Cut-off values of lesion and vessel quantitative flow ratio in *de novo* coronary lesion post-drug-coated balloon therapy predicting vessel restenosis at mid-term follow-up

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Abstract

Background: Drug-coated balloons (DCBs) have emerged as potential alternatives to drug-eluting stents in specific lesion subsets for *de novo* coronary lesions. Quantitative flow ratio (QFR) is a method based on the three-dimensional quantitative coronary angiography and contrast flow velocity during coronary angiography (CAG), obviating the need for an invasive fractional flow reserve procedural. This study aimed to assess the serial angiographic changes of *de novo* lesions post-DCB therapy and further explore the cut-off values of lesion and vessel QFR, which predict vessel restenosis (diameter stenosis [DS] ≥50%) at mid-term follow-up.

Methods: The data of patients who underwent DCB therapy between January 2014 and December 2019 from the multicenter hospital were retrospectively collected for QFR analysis. From their QFR performances, which were analyzed by CAG images at follow-up, we divided them into two groups: group A, showing target vessel DS ≥50%, and group B, showing target vessel DS <50%. The median follow-up time was 287 days in group A and 227 days in group B. We compared the clinical characteristics, parameters during DCB therapy, and QFR performances, which were analyzed by CAG images between the two groups, in need to explore the cut-off value of lesion/vessel QFR which can predict vessel restenosis. Student's *t* test was used for the comparison of normally distributed continuous data, Mann-Whitney *U* test for the comparison of non-normally distributed continuous data, and receiver operating characteristic (ROC) curves for the evaluation of QFR performance which can predict vessel restenosis (DS ≥50%) at mid-term follow-up using the area under the curve (AUC).

Results: A total of 112 patients with 112 target vessels were enrolled in this study. Group A had 41 patients, while group B had 71. Vessel QFR and lesion QFR were lower in group A than in group B post-DCB therapy, and the cut-off values of lesion QFR and vessel QFR in the ROC analysis to predict target vessel DS ≥50% post-DCB therapy were 0.905 (AUC, 0.741 [95% confidence interval, CI: 0.645, 0.837]; sensitivity, 0.817; specificity, 0.561; *P* < 0.001) and 0.890 (AUC, 0.796 [95% CI: 0.709, 0.882]; sensitivity, 0.746; specificity, 0.780; *P* < 0.001).

Conclusions: The cut-off values of lesion QFR and vessel QFR can assist in predicting the angiographic changes post-DCB therapy. When lesion/vessel QFR values are <0.905/0.890 post-DCB therapy, a higher risk of vessel restenosis is potentially predicted at follow-up.

Keywords: Quantitative flow ratio; Drug-coated balloons; *De novo* coronary lesions; Cut-off value; Receiver operating characteristic curves

Introduction

Drug-coated balloons (DCBs) coated with paclitaxel which could inhibit arterial smooth muscle cell proliferation, had emerged as an alternative therapeutic strategy for some selected coronary atherosclerotic lesions. DCBs therapy with bail-out stenting may be more suitable for in-stent restenosis and some *de novo* coronary lesions.[1-5]

Pei-Na Meng and Bin Liu contributed equally to this work.

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Accumulated clinical evidence shows that DCBs are safe and efficacious, but the key premise is well prepared for target lesions.[1-5] However, physiological assessment is a vital strategy to guide the procedure,[6] but the use of fractional flow reserve (FFR) remains lower, because of its invasive procedural and high-cost.[7-9] To further expand the use of physiological assessment during the percutaneous coronary intervention (PCI), coronary computed tomography angiography-based computation methods were developed.[10-12]

Quantitative flow ratio (QFR) is a method that is based on three-dimensional quantitative coronary angiography (3D-QCA) reconstructions and contrast flow velocity assessment during coronary angiography (CAG), obviating the need for invasive FFR. Several studies have shown that QFR has superior specificity and sensitivity with reference to FFR.[13-15] Physiological assessment during PCI is very important to predict major adverse cardiac events at follow-up. Bech *et al*[16] suggested that FFR >0.90 after angioplasty was a good indicator of immediate functional improvement and subsequent lower prevalence of restenosis at the 2-year follow-up, nevertheless, the relationship between physiological responses immediately post-DCB therapy and target vessel restenosis at follow-up had not been fully explored.

