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IMAGING INFORMATICS AND ARTIFICIAL INTELLIGENCE

A 2-year investigation of the impact of the computed tomography–derived fractional flow reserve calculated using a deep learning algorithm on routine decision-making for coronary artery disease management

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Abstract

Objective This study aims to investigate the safety and feasibility of using a deep learning algorithm to calculate computed tomography angiography–based fractional flow reserve (DL-FFRCT) as an alternative to invasive coronary angiography (ICA) in the selection of patients for coronary intervention.

Materials and methods Patients ($N = 296$) with symptomatic coronary artery disease identified by coronary computed tomography angiography (CTA) with stenosis over 50% were retrospectively enrolled from a single centre in this study. ICA-guided interventions were performed in patients at admission, and DL-FFRCT was conducted retrospectively. The influences on decision-making by using DL-FFRCT and the clinical outcome were compared to those of ICA-guided care for symptomatic CAD at the 2-year follow-up evaluation.

Result Two hundred forty-three patients were evaluated. Up to 72% of diagnostic ICA studies could have been avoided by using a DL-FFRCT value > 0.8 as a cut-off for intervention. A similar major adverse cardiovascular event (MACE) rate was observed in patients who underwent revascularisation with a DL-FFRCT value ≤ 0.8 (2.9%) compared to that of ICA-guided interventions (3.3%) (stented lesions with ICA stenosis > 75%) ($p = 0.838$).

Conclusion DL-FFRCT can reduce the need for diagnostic coronary angiography when identifying patients suitable for coronary intervention. A low MACE rate was found in a 2-year follow-up investigation.

Key Points

- *Seventy-two percent of diagnostic ICA studies could have been avoided by using a DL-FFRCT value > 0.8 as a cut-off for intervention.*
- *Coronary artery stenting based on the diagnosis by using a 320-detector row CT scanner and a positive DL-FFRCT value could potentially be associated with a lower occurrence rate of major adverse cardiovascular events (2.9%) within the first 2 years.*
- *A low event rate was found when intervention was performed in tandem lesions with haemodynamic significance based on DL-FFRCT < 0.8 as a cut-off value.*

Keywords Computed tomography angiography · Myocardial fractional flow reserve · Deep learning · Myocardial revascularisation · Coronary artery disease

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Abbreviations

CABG	Coronary artery bypass surgery
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CFD	Computed fluid dynamics
D L - FFRCT	Deep learning–based FFRCT
FFR	Fractional flow reserve
FFRCT	Coronary computed tomography angiography (CCTA)-derived fractional flow reserve
ICA	Invasive coronary angiography
LAD	Left anterior descending artery
MACEs	Major adverse cardiovascular events

Introduction

Coronary computed tomography angiography (CCTA)–derived fractional flow reserve (FFRCT) has been reported to yield better clinical outcomes in directing revascularisation than CCTA alone according to previous trials [1, 2]. Although FFRCT has demonstrated diagnostic accuracy and excellent correlations with invasive fractional flow reserve (FFR) [3], the long processing time and the complex parameter configurations needed to derive FFRCT are challenges for its further application in clinical practice. Therefore, a more convenient approach is becoming increasingly attractive to the cardiovascular community.

The current CT-derived FFR algorithm incorporates deep learning to learn patterns of stenotic coronary arteries and the FFR, which improves the efficiency of FFR prediction compared to that derived from CCTA through computed fluid dynamics (CFD). Several studies have validated that the diagnostic accuracy of discriminating haemodynamically significant stenosis using deep learning–based FFRCT (DL-FFRCT) was equivalent to that of CFD-based FFRCT [4–6]. However, few studies have investigated the safety associated with an alternative diagnostic strategy using DL-FFRCT in patients with planned invasive angiograms [7]. Further analysis is required to evaluate the clinical efficacy and safety of this method.

The purpose of this study was to investigate the prognostic value of a new DL-FFRCT algorithm using the invasive coronary angiography (ICA)–guided revascularisation strategy as a reference. Retrospective DL-FFRCT was performed and analysed with respect to 2-year clinical outcomes.

