



# Diagnostic performance of coronary computed tomography angiography-derived fractional flow reverse in lesion-specific ischemia patients with different Gensini score levels

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**Background:** Coronary pressure-derived fractional flow reverse (FFR) is the standard of the functional assessment of lesion severity. In spite of its strengths in determining ischemia-related coronary stenosis, the invasive operation involved still limits its clinical application. Coronary computed tomography angiography-derived FFR (CCTA-FFR) or computed tomography-derived FFR (CT-FFR) has been indicated as an effective and non-invasive index to evaluate lesion-specific ischemia. However, its diagnostic performance, especially in patients with different severity of coronary stenosis, remains unknown. The current research attempted to demonstrate this problem and provided the foundation for extensive clinical application of CCTA-FFR.

**Methods:** The design of this study was a diagnostic test. A total of 97 vessels from 91 patients who performed CCTA and coronary angiography (CAG) during a hospitalization collected from two research centers were included in this study. CCTA-FFR and FFR were obtained by CCTA and CAG separately. The Gensini score was calculated according to the CAG in each patient. FFR was indicated as the golden diagnosis of lesion-specific ischemia with a cut-off value of 0.80, which was consistent with most contemporary studies. A receiver-operating characteristic (ROC) curve, simple linear analysis, and Bland-Altman plot were performed to determine the diagnostic performance of CCTA-FFR.

**Results:** CCTA-FFR was well correlated with invasive FFR ( $R^2=0.745$ ,  $P<0.001$ ) and the area under the curve (AUC) was 0.976. The sensitivity was 94.6% and the specificity was 95.1%. The mean difference between FFR and CT-FFR was 0.011, and the 95% confidence interval was -0.173 to 0.196. The AUCs were 0.989 and 0.928 in the low and high Gensini groups, respectively, and there was no significant difference in the diagnostic accuracies between these two groups ( $Z=0.003$ ,  $P>0.500$ ). CT-FFR still exhibited a good correlation with FFR ( $R^2=0.713$ ,  $P<0.001$  in the low Gensini group and  $R^2=0.743$ ,  $P<0.001$  in the high Gensini group). The systematic differences were calculated, and the mean difference between FFR and CT-FFR was -0.005 and 0.025, respectively, in these two groups.

**Conclusions:** CCTA-FFR exhibited good diagnostic performance in patients with different Gensini score levels. Our results indicate that CCTA-FFR could be an effective tool to screen lesion-specific ischemia in patients with coronary artery disease.

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**Keywords:** Fractional flow reverse (FFR); coronary computed tomography angiography (CCTA); coronary artery disease; Gensini score

Submitted Jan 25, 2022. Accepted for publication Mar 07, 2022.

doi: 10.21037/atm-22-881

**View this article at:** <https://dx.doi.org/10.21037/atm-22-881>

## Introduction

Coronary heart disease (CHD) caused by atherosclerosis is a leading cause of morbidity and mortality worldwide (1). Coronary angiography (CAG) is still the gold standard for the identification of obstructive CHD (2). However, more than one-third of patients with suspected CHD are reported as no CHD (defined as <20% stenosis in all vessels) using CAG (3). Therefore, a more precise assessment system should be explored in order to determine a more effective risk stratification of patients and enhance the yield of diagnostic CAG.

CAG can not only reveal the angiographic degree of coronary stenosis, but can also demonstrate the relevant ischemia by means of intracoronary pressure wire assessment, typically measuring fractional flow reverse (FFR), which defines the ratio of the mean coronary artery pressure distal to the stenosis and the mean pressure in the aorta (4). At present, coronary pressure-derived FFR is the standard of the functional assessment of lesion severity, especially in patients with intermediate-grade stenosis, those without evidence of ischemia in non-invasive testing, or in those with multi-vessel disease, and has been recommended by guidelines (5). In spite of its strengths in determining ischemia-related coronary stenosis, the invasive operation involved still limits its clinical application.

