Original Article

Quantitative coronary computed tomography angiography assessment of chronic total occlusion percutaneous coronary intervention

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Background: Morphological and clinical characteristics are widely used to predict the success of percutaneous coronary intervention (PCI) in patients with chronic total occlusion (CTO). However, the impact of quantitative characteristics derived from coronary computed tomography angiography (CCTA) on guidewire crossing and PCI success is still unclear. This study aimed to explore the association between these quantitative characteristics and the difficulty of PCI for CTO.

Methods: A total of 207 CTO lesions from 201 patients (84.6% male; mean age 58.9 years) with pre-procedural CCTA scans who had undergone PCI for CTO were retrospectively enrolled in this case-control study. A semi-automated CCTA plaque-analysis software was adopted to obtain the total plaque volume and volume of each component according to the Hounsfield Unit (HU) value, including dense calcium (>351 HU), fibrous (131–350 HU), fibrofatty (76–130 HU), and necrotic core (–30–75 HU) tissue. Differences in the quantitative characteristics of the CTO lesions were compared between: (I) the group of lesions with successful guidewire crossing (≤30 min) and the group with failed guidewire crossing (≤30 min); (II) the group of lesions with procedural success [defined as achieving residual stenosis of <30% and a grade 3 thrombolysis in myocardial infarction (TIMI) flow] and the group with procedural failure. Logistic regression was used to explore the association of quantitative characteristics with successful guidewire crossing in ≤30 min and procedural success.

Results: A total of 131 (63.3%) lesions of 126 patients achieved successful guidewire crossing in ≤30 min and 157 (75.8%) lesions of 152 (75.6%) patients achieved procedural success. Quantitative characteristics such as occlusion length, plaque volume, volume of dense calcium, and fibrous and fibrofatty tissue showed significant differences between the groups of lesions with successful guidewire crossing in ≤30 min and with failed guidewire crossing in ≤30 min, as well as the groups of lesions with procedural success and with procedural failure. According to the results of logistic regression analysis, lower percentages of dense calcium [odds ratio (OR) =0.970, 95% confidence interval (CI): 0.950 to 0.991; P=0.004] and fibrous

(OR =0.970, 95% CI: 0.949 to 0.992; P=0.007) tissue and higher percentage of necrotic core tissue (OR =1.018, 95% CI: 1.005 to 1.030; P=0.005) were significantly associated with successful guidewire crossing in ≤30 min. Decreased percentages of dense calcium (OR =0.969; 95% CI: 0.949 to 0.989; P=0.002) and fibrous tissue (OR =0.966, 95% CI: 0.944 to 0.990; P=0.005) and higher percentage of necrotic core tissue (OR =1.022, 95% CI: 1.008 to 1.036; P=0.002) were associated with procedural success. After adjusting for cardiovascular risk factors, the percentages of dense calcium, fibrous, and necrotic core tissue were still associated with successful guidewire crossing in ≤30 min, and the quantitative parameters showed consistent association with procedural success.

Conclusions: Quantitative characteristics derived from CCTA for CTO are associated with successful guidewire crossing and procedural success of PCI.

Keywords: Coronary computed tomography angiography; percutaneous coronary intervention; chronic total occlusion; quantitative analysis

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Introduction

Recanalization of coronary chronic total occlusion (CTO) is associated with better clinical outcomes and improved quality of life (1-4). However, percutaneous coronary intervention (PCI) for CTO is challenging for cardiologists, given its complex procedures, low success rates, and high suboptimal and complication rates (5,6). To determine the optimal treatment strategy, it is necessary to conduct comprehensive preprocedural assessment for CTO patients.

The characteristics of blunt stump, lesion length >20 mm, calcification, and bending >45° derived from invasive coronary angiography (ICA) were recognized as risk factors of failed to achieve guidewire crossing ≤30 min in a multicenter Japanese study (J-CTO) (7). As a non-invasive modality, coronary computed tomography angiography (CCTA) has emerged as an accurate tool for grading the difficulty of PCI of CTO in scoring systems such as the Computed Tomography Registry of Chronic Total Occlusion Revascularization (CT-RECTOR), the Korean Multicenter Computed Tomography Registry (KCCT), and the CCTA-derived J-CTO scoring systems (8-10), and has been recommended to be conducted before initiation of CTO PCI (11). Recently, Hong *et al.* demonstrated that pre-procedural CCTA-guided CTO PCI resulted in higher success rates and lower complication rates compared with angiography guidance only (12).

Quantitative CCTA allows for the assessment of additional quantitative characteristics besides morphological characteristics (13,14). In previous studies, the potential of quantitative CCTA was demonstrated in the risk stratification and evaluation of treatment effects for coronary artery disease (CAD) patients (15-18). However, few studies have focused on CTO patients (19). Considering the gap in understanding of the relationship between quantitative characteristics and the difficulty of CTO PCI, this study sought to explore the impact of quantitative CTO plaque characteristics derived from CCTA on successful guidewire crossing in ≤30 min and the procedural success of CTO PCI. We present the following article in accordance with the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1050/rc).

Methods

Study design and population

This research was designed as a retrospective, case-control study. Between September 2015 and September 2019, patients from Beijing AnZhen Hospital and Beijing Friendship Hospital were retrospectively enrolled. CTO was defined as grade 0 Thrombolysis in Myocardial Infarction (TIMI) flow and estimated to have lasted for more than 3 months. The inclusion criteria were as follows: (I) CTO as confirmed by invasive coronary angiography, (II) accepted PCI for CTO lesion (s); (III) undergone pre-procedural CCTA scan within 2 months. The exclusion criteria were as follows: (I) in-stent CTO; (II) vessel diameter of <2.00 mm;

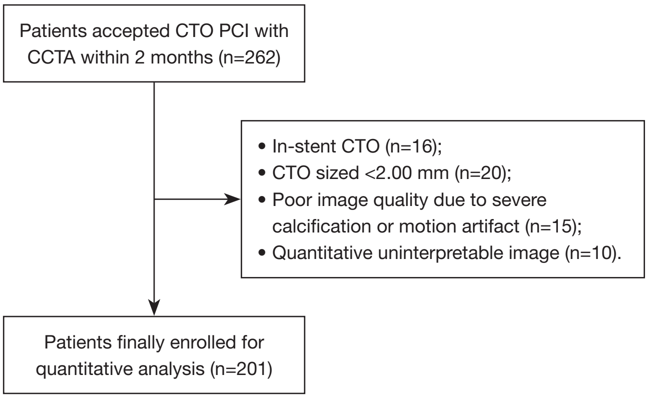

Figure 1 Patient selection flow chart. PCI, percutaneous coronary intervention; CCTA, coronary computed tomography angiography; CTO, chronic total occlusion.

