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Development and validation of a novel nomogram to predict chronic total occlusion before coronary angiography

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Abstract. – OBJECTIVE: Some previous studies have analyzed potential predictors related to the high incidence rate of coronary artery disease (CAD) and established a relevant nomogram for CAD in patients before coronary angiography (CAG). Nevertheless, there are still few models to predict chronic total occlusion (CTO). In this study, we aimed to construct a risk model and nomogram that could effectively predict the probability of CTO before CAG.

PATIENTS AND METHODS: In total, the derivation set (n=1,105) and the validation set (n=368), which included patients with CAG diagnosis of CTO, were collected. A statistical difference test was performed for clinical, demography, echocardiography, medication history, laboratory indexes, and angiography. Univariate and multivariate logistic regression analysis were performed to determine the independent risk factors that affect the diagnosis of CTO. A nomogram was established and validated based on the independent predictors. The area under the curve (AUC), the calibration curve, and the decision curve analysis (DCA) were used to evaluate the nomogram.

RESULTS: The incidence of CTO within CAD was 21.5%. Univariate and multivariate logistic regression analysis revealed that risk factors for gender (male), neutrophil percentage (NE%), hematocrit (HCT), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), ejection fraction (EF), troponin I (TnI), and N-terminal pro-B-type natriuretic peptide (NT-proBNP) were independent predictors of CTO. A nomogram was constructed incorporating these independent predictors with good discrimination (0.746 in the C-index) and external validation (0.741 in the C-index). The calibration curves and the DCA showed the reliability and accuracy of this clinical prediction model.

CONCLUSIONS: The nomogram, composed of gender, NE%, HCT, TC, HDL, EF, TnI, and NT-proBNP, can be used for the prediction of CTO in CAD patients, which opens a great possibility of enriching the means to predict the prognosis of these patients in clinical practice. More studies are needed to validate the effectiveness of this nomogram in other populations.

Key Words:
Chronic total occlusion, Coronary artery disease, Nomogram, Prediction.

Introduction

Chronic total occlusion (CTO) is defined as grade 0 thrombolysis in myocardial infarction flow for more than three months, which is often encountered during coronary angiography (CAG) in patients with coronary artery disease (CAD)[1]. CTO was called the "last fortress" of percutaneous coronary intervention (PCI) due to its complexity of the occluded lesion, a lower procedural success rate, and a higher incidence of restenosis. Previous studies[2] have found that 20% of patients with CAD complicated at least one CTO lesion simultaneously. Recently, advancements in new crossing equipment, techniques, and the improvement of operators' skills have incrementally elevated procedural success rates[3]. Successful CTO revascularization has proven to be beneficial in symptomatic relief, improvement in left ventricular function, reduced need for coronary artery bypass graft, and increased survival rate[4].

For better risk stratification of patients, efforts have been made to develop prognostic prediction tools or risk scores to identify CTO before CAG. Although some previous scholars[5] have analyzed

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potential predictors related to the high incidence rate of CAD and established a relevant nomogram for CAD in patients before CAG, there are still few models to predict CTO. The emergence of CTO is the result of various risk factors, such as sex, smoking, hypertension, dyslipidemia, and diabetes[6]. A preoperative model based on clinical demographic and preoperative blood biochemical parameters may help clinicians to distinguish high-risk CTO patients and optimize treatment strategies.

In this study, we collected the clinical features of patients with CTO diagnosed by CAG. Then, we constructed a risk model and analyzed the clinical risk factors that affect the diagnosis of CTO. Finally, we discussed the accuracy of this model in predicting CTO patients, with the hope of enriching the means of clinical prediction of diagnosis.

Patients and Methods

Study Cohort

In total, 1105 patients with chest pain and suspected CAD who underwent CAG, between January 2019 and December 2019 at Beijing Anzhen Hospital, Capital Medical University, were consecutively enrolled, which formed the derivation cohort in this study. Between January 2020 and December 2020, an independent cohort of 368 consecutive patients was prospectively enrolled using the same inclusion and exclusion criteria. These patients formed the validation cohort in this study. The entire patients were assigned to the CTO group (n = 317) or non-CTO (n=1156) group based on the procedural outcome. CTO was defined as an occlusion lasting more than three months based on the first onset of angina pectoris, previous angiogram, or previous infarction and thrombolysis in myocardial infarction grade 0. Non-CTO was defined as a stenosis of at least 50% of the luminal diameter in at least one major coronary artery branch. The study protocol was approved by the Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