Recently, increasing evidence has indicated that coronary computed tomography angiography (CCTA) and CCTA-derived FFR or computed tomography-derived FFR (CT-FFR) were effective tools to evaluate lesion-specific ischemia (5). However, the data for both remains limited. Di Jiang *et al.* have reported that coronary calcification did not affect diagnostic performance of CT-FFR (6). Michail and his colleagues also found that CT-FFR was feasible and valid in patients with severe aortic stenosis (7). Another study also affirmed its good diagnostic performance of CT-FFR in patients with or without diabetes mellitus (8). Therefore, the diagnostic performance of CT-FFR in patients with different severities of coronary stenosis has not been reported, which restricted its clinical use to a

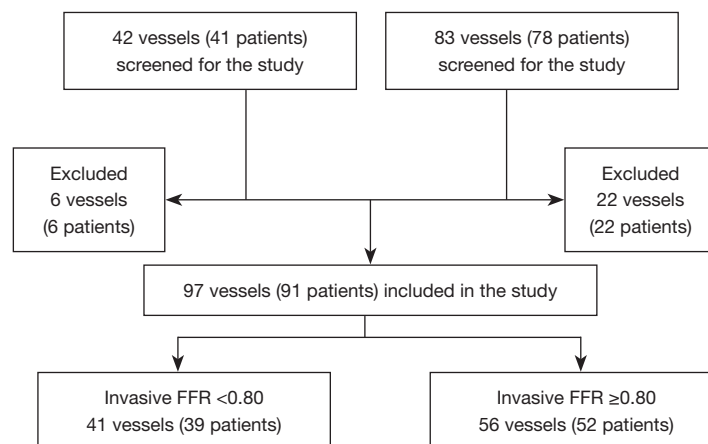
certain extent. The present study aims to investigate the diagnostic performance of CCTA-derived FFR, and explore whether it is consistent in patients with different severities of coronary stenosis. The current research attempted to provide the foundation for extensive clinical application of CCTA-FFR. We present the following article in accordance with the STARD reporting checklist (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-881/rc>).

## Methods

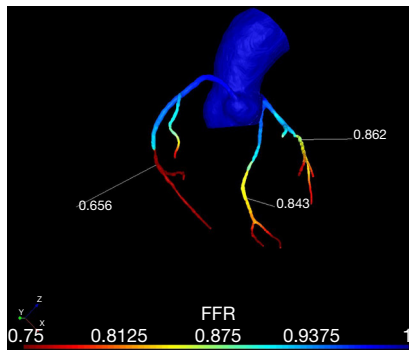
### *Study population*

A protocol was prepared before the study with registration (ID: ChiCTR1900026971). The design of the present study was a diagnostic test. From December 2019 to April 2021, a total of 36 vessels from 35 patients diagnosed by selective CAG participated in this study at the Cardiology Department of Shaanxi Provincial People's Hospital. Furthermore, 61 vessels from 56 patients obtained from West China Hospital of Sichuan University between July 2020 and April 2021 were also included. The inclusion criteria were as follows: (I) patients aged between 18 and 80; (II) patients who were able to understand the purpose of the study and signed the informed consent voluntarily; (III) patients who were suspected of having coronary artery stenosis and planned to have selective CAG; (IV) patients who underwent coronary computed tomography angiography (CTA) using CT scanners with  $\geq 64$ -row detectors; (V) clear and readable coronary CTA images; (VI) cases in which the degree of coronary artery stenosis was probably between 30% and 90% through coronary CTA; and (VII) the diameter of target vessel was greater than 2 mm through coronary CTA.

The exclusion criteria were as follows: (I) women who were pregnant, breastfeeding, or planning pregnancy; (II) patients with a history of myocardial infarction in the last 30 days prior to coronary CTA; (III) those who had previously undergone coronary artery bypass surgery or stenting, or had installed pacemakers, implantable



**Figure 1** Cohort selection flow diagram. FFR, fractional flow reverse.



**Figure 2** Schematic representation of the CT-FFR analysis. CT-FFR, computed tomography-derived fractional flow reverse.

cardioverter defibrillators, or artificial heart valves; (IV) patients with a history of allergies to contrast media; (V) those with hypertrophic obstructive cardiomyopathy or severe heart failure [New York Heart Association (NYHA)  $\geq$  III]; (VI) body mass index  $>35$  kg/m<sup>2</sup>; (VII) serum creatinine  $>178$   $\mu$ mol/L; (VIII) cases of non-diagnostic quality of CTA data; (IX) cases of chronic total occlusion; (X) cases of aneurysm or myocardial bridge involvement; (XI) an unqualified pressure curve for FFR analysis; and (XII) other circumstances that were not suitable for participating in the experiment.

The flowchart of the analysis is presented in *Figure 1*. This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China (No. 2019X005) and West China Hospital, Chengdu, Sichuan, China (No. 20202). Written informed consent was

obtained from all study participants.

