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# Exploring the Predictors of the Discrepancy Between Quantitative Flow Ratio and Fractional Flow Reserve Measurements

## ABSTRACT

**Background:** Quantitative flow ratio is a novel technology for the functional assessment of intermediate coronary stenoses. The authors sought to explore the influence of diabetes mellitus on the application of quantitative flow ratio and predictors of discrepancies between quantitative flow ratio and fractional flow reserve.

**Methods:** Quantitative flow ratio was calculated in 224 patients (317 vessels) who underwent fractional flow reserve measurement by professional technicians blinded to fractional flow reserve value. Patients were divided into the diabetes mellitus group and the non-diabetes mellitus group. The diagnostic performance of quantitative flow ratio was assessed using fractional flow reserve as a reference.

**Results:** Good correlation and agreement between quantitative flow ratio and fractional flow reserve can be found in the diabetes mellitus group ($r = 0.834$, $P < .001$; mean difference: 0.007 ± 0.108). Prior myocardial infarction showed a statistically significant association with increased classification discrepancy between quantitative flow ratio and fractional flow reserve [odds ratio 3.16 (95% confidence interval: 1.29-7.75), $P = .01$]. The area under the receiver-operating characteristic curve of quantitative flow ratio showed no significant difference in diabetes mellitus and non-diabetes mellitus groups, hemoglobin A1c ≥ 7% and hemoglobin A1c < 7% groups, diabetic duration ≥ 10 years and diabetic duration < 10 years groups (area under receiver-operating characteristic curve: 0.90 (95% confidence interval: 0.84-0.94) vs. 0.92 (95% confidence interval: 0.87-0.96), $P = .54$; 0.89 (95% confidence interval: 0.81-0.95) vs. 0.92 (95% confidence interval: 0.81-0.97), $P = .65$; 0.88 (95% confidence interval: 0.79-0.94) vs. 0.89 (95% confidence interval: 0.79-0.96), $P = .83$; respectively).

**Conclusions:** Clinical application of quantitative flow ratio is not limited to diabetic patients. The relationship between prior myocardial infarction and quantitative flow ratio needs to be further developed.

**Keywords:** