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Clinical risk score to predict poor coronary collateralization in type 2 diabetic patients with chronic total occlusion

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Abstract

Background This study sought to develop and externally validate a score that predicts the probability for poor coronary collateralization (CC) in stable angina patients with type 2 diabetes mellitus (T2DM).

Methods Clinical and laboratory variables were collected on admission in 1022 T2DM patients with chronic total occlusion (CTO). Coronary collaterals with Rentrop score 0 or 1 were considered as poor CC. Multivariable logistic regression analysis was used to identify independent predictors for poor CC. The external validation cohort comprised 234 T2DM patients with CTO selected randomly from an independent external center.

Results Eight predictors were independently associated with poor CC and applied to construct the risk model. A score incorporating these factors predicted poor CC, ranging from 7% when all factors were absent to 97% when ≥ 7 factors were present. Internal validation showed an AUC of 0.748 (95%CI, 0.695–0.795) and the external validation had an AUC of 0.754 (95%CI, 0.694–0.808). A cumulative predictive score was developed by summing points assigned to each factor based on its regression coefficient. Smoking and neutrophil > 6.5×10^9/L were assigned 3 points, female gender, hypercholesterolemia, and eGFR < 60 mL/min/1.73 m^2 were assigned 2 points, age > 65 years, hypertension, and HbA1c > 6.5% were assigned 1 point. The optimal cutoff score was 4 for predicting poor CC with sensitivity 75.4% and specificity 64.1%.

Conclusions We have demonstrated a risk score based on clinical and laboratory characteristics providing an easy-to-use tool to predict poor CC in T2DM patients with stable coronary artery disease.

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Keywords Coronary artery disease, Chronic total occlusion, Coronary collateral circulation, Type 2 diabetes mellitus, Risk score

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Introduction

Coronary collateralization (CC) is an adaptive response to occlusion of a coronary artery which is originally patent [1]. Chronic total occlusion (CTO) is a common entity in patients with stable coronary artery disease undergoing coronary angiography or percutaneous coronary intervention (PCI) with a point-prevalence between 15 and 30% [2]. CTO revascularization by PCI can be technically challenging due to the procedural complexity and low success rate compared to non-CTO PCI. Several scores have been developed to estimate the difficulty and the likelihood of success of CTO PCI. Dual arterial access and use of CTO crossing algorithms can increase the success and safety of CTO PCI. Intracoronary imaging is useful to optimize stent expansion and reduce major adverse cardiovascular events. While complications are more common during CTO PCI, careful planning and prompt diagnosis and treatment can prevent them or minimize their adverse consequences. Numerous studies have shown that coronary collateral status is crucial for decision-making of revascularization strategy of CTO, and robust coronary collaterals play a crucial role in improving clinical outcomes as they protect ischemic myocardium, enhance cardiac function, and reduce the incidence of future cardiovascular events and mortality [3–6].

Type 2 diabetes mellitus (T2DM) is associated with an increased risk for severe and diffuse coronary atherosclerosis and adverse clinical outcomes [7, 8]. It is well recognized that CC is significantly reduced in diabetic compared with non-diabetic patients [1], and T2DM has been identified as a major predictor of reduced CC in patients with CTO [9–11]. Previous studies have suggested that the dysregulation of pro- and anti-angiogenic factors contributes to the impaired arteriogenesis and angiogenesis in diabetic ischemic tissues, as demonstrated by a decrease in coronary collateral vessel growth [9–11]. Mechanistically, these pathologic features appear to be induced by a persistent low-grade inflammatory state in the diabetic vasculature and the myocardium, identified by the accumulation of advanced glycation end-products, elevated cholesterol levels, increased oxidative stress, endothelial dysfunction, and, among other factors, abnormal regulation of the renin-angiotensin system [7, 9–11].

An accurate assessment of CC requires measurement of collateral flow index, which needs simultaneous recording of aortic pressure and the distal pressure within the occluded segment of the culprit coronary artery [12]. The degree of collateral formation is often estimated visually at coronary angiography according to the Rentrop classification. Nevertheless, establishment of a clinical model using conventional factors for early noninvasive evaluation of CC would be applicable to widespread screening. Based on these considerations, our study aimed to provide an easy-to-use tool to identify T2DM CTO patients at higher risk of poor CC using simple clinical and laboratory variables available at admission.

Methods

This study was conducted as part of the COLLECT (COronary CoLLateralization in Type 2 diabEtic Patients with Chronic Total Occlusion) registry (Clinical Trials.gov: NCT06054126) retrospectively registered on September 19th, 2023, which aimed to investigate the risk factors and therapeutic strategies for poor CC in T2DM patients with CTO. The study protocol was approved by the Ethics Committee of Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and Shanghai Eastern Hospital, Tongji University School of Medicine. Written informed consent was obtained from all participants. The authors from each participating center guarantee the integrity of data.

Study population: derivation, internal and external validation cohorts

A total of 1079 stable angina patients who had T2DM and at least one lesion with coronary angiographic 100% occlusion for more than 3 months were consecutively recruited between January 2010 and April 2023 at Shanghai Ruijin Hospital. The exclusion criteria were as follows: previous history of coronary artery bypass grafting, percutaneous coronary intervention (PCI) within the previous 3 months, chronic severe renal or liver disease, malignancy, autoimmune disease, pulmonary heart disease or severe myocardiopathy. The remaining 1022 eligible patients were randomly allocated (in a 7:3 ratio) into a derivation cohort ($n = 716$) and an internal validation cohort ($n = 306$). For externally validating the model, an additional cohort of 234 consecutive patients with T2DM and CTO between January 2018 and July 2023 at Shanghai Eastern Hospital were enrolled. The validation cohorts were established using the same inclusion and exclusion criteria as the derivation cohort to ensure comparability. Clinical data and model variables were gathered from the Inpatient Medical Record Management Systems of each hospital using the standardized methods consistent with those applied to the derivation cohort (Fig. 1).

Blood samples were collected within 24 h of hospital admission, and laboratory parameters were assessed using standard methods. T2DM diagnosis was based on the American Diabetes Association criteria [13]. Hypertension was defined as systolic blood pressure value ≥ 140 mmHg and/or diastolic blood pressure value ≥ 90 mmHg or the use of antihypertensive medications for blood pressure control [14]. The diagnosis for hypercholesterolemia was made as total cholesterol levels over 200 mg/

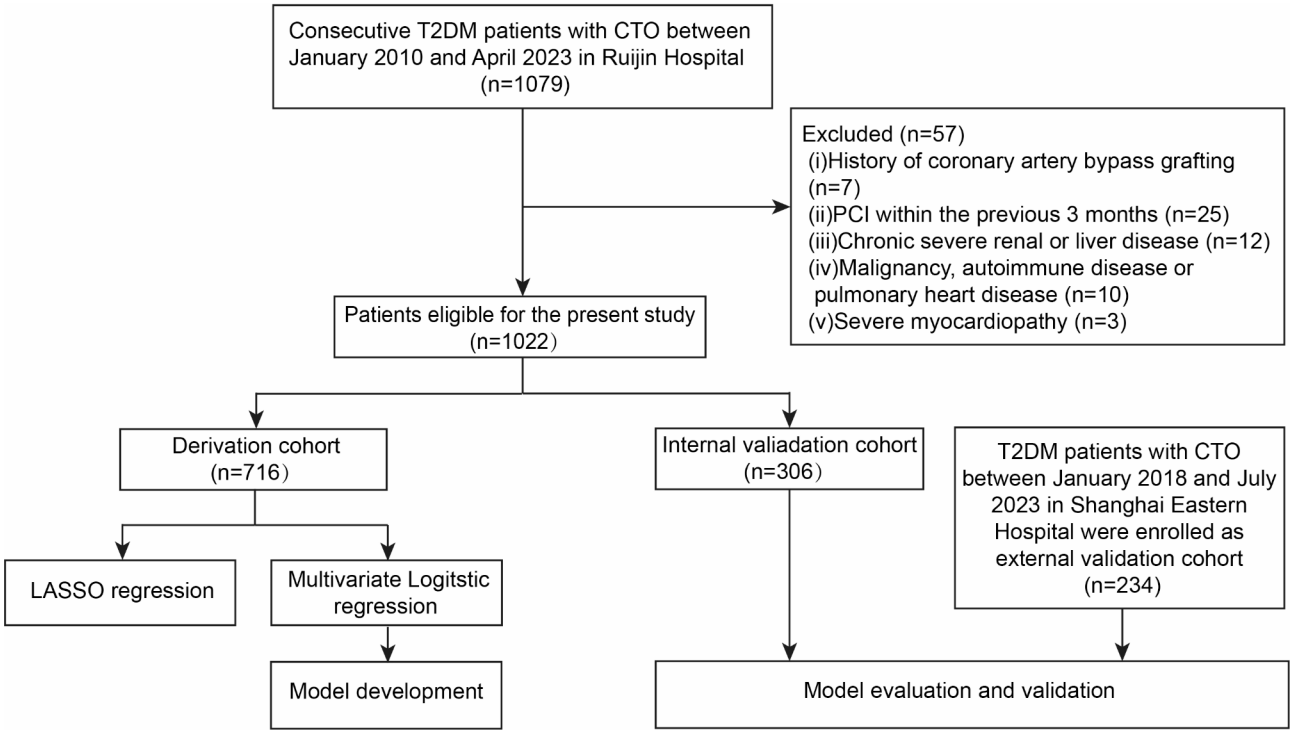

Fig. 1 Flowchart of patient enrollment. *T2DM* type 2 diabetes mellitus, *NYHA* New York Heart Association, *CTO* chronic total occlusion, *LASSO* Least Absolute Shrinkage and Selection Operator

dL or having medical treatment for hypercholesterolemia [15]. Smoking status was categorized as current or former smokers (smoking during the last one year or had a history of smoking before), and non-smokers [16].

Coronary angiography and collateral grading

Coronary angiography was performed using Judkins technique via either the radial or femoral access, and the extent of coronary artery stenosis was assessed by quantitative coronary analysis (QCA) [17]. Rentrop score system was used to classify coronary collateral formation [18]. Grade 0 = no visible filling of collateral vessels, grade 1 = filling of side branches without reaching the epicardial regions, grade 2 = filling of side branches with partial reaching the epicardial regions, grade 3 = complete filling of the epicardial artery. Grades 0 and 1 were defined as poor CC while grades 2 and 3 were considered as good CC. In patients with multiple chronic total occlusions, the highest Rentrop grade was used for analysis. Two experienced interventional cardiologists who were blinded to the clinical data of the patients evaluated all angiographic images. Any discrepancies between the cardiologists were resolved through consultation with a third reviewer.