Data Collection

Baseline clinical demographics, laboratory indexes, and angiography characteristics were collected. Baseline clinical demographics included sex, age, current tobacco use, alcohol consumption, body mass index (BMI), systolic blood pressure (SP), diastolic blood pressure (DP), hypertension, diabetes mellitus, dyslipidemia, previous stroke, echocardiography, and medication history. Laboratory indexes included white blood cell (WBC), red blood cell (RBC), hemoglobin (Hb), platelet (PLT), hematocrit (HCT), neutrophil (NE), neutrophil percentage (NE%), lymphocyte (LYM), monocyte (MONO), glucose (Glu), HbA1C, triglyceride (TG), total cholesterol (TC), high-density lipoprotein cholesterol (HDL), low-density lipoprotein cholesterol (LDL), Free Fatty Acids (FFA), Non-HDL, sdLDL, homocysteine (Hcy), uric acid (UA), creatinine (Cr), eGFR(CKD-EPI), brain natriuretic peptide (BNP), NT-proBNP, high-sensitivity C-reactive protein (hs-CRP), creatine kinase-MB (CK-MB), and troponin I (TnI). All laboratory indexes came from fasting venous blood from all participants and were analyzed by an automated biochemical analyzer. Angiography characteristics included the number of vessel lesions and the location of the CTO lesion, including the left main coronary artery (LM), left anterior descending branch (LAD), left circumflex artery (LCX), right coronary artery (RCA), and diagonal branch (D1). All angiography characteristics were calculated by two experienced interventional cardiologists.

Statistical Analysis

Continuous variables are expressed as mean ± standard deviation for normally distributed data or median and quartiles (Quartile 1-Quartile 3) for nonnormally distributed data. Student's *t*-test detected differences between continuous variables with a normal distribution. The Mann-Whitney U test detected differences between continuous variables with a nonnormal distribution. Categorical variables are expressed as frequency and percentage. The chi-square or Fisher's exact test was used to detect differences between categorical variables.

Univariate logistic regression analysis was performed to identify factors related to CTO prediction. Multivariate logistic regression analysis was performed with the selection of forward stepwise univariate logistic regression analysis, in which *p*-value levels for inclusion and exclusion criteria were established as 0.10 and 0.05, respectively. Then, a nomogram was formulated. To validate the nomogram, calibration curves were calculated from the multivariate logistic model; bootstrapping with 1000 resamples was used for these analyses. Decision curve analysis (DCA) was

performed to determine the clinical usefulness of the nomogram for the derivation and validation sets. The diagnostic value of the nomogram was tested by receiver operating characteristic (ROC) analysis. A two-sided *p*-value <0.05 was considered statistically significant. SPSS version 23.0 (SPSS Corp., Armonk, NY, USA) was used to perform statistical analyses in this study. The nomogram analysis and calibration curve were performed by using R software version 4.2.0 (R Foundation for Statistical Computing, Vienna, Austria).

Results

Baseline Characteristics

The baseline clinical demographics of the study population are shown in Table I. Compared to non-CTO controls, patients with CTO were more likely to be male and smokers. They also encountered more frequently a decreased ejection fraction (EF) and increased left ventricular end diastolic diameter (LVEDD). With the history of medication, CTO patients were more likely to take dual antiplatelet therapy, including clopidogrel or ticagrelor. In addition, β-blocker and nitrates are more used, but ACEI/ARB, statin, and calcium channel blocker are slightly less. Table II shows the baseline laboratory indexes between the two groups. The CTO group shows significantly higher WBC, NE%, TG, non-HDL, Hcy, UA, BNP, NT-proBNP, CK-MB, and TnI, but lower PLT and HDL. For the baseline clinical angiography characteristics in Table III, CTO patients have more multivessel lesions than non-CTO patients. The CTO lesions are RCA, LAD, LCX, and others.

Table I. Baseline clinical demographic of the study patients.

Variable	Overall (n = 1473)	CTO		*p*-value
		Yes (n = 317)	No (n = 1156)	
Clinical demographic				
Gender (male)	1049 (71.215%)	266 (83.912%)	783 (67.734%)	< 0.00001
Age (y)	61 (54-67)	61 (53-67)	61 (54-67)	0.51295
Current tobacco use	697 (47.318%)	181 (57.098%)	516 (44.637%)	0.00011
Alcohol consumption	479 (32.519%)	109 (34.385%)	370 (32.007%)	0.46356
BMI (kg/m^2)	25.712 (23.781-27.732)	25.817 (23.939-27.885)	25.649 (23.739-27.683)	0.17113
SP (mmHg)	130 (120-141)	128 (118-139)	130.000 (121-142)	0.00129
DP (mmHg)	78 (70-85)	77 (70-84)	78 (70-85)	0.12082
Hypertension	940 (63.815%)	201 (63.407%)	739 (63.927%)	0.864
Diabetes mellitus	475 (32.247%)	114 (35.962%)	361 (31.228%)	0.110
Dyslipidemia	1163 (78.955%)	244 (76.972%)	919 (79.498%)	0.328
Prior stroke	133 (9.029%)	29 (9.148%)	104 (8.997%)	0.933
Echocardiography				
EF (%)	65 (60-67)	62 (57-66)	65 (61-67)	< 0.00001
LVEDD (mm)	30 (28-32)	31 (28-35)	30 (28-32)	< 0.00001
Medication				
Aspirin	1473 (100%)	317 (100%)	1156 (100%)	–
Clopidogrel	685 (46.504%)	176 (55.521%)	509 (44.031%)	0.000
Ticagrelor	284 (19.280%)	117 (36.907%)	167 (14.446%)	0.000
β-blocker	728 (49.423%)	194 (61.199%)	534 (46.194%)	0.000
ACEI/ARB	478 (32.451%)	85 (26.814%)	393 (33.997%)	0.016
Statin	1406 (95.451%)	296 (93.375%)	1110 (96.021%)	0.045
Calcium channel blocker	414 (28.106%)	67 (21.136%)	347 (30.017%)	0.002
Nitrates	697 (47.318%)	186 (58.675%)	511 (44.204%)	0.000
PPIs	1034(70.197%)	224 (70.662%)	810 (70.069%)	0.838
Diuretics	249(16.904%)	86 (27.129%)	163 (14.100%)	0.000

