

The Clinical Prediction Factors of Non Chronic Total Occlusion Lesions Progression in Patients Underwent Percutaneous Coronary Intervention for Chronic Total Occlusion Lesions

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Research

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Abstract

Background :To investigate the clinical prediction factors of non chronic total occlusion lesions progression in patients underwent percutaneous coronary intervention(PCI) for chronic total occlusion lesions.

Methods: A total of 450 unstable angina patients (57.1 ± 9.2 years) underwent PCI from January 2016 to December 2018 in Beijing Anzhen Hospital were enrolled in this study. All patients underwent PCI as treatment for chronic total occlusion lesions. Clinical and angiographic follow-up were performed in 12 months. All patients were divided into **non chronic total occlusion lesions(NCTOL)** progression group (205 cases) and the control group (275 cases) according to angiographic follow-up outcome in 12 months. The clinical and angiographic features were analyzed.

Results: levels of adenosine diphosphate (ADP) induced platelet aggregation rate(ADP-IPA) (51.89 ± 14.81 vs 39.63 ± 17.12 , $P < 0.01$), lipoprotein(a)(Lp(a))(0.22 ± 0.26 vs 0.14 ± 0.18 , $P < 0.05$) in NCTOL progression group were significantly higher than those in the control group. Logistic regression showed that ADP induced PAR (odds ratio =1.047, 95% confidence interval:1.014-1.082, $P = 0.005$), Lp(a) (odds ratio =11.972, 95% confidence interval: 1.230 -116.570, $P = 0.033$) were independent predictors of NCTOL progression. Partial correlation analysis showed that ADP-IPA was positively correlated with NCTOL progression($r = 0.351$, $P < 0.001$). Receiver operating characteristic(ROC) curve showed that the boundary point of ADP-IPA to predict NCTOL progression was 30%, the sensitivity was 86.2% and the specificity was 68.9%.

Conclusions: ADP-IPA may be an valuable predictor for NCTOL progression .in unstable angina patients underwent percutaneous coronary intervention(PCI) for chronic total occlusion lesions.

1. Introduction

Chronic total occlusions (CTOs) are defined as coronary artery lesions with thrombolysis in myocardial infarction (TIMI) grade flow of 0 (true CTO) or TIMI grade flow 1 (functional CTO) and present for more than or equal to 3 months. CTOs are not seldom in coronary artery disease patients, Fefer et al found that CTOs were found in 14.7% coronary artery disease patients underwent coronary angiography. PCI for CTOs was a most challenging procedure in the field of PCI. However, with recent improvements in technology including the introduction of dedicated CTO wires, balloons, refinement in the operator technique and appropriate patient selection, success rate of PCI with CTOs has risen to 90% in some centers and PCI for CTOs was recommended as IIa class in 2011 ACCF/AHA/SCAI Guideline for Percutaneous Coronary Intervention.^[2] However, Park et al^[3] reported that the rate of nonculprit lesions(NCL) progression in patients underwent PCI for culprit lesions was 7% in one year, 14% in 2 years and 16% in 3 years. Non-culprit lesions(NCL) progression in coronary artery disease patients underwent PCI for culprit lesions indicated that diffuse and active inflammation occur in both vulnerable and stable

plaques of the entire coronary tree and NCL progression could be the most significant factor that affects the prognosis in coronary artery disease patients .

Recent studies about PCI for CTO lesions in coronary artery disease patients were not seldom however non chronic total occlusion lesions(NCTOL) progression in coronary artery disease patients underwent PCI for CTO lesions has not been studied. In this study ,we investigated the the clinical prediction factors of non chronic total occlusion lesions progression in coronary artery disease patients underwent percutaneous coronary intervention(PCI) for chronic total occlusion lesions .

2. Methods

All participants or their family members were informed about the potential publication of their identities and images, and all of them completed consent forms. All procedures and protocols were approved by the ethics committee of Beijing Anzhen Hospital, Capital Medical University, and the experiments were conducted in accordance with the Declaration of Helsinki (1975 and subsequent revisions).