(III) poor image quality for calcification or motion artifact, and (IV) quantitative uninterpretable CCTA (*Figure 1*). The CTO lesions were divided into groups according to the following features: (I) successful and failed guidewire crossing in ≤30 min; (II) lesions with procedural success (defined as achieving residual stenosis of <30% and a grade 3 TIMI flow) versus those with procedural failure (20). The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Beijing AnZhen Hospital and Beijing Friendship Hospital. Written informed consent was provided by all patients before participation in the study.

CCTA acquisition and analysis protocol

The CCTA scans were performed within 2 months (median interval of 6 days) before PCI was conducted with 64-slice or greater-slice dual-source scanners (Somatom Definition FLASH, Siemens Healthcare, Forchheim, Germany; Revolution CT, General Electric Healthcare, Milwaukee, WI, USA; Aquilion ONE, Toshiba Medical Systems, Tokyo, Japan). Tube voltage was set to either 100 or 120 kV, according to the body mass index (BMI) of patients (100 kV for BMI <24 kg/m^2 and 120 kV for BMI ≥24 kg/m^2). Automatic exposure control was chosen for the tube current. The region of interest (ROI) was placed in the root of the aorta for bolus-tracking, then the image acquisition was automatically started 6 seconds after a predefined threshold reached 100 Hounsfield units (HU). The area from the tracheal bifurcation to 1 cm below the diaphragm was scanned for patients. We injected 50–70 mL of a contrast agent (Ultravist, 370 mg iodine/mL; Bayer Schering Pharma, Berlin, Germany) was injected into the antecubital vein followed by a 30 mL saline flush at 4–6 mL/s with a dual-head power injector. The optimal phase with minimal artifacts was selected and transferred to the workstation for further analysis.

CCTA reconstruction and analysis

The evaluation of image quality was conducted by 2 experienced radiologists based on transaxial images following the guidelines of the Society of Cardiovascular Computed Tomography (21). After quality evaluation, the CCTA reconstruction and quantitative analysis were finished with a semi-automated plaque-analysis software (QAngio CT Research Edition version 3.1.4; Medical Imaging Systems [MEDIS], Leiden, The Netherlands), blinded to ICA results and PCI procedures (*Figure 2*). Qualitative morphological characteristics were evaluated according to the descriptions provided in previous studies (8,9). The coronary tree, including vessel and lumen contours, were extracted automatically and corrected manually, if necessary. A modified 18-segment model was adopted for the evaluation of CCTA, according to the Society of Cardiovascular Computed Tomography (21). Complete absence of contrast in the arterial lumen were identified as CTO segments and analyzed quantitatively. The percentage of atheroma volume (PAV) was defined as the proportion of the total plaque volume occupied by the compositional plaque volume (17). CTO plaque was categorized as dense calcium (DC) (>351 HU), fibrous (131 to 350 HU), fibrofatty (FF) (76 to 130 HU), and necrotic core (NC) (−30 to 75 HU) tissue, according to the HU value (22). Quantitative parameters, including lesion length, total plaque volume, and volume of each composition, were automatically calculated with the software. *Figure 2* illustrates the quantitative analysis and representative cross sections.

Coronary angiography and PCI procedural analysis

The PCI procedures were performed by experienced interventional cardiologists with a caseload of at least 50 CTO cases per year. The ICA and procedural characteristics were analyzed and agreed upon by 2 cardiologists. Qualitative features, such as stump morphology, occlusion length, bending, and calcification, were evaluated as described previously (7). Heavy calcification was defined as multiple, persisting opacifications of the coronary wall visible in more than one projection surrounding the complete lumen of the coronary

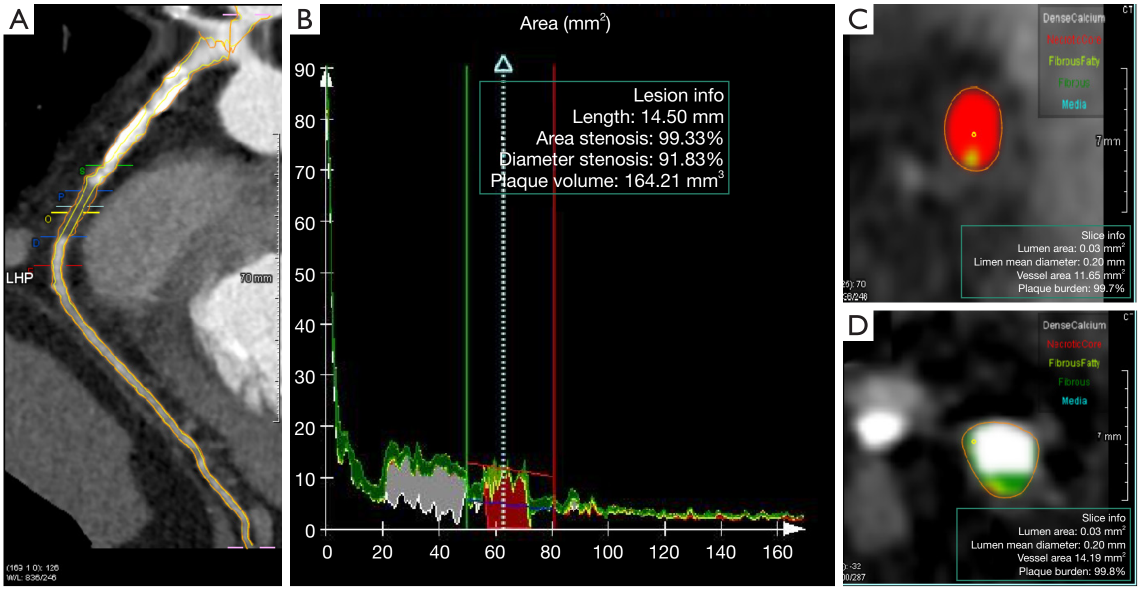

Figure 2 Example of quantitative CCTA analysis of an RCA CTO lesion. (A) Multiplanar reconstruction of an RCA vessel. "P (in blue)" is the proximal and "D (in blue)" is the distal section of the chronic total occlusion. "S (in green)" is the proximal normal reference section, and "E (in red)" is the distal normal reference section. (B) Lumen and vessel area line chart graph according to distance from the ostium of the target vessel. (C) Transverse section composed of necrotic core tissue (red area). (D) Transverse vessel section mainly composed of fibrous tissue (green area) and calcification (white area). CCTA, coronary computed tomography angiography; RCA, right coronary artery; CTO, chronic total occlusion.

artery at the site of the lesion (23). Complications were defined according to the 2020 American Heart Association/American College of Cardiology (AHA/ACC) Key Data Elements and Definitions for Coronary Revascularization (24).