BMI, body mass index; SP, systolic blood pressure; DP, diastolic blood pressure; EF, Ejection fraction; LVEDD, left ventricular end diastolic diameter; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blocker; PPI, proton pump inhibitors.

Table II. Baseline laboratory indexes of the study patients.

Variable	Overall (n = 1473)	CTO		p-value
		Yes (n = 317)	No (n = 1156)	
Laboratory indexes				
WBC (10^{12}/L)	6.840 (5.710-8.170)	7.260 (6.110-8.620)	6.710 (5.610-8.015)	< 0.00001
RBC (10^{12}/L)	4.580 (4.260-4.900)	4.550 (4.250-4.880)	4.580 (4.260-4.900)	0.5767
Hb (g/L)	141.000 (131.000-150.000)	141.000 (131.000-150.000)	141.000 (130.000-151.000)	0.55624
HCT (%)	40.800 (38.100-43.300)	40.700 (37.900-43.200)	40.800 (38.100-43.300)	0.42062
PLT (10^9/L)	216.000 (183.000-256.000)	213.000 (179.000-247.000)	219.000 (184.000-259.000)	0.01999
NE (10^9/L)	4.370 (3.510-5.430)	4.760 (3.870-6.230)	4.250 (3.428-5.300)	< 0.00001
NE% (%)	64.700 (59.000-70.100)	67.000 (60.400-72.500)	64.200 (58.575-69.400)	< 0.00001
LYM (10^9/L)	1.830 (1.480-2.250)	1.780 (1.450-2.220)	1.840 (1.490-2.260)	0.17446
MONO (10^9/L)	0.360 (0.280-0.460)	0.370 (0.300-0.480)	0.360 (0.280-0.460)	0.02469
Glu (mmol/L)	5.660 (5.090-7.130)	5.860 (5.140-7.500)	5.620 (5.080-7.060)	0.08821
HbA1C (%)	6.000 (5.600-6.800)	6.100 (5.700-7.000)	6.000 (5.600-6.800)	0.1216
TG (mmol/L)	1.440 (1.080-2.020)	1.540 (1.140-2.080)	1.420 (1.060-1.992)	0.02167
TC (mmol/L)	3.990 (3.430-4.750)	4.020 (3.460-4.990)	3.980 (3.430-4.703)	0.1619
HDL (mmol/L)	1.090 (0.930-1.270)	1.030 (0.890-1.190)	1.100 (0.940-1.280)	0.00002
LDL (mmol/L)	2.280 (1.800-2.940)	2.370 (1.870-3.130)	2.260 (1.800-2.890)	0.0619
FFA (mmol/L)	0.430 (0.300-0.610)	0.430 (0.290-0.620)	0.440 (0.300-0.610)	0.81339
non-HDL (mmol/L)	2.840 (2.320-3.600)	2.970 (2.390-3.820)	2.820 (2.310-3.540)	0.02141
sdLDL (mmol/L)	0.610 (0.440-0.880)	0.610 (0.440-0.930)	0.610 (0.440-0.870)	0.50908
Hcy (mmol/L)	13.400 (11.600-16.300)	13.800 (12.000-18.800)	13.300 (11.500-15.700)	0.00046
UA (mmol/L)	336.500 (281.600-391.500)	343.800 (292.100-407.900)	334.550 (278.600-387.325)	0.00496
Cr (μmol/L)	72.400 (62.700-82.500)	71.050 (61.800-81.525)	76.000 (66.300-86.400)	< 0.00001
eGFR (CKD-EPI)	93.960 (84.170-101.500)	92.660 (83.110-100.360)	94.165 (84.333-101.752)	0.05811
BNP (pg/ml)	34.000 (19.000-76.000)	53.000 (27.000-157.000)	32.000 (18.000-67.000)	< 0.00001
NT-proBNP (pg/ml)	85.400 (47.600-232.000)	160.000 (64.600-591.000)	75.700 (43.500-187.000)	< 0.00001
hs-CRP (mg/L)	1.080 (0.560-2.380)	1.120(0.590-2.910)	1.065 (0.550-2.288)	0.08794
CK-MB (U/L)	1.800 (1.200-2.500)	1.900 (1.300-2.600)	1.800 (1.200-2.500)	0.02579
TnI (μg/L)	0.010 (0.000-0.130)	0.030 (0.000-0.160)	0.010 (0.000-0.110)	0.00061

