

# Incidence, Predictors, and Prognosis of Coronary Slow-Flow and No-Reflow Phenomenon in Patients with Chronic Total Occlusion Who Underwent Percutaneous Coronary Intervention

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**Background:** The incidence and prognosis of coronary slow-flow (CSF) and no-reflow phenomenon (NRP) in patients with coronary chronic total occlusion (CTO) who underwent percutaneous coronary intervention (PCI) remain unclear.

**Methods:** This single-center prospective study aimed to investigate the incidence of CSF/NRP during CTO interventional therapy, determine predictors of CSF/NRP, and evaluate its effect on patient outcomes.

**Results:** In this study, 552 patients with CTO who underwent PCI were included. CSF/NRP occurred in 16.1% of them. They had higher incidences of diabetes mellitus (53.9% vs 36.3%,  $p=0.002$ ) and hypertension (50.6% vs 37.1%,  $p=0.018$ ) and a lower incidence of retrograde filling grade  $>2$  (34.8% vs 47.1%,  $p=0.036$ ). Patients with CSF/NRP had a higher neutrophil ratio ( $55.6\pm 19.4$  vs  $52.4\pm 18.3$ ,  $p=0.038$ ) and levels of low-density lipoprotein (LDL;  $3.0\pm 0.8$  vs  $2.8\pm 0.6$ ,  $p=0.029$ ), fasting glucose (FG;  $8.3\pm 1.3$  vs  $6.8\pm 1.1$ ,  $p=0.005$ ), uric acid ( $332.6\pm 82.9$  vs  $308.2\pm 62.8$ ,  $p=0.045$ ), and high-sensitivity C-reactive protein (Hs-CRP;  $9.8\pm 4.8$  vs  $7.3\pm 3.9$ ,  $p=0.036$ ). A multivariate logistic regression analysis revealed that diabetes mellitus (odds ratio [OR], 1.962; 95% confidence interval [CI]: 1.198–2.721;  $p=0.042$ ), mean platelet volume (MPV; OR, 1.284; 95% CI, 1.108–1.895;  $p=0.046$ ), LDL cholesterol (LDL-C; OR, 1.383; 95% CI, 1.105–2.491;  $p=0.036$ ), FG (OR, 2.095; 95% CI, 1.495–2.899;  $p=0.018$ ), Hs-CRP (OR, 2.218; 95% CI, 1.556–3.519;  $p=0.029$ ), and retrograde filling of grade  $>2$  (OR, 0.822; 95% CI, 0.622–0.907;  $p=0.037$ ) were independent predictors of CSF/NRP in CTO patients who underwent PCI. Kaplan-Meier analysis revealed that the patients in the CSF/NRP group had a significantly lower cumulative major cardiac and cerebrovascular events (MACCE)-free survival than those in the non-CSF/NRP group ( $p<0.0001$ ).

**Conclusion:** Of the patients with CTO who underwent PCI, 16.1% developed CSF/NRP and had a significantly lower cumulative MACCE-free survival rate. Diabetes mellitus; higher levels of MPV, LDL-C, FG, and Hs-CRP; and a lower incidence of retrograde filling grade  $>2$  were independent predictors of CSF/NRP in CTO patients who underwent PCI. Thus, they can be used for risk stratification.

**Keywords:** coronary slow-flow, no-reflow phenomenon, coronary chronic total occlusion, PCI, prognosis

## Introduction

Percutaneous coronary intervention (PCI) plays a crucial role in the management of coronary artery disease, especially in the setting of acute ST-elevation myocardial

infarction (STEMI). However, even if complete revascularization is achieved, adequate reperfusion in the myocardium as demonstrated on angiography is not necessarily maintained.<sup>1,2</sup> Previous studies showed that the prevalence of CSF/NRP in all patients who underwent PCI was 2–3.2%.<sup>3–5</sup> Studies also confirmed that CSF/NRP occurred in a significant proportion of patients with STEMI during emergency PCI with an incidence of 30–40%.<sup>6–8</sup> Increasing evidence has suggested that CSF/NRP is associated with PCI-related myocardial infarction, in-hospital mortality, and a poor prognosis.<sup>4,9,10</sup>

CTO is defined as thrombolysis in myocardial infarction (TIMI) grade 0 flow with a 3-month duration documented angiographically or clinically defined.<sup>11</sup> Previous studies showed that approximately 20% of patients with coronary heart disease have at least one vascular CTO lesion.<sup>11</sup> Accumulating evidence has confirmed that successful revascularization can effectively improve myocardial ischemia and relieve angina,<sup>12</sup> improve left ventricular function,<sup>13</sup> and improve clinical outcomes<sup>14,15</sup> in patients with CTO. However, a higher risk of CTO-PCI, longer procedure duration, and larger number of implanted stents made it different from routine interventional therapy, and the incidence of CSF/NRP and its effects on prognosis remain unclear.