Materials and methods

Study population

Symptomatic coronary artery disease (CAD) patients with a documented degree of stenosis > 50% on CCTA who visited the First Affiliated Hospital, Jinan University—Guangzhou Overseas Chinese Hospital, Guangzhou, Guangdong, P. R. China, between January 12, 2014, and December 26, 2016, were retrospectively reviewed. Patients who underwent ICA at the same site and who satisfied the following criteria were included: age > 18 years and the ability to provide informed consent. The exclusion criteria were as follows: patients with previous coronary artery revascularisation (coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI)), previous myocardial infarction, previous stroke, left main stem disease, chronic total occlusion (CTO), bifurcation lesion, and loss of contact by the end of the study. Revascularisation was performed following the standard clinical protocol with a clinical indication of > 75% stenosis estimated by ICA.

The follow-up investigation started from the first ICA procedure. CCTA was performed no earlier than 30 days before the planned invasive procedure. Clinical outcomes over the 24 months were recorded at the return visit through either a telephone call or a countercheck at the same site. The local institutional review boards approved this study on November 1, 2017.

CCTA protocol

All patients underwent CCTA with a 320-row multidetector CT scanner (Aquilion ONE, Toshiba Medical Systems). Beta-blockers were administered to patients with an elevated heart rate (over 70 bpm) 1 h before CT; sublingual nitroglycerine was given before the primary CT data acquisition for CCTA. Non-ionic contrast material (Iopamiro, 370 mg/ml, Bracco) was injected intravenously at an injection rate of 4 ml/s (median volume, 50 ml; range, 40–60 ml), followed by 30 ml of saline solution injected at the same speed. Details of the CT scanner parameters are shown in Table 1. CCTA studies were performed by observers with over 10 years of experience in cardiac CT. The degree of stenosis was defined as the ratio of the diameters of the stenotic and reference vessels, and the

Table 1 CT scanner parameters

Parameters	Value/descriptions
Collimation	320 × 0.5 mm
Gantry rotation time	350 ms
Temporal resolution	175 ms
Gating	Prospective or retrospective
Slice thickness	0.75 cm
Tube voltages	100 kVp or 120 kVp
Tube current	400–550 mA
Scan protocol	Either axial or helical
Noise index	145mAs or 120 mAs pr
Dose length products (DLP)	7.7 ± 2.1 mGy

vessels with a CCTA stenosis over 50% were referred for further evaluation by ICA.

Invasive procedures

ICA was performed according to societal guidelines [8] by certified interventional cardiologists. An iodinated contrast agent was applied, and a minimum bolus was used (range from 20 to 120 ml), with a mean dose area product (DAP) of 1.17 ± 0.72. The degree of stenosis was determined quantitatively based on diameter reduction during the procedure, with stenosis > 75% as a positive angiographic indication for revascularisation. The treatment strategy also relied on the location of the stenosis, the length of the stenosis, and the diameter of the target vessel. In cases with high-risk anatomies, three-vessel disease, or two vessels involving the left anterior descending (LAD) artery, a consensus reading by two reviewers determined the appropriate revascularisation strategy.

Retrospective DL-FFRCT evaluation

DL-FFRCT measurements were performed by an independent core laboratory at Keya Medical in a manner that was blinded to the clinical findings. Details of the DL-FFRCT algorithm have been previously described [9, 10]. In brief, a training dataset consisting of synthetic coronary artery networks that interpreted various characteristics of stenosis with the corresponding FFRCT value calculated using CFD was developed to train the deep learning algorithm [11–16]. The DL-FFRCT value was obtained directly as the output, and the threshold value of DL-FFRCT ≤ 0.80 was defined as positive [17]. DL-FFRCT values were obtained retrospectively and, therefore, did not interfere with clinical decision-making in the current study. Performance analysis for identifying obstructive CAD using DL-FFRCT ≤ 0.8 compared to CCTA and ICA was conducted, and the reference for significant stenosis was over 50% by CCTA and over 75% by ICA.