This study aimed to retrospectively assess the serial angiographic changes of *de novo* lesions post-DCB therapy based on QFR offline analysis and to explore the cut-off values of lesion QFR and vessel QFR[17] which can predict target vessel restenosis (diameter stenosis [DS] ≥50%) at mid-term follow-up.

Methods

Ethical approval

The study was retrospective, observational, and multicentered (Nanjing First Hospital, the Second Hospital of Jilin University, the First People's Hospital of Lianyungang, the First Affiliated Hospital of Bengbu Medical College, and the Affiliated Hospital of Xuzhou Medical University), which was approved by the local ethics committee of the Nanjing First Hospital. Informed consent was provided by all patients in this study before PCI.

Patients

Patients who underwent DCB therapy from January 2014 to December 2019 were retrospectively assessed for QFR analysis (post-DCB therapy and at follow-up). From their QFR performances, which were analyzed by CAG images at follow-up, we divided them into two groups: group A (target vessel DS ≥50%) and group B (target vessel DS <50%).

Inclusion criteria

Stable or unstable angina pectoris, *de novo* coronary lesions, target lesions treated with DCB and without any stents, images from CAG clear enough to enter into the QFR analysis software, the target vessels with two angiographic views with projection angles ≥25° for reconstructions in a 3D model in QFR analysis, had CAG review at follow-up.

Exclusion criteria

Left ventricular ejection fraction <40%, acute myocardial infarction, left main coronary artery (LMCA) disease, ostial lesion, heavily calcified or thrombotic lesion, life expectancy <1 year, end-stage renal failure (glomerular filtration rate <30 mL·min^{-1}·1.73 m^2), confused CAG images, and target vessels with excessive overlap and/or foreshortening.

Variables and QFR performances

Clinical presentation, demographics, laboratory results, and CAG characteristics were collected through medical records and coronary angiographic reviews. In this study, all QFR analyses were performed offline, using a software package (AngioPlus, Pulse Medical Imaging Technology, China). First, the selected arteries had two angiographic views with two different angles ≥25° apart. The target vessels, especially the target lesions, had to be clearly exposed (without excessive overlap and/or foreshortening) in the end-diastolic frames. Second, a 3D model reconstruction from a semi-automatic detection of the target vessel contours occurred. And importantly, the proximal segment of the LMCA was excluded; if stenosis lesions in the LMCA existed, the anatomical landmark was automatically located at the start of the stenosis lesions. The following QFR parameters were available for each target vessel: lesion length, DS%, area stenosis% (AS%), vessel QFR, lesion QFR, minimal lumen diameter, blood flow velocity in selected vessels, etc.

Statistics

Categorical variables were presented as percentages and were compared with the Chi-square test. The Student's *t* test was used to compare normally distributed continuous data, and Mann-Whitney *U* test was used to compare non-normally distributed continuous data. Data were presented as mean ± standard deviation or median (Q1, Q3). The relationship between vessel restenosis and risk factors was investigated using linear regression analysis. First, univariate linear regression analysis was used to investigate the association of every possible risk factor (age, hypertension, diabetes, smoking, lesion length, lesion covered by DCB, maximal diameter of the pre-dilation balloon, maximal inflation pressure with the pre-dilation balloon, maximal inflation pressure with DCB, diameter/length of DCB, minimal luminal diameter post-DCB dilatation, DS% post-DCB dilatation, and vessel/lesion QFR post-DCB dilatation). The variables with *P* value < 0.10 were used in the multivariate linear regression analysis. Receiver operating characteristic (ROC) curves were used to evaluate the diagnostic performance of lesion/vessel QFR values which can predict target vessel DS ≥50% at mid-term follow-up using the area under the curve (AUC). A two-sided *P* value < 0.05 was considered statistically significant. All statistical analyses were performed to use the SPSS version 20.0 (SPSS Inc., Chicago, IL, USA).