Model construction and internal validation

In the derivation cohort, Least Absolute Shrinkage and Selection Operator (LASSO) regression was employed to address potential collinearity among variables. Missing data were imputed when the proportion of missing values was less than 20%, using predictive mean matching for numerical variables. The most predictive factors were identified based on the 1 standard error (1-SE) of the minimum criteria, and variables that were statistically significant in multivariate logistic regression model were selected to construct the prediction model. A risk score for predicting poor CC was developed based on the results of the logistic regression analysis. The significant variable with the lowest regression coefficient (B-value) in the multivariate analysis was scored 1 point. The regression coefficients of the other significant variables were divided by the lowest regression coefficient and the results were rounded to whole numbers. Thus, each significant variable in the logistic regression analysis has a score associated with its impact [19]. These individual scores were then summed to give a total risk score for each patient. For derivation and internal validation cohorts, the discriminative ability of prediction model for poor CC was assessed using receiver-operator characteristic (ROC) curve analysis, and the calibration ability was evaluated using Hosmer–Lemeshow test.

External validation

The generalizability of the final prediction model was assessed by evaluating it externally in an independent validation cohort. The evaluation of external validity

performance involved using a calibration plot to assess calibration ability and the area under the curve(AUC) to assess discrimination ability.

General statistical analysis

Normally distributed variables were presented as mean ± standard deviation (SD) and nonnormally distributed variables were presented as the medians (interquartile ranges). The categorical variables were presented as numbers of cases with percentages. Student's t-test or Mann–Whitney U test was used for analysis of continuous variables that were normally or nonnormally distributed. respectively. The Chi-square test was used to compare the difference of categorical variables. The maximal Youden index was used to determine the optimal cutoff value. All statistical analyses were performed using SPSS version 26.0 (SPSS Inc., Chicago, IL, USA) and R software version 4.2.2 (https://cran.r-project.org). All analyses were two-tailed and a P value < 0.05 was considered statistically significant.

Results

Characteristics of the study cohort

The derivation and internal and external validation cohorts did not significantly differ with respect to age, gender distribution, risk factors for coronary artery disease, and laboratory measurements. Poor and good CC were detected in 301 and 415 patients for the derivation cohort, in 133 and 173 patients for the internal validation cohort, and in 79 and 155 patients for the external validation cohort, respectively. Compared to patients with good CC, those with poor CC were significantly older, higher proportion of females, hypertension, hypercholesterolemia, and cigarette smoking, and had lower lymphocyte to monocyte ratio (LMR) and estimated glomerular filtration rate (eGFR), and more elevated white blood cell count, neutrophil, neutrophil to lymphocyte ratio (NLR), fasting blood glucose (FBG), hemoglobin A1c (HbA1c) and low-density lipoprotein cholesterol (LDL-C) (Table 1).

Predictors of poor CC

In LASSO regression, a total of 32 variables were screened, and 9 candidate variables were associated with poor CC (Fig. 2). Multivariate logistic regression analysis identified the following 8 variables independently predicting poor CC, all of which were integrated into the final model: age > 65 years (OR, 1.560; 95%CI, 1.097–2.220; P = 0.013), female (OR, 2.469; 95%CI, 1.596–3.821; P < 0.001), smoking (OR, 3.239; 95%CI, 2.216–4.732; P < 0.001), hypertension (OR,1.905; 95%CI, 1.265–2.869; P = 0.002), hypercholesterolemia (OR, 2.425; 95%CI, 1.626–3.617; P < 0.001), neutrophil counts > 6.5×10^9/L (OR, 3.997; 95%CI, 2.575–6.205; P < 0.001), eGFR < 60 mL/min/1.73m^2 (OR, 2.306; 95%CI, 1.451–3.666; P < 0.001), and HbA1c > 6.5% (OR, 1.627; 95%CI, 1.160–2.283; P = 0.005) (Table 2).

Model presentation

The probability of poor CC of each patient was calculated using the following formulas obtained from the logistic model: Estimated probability of poor CC = 1/(1 + exp. -[− 2.575 + 0.445 × age > 65 years + 0.904 × female + 1.175 × smoking + 0.644 × hypertension + 0.886 × hypercholesterolemia + 1.386 × neutrophil > 6.5×10^9/L + 0.835 × eGFR < 60 mL/min/1.73m^2 + 0.487 × HbA1c > 6.5%]).

Internal validation

The Hosmer-Lemeshow test showed that there was no significant difference between the observed and predicted probabilities (P = 0.474). In ROC analysis, AUC was 0.755 (95% CI: 0.721–0.786 in the derivation cohort and a calibration slope was 1.00 (95% CI: 0.82–1.18). For internal validation cohort, AUC was 0.748 (95%CI: 0.695–0.795) with a calibration slope of 1.00 (95%CI: 0.72–1.28) (Fig. 3), suggesting that the model provided a good prediction of poor CC.

External validation

For external validation cohort, good discrimination of model was still exhibited with an AUC of 0.754 (95% CI:0.694–0.808) and a calibration slope of 1.00 (95%CI: 0.68–1.32) (Fig. 3).

Score performance

To facilitate the practical use of the model, we developed a cumulative predictive score for poor CC based on the 8 factors that independently predicted poor CC. The score is calculated by summing up the points assigned to each of the 8 factors in the final model. According to the regression coefficients observed with the 8 factors, each factor received its points in the cumulative predictive score: current smoking and higher level of neutrophil counts (> 6.5×10^9/L) was assigned with 3 points, female gender, presence of hypercholesterolemia and lower level of eGFR (< 60mL/min/1.73m^2) were assigned with 2 points; older age (> 65 years), presence of hypertension and higher level of HbA1c (> 6. 5%) were assigned with 1 point.