Reproducibility

Quantitative parameters, such as lesion length, plaque volume, and volume of each tissue component (NC, FF, fibrous, and DC) were extracted and analyzed. Intra-observer agreement was analyzed for all CTO lesions and again at an interval of 4 weeks or longer. Inter-observer agreement among 30 randomly selected CTO lesions was analyzed by 2 well trained radiologists blinded to the ICA results and PCI procedures.

Statistical analysis

Continuous variables were described using mean ± SD or median [interquartile range (IQR)] and categorical variables were expressed as absolute numbers and frequencies (%). Continuous variables were compared using the Student's *t*-test when normally distributed and the Mann-Whitney U test when not normally distributed. Categorical variables were compared using the Pearson's chi-squared test or Fisher's exact test. Clinical characteristics were compared at the patient level between lesions with successful guidewire crossing in ≤30 min and those with failed guidewire crossing. At the patient-level analysis, for patients with >1 CTO lesion, if 1 or more CTO lesions failed guidewire crossing in ≤30 min, the patients were classified into the failed guidewire crossing group. Quantitative variables were compared at the lesion level between the group with successful guidewire crossing in ≤30 min and the group with failed guidewire crossing and between the group with procedural success and the group with procedural failure. The influence of total volume was adjusted with the percentage of atheroma volume (PAV), which was defined as the proportion of the total plaque volume occupied by plaque volume of each component. The intraclass correlation coefficient (ICC) was used for comparing inter- and intra-observer variability. Univariate logistic regression was performed to investigate the association of the quantitative variables with successful guidewire crossing

≤30 min and procedural success. Multivariate analysis was adjusted for traditional cardiovascular risk factors such as age, gender, BMI, smoking history, diabetes mellitus, hypertension, triglyceride level, and low- and high-density lipoproteins. All statistical analyses were completed with the statistical software package, SPSS 20.0 (IBM Corp., Armonk, NY, USA). A 2-tailed P value of less than 0.05 was considered statistically significant.

Results

Clinical characteristics and procedural outcomes

A total of 201 patients with 207 CTO lesions and pre-procedural CCTA scans were finally enrolled. Exclusions were mainly due to CTO diameter <2.00 mm (n=20), in-stent CTO (n=16), and poor image quality (n=15) (*Figure 1*). The median interval from CCTA to PCI operation was 6 days. The mean age of participants was 58.9±10.8 years, and 170 (84.6%) were men. Successful guidewire crossing in ≤30 min was achieved in 131 (63.3%) lesions of 126 (62.7%) patients. Procedural success was achieved in 157 (75.8%) lesions of 152 (75.6%) patients. Compared with the group of lesions with successful guidewire crossings in ≤30 min, failed guidewire crossings predominantly occurred in patients with lower HDL levels (P=0.018) and who had experienced a prior failed attempt (P=0.003), while other clinical characteristics were similar between the 2 groups (*Table 1*).

Morphological and procedural characteristics

The right coronary artery (RCA; n=98, 47.3%) was the most common target vessel of CTO, followed by the left anterior descending artery (LAD; n=85; 41.1%) and the left circumflex artery (LCX; n=22, 10.6%). Most CTO lesions (n=180, 87.0%) were treated for the first time and with antegrade wiring technique (n=188, 90.8%). Compared to the group with successful guidewire crossings ≤30 min, lesions with failed guidewire crossings showed more proximal blunt stump (P<0.001), ostial location (P=0.01), proximal branches (P<0.001), heavy calcification (P=0.023), bending of more than 45° (P=0.029), occlusion length of >20 mm (P<0.001), and higher J-CTO scores (P<0.001) (*Table 2*). The distribution of successful guidewire crossing and procedural success by J-CTO score are presented in Table S1; CCTA characteristics are presented in Table S2.

Influence of quantitative characteristics on 30-min guidewire crossing

Overall, compared to the group with successful guidewire crossing in ≤30 min, the failed group presented with lesions of longer occlusion length (P<0.001) and larger volume (P<0.001). The volume difference was mostly driven by larger volumes of DC, fibrous, and FF tissue (P<0.001 for all). However, the difference in NC volume between the 2 groups was not significant (P=0.119) (*Figure 3A*).

The group with failed guidewire crossings showed higher PAV of DC and fibrous tissue (P≤0.05 for both), while lower PAV of NC tissue (P=0.006). The difference in the PAV of FF between the successful and failed guidewire crossing groups was not significant (P=0.306) (*Figure 3B*).

Influence of quantitative characteristics on procedural success

Compared to the group of lesions with procedural success, the lesions in the group with procedural failure showed longer occlusion length (P<0.001) and larger total volume (P<0.001). The lesions in the group with procedural failure also showed larger volumes of DC, fibrous, and FF tissue (P<0.05 for all). However, the difference in NC volume between the group of lesions with procedural failure and the group of lesions with procedural success was not significant (P=0.244).

Compared to the group with procedural success, the lesions in the group with procedural failure presented with higher PAV of DC and fibrous tissue (P<0.05 for both), but lower PAV of NC tissue (P=0.001). The difference in the PAV of FF between the group of lesions with procedural success and the group of lesions with procedural failure was not significant (P=0.507) (*Table 3*).