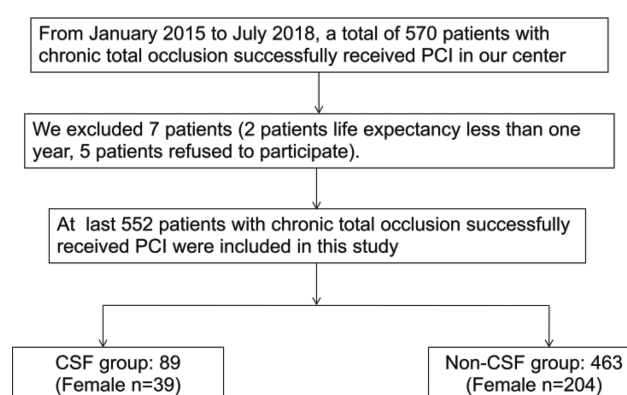
This study sought to investigate the incidence of CSF/NRP in patients with CTO who underwent PCI, determine the predictors of CSF/NRP, and assess its effects on patient outcomes.

## Methods

### Study Design and Patients

In this study, patients with a confirmed diagnosis of CTO were consecutively selected between January 2015 and May 2018 at our hospital. The exclusion criteria were as follows: current pregnancy; known allergy to aspirin, clopidogrel, or ticagrelor; refusal to accept interventional therapy or no stent implantation; life expectancy <1 year; and refusal to participate in the trial. CSF/NRP was defined as TIMI grade  $\leq 2$  by two experienced cardiologists (Ai-jie Hou and Bo Luan). A total of 552 patients were enrolled in the study, including 89 with CSF/NRP and 463 with normal blood flow (Figure 1).

The radial artery was the routine access point, but the physician determined the access as needed. During the procedure, a standard dose of unfractionated heparin 100 IU/kg was used as anticoagulant therapy, and unfractionated



**Figure 1** Study profile.

**Abbreviations:** PCI, percutaneous coronary intervention; CSF, coronary slow-flow.

heparin 2000 IU was added every hour. The use of glycoprotein IIb/IIIa inhibitor (GPI) was left to the physician's discretion. The study was approved by the Institutional Review Board of the People's Hospital of Liaoning Province and complied with the Declaration of Helsinki. All patients signed informed consent before participation.

### Study end points

The primary study end point was a composite of major cardiac and cerebrovascular events (MACCEs), including cardiac death, target vessel revascularization (TVR), stent thrombosis, nonfatal myocardial infarction (MI), PCI-associated MI (during the hospitalization period), and nonfatal stroke within 1 year of follow-up. MI was defined as the presence of pathological Q waves in at least two consecutive leads, or without a pathological Q wave, the markers of myocardial injury increased to more than twice the upper limit of normal but was not related to PCI or bypass.<sup>16</sup> PCI-related MI was defined as an elevated cardiac troponin T (cTn) value to more than five times the 99<sup>th</sup> percentile of cTn level in patients with normal baseline values.<sup>16</sup>

### Statistical Analysis

The Statistical Package for the Social Sciences for Windows version 20 (IBM SPSS Inc., Chicago, IL, USA) was used for the statistical analysis. Normally distributed continuous data are described as mean  $\pm$  standard deviation, while non-normally distributed data are shown as median (range). Categorical variables are shown as number and percentage. To compare continuous variables, Student's *t* test or the Mann–Whitney *U*-test was used. To compare categorical variables, the chi-square test and Fisher's exact test were used in the case of sparse data. Kaplan–Meier

graphs were used to assess survival without MACCEs. All tests were two-sided, and p values <0.05 were considered significant.