Study endpoints

The primary endpoint was revascularisation indicated by angiography at the initial admission. The secondary endpoint was all events recorded until December 30, 2018. These events included all-cause mortality and MACEs, which consisted of cardiac death, stroke, myocardial infarction (MI), and any secondary revascularisation, as a composite clinical endpoint.

Statistical analysis

Data are presented as the mean ± standard deviation or the median with the interquartile range (IQR) as appropriate, and variables were compared using Student's *t* test, the Mann-Whitney *U* test, ANOVA, or the Kruskal-Wallis *H* test as appropriate. Cox proportional hazards models were used to assess the relationship between the groups regarding the composite endpoint. All statistical tests were two-tailed, and a p value < 0.05 was defined as significant. Power analysis with 2-sample equivalence was conducted with a 2-sided test and alpha = 0.05%. The statistical analyses were carried out using IBM SPSS (SPSS Inc. Version 24).

Results

Study cohort

A total of 296 subjects were initially identified. Of the excluded patients, 42 had left main stem disease, and 11 were lost to follow-up. All of the remaining patients underwent successful DL-FFRCT analysis. The final population of the present study consisted of 243 patients with 567 lesions identified in 535 artery branches.

Patient characteristics

Patient characteristics are summarised in Table 2. Angiography-guided revascularisation was performed, during which 208 stents were placed in 157 vessels in 129 patients.

Risk stratification and revascularisation

The datasets were subdivided into four groups (Fig. 1). These groups were defined as (1) positively confirmed by both ICA and DL-FFRCT (DpFp), (2) positively confirmed by ICA but negative by DL-FFRCT (DpFn), (3) negatively confirmed by ICA but positive by DL-FFRCT (DnFp), and (4) negatively confirmed by both ICA and DL-FFRCT (DnFn). The analyses were then carried out based on lesion-wise and patient-wise distributions as follows.

The lesion-wise analysis and revascularisations

The lesion-wise distribution was 80 (14.1%), 161 (28.4%), 20 (3.5%), and 306 (54.0%) lesions in the DpFp, DpFn, DnFp, and DnFn groups, respectively. Of the lesions, 241 (42.5%) were ICA-positive, and 100 (17.6%) were DL-FFRCT-positive. The discordance rate of the risk stratification of DL-FFRCT for ICA-positive lesions was 66.8% (161) and that for ICA-negative lesions was 6.1% (20). Revascularisation was performed for 149 lesions (61.8%) in the ICA-positive groups (DpFp and DpFn), among which 107 (71.8%) lesions would have been suspended for revascularisation with a DL-FFRCT value > 0.8 (DpFn). For the ICA-negative groups (DnFp and DnFn), 20 (6.2%) lesions would have been reassigned for revascularisation with a DL-FFRCT value

Table 2 Baseline characteristics

Patient characteristics	243
Age (mean ± SD), year	63.5 ± 10.6
Male *n* (%)	143 (58.6)
Clinical characteristics	
Angina	
Stable, *n* (%)	151 (62.1)
Unstable, *n* (%)	92 (37.9)
Diabetes mellitus, *n* (%)	94 (38.7)
Hypertension	
I, *n* (%)	88 (36.2)
II, *n* (%)	61 (25.1)
III, *n* (%)	94 (38.7)
Hypercholesterolemia, *n* (%)	99 (40.7)
NYHA Heart function	
I, *n* (%)	96 (39.5)
II, *n* (%)	137 (56.4)
III, *n* (%)	7 (2.9)
IV, *n* (%)	3 (1.2)
Single vessel disease	61 (25.1)
Multiple vessel disease (without tandem lesion)	157 (64.6)
Multiple vessel disease (with tandem lesion)	25 (10.3)
Angiographic characteristics (inspected vessels/lesion)	**535/567**
Left anterior descending, n_v/n_l (%_v/%_l)	219/239 (41.0/42.2)
The first diagonal, n_v/n_l (%_v/%_l)	44/44 (8.2/7.8)
The second diagonal, n_v/n_l (%_v/%_l)	16/16 (3.0/2.8)
Middle branch, n_v/n_l (%_v/%_l)	8/8 (1.5/1.4)
Left circumflex, n_v/n_l (%_v/%_l)	101/104 (18.9/18.4)
Oculus margin, n_v/n_l (%_v/%_l)	14/14 (2.6/2.5)
Right coronary artery, n_v/n_l (%_v/%_l)	147/156 (27.5/27.6)
Posterior descending artery, n_v/n_l (%_v/%_l)	5/5 (0.9/0.9)
Posterior artery of the left ventricle, n_v/n_l (%_v/%_l)	1/1 (0.2/0.2)