### Data collection

The collected data included patients' demographics, medical history, vital signs, and results of laboratory testing at admission. Body mass index was calculated by dividing weight in kilograms by the square of height in meters. The CTA and CAG procedures, and the obtainment of CT-FFR and FFR have been published previously (9). Briefly, CT-FFR measurement was computed using a commercial software program (CAscope, EScope Ltd.), which adopted a deep learning method for vessel model creation from CCTA images. The patients' brachial artery diastolic (mmHg) and systolic (mmHg) blood pressure, as well as heart rate (bpm) measured before CCTA were used as inputs for CT-FFR calculation. The representative analysis of CT-FFR is illustrated in *Figure 2*. The vessel characteristics were also acquired during CAG. The Gensini score was calculated as described in the literature (10).

### Statistical analysis

Continuous variables were presented as the mean  $\pm$  standard deviation (SD) or median [lower quartile, upper quartile]. The Kolmogorov-Smirnov test was used to assess the normality of continuous variables distribution. Categorical variables were presented as frequencies (percentages). FFR was indicated as the golden diagnosis of lesion-specific ischemia with a cut-off value of 0.80, which was consistent with most contemporary studies. The diagnostic performance of CT-FFR was determined using the receiver-

**Table 1** Baseline patient characteristics (n=91)

Characteristics	Values
Male, %	59 (64.8)
Age, years	62.95±9.35
Body mass index, kg/m <sup>2</sup>	24.75±3.05
Heart rate, bpm	71 [64, 82]
Systolic blood pressure, mmHg	126 [118, 138]
Diastolic blood pressure, mmHg	78.14±11.05
Past medical history	
Diabetes mellitus, %	22 (24.2)
Hypertension, %	45 (49.5)
Hyperlipidemia, %	22 (24.2)
Peripheral vascular disease, %	8 (8.8)
Stroke, %	8 (8.8)
Smoking, %	19 (20.9)
Laboratory test	
White blood cell, 10 <sup>9</sup> /L	6.13 [5.43, 7.08]
Red blood cell, 10 <sup>12</sup> /L	4.31 [4.08, 4.85]
Platelet, 10 <sup>9</sup> /L	192.85±65.14
Hemoglobin, g/L	136.05±16.64
Serum creatinine, μmol/L	73.87±17.99
Blood urea nitrogen, mmol/L	5.72±1.49
Alanine aminotransferase, U/L	21 [13, 29]
Aspartate aminotransferase, U/L	22 [18, 27]

operating characteristic (ROC) curve. It was acceptable that if the area under the curve (AUC) was more than 0.70. Sensitivity and specificity of CT-FFR were also calculated. Simple linear analysis was performed by calculating the correlation between CT-FFR and FFR. The systematic difference between CT-FFR and FFR was represented using a Bland-Altman plot. As for the diagnostic performance on a per patient basis, the lowest values of FFR and CT-FFR were used in patients rather than one vessel (7). The Z test was performed to compare the diagnostic performance of CT-FFR in patients with low and high Gensini scores.

**Table 2** Vessel characteristics (n=97 vessels from 91 patients)

Characteristics	No. (%)
Target vessel	
Left anterior descending coronary artery	65 (67.0)
Right coronary artery	23 (23.7)
Left coronary circumflexus artery	7 (7.2)
Left main coronary artery	2 (2.1)
Plaque	
Combined plaque	49 (50.5)
Non-calcified plaque	33 (34.0)
Calcified plaque	15 (15.5)
Severity	
30–49%	29 (29.9)
50–69%	45 (46.4)
70–90%	23 (23.7)

## Results

### *Clinical and vessel characteristics of the study population*

A total of 91 patients were included in this analysis. Patient characteristics are presented in *Table 1*; 64.8% were males and the mean age was 63 years. Physical examinations, past medical history, and laboratory tests are also shown in the *Table 1*. A total of 97 vessels were analyzed in our study, and the vessel characteristics are listed in the *Table 2*. As for the target vessel, approximately two-thirds of the vessels were left anterior descending coronary arteries, and a quarter was right coronary arteries. More than half of the plaque was combined plaque. As for severity, nearly half of the vessels had 50–69% stenosis, and 30–49% and 70–90% stenosis also accounted for a certain percentage (29% and 23% separately).