Results

A total of 209 patients were enrolled, among whom 97 were excluded due to the insufficient image quality (excessive overlap and/or foreshortening of target vessels, absence of angiographic views with projection angles ≥25° apart). Finally, 112 patients and 112 target vessels were enrolled in this study. From their QFR performances, which were analyzed by CAG images at follow-up, we divided them into two groups: group A (DS ≥50%, 41 patients) and group B (DS <50%, 71 patients). The prevalence of vessel restenosis post-DCB therapy (DS ≥50%) at mid-term follow-up was 36.61% (41/112) in the population, and the median follow-up time was 287 days in group A and 227 days in group B ($P > 0.05$) [Figure 1].

Baseline clinical characteristics before DCB therapy between the two groups

No statistical differences of age, sex, hypertension, diabetes, current smoking, and history of PCI/coronary artery bypass graft/myocardial infarction at baseline were noted between the two groups ($P > 0.05$).

Parameters during DCB therapy between the two groups

No statistical differences of parameters during DCB therapy were noted between the two groups ($P > 0.05$) [Table 1].

QFR performances post-DCB therapy between the two groups

QFR performances based on CAG images (immediately post-DCB therapy) were similar between the two groups (including diameter of the proximal/distal vessel, minimal luminal diameter/area, and reference luminal diameter/area, $P > 0.05$) [Table 2], but the DS (%, 46.9 [39.60, 52.50] vs. 35.90 [33.00, 42.80]; $z = -4.325$, $P < 0.001$

and AS (%, 51.60 [37.80, 60.30] vs. 40.30 [29.40, 52.00]; $z = -2.763$, $P = 0.006$) were more severe in group A than in group B, and the vessel QFR (0.81 [0.56, 0.99] vs. 0.94 [0.67, 1.00], $z = -5.207$, $P < 0.001$) and lesion QFR (0.89 [0.64, 0.99] vs. 0.96 [0.68,1.00], $z = -4.257$, $P < 0.001$) were lower in group A than in group B [Figure 2A–D].

QFR performances at follow-up between the two groups

QFR performances based on CAG images (at follow-up) showed [Table 3]:

The minimal luminal diameter (mm, 1.20 [0.60, 2.90] vs. 1.70 [0.80, 3.40], $z = -4.212$, $P < 0.001$) and area (mm², 1.90 [0.80, 8.70] vs. 3.00 [0.70, 9.90], $z = -3.475$, $P = 0.001$) were smaller in group A than in group B.

DS (%, 53.00 [29.10, 77.30] vs. 33.00 [11.20, 48.80], $z = -8.009$, $P < 0.001$) and AS (%, 58.40 [15.20, 86.90] vs. 33.10 [15.40, 58.30], $z = -6.457$, $P < 0.001$) were more severe in group A than in group B, and the vessel QFR (0.78 [0.47, 0.99] vs. 0.96 [0.62, 1.00], $z = -7.136$, $P < 0.001$) and lesion QFR (0.88 [0.63, 1.00] vs. 0.98 [0.82, 1.00], $z = -6.806$, $P < 0.001$) were lower in group A than in group B.