## Results

A total of 552 CTO patients who underwent PCI were included in this study (Figure 1). CSF/NRP occurred in 16.1% of the patients. The patients with CSF/NRP had higher incidences of diabetes mellitus (53.9% vs 36.3%,  $p=0.002$ ) and hypertension (50.6% vs 37.1%,  $p=0.018$ ) and a lower rate of retrograde filling of grade >2 (34.8% vs 47.1%,  $p=0.036$ ; Tables 1 and 2). The patients with CSF/NRP had a higher neutrophil ratio (55.6±19.4 vs 52.4±18.3,  $p=0.038$ ) and higher levels of low-density lipoprotein (LDL; 3.0±0.8

**Table 1** Clinical Characteristics of the Study Population

Variable	CSF/NRP Group (n=89)	Non- CSF/NRP Group (n=463)	Pvalue
Age(years)	64.5±7.9	65.2±8.1	0.854
Sex (female), n(%)	39(43.8%)	204(44.1%)	1
Body mass index (kg/m <sup>2</sup> )	22.8±3.5	23.1±3.7	0.628
Diabetes mellitus, n(%)	48(53.9%)	168(36.3%)	<b>0.002</b>
Hypertension, n(%)	45(50.6%)	172(37.1%)	<b>0.018</b>
Current smoker, n(%)	32(36.0%)	142(30.7%)	0.383
Previous MI, n(%)	41(46.1%)	212(45.8%)	1
Previous ischemic CVA, n(%)	9(10.1%)	41(8.9%)	0.840
LVEF(%)	40.8±6.2	40.2±6.4	0.328
NYHA 2–3 on admission, n(%)	62(69.7%)	362(78.2%)	0.099
eGFR, mL/min/1.73 mm <sup>2</sup>	60.5±22.8	61.1±23.6	0.462
ACEIs/ARBs, n(%)	42(47.2%)	231(49.9%)	0.646
Beta-blockers, n(%)	40(44.9%)	229(49.5%)	0.488
Statin, n(%)	86(96.6%)	454(98.1%)	0.421
PPI, n(%)	84(94.4%)	449(97.0%)	0.210
WBC count (10 <sup>9</sup> /L)	6.8±1.9	6.7±1.7	0.764
MPV(fL)	10.1±0.8	10.4±0.9	0.195
Neutrophil ratio (%)	55.6±19.4	52.4±18.3	<b>0.038</b>
PDW (%)	11.9±1.8	11.2±1.5	0.214
HDL-C (mmol/L)	1.2±0.4	1.1±0.3	0.29
LDL-C (mmol/L)	3.0±0.8	2.8±0.6	<b>0.029</b>
TG (mmol/L)	1.6±0.9	1.5±0.8	0.682
TC (mmol/L)	4.6±0.9	4.4±0.8	0.692
FG (mmol/L)	8.3± 1.3	6.8±1.1	<b>0.005</b>
Creatinine (mg/dL)	58.4±11.9	57.9±11.6	0.328
UA (mmol/L)	332.6±82.9	308.2±62.8	<b>0.045</b>
Hs-CRP (mmol/L)	9.8±4.8	7.3±3.9	<b>0.037</b>

**Note:** Bold values are statistically significant ( $p < 0.05$ ).

**Abbreviations:** MI, myocardial infarction; CVA, cerebrovascular accident; GI, gastrointestinal; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; eGFR, estimated glomerular filtration rate; ACEIs, angiotensin-converting enzyme inhibitors; ARBs, angiotensin receptor blockers; PPI, proton pump inhibitor; MPV, mean platelet volume; PDW, platelet distribution width; HDL, high-density lipoprotein; LDL, low-density lipoprotein; TG, triglyceride; TC, total cholesterol; FG, fasting glucose; UA, uric acid; Hs-CRP, high-sensitivity C-reactive protein.

**Table 2** Procedure-Related Characteristics of the Studied Patients

Variables	CSF/NRP Group (n=89)	Non- CSF/NRP Group (n=463)	Pvalue
Procedural access			
Radial	32(36.0%)	146(31.5%)	0.242
Femoral	22(24.7%)	118(25.5%)	0.896
Radial and femoral	35(39.3%)	199(43.0%)	0.559
Total amount of contrast(mL)	245.8±123.6	239.4±119.7	0.681
Total time of procedure (min)	118.4±56.7	116.5±55.8	0.395
LAD occlusion, n (%)	23(25.8%)	126(27.2%)	0.797
LCX occlusion, n (%)	22(24.7%)	118(25.5%)	0.896
RCA occlusion, n (%)	47(52.8%)	225(48.6%)	0.489
Occlusion lesion length, mm	56.8±24.7	57.4±23.6	0.628
Retrograde filling > grade 2	31(34.8%)	218(47.1%)	<b>0.036</b>
Reverse wire technique	38(42.7%)	186(40.2%)	0.724
IABP, n(%)	6(6.7%)	36(7.8%)	0.813
IVUS, n(%)	17(19.1%)	102(22.0%)	0.577
Number of stents per patient	2.6±1.8	2.7±1.9	0.684
Stent length (mean, mm)	62.8±22.5	63.4±24.3	0.892
Glycoprotein IIb/IIIa receptor inhibitor, n(%)	42(47.2%)	252(54.4%)	0.246
LMWH (%)	29(32.6%)	135(29.2%)	0.528