WBC, white blood cell; RBC, red blood cell; Hb, hemoglobin; HCT, hematocrit; PLT, platelet; NE, neutrophil; NE%, neutrophil percentage; LYM, lymphocyte; MONO, monocyte; Glu, glucose; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; FFA, Free Fatty Acids; Hcy, homocysteine; UA, uric acid; Cr, creatinine; BNP, brain natriuretic peptide; NT-proBNP, N-terminal pro-B-type natriuretic peptide; hs-CRP, high-sensitivity C-reactive protein; CK-MB, creatine kinase-MB; TnI, troponin I.

Table III. Baseline clinical angiography characteristics of the study patients.

Variable	Overall (n = 1473)	CTO		p-value
		Yes (n = 317)	No (n = 1156)	
Angiography				
0-vessel	47 (3.191%)	0 (0%)	47 (4.066%)	0.000
1-vessel	592 (40.190%)	41 (12.934%)	551 (47.664%)	0.000
2-vessels	417 (28.310%)	97 (30.599%)	320 (27.682%)	0.307
3-vessels	417 (28.310%)	179 (56.467%)	238 (20.588%)	0.000
CTO-vessel				
LM	-	1 (0.315%)	-	-
LAD	-	119 (37.539%)	-	-
LCX	-	85 (26.814%)	-	-
RCA	-	138 (43.533%)	-	-
D1	-	4 (1.262%)	-	-

CTO, chronic total occlusion; LM, left main coronary artery; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; D1, diagonal branch.

The Derivation and Validation Sets

Table IV summarizes the clinical characteristics of the derivation set (n=1,105) and the validation set (n=368). The clinical demographics that included sex, age, current tobacco use, alcohol consumption, BMI, SP, and DP were not significantly different between both groups (all p >0.05). Additionally, the incidences of hypertension, diabetes mellitus, dyslipidemia, and a history of previous stroke had no significant differences between both groups (all p>0.05). Similarly, there was no statistical significance in echocardiography and laboratory indexes (all p>0.05).

Univariate Logistic Regression Analysis

Univariate logistic regression analysis was performed to explore the association between all clinical characteristics of the patients (Tables I and II) and CTO diagnosis. As shown in Table V, the result revealed that gender (p<0.0001) (OR: 2.929, 95% CI: 1.985-4.323), NE% (p <

Table IV. Clinical characteristics of the derivation and validation sets.