With this score, the probability of poor CC in the derivation cohort ranged from 10.3% for the 6 patients with risk score of 1, to 90.5% for the 19 patients with risk score of 10, and to 100% for the 6 patients with risk score of 11–13, showing a stepwise increase of poor CC with increasing risk score (P < 0.001). The probability of poor CC in the internal validation cohort ranged from 20.6% for the 7 patients with risk score of 2, to 77.3% for the 17 patients with risk score of 8, and to 100% for the

Table 1 Characteristics of the derivation, internal and external validation cohorts

	Derivation cohort		Internal validation cohort		External validation cohort	
Variables	**Poor CC (*n* = 301)**	**Good CC (*n* = 415)**	**Poor CC (*n* = 133)**	**Good CC (*n* = 173)**	**Poor CC (*n* = 79)**	**Good CC (*n* = 155)**
Variables	Poor CC (n = 301)	Good CC (n = 415)	Poor CC (n = 133)	Good CC (n = 173)	Poor CC (n = 79)	Good CC (n = 155)
Age, y	65.9 ± 10.1	62.8 ± 11.0***	66.7 ± 10.7	62.7 ± 10.8 ***	68.4 ± 11.1	64.6 ± 10.7*
Female, No. (%)	78(25.9)	75(18.1) *	38 (28.6)	26(15.0) **	28(35.4)	21(13.5)***
SBP, mmHg	137.1 ± 22.0	136.2 ± 20.9	137.1 ± 18.84	136.2 ± 16.8	135.3 ± 23.2	130.3 ± 18.1
DBP, mmHg	77.2 ± 13.1	76.7 ± 12.1	77.2 ± 12.4	76.8 ± 11.6	76.3 ± 9.2	76.2 ± 10.5
Body mass index, kg/m^2	25.1 ± 3.1	25.0 ± 3.0	25.7 ± 3.9	25.8 ± 3.9	25.4 ± 3.2	25.3 ± 2.3
Smoking, No. (%)	147(48.8)	125(30.1) ***	65(48.9)	61(35.3) *	38(48.1)	69(44.5)
Hypertension, No. (%)	250(83.1)	295(71.1) ***	115(86.5)	130(75.1) *	69(87.3)	121(78.1)
Hypercholesterolemia, No. (%)	88(29.2)	68(16.4) ***	42(31.6)	35(20.2) *	28(35.4)	34(21.9)*
Prior MI, No. (%)	66(21.9)	65(15.7) *	27(20.3)	29(16.8)	20(25.3)	24(15.5)
LVEF, %	58.0 ± 10.0	58.2 ± 10.3	57.9 ± 10.0	58.4 ± 10.9	58.1 ± 7.0	58.3 ± 8.0
Hemoglobin, g/L	132.7 ± 16.8	135.2 ± 17.7	132.5 ± 15.5	135.6 ± 15.5	130.9 ± 19.7	135.4 ± 18.0
Platelet count, 10^9 /L	193.2 ± 56.0	188.3 ± 57.0	189.2 ± 49.4	188.0 ± 49.1	219.8 ± 62.7	207.3 ± 54.7
White blood cell count, 10^9 /L	7.70(6.22–9.84)	6.88(5.71–8.30) ***	7.40(5.98–8.90)	6.49(5.70–7.62) ***	7.94(6.51–9.31)	6.47(5.39–7.83)**
Neutrophil, 10^9 /L	5.00(3.77–7.23)	4.28(3.40–5.50) ***	5.00(3.78–6.56)	4.24(3.60–5.13) ***	5.45(4.37–6.78)	4.39(3.57–5.56)**
Lymphocyte, 10^9 /L	1.60(1.20–2.13)	1.70(1.32–2.18)	1.58(1.30-2.00)	1.70(1.35–2.17)	1.50(1.16–1.96)	1.57(1.27–1.86)
Monocyte, 10^9 /L	0.50(0.40–0.66)	0.50(0.40–0.60)	0.51(0.41–0.70)	0.50(0.40–0.60)	0.58(0.49–0.76)	0.57(0.43–0.68)
NLR	3.00(2.09–4.98)	2.44(1.85–3.50) ***	2.98(2.16–4.82)	2.38(1.87–3.39) ***	3.60(2.85–5.29)	2.77(2.23–3.56) ***
LMR	3.21(2.20–4.25)	3.33(2.60–4.33) *	3.19(2.41–4.05)	3.33(2.50–4.52) *	2.48(1.94–3.41)	2.75(2.14–3.65)
Fasting glucose, mmol/L	6.90(5.53–8.71)	6.33(5.22–7.69) **	6.68(5.70–8.66)	6.32(5.28–7.71) *	6.84(5.41–8.77)	6.36(5.49–7.69)
HbA1c, %	6.90(6.15–8.05)	6.70(6.00-7.60) ***	6.90(6.20–8.20)	6.70(5.90–7.60) *	8.00(7.00-9.20)	7.70(6.60-8.00)**
Fasting insulin, pmol/mL	12.05(7.12–14.98)	11.72(7.14–14.28)	11.83(7.43–19.48)	11.78(7.12–19.48)	11.88(7.75–16.35)	11.73(7.86–16.76)
Triglyceride, mmol/L	1.54(1.07–2.05)	1.45(1.09–2.02)	1.55(1.05–2.11)	1.45(1.13–2.11)	1.50(1.10-2.00)	1.40(1.10–1.90)
Total cholesterol, mmol/L	4.08(3.36–4.87)	3.89(3.20–4.77)	4.06(3.33–5.19)	3.96(3.25–4.69)	3.83(3.07–4.58)	3.48(2.84–4.22)
LDL-C, mmol/L	2.41(1.83–3.08)	2.23(1.72–2.99) *	2.39(1.81–3.26)	2.25(1.77–2.88) *	2.09(1.49–2.94)	1.96(1.48–2.59)
HDL-C, mmol/L	0.98(0.85–1.14)	0.95(0.82–1.11)	1.01(0.89–1.13)	0.98(0.85–1.15)	0.97(0.83–1.15)	0.95(0.83–1.08)
Lp(a), mmol/L	0.16(0.09–0.36)	0.16(0.09–0.37)	0.21(0.10–0.42)	0.19(0.09–0.40)	0.20(0.12–0.36)	0.21(0.10–0.37)
BUN, mmol/L	5.90(4.80–7.30)	5.70(4.60–6.90)	6.00(4.75–7.60)	5.50(4.60–6.75)	6.59(4.60–8.06)	6.09(5.07–7.66)
Creatinine, μmol/L	82.00(69.00-95.50)	80.00(68.00–92.00)	82.00(68.50–98.00)	79.00(69.00-92.50)	83.00(68.70–102.00)	77.80(66.00-94.20)
BUN/SCr	17.55(14.25–21.59)	17.89(14.60-21.86)	17.47(14.82–20.88)	16.74(14.60–20.80)	21.43(16.33–26.15)	18.95(15.75–23.13)
Uric acid, μmol/L	340.70 ± 93.43	341.60 ± 97.17	336.65 ± 98.62	343.75 ± 84.27	337.26 ± 98.39	341.07 ± 87.77
eGFR, ml/min/1.73m^2	83.18(65.51–92.88)	88.10(74.56–97.62) ***	77.06(59.76–93.21)	88.42(73.16–98.38) ***	70.47(51.98–90.21)	83.79(66.77–97.87)**
hsCRP, mg/L	3.02(0.99–8.75)	2.55(0.80–6.97)	2.88(1.16–6.91)	2.30(0.89–5.86)	2.84(1.60–8.79)	2.36(1.21–7.79)