Between January 2016 and December 2018, 450 unstable angina patients (350 men and 100 women) who underwent successful PCI treatment for CTO lesions in Beijing Anzhen Hospital were enrolled in this retrospective study. Clinical and angiographic follow-up was performed in all patients for 12 months. The inclusion criteria were as follows. (1) ≥ 18 years old. (2) Coronary angiography indicated that an occlusive (100% stenosis) coronary lesion with antegrade Thrombolysis In Myocardial Infarction 0 flow for at least 3 months, and only one NCTOL was found.³ All patients underwent successful PCI treatment for CTO lesions.⁴ There was no contraindication for anticoagulation and antiplatelet therapy.

All patients were divided into non chronic total occlusion lesions(NCTOL) progression group (205 cases) and the control group (275 cases) according to angiographic follow-up outcome in 12 months.

The main exclusion criteria included the following: previous percutaneous coronary intervention (PCI) in CTO artery ($n = 6$) CTO artery with excessive proximal tortuosity or severe calcification ($n = 14$), left ventricular ejection fraction $< 35\%$ ($n = 15$), lack of clinical and angiographic follow-up ($n = 26$), in-hospital death after PCI ($n = 11$), myocardial infarction within 2 w of PCI to exclude potential subacute stent thrombosis of the intervened arterial segment ($n = 9$), and repeated PCI of CTO lesions for restenosis or progression ($n = 43$).

Coronary angiography was performed using the Judkins method, and coronary artery lesion classification was based on the American College of Cardiology/American Heart Association guidelines³. Stents were implanted using a routine method, and the procedure succeeded with residual stenosis $< 20\%$, TIMI flow grade of 3 and no acute complications (death, myocardial infarction, emergency coronary artery bypass grafting (CABG)), and no major adverse cardiac events (cardiac death, myocardial infarction, target vessel revascularization). Clinical and angiography follow-up was performed for 12 months.

NCTOLs were defined as those with a diameter of stenosis <70%. All patients underwent PCI for the CTO lesions.

Quantitative coronary angiography was performed during the first angiography. Follow-up angiography was performed by two independent investigators who were blinded to the results. We categorized the lesions in accordance with the American College of Cardiology/American Heart Association. Classification was performed on the basis of the morphological characteristics of lesions that cause significant stenosis of the coronary arteries.^[3] These include two categories of simple lesions (A or B1 lesions) and complex lesions (B2 or C).

The collected data included demographic information, medical history, coronary artery disease risk factor status, detailed coronary angiographic information, biomarkers associated with coronary atherosclerosis at the time of baseline PCI, and coronary angiographic information at the time of angiographic follow-up.

All clinical, laboratory, and coronary angiographic data were evaluated by two independent investigators who were not involved in the angiographic procedures.

Definition of NCTOL progression ^[3]: 1. The stenosis degree of the NCTOL was $\geq 50\%$ at the time of baseline PCI, and the degree of NCTOL progression was $\geq 10\%$ at the time of angiographic follow-up. 2. The stenosis degree of the NCTOL was <50% at the time of baseline PCI, and the degree of NCTOL progression was $\geq 30\%$ at the time of angiographic follow-up. 3. The degree of NCTOL progression $\geq 30\%$, while there were no NCTOLs at the time of baseline PCI. 4. NCTOL progression to total occlusion.

3. Results

Between January 2016 and December 2018, 964 unstable angina patients underwent PCI treatment for CTO lesions. Of those 450 patients (350 men and 100 women) underwent angiographic follow-up in 12 months. There were 305 (235 men and 70 women) patients without NCTOL progression (the control group) and 145 (115 men and 30 women) patients with NCTOL progression (the progression group) according to angiographic follow-up outcome in 12 months.

There were no significant differences in age, sex, BMI, current smoking, hypertension, hyperlipidemia, diabetes mellitus, prior myocardium infarction, prior PCI, prior CABG, heart rate, systolic arterial pressure (mmHg), left ventricular ejection fraction (LVEF), triglyceride (TG), total cholesterol (TCHO), high density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), homocysteine (Hcy), C reactive protein (CRP), serum creatinine (Scr), uric acid (UA), and arachidonic acid (AA)-induced platelet aggregation rate [AA-IPA] between the two groups (all $P > 0.05$).

There were significant differences in Lp(a) and adenosine diphosphate (ADP)-induced platelet aggregation rate [ADP-IPA] between the two groups (all $P < 0.0001$) (Table 1).