Association of quantitative parameters with guidewire crossing in ≤30 min and procedural success

Results of the univariate logistics regression showed that increasing the PAV of DC [odds ratio (OR) =0.970, 95% confidence interval (CI): 0.950 to 0.991; P=0.004] and fibrous tissue (OR =0.970, 95% CI: 0.949 to 0.992; P=0.007) was associated with lower likelihood of successful 30-min guidewire crossing, while higher PAV of NC tissue increased the likelihood of successful 30-min guidewire crossing (OR =1.018, 95% CI: 1.005 to 1.030; P=0.005). Elevated PAV of DC (OR =0.969, 95% CI: 0.949 to 0.989;

Table 1 Clinical characteristics according to guidewire crossing ≤30 min

Characteristics	All (n=201)	Success to Cross Guidewire in ≤30 min (n=126)	Fail to Cross Guidewire in ≤30 min (n=75)	P value
Age, years	58.88±10.77	58.84±11.20	58.95±10.07	0.947
Male gender	170 (84.6)	104 (82.5)	66 (88.0)	0.300
BMI, kg/m^2	26.27±3.35	26.30±3.22	26.23±3.58	0.896
LVEF, %	61.64±8.47	61.47±8.75	61.91±8.06	0.744
Diabetes mellitus	61 (30.3)	38 (30.2)	23 (30.7)	0.940
Hypertension	129 (64.2)	86 (68.3)	43 (57.3)	0.118
Hyperlipidemia	80 (39.8)	52 (41.3)	28 (37.3)	0.581
Smoking history	108 (53.7)	67 (53.2)	41 (54.7)	0.837
Prior failed attempt	27 (13.4)	10 (7.9)	17 (22.7)	0.003
Previous myocardial infarction	51 (25.4)	35 (27.8)	16 (21.3)	0.310
Occlusion time more than 12 months or unknown	131 (65.2)	76 (60.3)	55 (73.3)	0.061
Previous PCI	39 (19.4)	24 (19.0)	15 (20.0)	0.869
Previous CABG	2 (1.0)	0 (0)	2 (2.7)	0.138
Previous stroke or transient ischemic attack	18 (9.0)	12 (9.5)	6 (8.0)	0.714
Renal disease	12 (6.0)	7 (5.6)	5 (6.7)	0.989
eGFR, mL/min/1.73 m^2	94.07±16.08	93.91±16.47	94.34±15.52	0.856
TG, mmol/L	1.77±0.99	1.74±1.04	1.82±0.89	0.572
TC, mmol/L	3.89±0.95	3.97±0.95	3.76±0.95	0.141
HDL, mmol/L	1.01±0.22	1.04±0.23	0.97±0.19	0.018
LDL, mmol/L	2.27±0.78	2.30±0.78	2.22±0.79	0.504
FBG, mmol/L	6.66±2.31	6.62±2.13	6.74±2.59	0.730
HbA1c, %	6.44±1.14	6.48±1.15	6.36±1.10	0.524

Patients with >1 CTO lesion and with at least one failed 30-min guidewire crossing were classified into the failure group. Per patient analysis, values were expressed as mean ± standard deviation or n (%). BMI, body mass index; LVEF, left ventricular ejection fraction; PCI, percutaneous coronary intervention; CABG, coronary artery bypass grafting; eGFR, estimated glomerular filtration rate; TG, triglyceride; TC, total cholesterol; HDL, high-density lipoprotein; LDL, low-density lipoprotein; FBG, fasting blood glucose; HbA1c, hemoglobin A1C; CTO, chronic total occlusion.

P=0.002) and fibrous tissue (OR =0.966, 95% CI: 0.944 to 0.990; P=0.005) were related to a lower likelihood of procedural success. Higher PAV of NC tissue increased the likelihood of procedural success (OR =1.022, 95% CI: 1.008 to 1.036; P=0.002) (*Table 4*).

After adjusting for the influence of potential risk factors, multivariate analysis showed that elevated PAV of DC and fibrous tissue were still predictors of failed 30-min guidewire crossing (for every 1% increase in PAV; DC tissue, OR =0.966, 95% CI: 0.944 to 0.989; P=0.003; fibrous tissue, OR =0.965, 95% CI: 0.941 to 0.989; P=0.004, respectively) and procedural failure (for every 1% increase in PAV; DC tissue, OR =0.976, 95% CI: 0.955 to 0.998; P=0.033; fibrous tissue, OR =0.970, 95% CI: 0.945 to 0.995; P=0.021). Higher PAV of NC tissue was associated with increased likelihood of successful <30-min guidewire crossing (for every 1% increase in PAV; OR =1.022, 95% CI: 1.008 to 1.036; P=0.002) and procedural success (for every 1% increase in PAV; procedural success, OR =1.020, 95% CI: 1.004 to 1.035; P=0.012, respectively) (*Figure 4*).

Table 2 Coronary angiographic and procedural characteristics between groups with successful guidewire crossing (in ≤30 min) and failed guidewire crossing

Characteristics	All (n=207)	Success to cross guidewire in ≤30 min (n=131)	Fail to cross guidewire in ≤30 min (n=76)	P value
Angiographic characteristics				
Location				0.022
LM	2 (1.0)	2 (1.5)	0 (0)	
LAD	85 (41.1)	52 (39.7)	33 (43.4)	
LCX	22 (10.6)	20 (15.3)	2 (2.6)	
RCA	98 (47.3)	57 (43.5)	41 (53.9)	
Blunt stump	76 (36.7)	30 (22.9)	46 (60.5)	<0.001
Bending >45°	48 (23.2)	24 (18.3)	24 (31.6)	0.029
Ostial location	10 (4.8)	2 (1.5)	8 (10.5)	0.01
Length >20 mm	85 (41.1)	41 (31.3)	44 (57.9)	<0.001
Any calcification	45 (21.7)	20 (15.3)	25 (32.9)	0.003
Heavy calcification	20 (9.7)	8 (6.1)	12 (15.8)	0.023
Retrograde collaterals Rentrop grade ≥2	195 (94.2)	122 (93.1)	73 (96.1)	0.576
Multiple occlusion	9 (4.3)	3 (2.3)	6 (7.9)	0.121
Proximal branches	90 (43.5)	44 (33.6)	46 (60.5)	<0.001
Bridge collateral	21 (10.1)	10 (7.6)	11 (14.5)	0.116
J-CTO score	1.35±1.11	0.95±1.01	2.04±0.93	<0.001
J-CTO score = 0	57 (27.5)	54 (41.2)	3 (3.9)	<0.001
J-CTO score = 1	61 (29.5)	41 (31.3)	20 (26.3)	
J-CTO score = 2	52 (25.1)	26 (19.8)	26 (34.2)	
J-CTO score ≥ 3	37 (17.9)	10 (7.6)	27 (35.5)	
Procedural characteristics				
Guiding catheter				0.016
6-Fr	136 (65.7)	94 (71.8)	42 (55.3)	
7-Fr	71 (34.3)	37 (28.2)	34 (44.7)	
Simultaneous PCI for other lesions	73 (35.3)	49 (37.4)	24 (31.6)	0.398
Retrograde injection	97 (46.9)	49 (37.4)	48 (63.2)	<0.001
Retrograde wiring approach	19 (9.2)	0 (0)	19 (25.0)	<0.001
Mean number of guidewires	3.60±1.85	2.85±1.21	4.88±2.05	<0.001
Procedural success	157 (75.8)	128 (97.7)	29 (38.2)	<0.001
Complications	9 (4.3)	5 (3.8)	4 (5.3)	0.890