(*$P < 0.05$; **$P < 0.01$; ***$P < 0.001$)

CC coronary collateralization, *SBP* Systolic blood pressure, *DBP* diastolic blood pressure, *MI* myocardial infarction, *LVEF* left ventricular ejection fraction, *NLR* neutrophil-to-lymphocyte ratio, *LMR* lymphocyte to monocyte ratio, *HbA1c* glycosylated hemoglobin A1c, *LDL-C* low-density lipoprotein cholesterol, *HDL-C* high-density lipoprotein cholesterol, *Lp(a)* lipoprotein a, *BUN* blood urea nitrogen, *SCr* serum creatinine, e*GFR* estimated glomerular filtration rate, *hsCRP* high-sensitivity C reactive protein

14 patients with risk score of 9–13, showing a stepwise increase of poor CC with increasing risk score ($P < 0.001$). Similarly, the external cohort indicated a stepwise increase of poor CC with increasing risk score ranging from 11.1% for the 1 patient with risk score of 1 to 100% for the 17 patients with risk score of 10–13 ($P < 0.001$). None of the individuals in the external validation cohort had a score of 0 (Table 3). We identified the optimal cut-off value by using the maximal Youden index in the ROC curve analysis of derivation cohort. An optimal predictive score threshold of 4 could differentiate patients with poor CC with a sensitivity of 75.4% and a specificity of 64.1%. Patients with a predictive score higher than 4 points were considered to have a greater likelihood of developing poor CC.

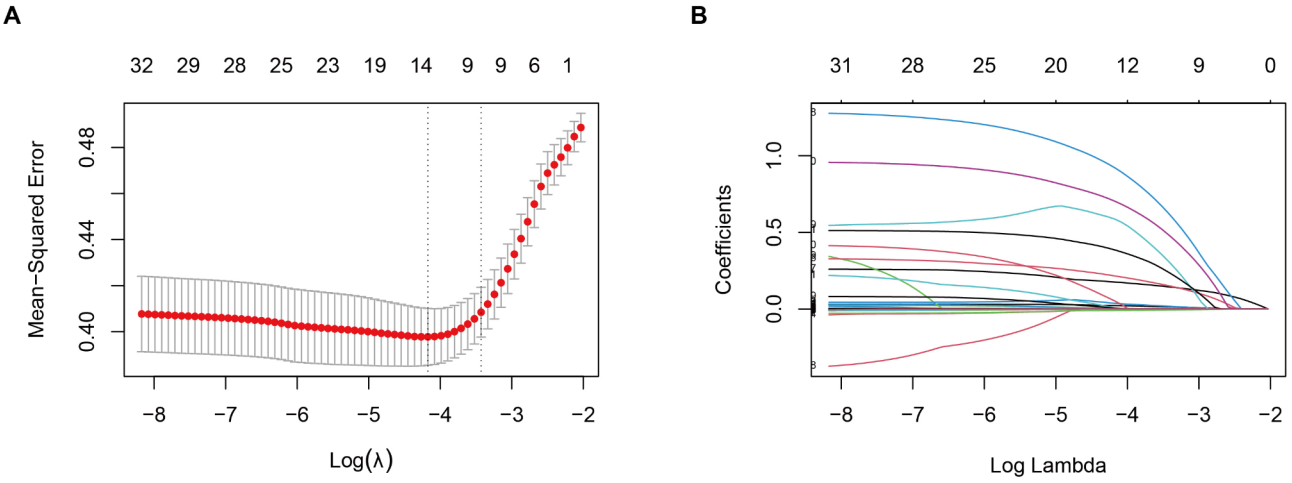

Fig. 2 LASSO regression model for screening predictors. **(A)** Vertical lines are plotted at the most available parameter value, and the number of selected variables is 10. **(B)** Plot of each clinical characteristic coefficient against log(λ) by adjusting the parameter λ

Table 2 Multivariate logistic regression analysis for the occurrence of poor CC in T2DM patients with CTO in the derivation cohort