**Abbreviations:** LAD, left anterior descending artery; LCX, left circumflex coronary artery; RCA, right coronary artery; IABP, intra-aortic balloon pump; IVUS, intravascular ultrasonography; TIMI, thrombolysis in myocardial infarction; LMWH, low-molecular-weight heparin.

vs 2.8±0.6,  $p=0.029$ ), FG (8.3± 1.3 vs 6.8 ±1.1,  $p=0.005$ ), uric acid (332.6±82.9 vs 308.2±62.8,  $p=0.045$ ), and high-sensitivity C-reactive protein (Hs-CRP; 9.8±4.8 vs 7.3±3.9,  $p=0.036$ ; Table 2).

Age, female sex, smoking, body mass index, diabetes mellitus, hypertension, mean platelet volume (MPV), neutrophil ratio, platelet distribution width (PDW), LDL cholesterol (LDL-C), fasting glucose (FG), uric acid, Hs-CRP, retrograde filling of grade >2, and GPI were analyzed in univariate analysis. Diabetes mellitus, hypertension, MPV, neutrophil ratio, PDW, LDL-C, FG, Hs-CRP, and retrograde filling of grade >2 were included in the multivariate logistic regression analysis. Diabetes mellitus (odds ratio [OR], 1.962; 95% confidence interval [CI], 1.198–2.721;  $p=0.042$ ), MPV(OR, 1.284; 95% CI, 1.108–1.895,  $p = 0.046$ ), LDL-C (OR, 1.383; 95% CI, 1.105–2.491,  $p = 0.036$ ), FG(OR, 2.095; 95% CI, 1.495–2.899,  $p = 0.018$ ), Hs-CRP (OR, 2.218; 95% CI, 1.556–3.519;  $p = 0.029$ ), and retrograde filling of grade >2 (OR, 0.822; 95% CI, 0.622–0.907;  $p = 0.037$ ) were independent predictors of CSF/NRP in patients with CTO treated with PCI (Table 3).

**Table 3** Univariate and Stepwise Multivariate Logistic Regression Analysis of Risk Factors of CSF/NRP

	Univariate Analysis			Multivariate Analysis		
	OR	95% CI	P value	OR	95% CI	P value
Age	1.000	0.729–1.213	0.782	–	–	–
Female sex	0.892	0.658–1.869	0.692	–	–	–
Current smoking	1.124	0.732–1.685	0.358	–	–	–
Body mass index	1.097	0.912–2.289	0.529	–	–	–
Diabetes mellitus	1.895	1.271–2.826	<b>0.035</b>	1.962	1.198–2.721	<b>0.042</b>
Hypertension	1.684	1.118–1.959	<b>0.029</b>	1.375	1.122–1.899	0.182
PDW	1.321	1.09–1.59	<b>0.029</b>	1.204	1.181–1.688	0.089
Neutrophil ratio	1.294	1.112–1.985	<b>0.034</b>	1.182	1.091–1.979	0.132
MPV	1.307	1.092–1.995	<b>0.026</b>	1.284	1.108–1.895	<b>0.046</b>
LDL-C	1.422	1.166–2.521	<b>0.019</b>	1.383	1.105–2.491	<b>0.036</b>
FG	2.114	1.562–3.095	<b>0.028</b>	2.095	1.495–2.899	<b>0.018</b>
UA	1.186	0.897–1.568	0.624	–	–	–
Hs-CRP	2.323	1.629–3.592	<b>0.012</b>	2.218	1.556–3.519	<b>0.029</b>
Retrograde filling > grade 2	0.782	0.556–0.925	<b>0.025</b>	0.822	0.622–0.907	<b>0.037</b>
GPI	1.195	0.893–1.688	0.329	–	–	–

**Note:** Bold values are statistically significant ( $p < 0.05$ ).

**Abbreviations:** MPV, mean platelet volume; PDW, platelet distribution width; LDL, low-density lipoprotein; FG, fasting glucose; UA, uric acid; Hs-CRP, high-sensitivity C-reactive protein; GPI, glycoprotein IIb/IIIa receptor inhibitor.