The association of vessel restenosis (DS%) and risk factors

From univariate linear regression analysis (including age, hypertension, diabetes, smoking, maximal pre-dilatation pressure with the pre-dilatation balloon, a diameter of DCB, maximal inflation pressure with DCB, length of DCB, minimal luminal diameter/area post-DCB dilatation, DS% post-DCB dilatation, and vessel/lesion QFR post-DCB dilatation), maximal pre-dilatation pressure ($\beta = 0.926$, $t = 2.088$, $P = 0.039$), maximal inflation pressure with DCB ($\beta = 1.291$, $t = 2.158$, $P = 0.033$), DS% post-DCB dilatation ($\beta = 0.455$, $t = 4.027$, $P < 0.001$), vessel QFR post-DCB dilatation ($\beta = -0.360$, $t = -4.047$,
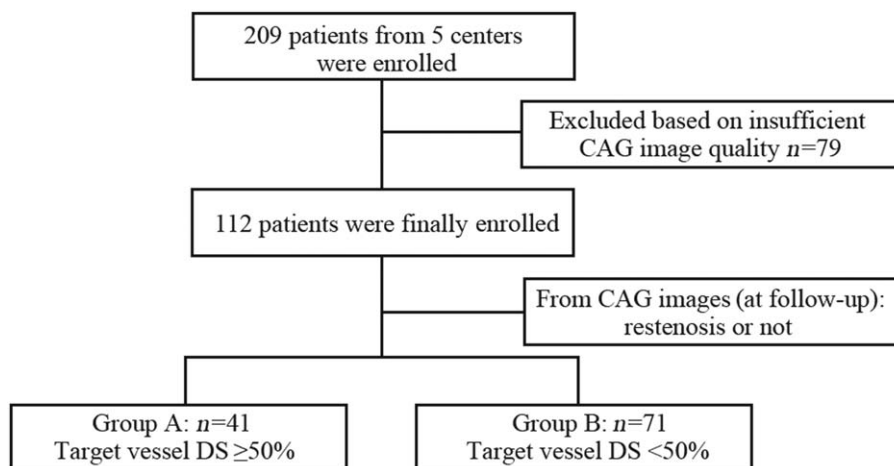
Figure 1: Study enrolment of flowchart. Patients who underwent DCB therapy between January 2014 and December 2019 from the multicenter hospital were retrospectively assessed for QFR analysis (post-DCB therapy and at follow-up). According to the inclusion and exclusion criteria, 209 patients were included, but based on insufficient CAG image quality not clear enough to enter into the QFR analysis software, 112 patients and 112 target vessels were finally enrolled. From their QFR performances analyzed by CAG images at follow-up, we divided them into two groups: group A (target vessel DS ≥50%) and group B (target vessel DS <50%). CAG: Coronary angiography; DCB: Drug-coated balloon; DS: Diameter stenosis; QFR: Quantitative flow ratio.

Table 1: Parameters during DCB therapy between group A (target vessel DS ≥50%) and group B (target vessel DS <50%).

Variables	Group A (n = 41)	Group B (n = 71)	Statistics	P
Target vessel			−0.814	0.582
LAD (%)	15 (36.6)	33 (46.5)		
LCX (%)	13 (31.7)	20 (28.2)		
RCA (%)	13 (31.7)	18 (25.4)		
Lesion length (mm)	25.80 (17.30, 42.90)	23.90 (14.80, 39.40)	−1.537	0.124
Lesion covered by DCB (%)	36 (87.8)	62 (87.3)	0.005	1.000
Maximal diameter of pre-dilation balloon (mm)	2.50 (1.50, 3.50)	2.50 (1.50, 4.00)	−1.727	0.084
Maximal inflation pressure with pre-dilation balloon (atm)	12.00 (6.00, 20.00)	12.00 (6.00, 16.00)	−0.448	0.654
Residual stenosis post-dilatation (%)	10.00 (5.00, 10.00)	10.00 (5.00, 10.00)	−0.401	0.689
Diameter of DCB (mm)	2.50 (2.00, 3.50)	2.75 (2.00, 4.00)	−1.752	0.080
Maximal inflation pressure with DCB (atm)	10.00 (6.00, 16.00)	10.00 (6.00, 16.00)	−1.132	0.258
Duration of inflation with DCB (s)	60.00 (50.00, 60.00)	60.00 (30.00, 60.00)	−0.819	0.413
Length of DCB (mm)	20.00 (15.00, 30.00)	25.00 (10.00, 30.00)	−0.124	0.901

Data are presented as n (%) or median (Q1, Q3), respectively. The differences of quantitative indexes or categorical variables between the two groups were analyzed using Mann-Whitney U test or χ^2 test. DCB: Drug-coated balloon; DS: Diameter stenosis; LAD: Left anterior descending branch; LCX: Left circumflex artery; RCA: Right coronary artery.

Table 2: QFR performances post-DCB therapy between group A (target vessel DS ≥50%) and group B (target vessel DS <50%).

