stage, preoperative systolic blood pressure (SBP) was lower, the level of high-sensitivity C-reactive proteins (hs-CRP) were higher [18.15±3.42 vs. 8.20±2.54 (mg/l)] in the no-reflow than those in the reflow group, and differences in all the above factors between the two groups were significant (P<0.05). In addition, the preoperative Killip classification of the two groups was significantly different (P<0.05).

Table II shows the coronary angiography and PCI data of the two groups of patients. There were no differences between the reflow and no-reflow groups in the IRA, TIMI flow grading before intervention, the target vessel diameter, the number of implanted stents and the thrombus aspiration before reperfusion (P>0.05 for all the above factors); namely, the above factors did not affect the incidence rate of the no-reflow phenomenon. Thrombus loads and the length of blood vessels in the no-flow group were significantly different from those in the reflow group (P<0.05 for the above two factors).

As shown in Table III, the above 10 related factors were introduced into the univariate analysis and multivariate logistic regression analysis, which showed that the IRA ≥8 h [odds ratio (OR)=1.349, 95% confidence interval (CI)=1.164-1.435, P=0.001], and the preoperative SBP <100 mmHg (OR=1.698, 95% CI=1.062-2.984, P=0.001), hs-CRP >18 mg/l (OR=1.852, 95% CI=1.529-1.972, P=0.011), thrombus loads (OR=1.597, 95% CI=1.354-1.931, P=0.015) and the length of the culprit vessel ≥20 mm (OR=1.987, 95% CI=1.854-2.110, P=0.011) were independent risk factors for no-reflow phenomenon of STEMI after direct PCI.

Prediction of the occurrence of no-reflow phenomenon by the score allocation analysis of related factors in no-reflow group. The scores of 38 patients with no-reflow phenomenon and the above-mentioned 10 related factors were quantified [1 point each (age >65 years, Killip classification > Class 2, white blood cell count >13,000/mm^3, preoperative blood glucose >11.8 mmol/l, elevation amplitude peak of the ST-segment >35 mm) and 3 points each (the IRA ≥10 h, preoperative SBP <100 mmHg, high sensitivity C-reactive protein >18 mg/l, thrombus loads, the length of culprit vessel

Table II. Coronary angiography and PCI data of two groups of patients (mean ± SD).

Variable	Reflow (n=165)	No-reflow (n=38)	t/χ^2 test	P-value
IRA			1.509	0.219
Left coronary artery	95 (57.6)	26 (68.4)		
Right coronary artery	70 (42.4)	12 (31.6)		
TIMI flow grading before intervention			2.272	0.132
≤1	130 (78.8)	34 (89.5)		
≥2	35 (21.2)	4 (10.5)		
Thrombus loads			8.720	0.003
Light	100 (60.6)	13 (34.2)		
Heavy	65 (39.4)	25 (65.8)		
Target vessel diameter (mm)	3.21±0.3	3.26±0.4	0.866	0.490
The number of implanted stents (n)			1.055	0.304
≤1	130 (78.8)	27 (71.1)		
≥2	35 (21.2)	11 (28.9)		
The length of the culprit vessel (mm)	16.2±5.2	21.4±6.4	3.728	<0.001
Thrombus aspiration before reperfusion	20 (12.1)	8 (21.1)	2.072	0.150

Table III. The univariate and multivariate logical regression analysis of independent risk factors of no-reflow phenomenon.

	Univariate analysis		Multivariate analysis	
Variable	P-value	OR (95% CI)	P-value	OR (95% CI)
IRA open-up time ≥8 h	0.004	1.568 (1.359-1.863)	0.001	1.349 (1.164-1.435)
SBP <100 mmHg	0.005	1.562 (1.387-1.846)	0.005	1.698 (1.062-2.984)
Hs-CRP >18 mg/l	0.003	1.694 (1.328-1.896)	0.011	1.852 (1.529-1.972)
Thrombus loads	0.024	1.348 (1.142-1.401)	0.015	1.597 (1.354-1.931)
Length of the culprit vessel ≥20 mm	0.019 1	394 (1.248-1.436)	0.011	1.987 (1.854-2.110)

Table IV. Score allocation analysis of related factors of no-reflow phenomenon in 38 patients.

Related factor	Score	Scores of 38 patients	mean ± SD	95% CI
Age >65 years old	1			
Killip classification > Class 2	1			
White blood cell count >13,000/mm^3	1			
Preoperative blood glucose >11.8 mmol/l	1			
Elevation amplitude peak of ST-segment (mm) >3.5 mm	1	Approximately	11.5±1.57	>8.93
IRA open-up time ≥8 h	3	normal		
SBP <100 mmHg	3	distribution		
Hs-CRP >18 mg/l	3			
Thrombus loads	3			
The length of the culprit vessel ≥20 mm	3			

≥20 mm)]. The statistical analysis was conducted for the scores of 38 patients, which showed an approximately normal distribution with the average of 11.5±1.57 points and 95% confidence interval lower limit (>8.93 points) (Table IV).