In terms of medications, patients received a similar amount of aspirin (100% vs. 100%), β -blockers (65.2% vs. 67.2%), calcium antagonists (27.6% vs. 28.9%), and statins (100% vs. 100%) in each group (all $P>0.05$). However, patients received a different amount of clopidogrel (62.1% vs. 83.6%), ticagrelor (37.9% vs. 16.4%), and ACEI/ARB (37.9% vs. 62.3%) between the two groups (all $P<0.0001$) (Table 1).

Angiographic characteristics between two groups showed that Stent length in NCTOL progression group was shorter than that in the control group [28.79 ± 23.93 vs 43.87 ± 30.35 , $P< 0.05$]. There were no significant differences in other angiographic characteristics between two groups (Table 2).

Multivariate logistic regression analysis indicated that ADP (OR: 1.047, 95% CI: 1.0141–1.082, $P=0.005$) and Lp[a] (OR: 11.972, 95% CI: 1.230–116.570, $P=0.033$) were independent predictors of the progression of NCTOL in patients underwent PCI for chronic total occlusion lesions ($P<0.05$) (Table 3).

Partial correlation analysis showed that ADP was positively correlated with NCTOL progression ($r= 0.231$, $P=0.001$) (Table 4).

ROC analysis for the predictors of NCTOL progression indicated that an ADP level $\geq 30\%$ may predict NCL progression. The sensitivity was 86.2% and the specificity was 68.9% (AUC: 0.613, CI: 0.532–0.693, $P<0.008$) (Table 4 Fig1).

4. Discussion

In this study, there were 450 patients underwent angiographic follow-up after PCI for CTO lesion in 12 months, and there were 145 patients with NCTOL progression, the progression rate of NCTOL was 32.2%. However, Park et al investigated the progression rate of non-culprit lesions in STEMI patients after primary PCI, and showed that the progression rate of NCL in STEMI patients after primary PCI was 7.7%^[3]. It indicated that the progression of NCTOL was an important factor that affected the prognosis of CAD patients after successful PCI for CTO lesions.

In this study, we found that ADP-induced PAR may be a predictor of the progression of NCTOL in patients underwent PCI for chronic total occlusion lesions and partial correlation analysis also indicated that ADP-induced PAR was positively correlated with NCTOL progression ($r= 0.231$, $P=0.001$).

ADP is one of the most important agonists of platelet activation. ADP induces platelet shape change, exposure of fibrinogen binding sites, aggregation, and influx and intracellular mobilization of Ca^{2+} . ADP-induced platelet aggregation is important for maintaining normal hemostasis, but aberrant platelet aggregation manifests itself pathophysiologically in myocardial ischemia, stroke, and atherosclerosis. Clopidogrel is an ADP receptor antagonist and can irreversibly inhibit adenosine diphosphate (ADP)-induced platelet aggregation, long-term administration of clopidogrel was associated with a modest but statistically significant advantage over aspirin in reducing adverse cardiovascular outcomes in CAD patients underwent PCI. However, there were 25–50% CAD patients received clopidogrel therapy without adequate inhibition of ADP-induced platelet aggregation^[4], and the poor inhibition of ADP-induced

platelet aggregation may be associated with adverse cardiovascular outcomes. Li Q and colleagues^[5] found that CAD patients with high ADP-induced platelet aggregation have high risk of *major adverse cardiac and cerebrovascular event (MACCE)* after PCI. PCI procedure may cause endothelial cells injury, activate the excessive proliferation of smooth muscle cells and platelet adhesion and aggregation, leading to stenosis and thrombosis^[6-8]. Complex PCI may cause more endothelial cells injury than simple PCI—it was essential for patients underwent complex PCI—such as PCI for CTO lesions—to detect platelet function. Moreover, *coronary* artery lesions were not fully covered by stents may cause *in-stent thrombus*, it was involved in platelet activation^[9,10]. This study showed that stent length in NCTOL progression group was shorter than that in the control group, it indicated that *coronary* artery lesions were not fully covered by stents may be involved in NCTOL progression.

This study showed that **NCTOL** progression was important cause of recurrent PCI in CAD patients after PCI for CTO lesions and **NCTOL** progression may be the most important factor that affects the prognosis of CAD patients after successful PCI for CTO lesions. ADP-IPA may be a predictor of the progression of NCTOL. In patients underwent PCI for chronic total occlusion lesions, and it was essential to detect platelet function and adequate antiplatelet therapy.

5. Conclusions

ADP-IPA may be a valuable predictor for NCTOL progression. In unstable angina patients underwent percutaneous coronary intervention (PCI) for chronic total occlusion lesions.

Declarations

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Ethics approval and consent to participate

This study conformed to the ethical guidelines of the 1975 Declaration of Helsinki as reflected in approval by the Ethics Committee of Peking University. Informed consent was exempted by the board for this study.

Consent for publication

Not applicable

Availability of data and material

Please contact author for data requests.

Competing interests

The authors declare that they have no competing interests.

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Authors' contributions

X.X. designed and coordinated the study, X.X. wrote the main manuscript text. X.-X.X. collected samples. All authors reviewed the manuscript.

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Tables

Table 1. Baseline clinical characteristics [n=450]

n=450	NCTOL progression group	The control group	P value
	n=145	n=305	
Age	56.24 ± 11.5	56.44 ± 8.2	NS
Male	115(79.3)	235(77.0)	NS
BMI	25.37 ± 2.72	25.84 ± 3.57	NS
Current somking(%)	85(58.6)	150(49.2)	NS
Hypertension	85(58.6)	195(63.9)	NS
Hyperlipidemia	37(25.5)108	82(26.9)223	NS
Diabetes mellitu	35(24.1)	115(37.7)	NS
Prior myocardium infarction(%)	35(24.1)	100(32.8)	NS
Prior PCI(%)	50(34.5)	60(19.7)	NS
Prior CABG(%)	49(3.4)	10(3.3)	NS
Aspirin	145(100)	305(100)	NS
Clopidogrel	90(62.1)	255(83.6)	<0.0001
Ticagrelor	55(37.9)	50(16.4)	<0.0001
β-blockers(%)	95(65.2)	205(67.2)	NS
Calcium antagonists(%)	40(27.6)	88(28.9)	NS
ACEI/ARB(%)	55(37.9)	190(62.3)	<0.0001
Statins(%)	145(100)	305(100)	NS
Heart rate, beats/min	82 ± 11	80 ± 12	NS
Systolic arterial pressure(mmHg)	132±21	133±20	NS
LVEF(%)	62 ± 9	60 ± 10	NS
TG(mmol/L)	1.86 ± 1.27	2.01 ± 2.54	NS
TCHO(mmol/L)	4.07 ± 1.15	4.12 ± 1.70	NS
HDL-C(mmol/L)	0.97 ± 0.22	0.99 ± 0.22	NS
LDL-C(mmol/L)	2.42 ± 1.04	2.40 ± 1.42	NS
Lp(a)	0.22 ± 0.18	0.14 ± 0.12	<0.0001
Hcy((umol/L)	16.97 ± 5.48 145	15.77 ± 11.54 305	NS
CRP(mg/L)	5.50 ± 4.73	5.20 ± 4.20	NS
Scr (umol/L)	68.35 ± 14.83	66.39 ± 14.33	NS

UA(umol/L)	339.68 ± 102.44	326.88 ± 77.72	NS
AA-IPA[%]	11.57 ± 9.24	10.96 ± 8.93	NS
ADP-IPA[%]	51.89 ± 14.81	17.12 ± 9.63	<0.0001

Table 2. Angiographic characteristics between two groups

CTO lesion (n(%))	NCTOL progression group [n=145]	The control group [n=305]	P value
LM	3 (2.07)	6 (1.97)	NS
LAD	52 (.35.86)	105 (34.43)	NS
LCX	35 (24.14)	75 (24.59)	NS
RCA	55 (37.93) 90	119(39.01) 186	NS
Lesion length	26.38 ± 13.98	24.93 ± 10.97	NS
Stent length	28.79 ± 23.93	43.87 ± 30.35	<0.0001
CTO score≥2 (n(%))	110[75.9]	217[71.1]	NS
≥ 2 vessel lesion rate(n(%))	100(69.0)	189(62.0)	NS
Retrograde approach(n(%))	15 (10.3)	45 (14.8)	NS

Table 3. Multivariate logistic regression analysis

Factor	B value	SE value	Wald value	OR value	95%CI	P value
ADP	0.046	0.017	7.852	1.047	1.014-1.082	0.005
Lp[a]	2.483	1.161	4.571	11.972	1.230-116.570	0.033
Stent length	-0.020	0.010	3.706	0.980	0.961-1.000	0.054