Variable	B	SE	OR (95%CI)	*P* value
Age (> 65 years)	0.445	0.180	1.560 (1.097–2.220)	0.013
Female	0.904	0.223	2.469(1.596–3.821)	< 0.001
Smoking	1.175	0.194	3.239(2.216–4.732)	< 0.001
Hypertension	0.644	0.209	1.905(1.265–2.869)	0.002
Hypercholesterolemia	0.886	0.204	2.425(1.626–3.617)	< 0.001
Neutrophil ($> 6.5 \times 10^9$/L)	1.386	0.224	3.997(2.575–6.205)	< 0.001
eGFR(< 60 mL/min/1.73m^2)	0.835	0.237	2.306(1.451–3.666)	< 0.001
HbA1c (> 6.5%)	0.487	0.173	1.627(1.160–2.283)	0.005

CC coronary collateralization, *T2DM* type 2 diabetes mellitus, *CTO* chronic total occlusion, e*GFR* estimated glomerular filtration rate, *HbA1c* glycosylated hemoglobin A1c

Construction of Web-based calculator

An online calculator was developed to allow clinicians to enter the values of the eight variables required for the risk score with automatic calculation of the probability that a T2DM patient with CTO will develop poor CC (Fig. 4). Patients with a risk score higher than cutoff value were considered to have a greater likelihood of developing poor CC. In contrast, those with lower risk score than cutoff value were considered to have good CC.

Discussion

In the present study, we develop and validate a novel prediction model to assess the probability of poor CC in patients with T2DM and stable coronary artery disease based on clinical characteristics and laboratory measurements which were easy to assess and readily available at hospital admission. The derivation cohort comprised a large sample size, allowing the evaluation of a comprehensive range of candidate predictors to develop a score that predicts poor CC with strong discrimination abilities, which was subsequently validated in an independent external cohort.

The status of coronary collateral circulation has prognostic value in T2DM patients with coronary artery disease; those with poor CC have a significantly higher incidence of major adverse cardiac events during long-term follow-up than those with well-formed coronary collaterals [3–7]. Previous reports supported the indication for assessing CC in all T2DM patients with coronary artery disease [8]. Coronary collateral circulation can be accurately assessed by measurement of collateral flow index, but it requires simultaneous recording of aortic pressure and the distal pressure within the occluded segment of the culprit coronary artery [12]. The degree of collateral formation is also estimated visually at coronary angiography, which is an invasive procedure and needs multiple injections of contrast medium. In this context, establishment of a clinical model using clinical factors and laboratory measurements has been designed to facilitate non-invasive identification of those patients at a higher risk of developing poor CC, who would likely benefit most from targeted interventions. CTO patients undergoing recanalization are at increased risk for adverse events, which can be mitigated to some extent by antithrombotic therapy. However, achieving a balance