Values are expressed as mean ± standard deviation or n (%). LM, left main; LAD, left anterior descending; LCX, left circumflex; RCA, right coronary artery; Fr, French; PCI, percutaneous coronary intervention; J-CTO, Multicenter CTO Registry of Japan.

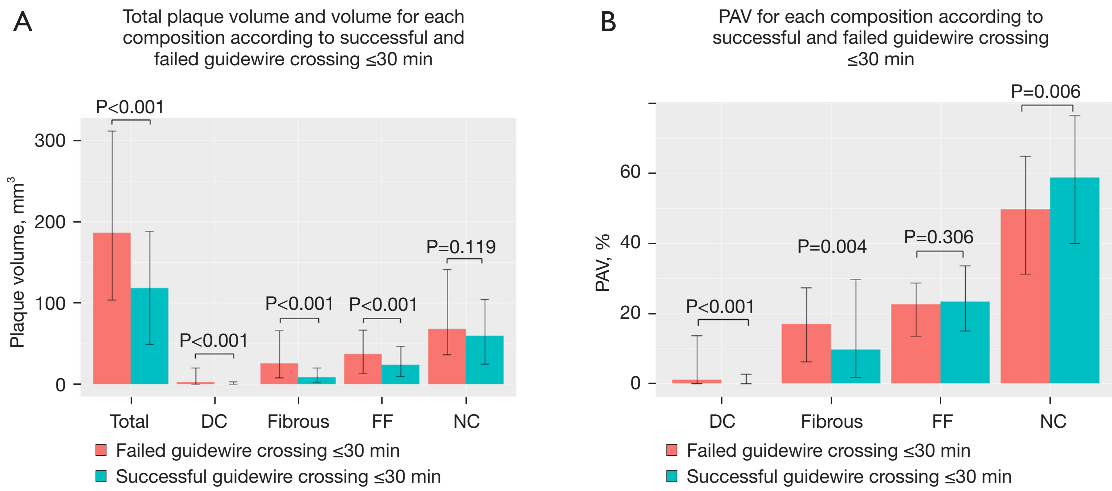

Figure 3 Comparison of plaque volume and PAV differences between successful and failed guidewire crossing in ≤30 min groups. (A) Per lesion medians and interquartile ranges of total plaque volume and volume distribution for each composition of the successful guidewire crossing (in ≤30 min) and failed guidewire crossing (in ≤30 min) group. (B) Per lesion analysis of median and interquartile range of the PAV for each composition (%) of the successful guidewire crossing in ≤30 min and failed guidewire crossing group. PAV, percentage of atheroma volume; NC, necrotic core; FF, fibrofatty; DC, dense calcium.

Intra- and inter-observer variability of quantitative coronary plaque analysis

The intra-observer reproducibility between the first and second evaluations was excellent: lesion length, ICC 0.965; plaque volume, ICC 0.980; NC volume, ICC 0.969; FF volume, ICC 0.984; fibrous volume, ICC 0.974; and DC volume, ICC 0.975. The inter-observer variability between 2 observers for 30 selected lesions was good: lesion length, ICC 0.953; plaque volume, CC 0.673; NC volume, ICC 0.678; FF volume, ICC 0.872; fibrous volume, ICC 0.871; and DC volume, ICC 0.788 for DC.

Discussion

Major findings of this study were as follows: (I) larger volume of DC, fibrous, and FF tissue were observed in the groups of lesions with failed guidewire crossing in ≤30 min and procedural failure compared with the successful groups; (II) higher PAVs of DC and fibrous tissue while lower PAV of NC tissue were found in the groups of lesions with failed guidewire crossing in ≤30 min and with procedural failure compared with the successful groups; (III) increasing PAVs of DC and fibrous tissue were associated with higher risk of failed guidewire crossing in ≤30 min and procedural failure, while higher PAV of NC was associated with decreased risk of failed guidewire crossing and greater likelihood of procedural success.

Currently, difficulty of CTO PCI is mainly assessed through qualitative morphological and anatomical characteristics from ICA or CCTA (7-9,19). The presence of blunt stump, proximal branch, occlusion length <15 mm or multiple occlusions, bending >45°, and severe calcification identified from CCTA were recognized in the previous CT-RECTOR and KCTT studies as risk factors in predicting difficulty of CTO PCI (8,9). However, routine evaluation of CCTA has mostly focused on stenosis severity, anatomical location, and plaque quality, such as calcified, mixed, or non-calcified plaque. With the aid of quantitative analysis, we conducted a more comprehensive analysis of CTO plaque by differentiating plaque quality according to the HU value (13,14,21). The results of our study showed that certain quantitative characteristics were significantly different between CTO lesions from successful and failed guidewire crossing in ≤30 min groups, as well as CTO lesions from procedural success and procedural failure groups, indicating a novel assessment approach for CTO PCI.