Table 4. Partial correlation analysis between ADP and NCL progression

Factor	Partial correlation coefficient	<i>P</i> value
ADP	0.351	<0.001

Table 5. ROC analysis for the predictors of NCL progression

The area under the ROC curve	SEM	95% CI	<i>P</i> value
0.726	0.058	0.611-0.840	0.001

Figures

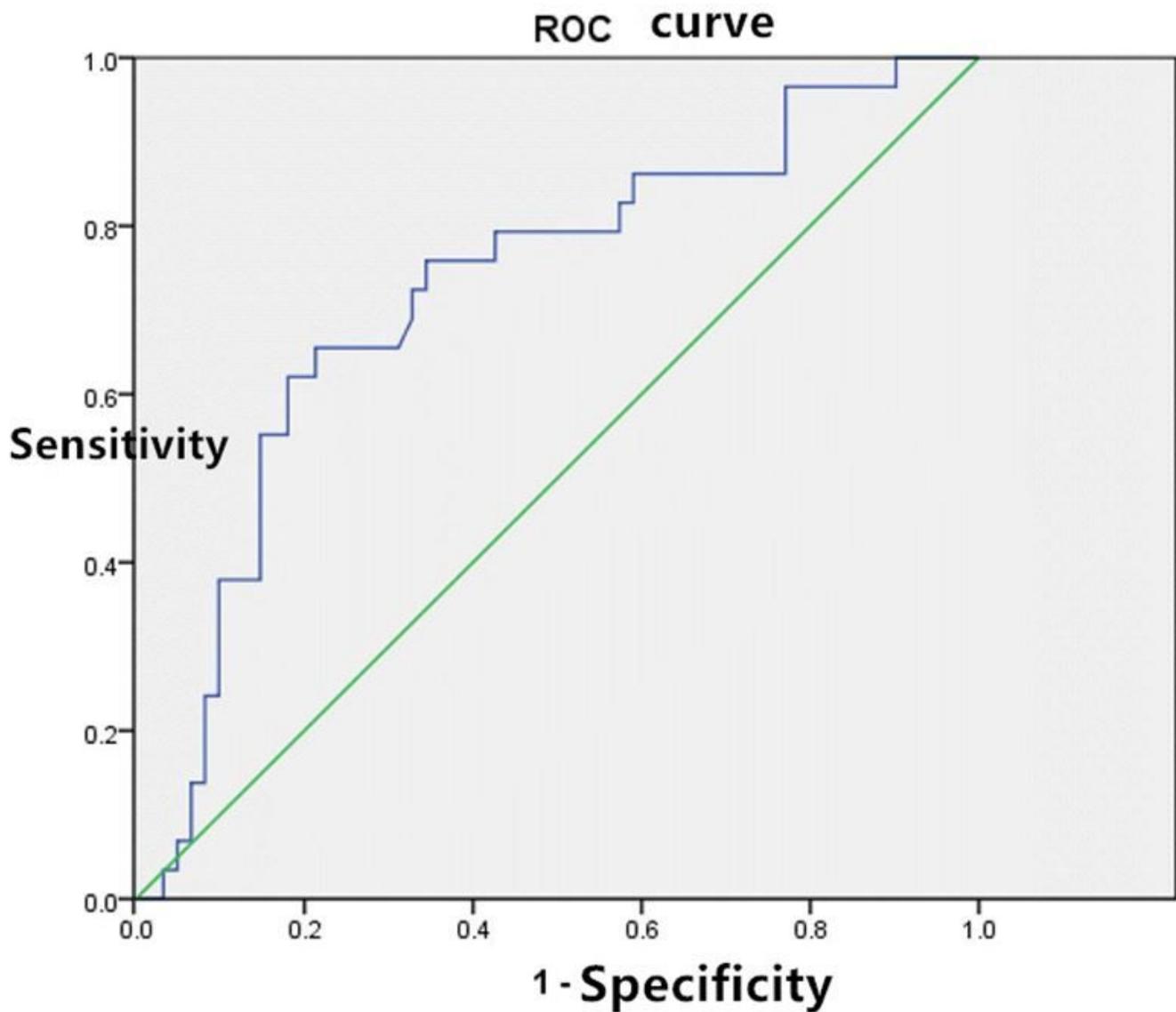


Figure 1

ROC curve for the predictors of NCTOL progression