≤ 0.8 (DnFp), while 2 lesions underwent revascularisation due to unstable chest pain. Five lesions (1.6%) in the DnFn group underwent revascularisation with a median DL-FFRCT value of 0.9 (IQR: 0.81 to 0.93), and the median degree of stenosis by ICA was 60% (IQR: 50% to 70%). A case review showed that 3 patients had unstable chest pain and medium- to high-grade hypertension, whereas the remaining 2 patients had stable chest pain and low-grade hypertension.

The patient-wise analysis and clinical outcomes

The patient-wise distribution was 59 (24.3%), 93 (38.3%), 9 (3.7%), and 82 (33.7%) patients in the DpFp, DpFn, DnFp, and DnFn groups, respectively. Of the patients, 152 (62.5%) were ICA-positive, and 65 (26.7%) were DL-FFRCT-positive. The discordance rate of the risk stratification of DL-FFRCT for ICA-positive patients was 61.2% and that for ICA-negative patients was 9.9%. As a result, the rate of ICA could potentially be reduced by 72% (175 patients from the DpFn and DnFn groups out of 243) according to DL-FFRCT-positive indications.

Tandem lesions were observed in 10.3% of the patients (*N* = 25), while no significant differences were observed in patient characteristics (Table 3). Similarly, patients with tandem lesions tended to be identified as positive by both ICA and DL-FFRCT, and consistency in the management strategy of revascularisation was observed (Fig. 2). In contrast, differences were observed in patients with single and multiple lesions, for which DL-FFRCT tended to reject ICA-guided revascularisation (Fig. 2).

The clinical outcome analysis showed that the event rate was 3.3% (8 patients), including 1 (0.41%) suicide, 2 (0.82%) deaths from heart failure, 1 (0.41%) death from MI, 3 (1.23%) strokes, and 1 (0.41%) revascularisation. Of the eight patients who recorded events (Table 4), 4 patients were categorised as DpFp, and the remainder were categorised as