Variable	Overall (n = 1473)	Derivation set (n = 1105)	Validation set (n = 368)	p-value
Clinical demographic				
Gender (male)	1049 (71.215%)	254 (69.022%)	795 (71.946%)	0.31415
Age (y)	61 (54-67)	61 (53-67)	61 (54-67)	0.51295
Current tobacco use	697 (47.318%)	185 (50.272%)	512 (46.335%)	0.21135
Alcohol consumption	479 (32.519%)	109 (29.620%)	370 (33.484%)	0.19139
BMI (kg/m^2)	25.712 (23.781-27.732)	25.728 (23.847-27.968)	25.649 (23.781-27.701)	0.46602
SP (mmHg)	130 (120-141)	130 (120-141)	130 (120-142)	0.30211
DP (mmHg)	78 (70-85)	77.5 (70-85)	78 (70-85)	0.12082
Hypertension	940 (63.815%)	201 (63.407%)	739 (63.927%)	0.97007
Diabetes mellitus	475 (32.247%)	117 (31.793%)	358 (32.398%)	0.88031
Dyslipidemia	1163 (78.955%)	286 (77.717%)	877 (79.367%)	0.5496
Prior stroke	133 (9.029%)	40 (10.870%)	93 (8.416%)	0.18776
Echocardiography				
EF (%)	65 (60-67)	64 (60-67)	65 (60-67)	0.4192
LVEDD (mm)	30 (28-32)	30 (28-33)	30 (28-32)	0.84197
Laboratory indexes				
WBC (10^{12}/L)	6.840 (5.710-8.170)	6.930 (5.745-8.285)	6.790 (5.690-8.130)	0.62044
RBC (10^{12}/L)	4.580 (4.260-4.900)	4.595 (4.260-4.912)	4.580 (4.260-4.900)	0.65744
Hb (g/L)	141.000 (131.000-150.000)	141.000 (129.750-151.000)	141.000 (131.000-150.000)	0.91934
PLT (10^9/L)	216.000 (183.000-256.000)	216.000 (183.500-252.000)	217.000 (183.000-257.000)	0.96146
NE% (%)	64.700 (59.000-70.100)	64.800 (59.100-70.000)	64.450 (58.575-70.100)	0.61451
LYM (10^9/L)	1.830 (1.480-2.250)	216.000 (183.500-252.000)	217.000 (183.000-257.000)	0.96146
MONO (10^9/L)	0.360 (0.280-0.460)	216.000 (183.500-252.000)	217.000 (183.000-257.000)	0.96146
Glu (mmol/L)	5.660 (5.090-7.130)	5.750 (5.128-7.400)	5.640 (5.080-7.080)	0.3331
HbA1C (%)	6.000 (5.600-6.800)	6.100 (5.600-6.900)	6.000 (5.600-6.800)	0.29597
TG (mmol/L)	1.440 (1.080-2.020)	1.495 (1.160-2.090)	1.430 (1.060-2.010)	0.08011
TC (mmol/L)	3.990 (3.430-4.750)	3.900 (3.340-4.680)	4.010 (3.470-4.770)	0.13557
HDL (mmol/L)	1.090 (0.930-1.270)	1.060 (0.927-1.250)	1.090 (0.940-1.270)	0.09305
LDL (mmol/L)	2.280 (1.800-2.940)	2.205 (1.740-2.940)	2.310 (1.830-2.950)	0.18773
FFA (mmol/L)	0.430 (0.300-0.610)	0.455 (0.290-0.613)	0.430 (0.300-0.610)	0.94494
nonHDL (mmol/L)	2.840 (2.320-3.600)	2.770 (2.280-3.570)	2.860 (2.340-3.610)	0.33696
sdLDL (mmol/L)	0.610 (0.440-0.880)	0.610 (0.430-0.870)	0.610 (0.440-0.890)	0.92576
Hcy (mmol/L)	13.400 (11.600-16.300)	13.500 (11.300-15.850)	13.400 (11.600-16.500)	0.28687
UA (mmol/L)	336.500 (281.600-391.500)	334.550 (285.550-391.225)	336.900 (280.700-391.700)	0.94557
Cr (μmol/L)	72.400 (62.700-82.500)	72.550 (62.600-82.425)	72.400 (62.800-82.500)	0.75413
eGFR (CKD-EPI)	93.960 (84.170-101.500)	93.685 (83.945-101.698)	94.020 (84.200-101.360)	0.75698
BNP (pg/ml)	34.000 (19.000-76.000)	37.500 (20.000-82.000)	34.000 (19.000-73.000)	0.18909
hs-CRP (mg/L)	1.080 (0.560-2.380)	1.070 (0.540-2.478)	1.080 (0.560-2.360)	0.87698
CK-MB (U/L)	1.800 (1.200-2.500)	1.900 (1.300-2.500)	1.800 (1.200-2.500)	0.11103
TnI (μg/L)	0.010 (0.000-0.130)	0.010 (0.000-0.140)	0.010 (0.000-0.120)	0.83763

Table V. Univariate and multivariate logistic regression analyses for CTO predictors.

Variables	Univariate logistic regression			Multivariate logistic regression		
	OR	95% CI	*p*	OR	95% CI	*p*
Gender (male)	2.929	1.985-4.323	0.000	2.860	1.949-4.197	0.000
NE% (%)	1.173	1.086-1.267	0.000	0.849	0.787-0.915	0.000
HCT (%)	0.957	0.925-0.991	0.013	1.041	1.006-1.077	0.021
TC (mmol/L)	3.693	1.14-11.964	0.029	0.262	0.081-0.849	0.026
HDL (mmol/L)	0.129	0.036-0.458	0.002	7.658	2.158-27.180	0.002
EF (%)	0.965	0.947-0.984	0.000	1.036	1.016-1.056	0.000
TnI (μg/L)	0.645	0.484-0.859	0.003	1.580	1.185-2.107	0.002
CK-MB (U/L)	1.002	1.001-1.003	0.000	0.998	0.997-1.002	0.064
NT-proBNP(pg/ml)	1.000	1.000-1.001	0.000	1.000	0.999-1.000	0.000

0.0001) (OR: 1.173, 95% CI: 1.086-1.267), HCT (p=0.013) (OR: 0.957, 95% CI: 0.925-0.991), TC (p =0.029) (OR: 3.693, 95% CI: 1.14-11.964), HDL (p=0.002) (OR: 0.129, 95% CI: 0.036-0.458), EF (p<0.0001) (OR: 0.965, 95% CI: 0.947-0.984), TnI (p=0.003) (OR: 0.645, 95% CI: 0.484-0.859), CK-MB (p<0.0001) (OR: 1.002, 95% CI: 1.001-1.003), and NT-proBNP (p<0.0001) (OR: 1.000, 95% CI: 1.000-1.001) were implicated in the risk of CTO patients.

Multivariate Logistic Regression Analysis

Multivariate logistic regression analysis was used to determine the significant independent predictors of CTO. According to the multivariate logistic regression analysis in Table V, gender (p<0.0001) (OR: 2.860, 95% CI: 1.949-4.197), NE% (p < 0:0001) (OR: 0.849, 95% CI: 0.787-0.915), HCT (p=0.021) (OR: 1.041, 95% CI: 1.006-1.077), TC (p =0.026) (OR: 0.262, 95% CI: 0.081-0.849), HDL (p=0.002) (OR: 7.658, 95% CI: 2.158-27.180), EF (p < 0:0001) (OR: 1.036, 95% CI: 1.016-1.056), TnI (p=0.002) (OR: 1.580, 95% CI: 1.185-2.107), and NT-proBNP (p < 0:0001) (OR: 1.000, 95% CI: 0.999-1.000) were identified as independent factors affecting CTO diagnosis.

Construction of a Novel Nomogram Scoring System

According to the results of multivariate logistic regression analysis, gender (male), NE%, HCT, TC, HDL, EF, TnI, and NT-proBNP were included as influencing factors to construct a nomogram (Figure 1). Each influencing factor corresponded to a score, and the total score was mapped to the axis of prediction of the diagnosis, which could reflect the risk factors for CTO. As an example to better explain the nomogram model, if the patient is male (34 points), NE% of 40% (6 points), HCT of 35% (32 points), TC of 2.0 mmol/L (10 points), HDL of 0.8 mmol/L (58 points), EF of 35% (57 points), TnI of 0 μg/L (73 points), and NT-proBNP of 1000 pg/ml (12 points), the total points is 282 and the probability of CTO is estimated to be 30%.

Evaluation and Validation of the Nomogram

368 patients were included in the validation set between January 2020 and December 2020. The calibration curves were drawn to evaluate the calibration of the model in the derivation set (Figure 2A) and the validation set (Figure 2B). The ROC curve analysis was used to evaluate the discrimination of the model in the derivation set and validation set. The areas under the curves

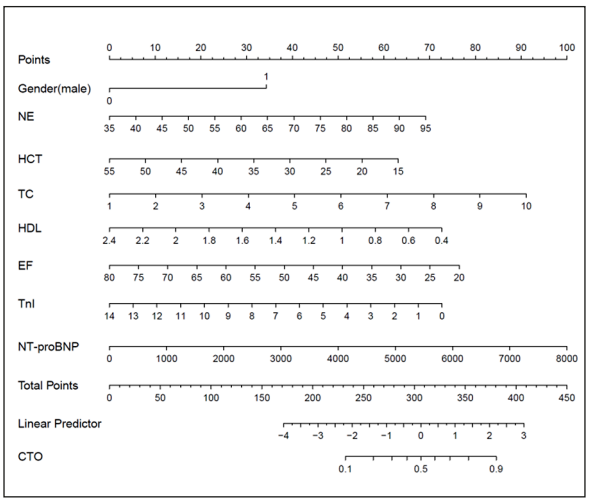

Figure 1. A nomogram prediction model for the probability of CTO.

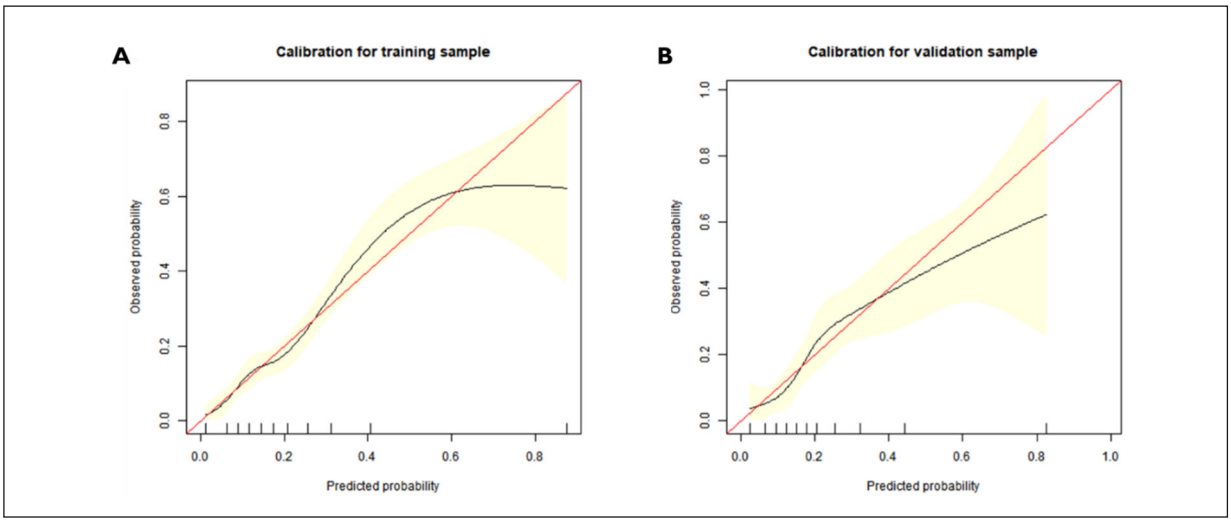

Figure 2. Calibration curves of the nomogram in the derivation set (**A**) and validation sets (**B**).