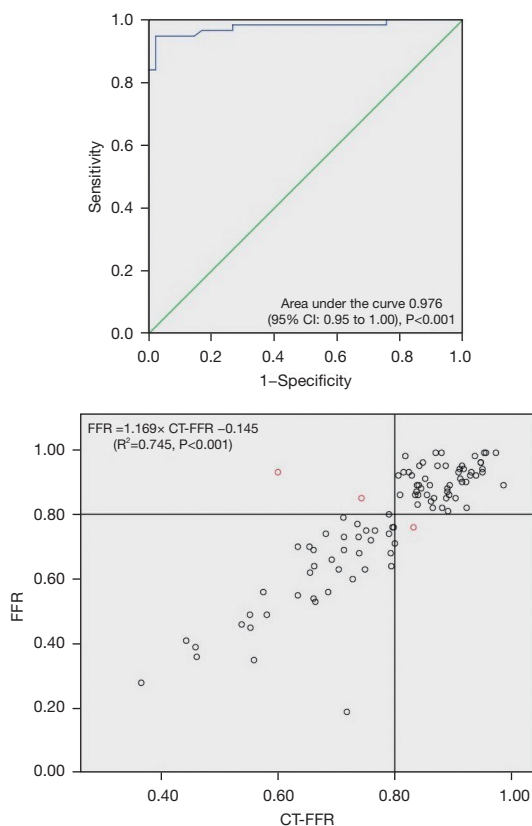
### *Diagnostic accuracy of CT-FFR compared with FFR*

Consistent with most contemporary studies, we used an FFR cut-off of 0.80, and the following analysis was performed at the per-vessel level (5). *Table 3* shows CT-FFR in relation to FFR and the sensitivity was 94.6% and

**Table 3** The relationship between CT-FFR and FFR in diagnosis of coronary ischemia

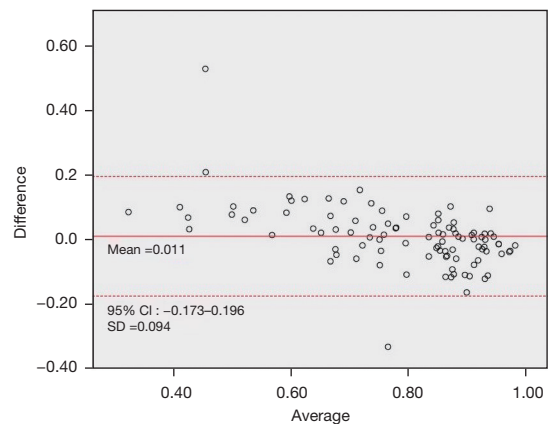
CT-FFR	FFR		Total
	Positive	Negative	
Positive	53	2	55
Negative	3	39	42
Total	56	41	97

CT-FFR, computed tomography-derived fractional flow reverse.  
FFR, fractional flow reverse.



**Figure 3** Diagnostic accuracy of resting CT-FFR versus FFR. Black circle means that the test result of CT-FFR is consistent with that of FFR; red circles means that they are inconsistent. CT-FFR, computed tomography-derived fractional flow reverse.

the specificity was 95.1%. As shown in *Figure 3*, CT-FFR was well correlated with invasive FFR ( $R^2=0.745$ ,  $P<0.001$ ) and the AUC was 0.976. Further analysis of the systematic difference was performed, which indicated that the mean difference between FFR and CT-FFR was 0.011, and the 95% confidence interval was  $-0.173$  to  $0.196$  (*Figure 4*).