Table V. Effects of three treatments for no-reflow phenomenon.

Treatment	Effective	Ineffective	Total	Effective rate (%)
A[a]	20	18	38	52.63[b]
A+B[a]	23	15	38	60.53[b]
A+B+C[a]	33	5	38	86.84[b]
Total	76	38	114	66.67

[a][A = diltiazem (150 μg) group; B = diltiazem (150 μg) + nitroglycerin (200 μg) group; C = diltiazem (150 μg) + nitroglycerin (200 μg) + tirofiban (500 μg) group]. [b]χ^2=10.974; P=0.004<0.01; the effective rates of the three treatments are statistically significant, thus the effective rates of the three treatments were not exactly the same.

Therefore, we comprehensively analyzed the related factors of no-reflow phenomenon and quantified related indicators, which can provide a reference for clinical prediction of no-reflow phenomenon. In other words, a score of ≥9 points can be clinically used as a reference for the prediction of no-reflow phenomenon in STEMI after direct PCI.

Evaluation of no-reflow drug treatments. As shown in Table V, among 38 patients with the non-reflow phenomenon receiving drug treatments, there were a total of 20 patients whose TIMI flow was restored to grade 3 after receiving diltiazem. After the addition of nitroglycerin, the number was increased to 23, and after the addition of tirofiban, the number was increased to 33. The effective rates of the three treatments were 52.63, 60.53, 86.84%, respectively (χ^2=10.974, P=0.004 <0.01), and were statistically different, which indicated that the effective rates of the three treatments were not exactly the same.

Table VI shows the pairwise comparisons of the effective rate. There was no statistically significant difference between group A (diltiazem) and group B (diltiazem + nitroglycerin), but there were statistically significant differences between group A (diltiazem) and group C (diltiazem + nitroglycerin + tirofiban) and between group B (diltiazem + nitroglycerin) and group C (diltiazem + nitroglycerin + tirofiban). In other words, diltiazem and tirofiban were effective in the treatment of no-reflow phenomenon, and nitroglycerin may be effective (as after the addition of nitroglycerin, the TIMI flows of another 3 patients were restored to grade 3, but there was no statistical difference between group C and A).

Discussion

General. The key of acute STEMI treatment is to quickly restore the IRA perfusion, resulting in the slogan 'Time is the Myocardium, Time is Life'. As the body has a complex regulatory mechanism, where, on the one hand, the necrotic myocardium cannot be restored, and on the other hand, it is accompanied with reperfusion injuries and even the no-reflow phenomenon, the occurrence and development of the no-reflow phenomenon contain reperfusion injuries (7). Previous studies have shown that reperfusion injury mechanisms include calcium overload, increased oxygen free radicals and, inflammatory responses, and no-reflow phenomenon is a complex and multivariate-related pathophysiological process, and the exact mechanism is unknown, but now it is believed that this phenomenon is associated with microcirculation, reperfusion injury and microthrombosis (8,9). No-reflow phenomenon is a common and severe complication of patients with acute myocardial infarction (AMI) after direct PCI. As its occurrence hinders the effective myocardial reperfusion, it has become an independent predicative indicator for short-term prognosis as well as long-term heart failure, arrhythmia, sudden cardiac death and other cardiac events (10).

Related factors of the no-reflow phenomenon in acute STEMI after direct PCI. Delayed IRA reperfusion time (prolonged time from onset to reperfusion) is an independent risk factor for the no-reflow phenomenon. Our study has shown that thrombus loads of patients with prolonged reperfusion (≥8 h) were heavier than those of patients with short-term reperfusion, and increased the

Table VI. Pairwise comparisons of the effective rates of three treatments.

Treatment	Effective	Ineffective	Total	α' *	χ^2 test	P-value
A	20	18	38			
A+B	23	15	38			
Total	43	33	76	0.017	0.482	0.488>0.05[a]
A	20	18	38			
A+B+C	33	5	38			
Total	53	23	76	0.017	10.537	0.001<0.005[a]
A+B	23	15	38			
A+B+C	33	5	38			
Total	56	20	76	0.017	6.786	0.009<0.01[a]

[a]There is no significant difference between group A and B (P>0.05), but the differences between A and C and between B and C were statistically significant. In order to ensure that the total probability α of the I-type error is unchanged, the test criterion $\alpha' = 1 - \sqrt[3]{1 - \alpha} = 0.017$ is reassigned.

probability of 1.3-fold no-reflow. Within 6 h after the coronary artery occlusion, myocardial necrosis occurred, and it was found that there was no statistically significant difference between ≤6 h and >6 h in the occurrence rate of myocardial necrosis, but there was a statistically significant difference between >8 h and ≤8 h. It has been reported that prolonged ischemic time leads to edema and swelling of the distal capillary bed, blocks myocardial cells and neutrophils and changes the capillary integrity, thereby undermining the microvascular bed, all of which are conducive to the occurrence of no-reflow phenomenon (11).