Although quantitative analysis enables more detailed analysis of coronary plaques according to plaque HU distribution, few studies have focused on the association between the results of quantitative analysis and guidewire crossing or procedural success of CTO PCI. Choi *et al.* conducted a 3-dimensional, volumetric, radiologic density

Table 3 Quantitative CCTA characteristics of groups according to 30-min guidewire crossing and procedure success

	All	Success to Cross Guidewire in ≤30 min (n=131)	Fail to Cross Guidewire in ≤30 min (n=76)	P value	Procedural succes (n=157)	Procedural failure (n=50)	P value
Occlusion length, mm	16.45 (9.50–27.00)	12.97 (7.00–21.80)	24.79 (13.08–34.95)	<0.001	13.85 (7.79–23.83)	24.79 (13.24–35.45)	<0.001
Total plaque volume, mm^3	138.69 (64.08–216.49)	118.37 (49.54–188.42)	186.55 (103.96–312.10)	<0.001	126.82 (52.36–196.72)	181.99 (121.65–331.76)	<0.001
DC volume, mm^3	0.12 (0–7.38)	0 (0–3.41)	2.39 (0–20.08)	<0.001	0 (0–5.43)	3.61 (0.08–38.13)	<0.001
Non-calcified volume, mm^3	126.00 (59.92–198.76)	102.05 (48.76–179.97)	149.12 (97.48–267.21)	<0.001	108.87 (51.45–17.48)	154.74 (98.08–252.03)	<0.001
Fibrous volume, mm^3	12.53 (3.18–39.37)	8.84(2.02–19.97)	25.64 (8.15–66.04)	<0.001	9.12 (2.57–25.11)	28.49 (13.63–67.22)	<0.001
FF volume, mm^3	26.78 (12.5–54.81)	23.96(9.86–46.88)	36.98 (13.60–66.91)	<0.001	24.25 (10.86–52.70)	33.78 (16.87–72.32)	0.019
NC volume, mm^3	61.03 (29.56–115.12)	59.73 (25.15–104.61)	67.85 (36.50–141.66)	0.119	59.73 (26.50–107.94)	68.30 (37.52–134.78)	0.244
DC PAV, %	0.11 (0–4.45)	0 (0–2.76)	1.13 (0–13.67)	<0.001	0 (0–3.15)	2.25 (0.10–22.68)	<0.001
Fibrous PAV, %	11.42 (3.52–25.52)	9.68 (1.87–29.74)	16.93 (6.26–27.34)	0.004	9.68 (2.39–23.33)	18.11 (7.48–28.57)	0.002
FF PAV, %	22.66 (14.18–31.67)	23.40 (15.03–33.68)	22.63 (13.59–28.69)	0.306	22.66 (14.51–32.11)	22.55 (12.54–31.59)	0.507
NC PAV, %	56.26 (35.44–70.35)	58.77 (40.01–76.46)	49.66 (31.49–64.74)	0.006	59.49 (39.98–74.94)	43.43 (30.70–62.49)	0.001

Values are expressed as median (1st quartile to 3rd quartile). CCTA, coronary computed tomography angiography; DC, dense calcium; FF, fibrofatty; NC, necrotic core; PAV, percentage of atheroma volume.

Table 4 Univariable and multivariable logistic regression analyses of the association between the quantitative characteristics and Success to Cross Guidewire in ≤30 min and procedural success

	Prediction of 30-min guidewire crossing				Prediction of procedural success			
	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value	Unadjusted OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Occlusion length, mm	0.955 (0.934–0.976)	<0.001	0.953 (0.931–0.975)	<0.001	0.960 (0.940–0.980)	<0.001	0.955 (0.933–0.977)	<0.001
Total plaque volume, mm^3	0.998 (0.996–0.999)	0.01	0.998 (0.996–0.999)	0.008	0.998 (0.996–1.000)	0.016	0.998 (0.996–1.000)	0.018
DC volume, mm^3	0.997 (0.992–1.001)	0.12	0.996 (0.992–1.001)	0.092	0.997 (0.993–1.001)	0.103	0.998 (0.994–1.002)	0.301
DC volume >0	0.302 (0.163–0.559)	<0.001	0.252 (0.128–0.496)	<0.001	0.235 (0.110–0.502)	<0.001	0.244 (0.109–0.544)	0.001
Fibrous volume, mm^3	0.989 (0.982–0.996)	0.003	0.988 (0.981–0.996)	0.002	0.990 (0.983–0.997)	0.004	0.991 (0.984–0.998)	0.012
FF volume, mm^3	0.991 (0.984–0.999)	0.02	0.990 (0.982–0.998)	0.011	0.992 (0.984–0.999)	0.028	0.988 (0.980–0.997)	0.006
NC volume, mm^3	0.998 (0.995–1.001)	0.216	0.998 (0.994–1.001)	0.186	0.998 (0.995–1.002)	0.354	0.997 (0.993–1.001)	0.124
DC PAV, %	0.970 (0.950–0.991)	0.004	0.966 (0.944–0.989)	0.003	0.969 (0.949–0.989)	0.002	0.976 (0.955–0.998)	0.033
Fibrous PAV, %	0.970 (0.949–0.992)	0.007	0.965 (0.941–0.989)	0.004	0.966 (0.944–0.990)	0.005	0.970 (0.945–0.995)	0.021
FF PAV, %	1.014 (0.990–1.039)	0.257	1.012 (0.986–1.039)	0.358	1.009 (0.982–1.037)	0.509	1.004 (0.975–1.035)	0.786
NC PAV, %	1.018 (1.005–1.030)	0.005	1.022 (1.008–1.036)	0.002	1.022 (1.008–1.036)	0.002	1.020 (1.004–1.035)	0.012

Multivariate analysis adjusted for the following traditional cardiovascular risk factors: age, gender, body mass index, hypertension, diabetes mellitus, and smoking history. DC, dense calcium; FF, fibrofatty; NC, necrotic core; PAV, percentage of atheroma volume; OR, odds ratio; CI, confidence interval.