(AUC) were 0.746 and 0.741, respectively (Figure 3). Furthermore, the DCA curves demonstrated that the novel nomogram also included a higher clinical net (Figure 4).

Discussion

In this study, clinical demographics, echocardiography, and laboratory indexes were analyzed to examine the association between predictive factors and CTO diagnosis. New predictive models, including a nomogram based on univariate and multivariate logistic regression analysis, were developed and validated. Our results provide a unique perspective on relevant predictive factors with better discriminatory power. To the best of our knowledge, this is the first attempt to develop a predictive method for diagnosing CTO based on a nomogram. The nomogram formed by gender (male), NE, HCT, TC, HDL, EF, TnI, and NT-proBNP may provide critical clues for the risk evaluation and diagnosis of CTO (Figure 1).

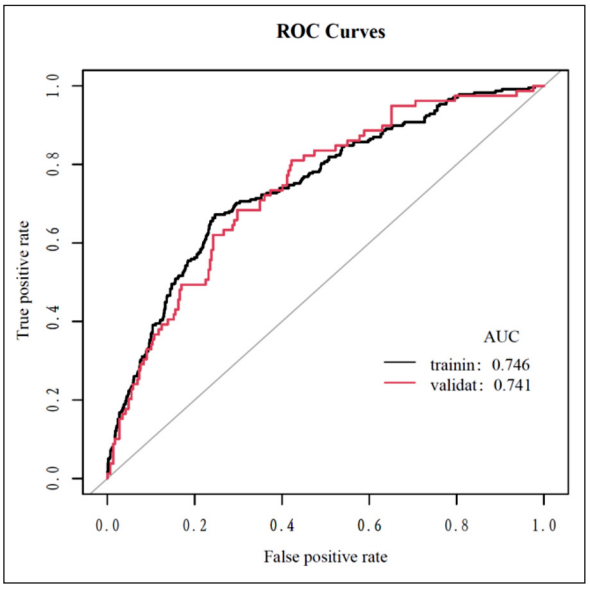

Figure 3. Receiver-operating characteristics curve in the derivation cohort (*blank*) and validation (*red*) cohort for the nomogram.

Although the development of CAD has been associated with various traditional risk factors, including sex (male) and lipid metabolism, their role in the etiology of CTO remains less understood[7]. Most studies[8] have focused on stable CAD or acute coronary syndrome; information on risk factors for CTO patients is lacking. In addition, there has not been a satisfactory model to predict CTO before CAG. The advent of clinical demographic nomogram analysis provides detailed information on traditional risk factors with unprecedented coverage, enhancing our understanding and management of cardiovascular diseases[9]. By converting the total score into a continuum of individual scores using a logarithmic formula, we developed a relatively accurate nomogram to predict the probability of CTO before CAG. Since recanalization of a totally occluded vessel requires a great amount of time and finance, it would be necessary to find a method that effectively stratifies cardiovascular risks and guides clinical practice[10].

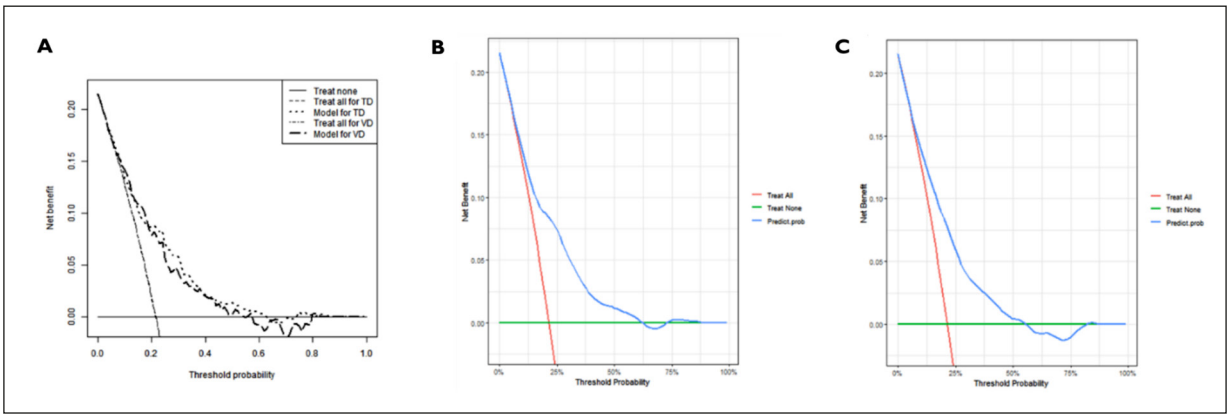

Figure 4. Decision curve analysis of the nomogram (**A**) and in the derivation set (**B**) and validation set (**C**), respectively.