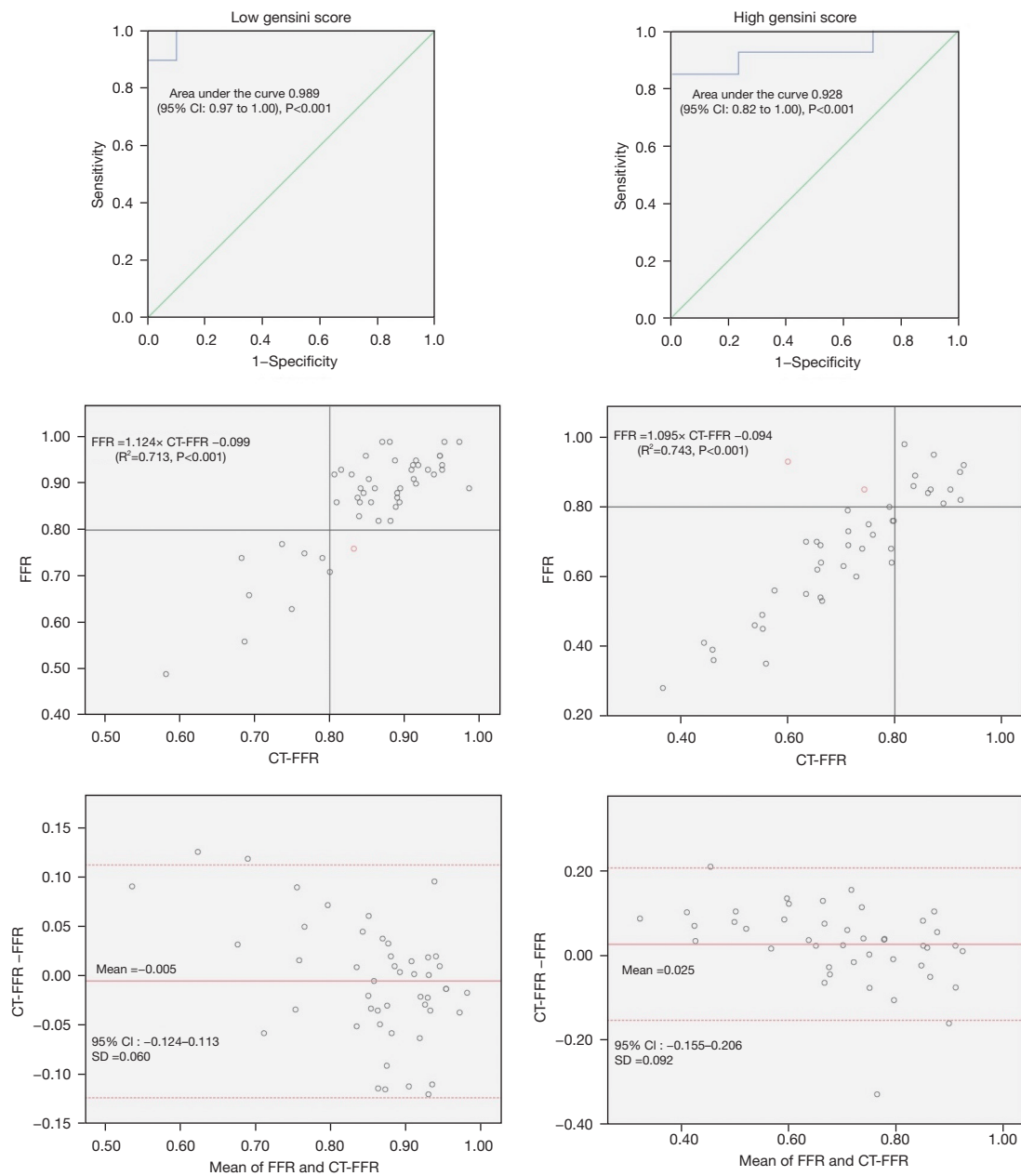
**Figure 4** Bland-Altman plot of CT-FFR and invasive FFR on a per-vessel basis. CT-FFR, computed tomography-derived fractional flow reverse.

### *Diagnostic performance of CT-FFR in different degrees of coronary stenosis*

We utilized the Gensini score as an evaluation method of the severity of coronary stenosis. According to the median scores, all participants were divided into a low Gensini group (Gensini score: 1.5–21,  $n=48$ ) and a high Gensini group (Gensini score: 21.5–99.5,  $n=43$ ). Subsequent analysis was performed at the per-patient level and the results are shown in *Figure 5*. Firstly, the AUCs were 0.989 and 0.928 in low and high Gensini groups, respectively. However, there was no significant difference in the diagnostic accuracies between these two groups ( $Z=0.003$ ,  $P>0.500$ ). Secondly, CT-FFR still exhibited a good correlation with FFR ( $R^2=0.713$ ,  $P<0.001$  in the low Gensini group and  $R^2=0.743$ ,  $P<0.001$  in the high Gensini group). Thirdly, the systematic differences were calculated, and the mean difference between FFR and CT-FFR was  $-0.005$  and  $0.025$ , respectively, in these two groups.

### Discussion

Although CT-FFR has been indicated as an effective index to assess lesion-specific ischemia, relevant research remains limited at present. Our current study focused on the diagnostic performance of CT-FFR and found that CT-FFR had a good diagnostic accuracy compared with FFR, which was maintained in the subgroup analysis of different degrees of coronary stenosis. To the best of our knowledge, our study is the first analysis of the diagnostic performance of CT-FFR in patients with different Gensini score levels.