Variables	Group A (n = 41)	Group B (n = 71)	Statistics	P
Diameter of proximal vessel (mm)	2.69 ± 0.81	2.47 ± 0.67	−1.503	0.136
Diameter of distal vessel (mm)	2.23 ± 0.92	2.18 ± 0.57	−0.367	0.714
Minimal luminal diameter (mm)	1.20 (0.60, 2.70)	1.50 (0.60, 3.40)	−1.635	0.102
Reference luminal diameter (mm)	2.50 (1.40, 5.40)	2.40 (1.20, 5.60)	−0.541	0.588
Minimal luminal area (mm^2)	2.50 (0.40, 13.10)	2.80 (0.60, 9.80)	−0.819	0.413
Reference luminal area (mm^2)	4.60 (1.50, 23.10)	4.60 (1.10, 24.90)	−0.048	0.961
DS (%)	46.9 (39.60, 52.50)	35.90 (33.00, 42.80)	−4.325	<0.001
AS (%)	51.60 (37.80, 60.30)	40.30 (29.40, 52.00)	−2.763	0.006
Vessel QFR	0.81 (0.56, 0.99)	0.94 (0.67, 1.00)	−5.207	<0.001
Lesion QFR	0.89 (0.64, 0.99)	0.96 (0.68, 1.00)	−4.257	<0.001

Data are presented as mean ± standard deviation or median (Q1, Q3), respectively. The differences of quantitative indexes or categorical variables between the two groups were analyzed by Student's t test or Mann-Whitney U test (χ^2 test). Vessel QFR, QFR value of the entire interrogated segment. Segments proximal to the contoured segment are considered non-stenotic; Lesion QFR, QFR value of the lesion segment between the two green lesion delimiters. AS: Area stenosis; DS: Diameter stenosis; QFR: Quantitative flow ratio.

$P < 0.001$), and lesion QFR post-DCB dilatation ($\beta = -0.299$, $t = -3.285$, $P = 0.001$) were associated with the DS%.

From multivariate linear regression analysis (including maximal pre-dilatation pressure, maximal inflation pressure with DCB, DS% post-DCB dilatation, vessel QFR post-DCB dilatation [the clinical significance and value were very similar of vessel QFR and lesion QFR, so we had chosen vessel QFR to enter into multivariate linear regression analysis]), the only vessel QFR was independently associated with the DS% ($\beta = -0.233$, $t = -2.002$, $P = 0.048$) [Table 4].

### Cut-off values of QFR which can predict target vessel DS ≥50% at follow-up

The cut-off values of lesion/vessel QFR which can predict target vessel DS ≥50% at follow-up were 0.905 (AUC, 0.741 [95% confidence interval, CI: 0.645, 0.837]; sensitivity, 0.817; specificity, 0.561; $P < 0.001$) and 0.890 (AUC, 0.796 [95% CI: 0.709, 0.882]; sensitivity,

0.746; specificity, 0.780; $P < 0.001$). The results showed that when lesion QFR is <0.905 or vessel QFR <0.890 post-DCB therapy, it may predict target vessel restenosis at follow-up [Figure 3A and 3B].

Discussion

The main findings of this study are as follows: (1) Lower QFR value post-DCB therapy potentially predicts a higher risk of vessel restenosis at mid-term follow-up. (2) The cut-off values of lesion QFR and vessel QFR for the ROC analysis to predict vessel restenosis ≥50% at mid-term follow-up were 0.905 and 0.890, respectively.