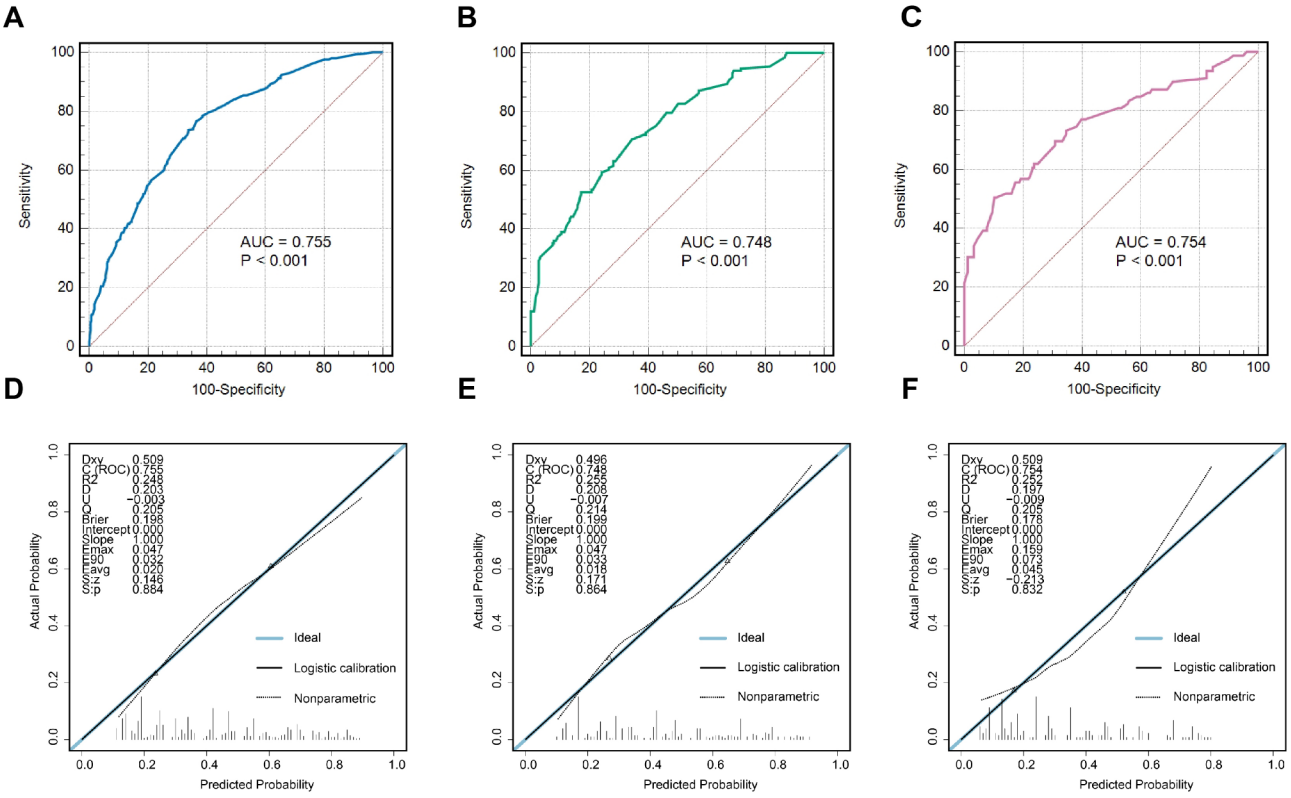

Fig. 3 ROC curve analysis of predicting coronary collateral formation. **(A)** Derivation cohort; **(B)** Internal validation cohort. **(C)** External validation cohort; Calibration curve of the prediction model. The X-axis represents the overall predicted probability of poor collateralization and the Y -axis represents the observed probability. Model calibration is indicated by the degree of fitting of the curve and the diagonal. **(D)** Derivation cohort; **(E)** Internal validation cohort. **(F)** External validation cohort

Table 3 Coronary collateralization yield for each of the scores in the derivation, internal and external validation cohorts

Total Score	Derivation cohort			Internal validation cohort			External validation cohort		
	Poor CC (*n* = 301)	Good CC (*n* = 415)	Total (*n* = 716)	Poor CC (*n* = 133)	Good CC (*n* = 173)	Total (*n* = 306)	Poor CC (*n* = 79)	Good CC (155)	Total (*n* = 234)
0	0	14(100)	14(2.0)	0	2(100)	2(0.7)			
1	6(10.3)	52(89.7)	58(8.1)	0	20(100)	20(6.9)	1(11.1)	8(88.9)	9(3.8)
2	15(18.8)	65(81.3)	80(11.2)	7(20.6)	27(79.4)	34(11.1)	3(15.8)	16(84.2)	19(8.1)
3	23(27.4)	61(72.6)	84(11.7)	9(32.1)	19(67.9)	28(9.2)	4(16.7)	20(83.3)	24(10.3)
4	30(28.8)	74(71.2)	104(14.5)	18(35.3)	33(64.7)	51(16.7)	6(19.4)	25(80.6)	31(13.2)
5	62(48.1)	67(51.9)	129(18.0)	28(43.1)	37(56.9)	65(21.2)	9(20.9)	34(79.1)	43(18.4)
6	49(57.6)	36(42.4)	85(11.9	19(55.9)	15(44.1)	34(11.1)	10(34.5)	19(65.5)	29(12.4)
7	54(66.7)	27(33.3)	81(11.3)	21(58.3)	15(41.7)	36(11.8)	15(41.7)	21(58.3)	36(15.4)
8	23(67.6)	11(32.4)	34(4.7)	17(77.3)	5(22.7)	22(7.2)	7(50.0)	7(50.0)	14(6.0)
9	14(70.0)	6(30.0	20(2.8)	4(100)	0	4(1.3)	7(58.3)	5(41.7)	12(5.1)
10	19(90.5)	2(9.5)	21(2.9)	6(100)	0	6(2.0)	9(100)	0(0)	9(3.8)
11	3(100)	0	3(0.4)	2(100)	0	2(1.0)	5(100)	0(0)	5(2.1)
12	1(100)	0	1(0.1)	1(100)	0	1(0.3)	2(100)	0(0)	2(0.9)
13	2(100)	0	2(0.3)	1(100)	0	1(0.3)	1(100)	0(0)	1(0.4)

CC coronary collateralization

between ischemia and bleeding is challenging especially in complex PCI patients. A meta-analysis demonstrated that P2Y12 inhibitor monotherapy potentially overcomes the bleeding liability of standard dual antiplatelet therapy and provides additional benefit of reducing the risk of myocardial infarction in patients undergoing complex PCI [20]. Therefore, assessment of coronary collaterals before CTO PCI, together with optimal antithrombotic therapy after the procedure, could improve the prognosis of patients with CTO. In this study, a predictive score