CTO and CAD share common pathological processes; nevertheless, the underlying mechanism of coronary artery progressing from stenosis to complete obstruction has not been fully clarified[11]. Therefore, we recruited the CAD and CTO patients to find out some differences that were uniquely altered in CTO. However, compared to patients with CAD, the demographic characteristics between patients with CAD and CTO were pretty much comparable. In some ways, this confirmed that the change in CTO patients was not solely attributed to the discrepancy in baseline features, but to independent pathogenic factors on their own[12].

Our study shows that the incidence of CTO was 21.5%, which is within the range reported by recent studies (18.0% to 52%)[13]. Male sex and lipid metabolism have previously been reported to be associated with the incidence of CTO in patients[14]. Consistent with previous reports[15], the sex and lipid elements in our nomogram were significant predictors of CTO. Especially for HDL, it has been proposed that reduced HDL could alter the stability of HDL particles, resulting in the disruption of reverse cholesterol transport and in part, at least, enhance the progression of CAD to CTO.

Besides CAD risk factors, our study revealed that EF and NT-proBNP were independently positively associated with the prediction of CTO[16]. Some CTO lesions develop from an undetected acute myocardial infarction[17]. Acute myocardial ischemia and its early pathological changes often damage left ventricular systolic function, and gradually develop into ischemic cardiomyopathy after three months[18]. By contrast, TnI was independently negatively associated with predicting CTO. Notably, TnI is a biomarker of acute myocardial ischemia[19]. Given this, the increase in TnI may imply a total occlusion lesion less than three months. Taken together, EF, NT-proBNP, and TnI may predict the probability of CTO in patients with CAD.

In addition to non-modifiable variables (male sex) and traditional risk factors for CAD (TC, HDL, EF, NT-proBNP, and TnI) of the individual patient, blood routine levels including HCT and NE%, were also predictors in the nomogram. HCT is an indicator that reflects the extent of hemoconcentration[20]. It seems plausible that a higher HCT with increased blood viscosity will predict a more increased risk of first incident acute myocardial ischemia than a lower HCT[21]. On the contrary, the lower HCT may refer to CTO rather than acute total occlusion. For NE%, CTO has long been regarded a low-grade, subclinical, systemic inflammatory chronic disease[22]. Inflammation is at the forefront in the initiation and development of the entire course of CTO[23]. CTO develops from total luminal obstruction of an artery by a thrombus, with subsequent organization and varying degrees of recanalization; often, these events are clinically silent[24]. The thrombus organization process coincides with the development of intraluminal microvessels accompanied by inflammatory cells, infiltrating smooth muscle cells, and the deposition of the proteoglycan matrix[25]. In CTO of all ages, a close relationship has been observed, in both location and intensity, between cellular inflammation and vessel wall neovascularization[26]. NE% is an indicator of inflammatory status. Therefore, it may predict the probability of CTO in patients with CAD.

Taken together, noninvasive tests have been increasingly used for risk stratification and to

aid in clinical decision-making in patients with suspected diseases[27]. Subsequently, nomograms have been developed in various diseases, showing to be more accurate than conventional staging systems to predict the prognosis[28]. To our knowledge, this is the pioneering research to investigate the predictability of CTO in patients with CAD with well performed. These results supported that the nomograms could better understand the risk factors for CTO and even predict the diagnosis in patients with CTO before CAG.

Limitations

There are several limitations in our study. First, we only included patients of Asian ethnicity, which may limit the generalizability of the nomogram. Second, some selection bias was inevitable due to the retrospective design and single-center nature of the study. Third, although we implemented external validation, multicenter validated research is needed to draw more persuasive conclusions. Finally, there is still room for optimization of this predictive model using other advanced statistical methods, such as the least absolute shrinkage and selection operator (LASSO), which may help develop a more accurate prognostic prediction model.

Conclusions

In summary, we constructed and validated a relatively accurate clinical nomogram that demonstrated adequate discrimination and calibration, to predict the probability of CTO in patients with CAD. This work will generate fresh insight into developing a preoperative risk factor nomogram that may help clinicians discern CTO in CAD patients.

Conflict of Interest

The Authors declare that they have no conflict of interests.

Acknowledgements

Not applicable.

Ethics Approval

The study protocol was approved by the Institutional Review Board of Beijing Anzhen Hospital, Capital Medical University, Beijing, China.

Availability of Data and Materials

The data sets used during the study are available from the corresponding author on reasonable request.

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Authors' Contribution

Yuchen Shi, Ze Zheng, and Jinghua Liu conceived the study and designed the protocol. Yuchen Shi and Ping Wang integrated the data and wrote the manuscript. Yongxin Wu and Zichao Cheng were responsible for the selection of the study, the extraction of data, and the evaluation of the quality of the study. Wen Jian, Yanci Liu and Jinghua Liu critically revised the manuscript. All authors read and approved the final manuscript.

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