During the hospitalization period, the incidence of PCI-related MI was significantly higher in the CSF/NRP group than in the non-CSF/NRP group (32.6% vs 14.9%,  $p < 0.001$ ), and the incidence of MACCEs was also significantly higher in the CSF/NRP group than in the non-CSF/NRP group (37.1% vs 18.6%,  $p < 0.001$ ). At 1-year follow-up, the incidences of TVR (22.0% vs 5.8%,  $p < 0.001$ ) and MACCE (47.2% vs 21.4%,  $p < 0.001$ ) were significantly higher in the CSF/NRP group than in the non-CSF/NRP group (Table 4). Kaplan-Meier analysis revealed that the cumulative MACCE-free survival was significantly lower in the CSF/NRP group than in the non-CSF/NRP group ( $p < 0.0001$ ; Figure 2).

## Discussion

This study was the first to investigate the incidence, predictive factors, and prognosis of CSF/NRP inpatients with CTO who successfully underwent PCI. The study confirmed that 16.1% of patients with CTO who underwent PCI developed CSF, which had a significantly lower cumulative MACCE-free survival rate. Diabetes mellitus; higher MPV and levels of LDL-C, FG, and Hs-CRP; and a lower retrograde filling level (grade >2) were independent predictors of CSF/NRP in patients with CTO who underwent PCI. Thus, these factors can be used for risk stratification.

The etiology of CSF/NRP is complex and still not fully understood. Its possible mechanisms include endothelial

**Table 4** MACCE During Hospital Stay and at 12-Month follow-Up

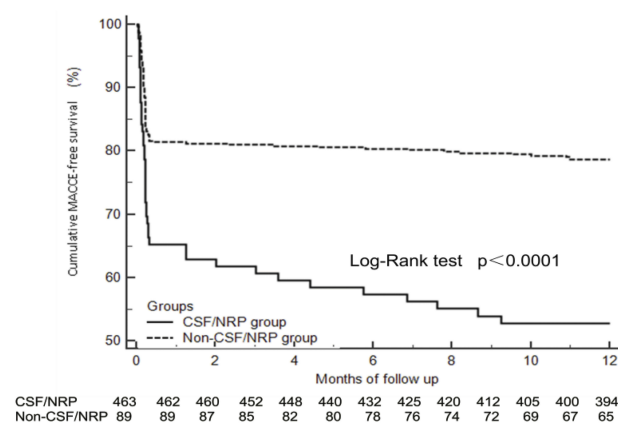
Variable	CSF/NRP Group (n=89)	Non-CSF/NRP Group (n=463)	P value
MACCE during hospitalization			
Cardiogenic death, n(%)	1(1.1%)	4(0.9%)	1
AMI, n(%)	1(1.1%)	6(1.3%)	1
PCI-related MI, n(%)	29(32.6%)	69(14.9%)	<b>&lt;0.001</b>
Stent thrombosis, n(%)	1(1.1%)	7(1.5%)	1
Stroke, n(%)	0	2(0.4%)	1
TVR, n(%)	3(3.4%)	13(2.8%)	0.731
Overall MACCE, n(%)	33(37.1%)	86(18.6%)	<b>&lt;0.001</b>
MACCE at 12-month follow-up			
Cardiogenic death, n(%)	1(1.1%)	6(1.3%)	1
AMI, n(%)	2(2.2%)	16(3.5%)	0.751
Stent thrombosis, n(%)	6(6.7%)	22(4.8%)	0.430
Stroke, n(%)	1(1.1%)	3(0.6%)	0.506
TVR, n(%)	11(22.0%)	27(5.8%)	<b>&lt;0.001</b>
Overall MACCE, n(%)	42(47.2%)	99(21.4%)	<b>&lt;0.001</b>

**Note:** Bold values are statistically significant ( $p < 0.05$ ).

**Abbreviations:** MACCE, major adverse cardiac and cerebral events; PCI, percutaneous coronary intervention; TVR, target vessel revascularization; AMI, acute myocardial infarction.

dysfunction, microvascular ischemia and edema, embolization, and reperfusion injury.<sup>17</sup> Currently, the incidence of CSF/NRP varies widely among different study populations. Most of these studies were in STEMI patients. Some recent studies demonstrated that the proportion of NRP in all PCI patients was 2–3.2%.<sup>3–5</sup> Studies also confirmed that CSF/NRP occurred at a prevalence of 30–40%





**Figure 2** Cumulative MACCE-free survival.

in STEMI patients during emergency PCI.<sup>6–8</sup> The present study showed that the incidence of CSF/NRP in such patients was as high as 16.1%. We speculated that the guide wire may penetrate the proximal or distal fibrous cap during antegrade interventional therapy or the retrograde wire technique, causing the release of lipids from atherosclerotic plaques that may lead to the occlusion of distal blood vessels, especially micro vessels.