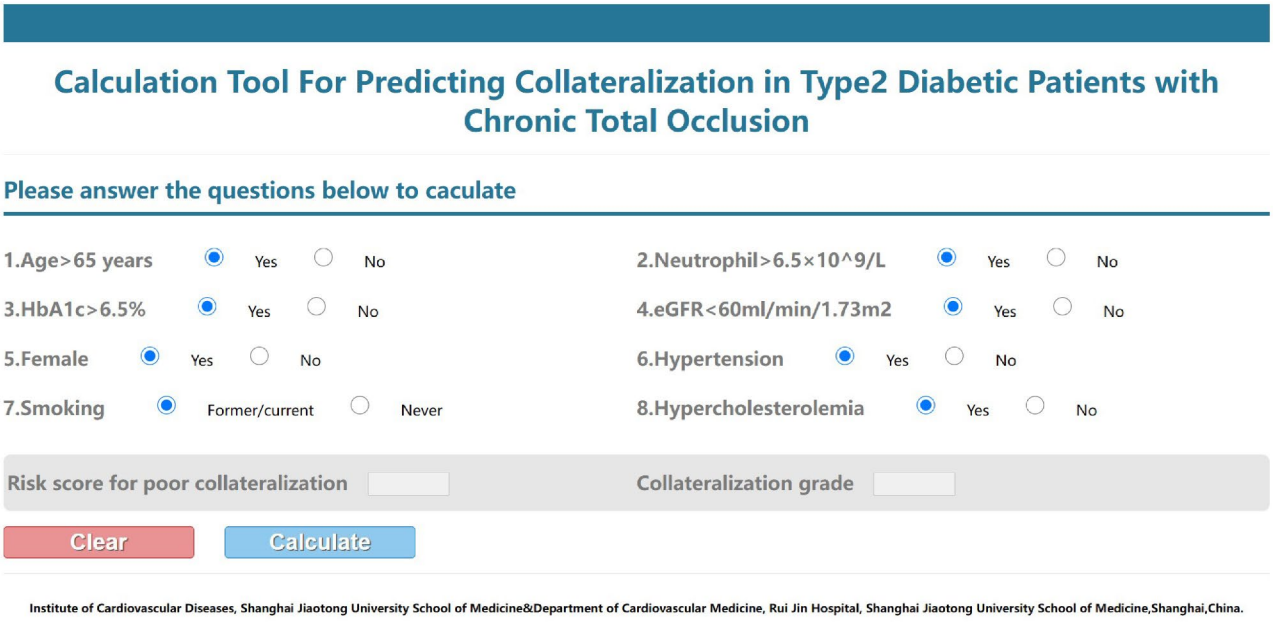

Fig. 4 Online Web calculator for predicting coronary collateralization in type 2 diabetic patients with chronic total occlusion (http://124.220.98.250/)

based on 8 readily available factors (older age, female gender, hypertension, hypercholesterolemia, smoking, neutrophil count, eGFR, and HbA1c) was constructed and provided fairly accurate predictions.

The findings regarding these strong independent predictors of poor CC are biologically plausible and align with previous studies. Aging negatively affects collateral remodeling via impaired endothelial nitric oxide synthase pathways and by increased oxidative stress in coronary arterioles [21]. Female gender particularly in post-menopausal period has been shown to be another risk factor for poor CC in addition to diabetes in patients with CTO [22]. Koreselman et al. found that smoking habits and high blood pressure cause impaired collateral formation [16, 23]. Because coronary blood flow occurs predominantly in diastole and there exists some extent of microvascular disease in the diabetic myocardium, the optimal diastolic blood pressure ranges with the lowest risk of poor CC differed between T2DM patients (80–89 mm Hg) and non-diabetic counterparts (90–99 mm Hg) [24, 25]; too low or too high diastolic blood pressure decreasing the perfusion of coronary collaterals. Hypercholesterolemia inhibits angiogenesis and arteriogenesis, primarily due to the negative impact of LDL-C on the ability of endothelial cells to respond to growth factors [26]. Notably, a significant relationship has been observed between the lipoprotein(a) and cholesterol-containing lipids in promoting the formation of coronary collaterals in patients with T2DM and stable coronary artery disease [27]. Furthermore, glycoxidative modification of LDL hampers the process of new vessel growth and maturation. Reduced high-density lipoprotein cholesterol levels, and more importantly, impaired high-density lipoprotein function may synergistically contribute to a decrease in collateral formation [28]. Renal insufficiency is one of the most important prognostic variables in assessing the risk factors of cardiovascular disease [29]. Mildly reduced eGFR was observed in patients with impaired development of coronary collateral circulation and may be associated with endothelial dysfunction and increased inflammatory activity in these patients [8, 30]. Neutrophils and lymphocytes as well as NLR are indicators of inflammatory reaction [31, 32]. Previous studies have shown that persistent low-grade inflammation in diabetic ischemic tissues impairs endothelial function, leading to dysregulation of pro- and anti-angiogenic factors and hampering the growth and maturation of collateral vessels [33–35]. Consistent with previous findings [36], our study demonstrated a close relationship between higher levels of HbA1c and poor CC. Mechanistically, hyperglycemia downregulates key promoters of angiogenesis, impairs endothelium-dependent vasodilatory function, and thereby inhibits new vessel formation [37].

The findings of this study may have clinical implications. Although the trade-off between diagnostic sensitivity and specificity and between the cost and effectiveness of angiographic examination is not avoidable, our results suggest that if appropriately used before coronary angiography, the novel clinical risk score generated in this study could help physicians to predict the choice of revascularization strategy.

Limitations

Our study has several limitations. First, this is a retrospective analysis, thus patient selection bias may have occurred. Patients in the derivation, internal and external validation cohorts were all enrolled from the tertial hospitals, potentially limiting the generalized application of the score to other regional or community centers. Second, although a number of traditional risk factors were considered, some confounding variables were not measured in this study. Third, the method of Rentrop classification to evaluate CC development has limitations, whereas use of collateral flow index, an objective method for measuring CC, could more accurately assess outcomes. Fourth, further research is required to determine whether CC in the high-risk patients identified by the model would benefit from target strategies, such as better glycemic control or inflammation reduction. Finally, although both internal and external validation have been conducted, prospective multicenter studies are essential to verify the predictive value and clinical applicability of the model.

Conclusion

Our results suggest that a risk score by incorporating eight readily available clinical and laboratory measurements at the initial presentation may predict poor CC with good discrimination in T2DM patients with CTO. Thus, the proposed predictor score provides an easy-to-use tool to guide treatment strategy. Further multicenter, prospective studies are warranted to confirm the predictive performance of the model and its role in the management of T2DM patients with stable coronary artery disease.

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Author contributions
All authors made a significant contribution to the study. LSM, LG, YXW, YQ, MHW, FHD, YD, LL, QZ, WFS and YS participated in study design, data analysis, interpretation, and drafting manuscript. LSM, LG, YXW, YQ, MHW, FHD, YD, LL, QZ and WFS performed data collection. YS revised the manuscript before final approval. All authors have read and approved the final manuscript.

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Data availability
The datasets from the current study are available from the corresponding author upon request.

Declarations

Ethics approval and consent to participate
The study protocol was approved by the Ethics Committee of Shanghai Ruijin Hospital, Shanghai Jiao Tong University School of Medicine, and Shanghai Eastern Hospital, Tongji University School of Medicine. The study was conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all participants.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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