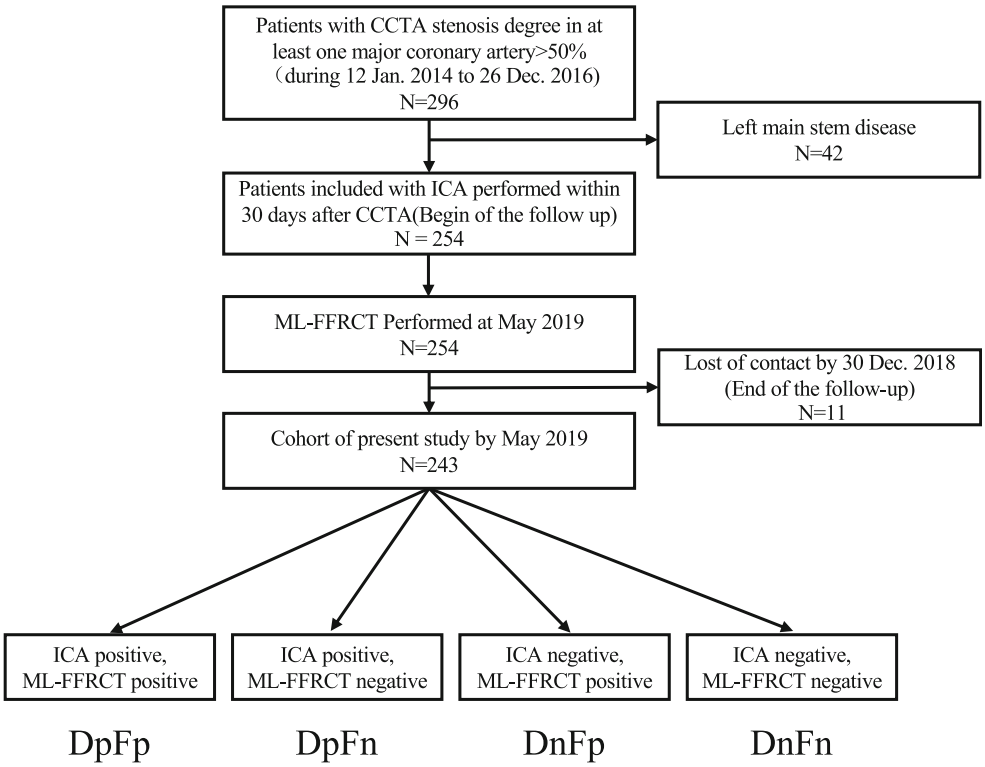

Fig. 1 Flow diagram showing the selection and analysis of patients with CAD

DpFn. In the DpFp group, two patients were managed without revascularisation, 1 patient died from heart failure within the first year, and 1 patient died from MI in the second year. Additionally, 1 patient with treated tandem lesion died from heart failure, and 1 patient treated with revascularisation experienced stroke in the second year. In the DpFn group, no MACEs were observed within 1 year, and 1 patient died from suicide at 10 months. There was 1 patient in whom a secondary revascularisation was performed by placing two stents in the right coronary artery, while no restenosis was observed in the LAD, where a stent was placed during the first ICA procedure. Thus, among the 7 MACEs of the 243 patients included in the DL-FFRCT analysis in this study (MACE rate: 2.9%), 4 (out of 68) occurred in patients with DL-FFRCT ≤ 0.8, and 3 (out of 175) occurred in patients with DL-FFRCT > 0.8 (RR: 3.43, 95% [CI]: 0.79 to 14.93). In particular, the MACE rate of the patients with DL-FFRCT values ≤ 0.8 who had undergone revascularisation was 2.9% (2 out of 68), while no MACEs were observed in patients with DL-FFRCT values > 0.8 who were treated without revascularisation within two years. The MACE rate of the patients with ICA ≥ 75% who had undergone revascularisation was 3.3% (5 out of 152), and there were no MACEs in patients with ICA < 75% who were treated without revascularisation for 2 years. Power analysis with 2-sample equivalence showed that the cardiovascular-related clinical outcome after revascularisation indicated by positive ICA (3.3%) and positive DL-FFRCT (2.9%) was associated with a power of 0.83 and an alpha value = 0.05% (2-sided test in the cohort of 243 patients) (95% CI [-0.045, 0.053]). A similar MACE rate was observed between the ICA-guided and DL-FFRCT-indicated interventions according to Cox regression analysis (p value = 0.838).

Table 3 Patient characteristics in different lesion types (N = 243)

	Single (N = 61)	Multiple (N = 157)	Tandem (N = 25)	p value
Age mean (SD)	66.4 (9.6)	65.5 (9.3)	65.6 (7.4)	.866
Gender, n (%)	33 (54.1)	92 (58.6)	18 (72.0)	.309
Stable, n (%)	34 (55.7)	100 (63.7)	17 (68.0)	.453
Diabetes, n (%)	20 (32.8)	66 (42.0)	4 (16.0)	.350
Hypertension (high risk, I), n (%)	22 (36.1)	54 (34.4)	12 (48.0)	.249
Hypercholesterolaemia, n (%)	28 (45.9)	64 (40.8)	3 (12.0)	.310
NYHA heart function (high risk, over II), n (%)	1 (1.7)	6 (3.8)	0 (0)	.855