Preoperative SBP is another independent risk factor for the no-reflow phenomenon. It has been reported that the mortality rate of AMI patients with SBP <100 mmHg was higher than that of those with SBP ≥100 mmHg (12). A previous study showed that low SBP <100 mmHg decreases the CBF and collateral circulation blood flow, and increases the infarct size (13). Findings of that study suggested that hypotension is associated with reduced CBF (13). In addition, decreased CBF accelerates leukocyte aggregation, and increases capillary capture of white blood cells, thus leading to vein adhesion and resulting in the increased occurrence rate of no-reflow phenomenon (14). The present study also confirmed that the difference in the low SBP (<100 mmHg) between the no-reflow and reflow groups was statistically significant.

Hs-CRP is also an independent risk factor for no-reflow phenomenon. CRP is a non-specific marker of acute systemic inflammatory response synthesized by the liver (15). A previous study showed that the low-level CRP is associated with inflammatory responses of atherosclerosis, which are also important reasons for plate rupture and instability (16). CRP can be combined with lipoproteins, activate the complement system, produce a large number of inflammatory mediators and release oxygen free radicals, thus resulting in vascular intimal injuries, vasospasm and unstable plaque shedding and aggravating luminal stenosis caused by atherosclerosis (17). In this study, hs-CRP in the blood of patients with no-reflow phenomenon was significantly increased, which may also be similar to the above mechanism.

IRA thrombus loads and the length of the culprit vessel are two independent risk factors of no-reflow phenomenon, and acute coronary syndromes are plaque rupture and thrombosis superposition (18). Plaque and thrombus microvessel formation can be spontaneously formed or caused during PCI. It has been reported that the thrombus blockage of the capillary cavity >50% of the distal vessel can cause irreversible myocardial injuries. In addition to distal embolization, thrombosis may be accompanied by vasoconstriction, cardiac sympathetic reflexes and increased local release of substances with microvascular dysfunction (19), which are closely related to no-reflow phenomenon. It was more likely occur to patients with lesions >20 mm after PCI. The longer the lesion is, the greater the weight of the lipid plaque is, and the growth of lesions needs multiple balloon dilatations to increase endothelial dysfunction, which can explain the higher risk of no-reflow phenomenon in patients with long lesions after PCI.

Drug treatments for no-reflow phenomenon. Diltiazem can significantly improve no-reflow phenomenon, which may be related to the improvement of microcirculation through stretching vasospasm. Calcium antagonists have a great advantage in improving coronary spasm (20). In addition, these antagonists open the microcirculation pathway, thus blocking the formation of microthrombosis and playing the anti-no-reflow role.

Nitroglycerin did not significantly improve no-reflow phenomenon in those studies, but a study showed that nitroglycerin can improve no-reflow phenomenon (21). Its mechanism may be to directly expand the coronary artery and improve ischemic blood supply of microcirculation, thus playing the anti-no-reflow role. The current study showed that there was no statistically significant difference due to the small size of patients with no-reflow phenomenon. However, the use of nitroglycerin improves the no-reflow phenomenon in several patients. Thus, a large-scale observation is expected to obtain reliable conclusions in the future.

Tirofiban is a peptide glycoprotein IIb/IIIa receptor antagonist, and this study revealed that it significantly improved the no-reflow phenomenon, which may be due to the timely inhibition of the formation of the microthrombosis process (22), the improvement of microcirculation and anti-inflammatory and other factors.

No-reflow phenomenon often occurs in PCI, which affects the treatment effect of PCI. Related factors and risk factors were obtained from the above studies, and the scores were quantified to assess each acute STEMI patient before PCI according to the score, thus selecting a more appropriate time to conduct improved treatments in time. As for drug treatments for no-reflow phenomenon, diltiazem and tirofiban are obviously effective, and nitroglycerin may be effective. In addition, due to the relatively small number of patients in this study, the corresponding results may have limitations, but can be used as clinical references.

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Availability of data and materials

The datasets used and/or analyzed during the present study are available from the corresponding author on reasonable request.

Authors' contributions

HL contributed to the conception and wrote the manuscript. DGF made contributions to analysis and interpretation of data. FYL and HZ were responsible for score allocation analyses and revised the manuscript for critically important intellectual content. XML contributed to evaluations of no-reflow drug treatments and gave final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The present study was approved by the Ethics Committee of Xiangyang No. 1 People's Hospital, Hubei University of

Medicine (Xiangyang, China). Patients signed the informed consent or the form was signed by their family members.

Consent for publication

Not applicable

Competing interests

The authors declare that they have no competing interests.

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