The main effect of DCB therapy is the rapid delivery of an antiproliferative agent to the vessel wall to further inhibit smooth muscle cell proliferation and avoid acute or subacute vessel elastic recoil.[18] DCBs have smaller profiles than stents, so they often have easier access to some complex lesions and small vessels. The absence of a foreign body in coronary arteries potentially shortens the duration of double antiplatelet therapy[5] and avoids
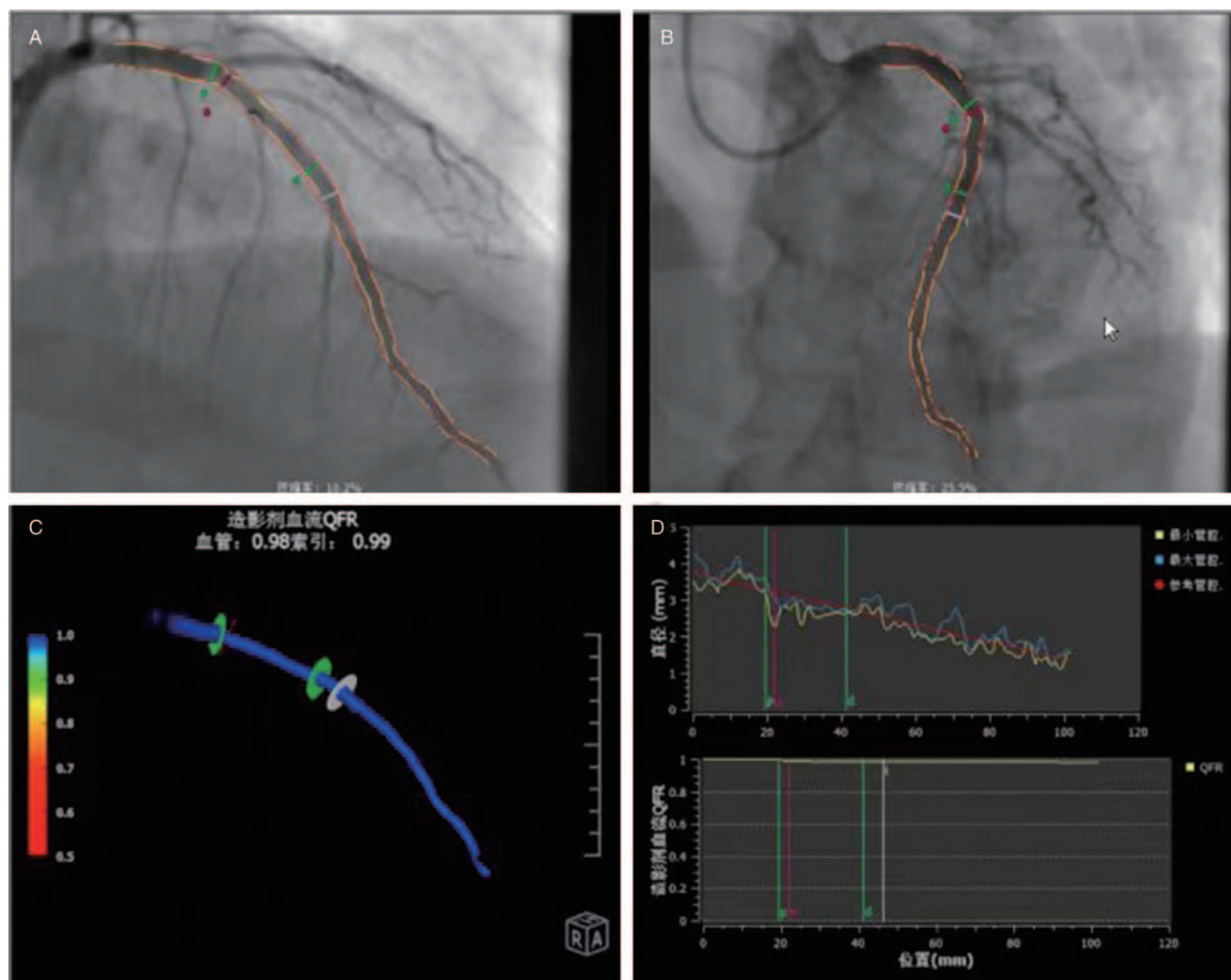
Figure 2: QFR results from a patient (post-DCB therapy). (A and B) Two angiographic views were used for QFR analysis, including the lumen and reference contours. (C) Three-dimensional model of the coronary artery. (D) Diameter curves: yellow curve (the minimum lumen), blue curve (the maximum curve), and red curve (reference lumen). DCB: Drug-coated balloon; QFR: Quantitative flow ratio.

Table 3: QFR results at mid-term follow-up between group A (target vessel DS ≥50%) and group B (target vessel DS <50%).