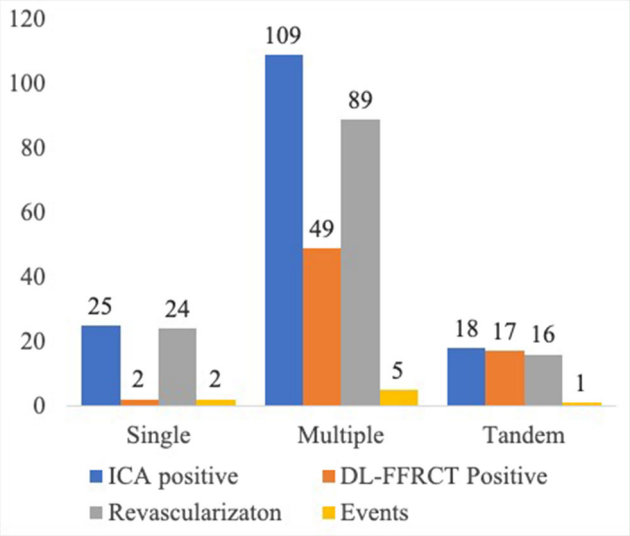

Fig. 2 Distributions of cases categorised into 3 groups. Group 1: Single indicating patients with only one lesion. Group 2: Multiple indicating patients with more than one lesion that was observed in arteries without tandem lesions. Group 3: Tandem indicating patients with tandem lesions observed in at least one artery

Discussion

The main finding of this retrospective study was that revascularisation for symptomatic CAD patients guided by the combination of CCTA stenosis ≥ 50% and DL-FFRCT ≤ 0.8 was associated with a MACE rate (2.9%) similar to that when guided by ICA stenosis ≥ 75% (3.3%) in a 2-year follow-up investigation. In addition, the use of DL-FFRCT to determine a functionally significant lesion in comparison with ICA-guided anatomical indications could lead to a high cancellation rate (72%) of invasive diagnostic procedures. Thus, a reduction in overall clinical cost in CAD management could be expected, as demonstrated in the Prospective Longitudinal Trial of FFRCT: Outcomes and Resource Impacts (PLATFORM) study [18].

Our results showed that DL-FFRCT could potentially improve the efficiency of CCTA-guided decision-making for invasive inspection. Previous studies of CAD management screened by using CCTA have demonstrated a low event rate during the first year [17, 19, 20]. Our results showed a better predictive ability in finding non-ischaemic lesions in patients with the use of CCTA stenosis ≥ 50% in combination with DL-FFRCT ≤ 0.8 than the use of CCTA alone, and a similar MACE rate was observed compared to ICA-guided revascularisation within 1 and 2 years. This observation is consistent with the Assessing Diagnostic Value of Non-invasive FFRCT in Coronary Care (ADVANCE) trial, in which FFRCT was capable of better determining the appropriateness of invasive intervention and was associated with a low MACE rate [21].

In this study, the discordance between DL-FFRCT and ICA for classifying the functional and anatomical severity of a lesion aligns with the previous study of the PROspective Multicenter Imaging Study for Evaluation of Chest Pains (PROMISE) trial [22], although the cancellation rate of ICA was higher than that in previous studies [19, 23]. Two factors might contribute to this finding. First, the current study utilised a 320-detector row CT scanner for all symptomatic patients to obtain high-quality images. Hence, a more accurate DL-FFRCT calculation could be achieved based on more precise anatomic analysis [24, 25]. In comparison to earlier trials for FFRCT evaluation in which a minimum 64-detector row CT scanner was utilised, the accuracy of anatomic analysis might be reduced due to stair-step artefacts caused by a mismatch between cardiac cycles [26]. Second, our deep learning–based algorithm could have improved the accuracy of the FFRCT calculation. By learning the anatomic features extracted from CCTA to calculate the pressure gradient along the coronary artery tree, DL-FFRCT could provide a more objective and reproducible result [27]. In comparison, the accuracy of pressure distribution could be influenced by the parameter calibration due to the different number of outflow boundaries between cases and individual blood flow volume in the coronary artery tree when calculating CFD-based FFRCT. These results suggest an added value in potentially preventing unnecessary ICA by using a combination of high-performance CCTA with DL-FFRCT [24].