**Figure 5** Diagnostic accuracy of resting CT-FFR versus FFR and Bland-Altman plot of CT-FFR and invasive FFR on a per-vessel basis in (left-hand) low and (right-hand) high Gensini score subgroups separately. Black circle means that the test result of CT-FFR is consistent with that of FFR; red circles means that they are inconsistent. CT-FFR, computed tomography-derived fractional flow reverse.

DISCOVER-FLOW is the first multi-center clinical trial to evaluate the diagnostic value of CT-FFR. It included 103 patients suspected with complete CHD, and the results showed that the diagnostic performance of CT-FFR in coronary stenosis was better than CCTA, especially in terms of specificity (CT-FFR: 82.2% *vs.* CCTA: 39.6%).

Furthermore, there was a strong correlation between CT-FFR and invasive FFR ( $r=0.678$ ,  $P<0.001$ ), which indicated that CCTA-derived non-invasive FFR was an effective method with high diagnostic performance for the detection and exclusion of ischemia-causing coronary lesions (11). Multiple subsequent studies also confirmed

similar conclusions. Several studies have shown that CT-FFR is a useful method to recognize hemodynamically-significant CHD (12-16). Rasoul *et al.* also suggested that CT-FFR could preliminarily screen patients for CAG (17-19). Other researchers also reported that CT-FFR improved the diagnostic performance of CTA (20-26). In the current study, we also showed (using a ROC curve) that CT-FFR was an excellent tool to evaluate ischemia-causing coronary stenosis compared with invasive FFR. In addition, we observed a good correlation between non-invasive CT-FFR and invasive FFR through simple linear analysis and the Bland-Altman plot. These results were consistent with previous research.

Recent studies have increasingly been paying attention to the diagnostic value of CT-FFR in different kinds of coronary stenosis (7,27). The aim of the DeFACTO study was to focus on the diagnostic performance of CT-FFR for lesions of intermediate stenosis severity and draw a consistent conclusion. Nevertheless, the researchers suggested that CT-FFR might serve as an excluded index for ischemia due to its high sensitivity and negative predictive value (27). However, the severity of CHD is amazingly varied, regardless of whether it is measured at the per-vessel or per-patient levels, and whether the diagnostic performance of CT-FFR is still high in different degrees of coronary stenosis has not been reported. In our present study, we calculated the Gensini score for each patient according to CAG and divided them into two groups on the basis of the median Gensini score. Statistical analyses were performed in the low and high Gensini groups, respectively, and the results revealed that CT-FFR showed eminent diagnostic performance in both the low and high Gensini score groups, and there was no statistical difference between them.

The current study has several limitations that should be noted. Firstly, the sample size was relatively small, and thus, the results still need to be confirmed in a larger sample size study. Secondly, the Gensini score was the only metric used to evaluate the severity of coronary stenosis. Subsequent studies could determine the diagnostic performance of CT-FFR in varied severity of CHD according to other scoring systems, such as the Syntax score. Thirdly, we only investigated the diagnostic performance of CT-FFR in different levels of CHD. Long-term follow-up could determine the prognostic value of CT-FFR in CHD and guide clinical decision-making.

In conclusion, CT-FFR showed good prognostic performance in patients with different Gensini score levels. CT-FFR is an excellent non-invasive index to evaluate

coronary ischemia, regardless of the severity of stenosis.

## Acknowledgments

*Funding:* None.

## Footnote

*Reporting Checklist:* The authors have completed the STARD reporting checklist. Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-881/rc>

*Data Sharing Statement:* Available at <https://atm.amegroups.com/article/view/10.21037/atm-22-881/dss>

*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <https://atm.amegroups.com/article/view/10.21037/atm-22-881/coif>). QZ and YL report that they are from Beijing Escape Tech Co., Ltd. The other 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. This study complied with the Declaration of Helsinki (as revised in 2013) and was approved by the Ethics Committee of the Shaanxi Provincial People's Hospital, Xi'an, Shaanxi, China (No. 2019X005) and West China Hospital, Chengdu, Sichuan, China (No. 20202). Written informed consent was obtained from all study participants.

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- (English Language Editor: A. Kassem)

**Cite this article as:** Dong M, Li C, Yang G, Gou Q, Zhao Q, Liu Y, Shou X. Diagnostic performance of coronary computed tomography angiography-derived fractional flow reverse in lesion-specific ischemia patients with different Gensini score levels. *Ann Transl Med* 2022;10(7):412. doi: 10.21037/atm-22-881