Variables	Group A (n = 41)	Group B (n = 71)	Statistics	P
Diameter of proximal vessel (mm)	2.60 (1.20, 7.30)	2.60 (1.20, 4.40)	−0.206	0.837
Diameter of distal vessel (mm)	2.10 (1.10, 7.30)	2.20 (1.30, 3.90)	−0.024	0.981
Minimal luminal diameter (mm)	1.20 (0.60, 2.90)	1.70 (0.80, 3.40)	−4.212	<0.001
Reference luminal diameter (mm)	2.60 (1.40, 7.50)	2.40 (1.30, 5.40)	−0.768	0.442
Minimal luminal area (mm^2)	1.90 (0.80, 8.70)	3.00 (0.70, 9.90)	−3.475	0.001
Reference luminal area (mm^2)	5.20 (1.50, 44.60)	4.80 (1.40, 22.90)	−0.565	0.572
DS (%)	53.00 (29.10, 77.30)	33.00 (11.20, 48.80)	−8.009	<0.001
AS (%)	58.40 (15.20, 86.90)	33.10 (15.40, 58.30)	−6.457	<0.001
Vessel QFR	0.78 (0.47, 0.99)	0.96 (0.62, 1.00)	−7.136	<0.001
Lesion QFR	0.88 (0.63, 1.00)	0.98 (0.82, 1.00)	−6.806	<0.001

Data are presented as median (Q1, Q3), respectively. The differences of quantitative indexes or categorical variables between the two groups were analyzed using Mann-Whitney U test (χ^2 test). Vessel QFR, QFR value of the entire interrogated segment. Segments proximal to the contoured segment are considered non-stenotic; Lesion QFR, QFR value of the lesion segment between the two green lesion delimiters. AS: Area stenosis; DS: Diameter stenosis; QFR: Quantitative flow ratio.

chronic inflammation in the vessel wall, thereby decreasing the risk of hemorrhage and revascularization. Thus, DCBs might be an alternative option to some *de novo* lesions that are not suitable for stents. The encouraging results with DCB therapy of *de novo* lesions in recent years have been attributed to the improvements of DCB's design.[19-21]

Table 4: Association of restenosis (DS%) and risk factors.

Model	β	t	P
Maximal pre-dilatation pressure	0.112	1.214	0.227
Maximal inflation pressure with DCB	0.167	1.819	0.072
DS% post-DCB dilatation	0.189	1.606	0.111
Vessel QFR post-DCB dilatation	−0.233	−2.002	0.048

Linear regression analysis was used for assessing the association of restenosis (DS%) and risk factors (maximal pre-dilatation pressure, maximal inflation pressure with DCB, DS% post-DCB dilatation, vessel QFR post-DCB dilatation). DCB: Drug-coated balloon; DS: Diameter stenosis; QFR: Quantitative flow ratio.
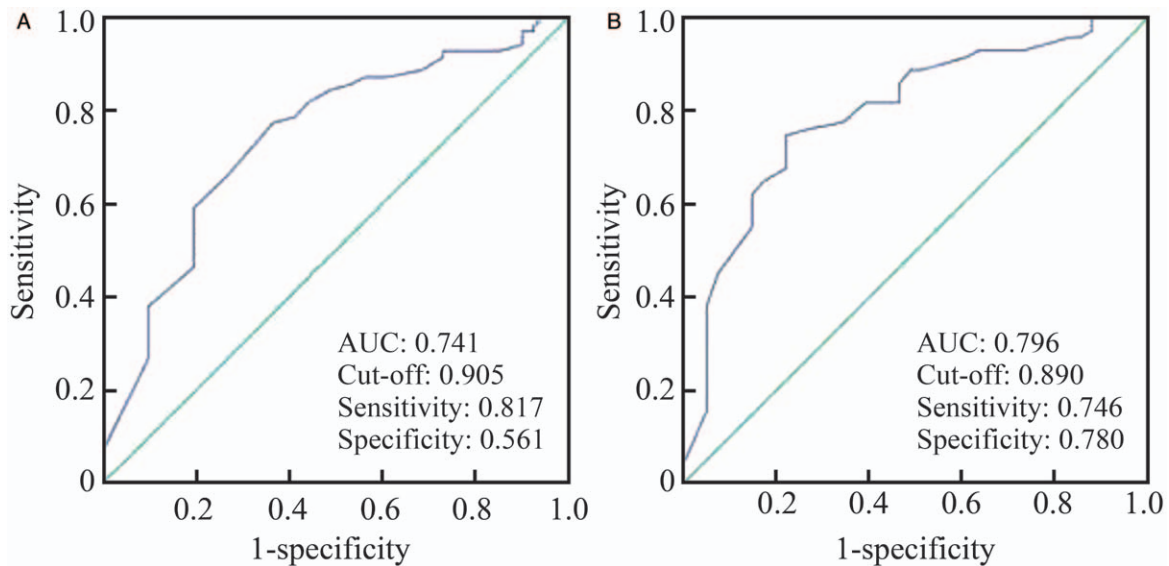
Figure 3: ROC curves of lesion/vessel QFR to predict target vessel DS ≥50% at mid-term follow-up. (A) The cut-off values of lesion QFR which can predict target vessel DS ≥50% at follow-up was 0.905 (AUC, 0.741 [95% CI: 0.645, 0.837]; sensitivity, 0.817; specificity, 0.561; $P < 0.001$). (B) The cut-off value of vessel QFR which can predict target vessel DS ≥50% at follow-up was 0.890 (AUC, 0.796 [95% CI: 0.709, 0.882]; sensitivity, 0.746; specificity, 0.780; $P < 0.001$). CI: Confidence interval; DS: Diameter stenosis; QFR: Quantitative flow ratio; ROC: Receiver operating characteristic.