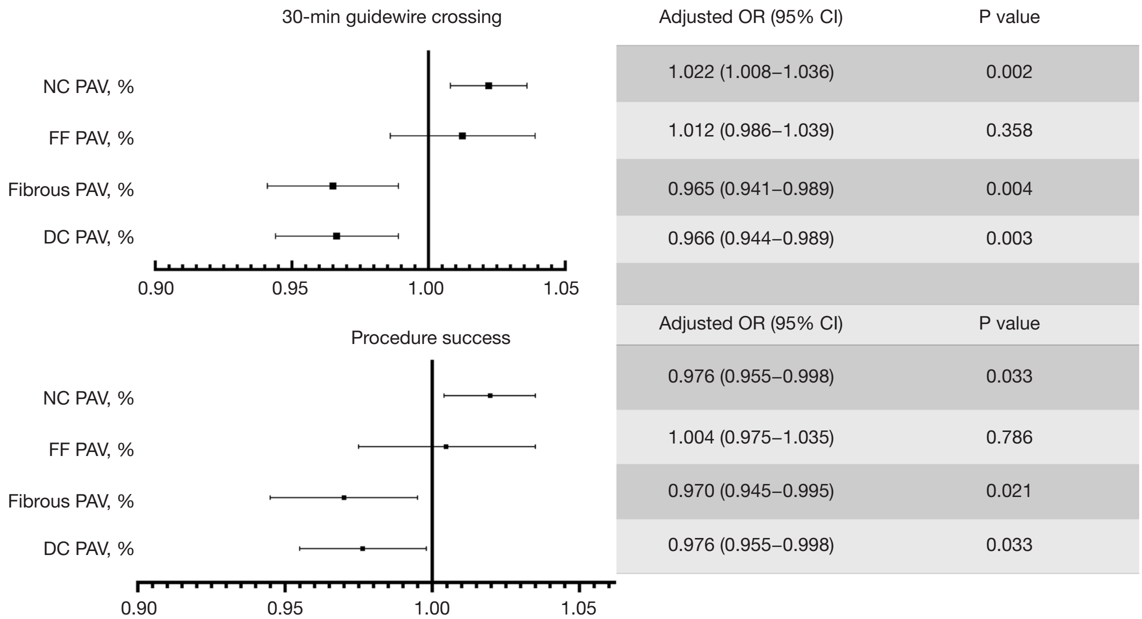

Figure 4 Main results of multivariate analysis, including OR. OR, odds ratio; CI, confidence interval; DC, dense calcium; FF, fibrofatty; NC, necrotic core; PAV, percentage of atheroma volume.

analysis of 186 CTO lesions, and found that high segmental radiologic density as well as occlusion duration and occlusion length were significant predictors of PCI failure (19). However, the CCTA measurement algorithm and HU threshold they adopted were not well defined and validated with other imaging modalities, such as intravascular ultrasound (IVUS). Software in this study was well validated with the results of intravascular ultrasound virtual histology (IVUS-VH) in previous research (13,14), and presented good correlation of quantitative CCTA with IVUS for lumen, vessel, and plaque volume, confirming the feasibility of estimating coronary tissue characterization noninvasively. Furthermore, the key quantitative method we used had been previously adopted in several clinical researches and presented promising results in non-CTO patients (16,17,21). Results from this study narrowed the gap between the quantitative characteristics of CCTA and CTO PCI, providing a potential technique for CTO pre-procedural assessment.

Calcification is a generally accepted obstacle for CTO PCI, and its degree of influence depends on both its extent and distribution. Our results demonstrated that greater PAV of DC tissue was related with higher risk of failed guidewire crossing in ≤30 min and procedural failure (for every 1% increase in PAV; successful 30-min guidewire crossing, OR =0.966, P=0.003; procedural success, OR =0.976, P=0.033), verifying the prior findings with PAV parameters (*Figure 5*).

Notably, although not identifiable on routine CCTA scan, high-density, non-calcified component showed a similar impact on PCI procedure as that of DC (*Figure 5*). Wu *et al.* observed CCTA of 31 untreated CTO lesions and found that later stages of CTO presented with higher density of non-calcified components (25). Prior studies have shown that occlusion time >12 months is also an independent risk factor for CTO PCI difficulty (8,9). However, the relationship between high-density non-calcified components and PCI procedure is still unclear. Our results revealed that increased volume and PAV of fibrous tissue indicates a greater likelihood of failed ≤30-min guidewire crossing and procedural failure.

Low-attenuation plaques are thought to be high-risk characteristic of plaques in non-CTO lesions, indicating an increased risk of future acute coronary syndrome (ACS) and acting as a precursor of CTO lesions (16,26). Kang *et al.* reported that mean plaque attenuation <50 HU was an independent predictor of progression to CTO for patients with vessel diameter stenosis ≥70% under ICA (26). Additionally, prior studies revealed that short-duration CTO lesions presented with greater NC compared with long-duration CTO lesions (27). Hence, as the component with the lowest HU value (−30–75 HU), increased PAV of NC tissue was a predictor of short occlusion time and

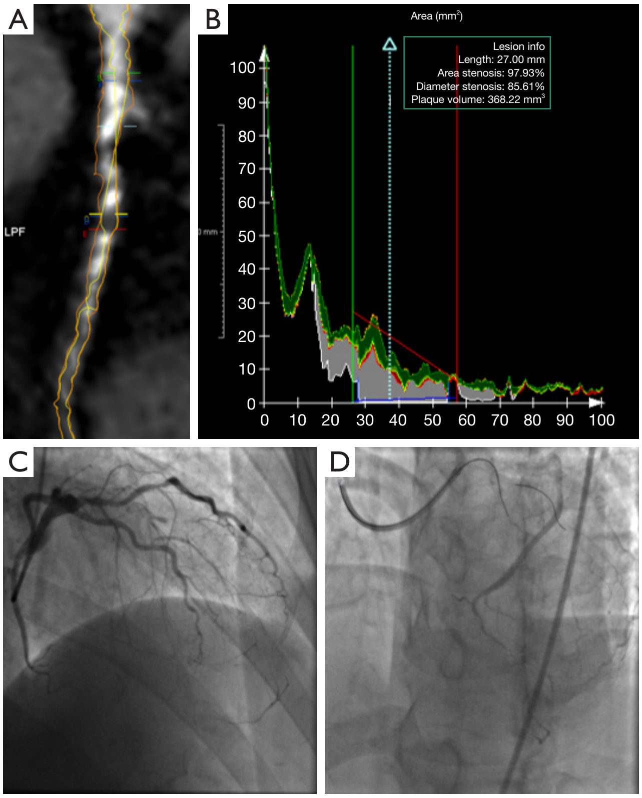

Figure 5 Representative cases. (A) Example of a fibrous and DC rich CTO lesion located in LAD with length of 27.00 mm, 58.92% DC and 29.66% fibrous, which was finally failed after 39 min's trying. Outer vessel wall was represented with orange line and lumen of the coronary artery was presented with yellow line. (B) Component analysis of target vessel according to distance from ostium. (C) Diagnostic invasive coronary angiography. (D) Final coronary angiography after PCI. DC, dense calcium; CTO, chronic total occlusion; LAD, left anterior descending artery; PCI, percutaneous coronary intervention.