Although many researchers have proposed several predictors of CSF/NRP,<sup>18</sup> their predictive value in different study populations requires further investigation. Studies have confirmed that >50% of patients with STEMI have abnormal glucose metabolism. Although early revascularization can achieve significant clinical results, patients with abnormal glucose metabolism have poorer microvascular perfusion and a higher risk of developing CSF/NRP.<sup>19</sup> The present study also found that diabetes mellitus and a high fasting blood glucose level are independent predictors of CSF/NRP as shown in previous studies. The present study demonstrated that a high LDL-C level is associated with CSF/NRP. Previous studies confirmed that hypercholesterolemia is associated with endothelial dysfunction because it reduces the bioavailability of vascular nitric oxide.<sup>20</sup> Pretreatment with statins effectively prevents CSF/NRP,<sup>21</sup> reduces the incidence of postoperative MI,<sup>22</sup> and improves myocardial perfusion after PCI.<sup>23</sup> These findings also indirectly confirm that hyperlipidemia is involved in the pathogenesis of CSF/NRP.

Studies have shown that a higher inflammation status plays an important role in the development of CSF/NRP during emergency PCI for STEMI.<sup>24</sup> Oduncuet al<sup>25</sup> showed that patients with NRP have a higher baseline Hs-CRP level. The independent relationship between Hs-CRP and NRP development, which was discovered in this study, has

also been reported previously.<sup>26</sup> The present study confirmed that MPV was significantly elevated in the CSF/NRP group and is an independent predictor of CSF/NRP. We suggest that MPV is an indicator of platelet activation that plays an important role in the pathophysiology of cardiovascular disease; previous studies also confirmed its association with CSF/NRP.<sup>18</sup> We also found that patients with better collateral circulation had a lower incidence of CSF/NRP, presumably because the collateral circulation provides better myocardial perfusion to occluded vessels and its endothelial and microvascular functions are relatively less damaged; thus, the incidence of CSF/NRP is lower because reperfusion-related damage is less severe.

CSF/NRP is clinically important, as increasing evidence has suggested that it is associated with PCI-related MI, in-hospital mortality, and poor prognosis.<sup>4,9,10</sup> In addition, Butler et al reported that transient CSF/NRP is even more common than persistent CSF/NRP and results in significantly increased 30-day morbidity and mortality rates.<sup>27</sup> Our study found that CTO-PCI patients with CSF/NRPs had significantly increased incidences of perioperative MI, MACCEs during hospitalization and the 1-year follow-up period, and TVR at 1-year follow-up. Their MACCE-free survival rate was significantly lower than that of non-CSF/NRP patients.

The CSF/NRP condition of CTO-PCI patients warrants additional attention due to its unique pathophysiology and complex interventional procedures. We recommend that these conditions be identified separately from acute MI. As this was a small-sample single-center study, some bias exists. In the future, a large-sample multicenter prospective randomized controlled trial is needed to validate our conclusions.

## Conclusion

Of the patients with CTO who underwent PCI, 16.1% developed CSF/NRP and had a significantly lower cumulative MACCE-free survival rate. Diabetes mellitus; higher MPV, LDL-C, FG, and Hs-CRP levels; and a lower incidence of retrograde filling grade >2 were independent predictors of CSF/NRP in CTO patients who underwent PCI. Thus, these factors can be used for risk stratification.

## Abbreviations

CSF, coronary slow-flow; NRP, no-reflow phenomenon; TIMI, thrombolysis in myocardial infarction; CTO, coronary chronic total occlusion; PCI, percutaneous coronary intervention; MACCE, major adverse cardiac and cerebral events; TVR, target vessel revascularization; GPI, glycoprotein IIb/IIIa inhibitor.

## Ethics Approval and Informed Consent

The study had already been approved by Ethics Committee of the People's Hospital of China Medical University and all subjects provided their informed, written consent before participation.

## Data Sharing Statement

The data supporting the results in the current study are available from the corresponding author on reasonable request.

## Author Contributions

All authors contributed to data analysis, drafting or revising the article, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

## Disclosure

The authors report no conflicts of interest in this work.

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