Several studies have even indicated that DCB-treated *de novo* lesions had favorable vessel remodeling without chronic elastic recoil during follow-up[22,23] and that the majority of plaque composition is fibrous, with an increasing trend in the fibrofatty tissue from baseline to 9 months follow-up.[22]

To evaluate the effectiveness of DCB therapy on *de novo* lesions, except for optimal lesion preparation, acceptable angiographic results after pre-dilation during the intervention and reliable predictors immediately post-DCB treatment are necessary too. Fewer studies explored the predictors of post-DCB therapy for restenosis. Reductions in the pressure gradient and the final angioplasty pressure gradient are known useful indicators of initial angiographic outcomes.[24] FFR is a reliable index to calculate the pressure gradient changes. Bech *et al*[16] suggested that FFR >0.90 after final angioplasty could predict immediate functional improvement and subsequent lower prevalence of restenosis at 2-year follow-up, but it must be performed on the premise of hyperemia induction and should use an invasive pressure-wire; besides that, it is costly. To overcome the above disadvantages, QFR was developed, which is a method based on 3D-QCA reconstruction and

contrast flow velocity during CAG, obviating the need for invasive FFR. It depends on optimal CAG images, which had complete exposure of target vessels and lesions. It can also provide the information by both QCA and FFR. FAVOR and FAVOR Europe-Japan and FAVOR-China studies showed that QFR has superior specificity and sensitivity than FFR.[13-15] Furthermore, QFR could support real-time and offline analyses, with less time than FFR. Thus, with QFR having superior accessibility in clinical work, QFR is believed to be easily adopted in future clinical work.

Our study showed that when vessel QFR or lesion QFR was up to 0.890 or 0.905, it was a valuable indicator of the prediction of angiographic outcomes of DCB treatment on *de novo* lesions. Therefore, QFR could provide us easier and faster information of the lesions' functional and angiographic performance than FFR, and their cut-off value can help us predict vessel restenosis post-DCB therapy.

Limitations

This study has several limitations: (1) It is a retrospective design, we had selection bias of patients and lack of some

parameters of them. Subsequently, the results should be considered exploratory. (2) The patients were not divided into several subgroups due to our small sample, so it is not known whether any difference exists among them. The results cannot be applied to all types of patients with DCB therapy. (3) No clinical outcomes were noted in the study; thus, these findings strongly suggest the need for further, larger, randomized registry studies to validate the clinical implication of QFR values.

Conflicts of interest

None.

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