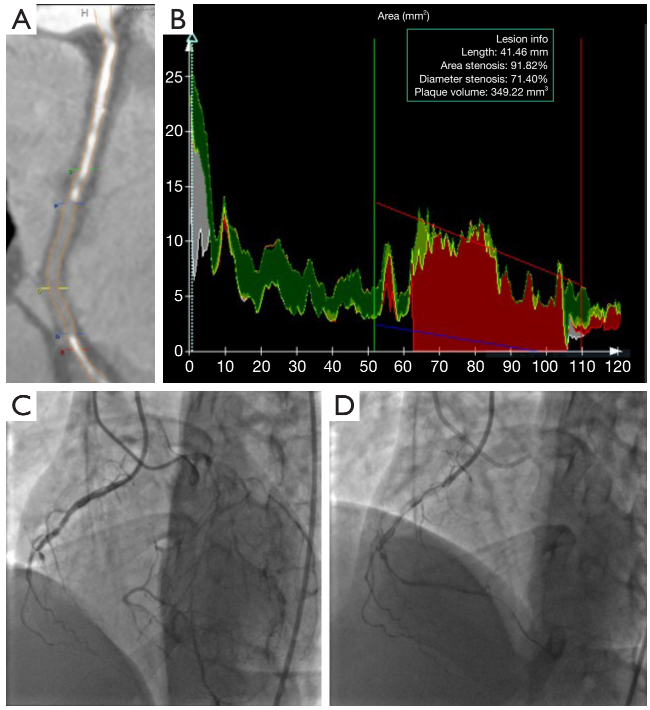

Figure 6 Representative cases. (A) Example of a NC rich CTO lesion located in RCA with length of 41.46 mm and bending >45°, guidewire crossing time was 11 min for 92.53% NC and 7.39% Fibrofatty. Outer vessel wall was represented with orange line. (B) Component analysis of target vessel according to distance from ostium, red represented NC, green represented fibrous, white represented DC and light green represented FF. (C) Diagnostic invasive coronary angiography. (D) Guidewire crossed to distal true lumen within 30 min. NC, necrotic core; CTO, chronic total occlusion; RCA, right coronary artery; FF, fibrofatty; DC, dense calcium.

more similar to the acute coronary syndrome lesion in histopathology. Our study also showed that increasing the volume of NC tissue was not associated with guidewire crossing and procedural success as with other components, while increasing PAV of NC was a predictor of successful guidewire crossing in ≤30 min as well as procedural success (*Figure 6*). Taking the above into consideration, the quantitative evaluation of NC shows promising for speculating on the stage of CTO progression as well as PCI difficulty in further study.

Results of this study indicated that plaque characteristics derived from quantitative CCTA are associated with the difficulty of CTO PCI. With this more accessible modality, quantitative characteristics from quantitative analysis might help with understanding the nature of CTO progression and optimizing interventional strategy.

Study limitations

This study had several limitations that should be noted. First, as a retrospective observational study, it was hard to avoid case-selection bias, and detailed reasons for recanalization failure could not be collected by reviewing the medical records of all cases. Second, some cases could not be reconstructed and analyzed for quantitative analysis, which requires more strict for image quality, vessel diameter, and degree of calcification. Third, the incremental value of the quantitative characteristics in a prediction model was not discussed in this study. With current sample size, a prediction model with a novel, quantitative, continuous variable might not be sufficient for clinical application. Hence, we toned down our conclusion and illustrated the association first. However, as a potential risk factor for CTO PCI, the incremental value of quantitative characteristics in a prediction model will be explored in our further work. Fourth, quantitative analysis also requires extra technical work, specific post-processing software, and longer time than routine assessment, which impacts clinical application.

Conclusions

This study demonstrated that quantitative characteristics derived from CCTA of CTO patients were associated with successful guidewire crossing in ≤30 min and procedural success. Increased percentages of high-attenuation components (of DC and fibrous tissue) were associated with higher risk of failed guidewire crossing in ≤30 min and procedural failure while decreased volume of low-attenuation plaque (NC) was related with higher risk of failed guidewire crossing (in ≤30 min) and procedural failure.

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Footnote

Reporting Checklist: The authors have completed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting checklist. Available at https://qims.amegroups.com/article/view/10.21037/qims-21-1050/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://qims.amegroups.com/article/view/10.21037/qims-21-1050/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study protocol was approved by the Ethics Committee of Beijing Anzhen Hospital and Beijing Friendship Hospital. Written informed consent was provided by all patients before commencement of the study.

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Supplementary

Table S1 distribution of procedural success by J-CTO score

J-CTO Score	Total	Procedural success	Procedural failure	P value
0	57	56	1	<0.001
1	61	49	12	
2	52	34	18	
≥3	37	18	19	

J-CTO, Multicenter CTO Registry of Japan.

Table S2 CCTA characteristics

	Total(N=207)	Successful guidewire crossing ≤30 min (n=131)	Failed guidewire crossing ≤30 min (n=76)	P value
Proximal branch	65 (31.4)	29 (22.1)	36 (47.4)	0.001
Proximal blunt stump	74 (35.7)	31 (23.7)	43 (56.6)	0.001
Lesion length ≥15 mm	107 (51.7)	55 (42.0)	52 (68.4)	<0.001
Lesion length ≥20 mm	80 (38.6)	42 (32.1)	38 (50.5)	<0.001
Bending >45°	42 (20.3)	17 (13.0)	25 (32.9)	0.001
Any calcification	80 (38.6)	37 (28.2)	43 (56.6)	<0.001
Severe calcification	63 (30.4)	26 (19.8)	37 (48.7)	<0.001
Distal branch	48 (23.2)	23 (17.6)	25 (32.9)	0.019
Multiple occlusion	10 (4.8)	6 (4.6)	4 (52.6)	1.000
CTA-JCTO score	1.45±1.30	1.01±1.09	2.22±1.26	<0.001
CTA-JCTO score = 0	58 (28.0)	53 (40.5)	5 (6.6)	<0.001
CTA-JCTO score = 1	62 (30.0)	42 (32.1)	20 (26.3)	
CTA-JCTO score = 2	45 (21.7)	23 (17.6)	22 (28.9)	
CTA-JCTO score ≥ 3	42 (20.3)	13 (9.9)	29 (38.2)	

Severe calcification was defined as presence of any calcification involving more than 50% cross section area in CTO segment. CCTA, coronary computed tomography angiography; J-CTO, Multicenter CTO Registry of Japan.

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