Table 4 Cumulative event counts during the period of 24 months

Events	DpFp (59)		DpFn (93)	
	Treatment (*n*, %)			
	Stented (48, 81.4%)	Not stented (11, 18.6%)	Stented (76, 81.7%)	Not stented (17, 18.3%)
HF, *n* (months)	1 (22)	1 (12)	0	0
MI, *n* (months)	0	1 (16)	0	0
Stroke, *n* (months)	1 (21)	0	2 (21, 24)	0
Revascularisation, *n* (months)	0	0	1 (17)	0

A total of 8 events was recorded namely 1 suicide, 2 deaths from heart failure, 1 death from myocardial infarction, 1 revascularization, and 3 cases of stroke

Treatment for tandem lesions is one of the major challenges in CAD management. Clinical studies have reported an underestimation of stenotic severity when using the invasive FFR procedure [1, 3, 28]. The increasing vessel resistance from distal stenosis could mask the true pressure gradient over proximal stenoses [3]. Consequently, the culprit lesion could be masked, especially for lesions with DL-FFRCT values within the grey zone of the FFR (0.75 to 0.8). In this study, 10.3% of the patients were diagnosed with tandem lesions based on ICA. There was no significant difference between the decision-making for intervention in tandem lesions based on the positive criteria of both ICA and DL-FFRCT, which contributed to a favourable outcome (i.e. 1 MACE within 2 years) (Fig. 2). This finding suggested that the application of DL-FFRCT in coronary intervention for tandem lesions is safe. With time efficiency advancement by using DL-FFRCT, the procedure time and overall medical cost for the evaluation of tandem lesions could be reduced.

Study limitations

Patients from daily practice were included in the present study in a retrospective, single-centre setting. Several limitations might have impacted the conclusion according to the results we obtained. First, the single-centre setting could have introduced a site bias. Therefore, the results of the present study may not be generalizable to other medical centres. Second, the sample size was small (n = 243) compared to that in previous clinical trials [29]. Additionally, the number of MACEs was relatively low. The statistical power of the categorical data could be insufficient to validate the outcome of DL-FFRCT. However, the 1-year event rate in our study was consistent with a global trial with a larger sample size. Third, the results of the present study cannot be applied to patients with left main CAD, bifurcation lesions, CTO, or acute MI [30]. Further studies are required to investigate the effectiveness and safety of DL-FFRCT in these cohorts. Finally, patients with CTA stenosis over 50% were referred for ICA, while those with stenosis less than 50% were not investigated in the present study. However, a previous study reported that 5 to 10% of lesions with a CCTA degree of stenosis between 30 and 50% presented with an FFR $\leq$ 0.8 [31]. Therefore, the performance of DL-FFRCT on patients with a CCTA degree of stenosis between 30 and 50% requires further study.

Conclusion

The 2-year outcomes analysed in the present study indicated that DL-FFRCT could serve as an alternative tool in guiding revascularisation, with a high cancellation rate of coronary intervention procedures and a low event rate. Importantly, a positive DL-FFRCT in guiding intervention for tandem lesions was associated with low MACEs within 2 years.

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Declarations

Guarantor The scientific guarantor of this publication is Changzheng Shi.

Conflict of interest The authors report no relationships that could be construed as a conflict of interest.

Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was obtained.

Ethical approval Institutional Review Board approved the present study.

Methodology
- retrospective
- observational
- performed at one institution

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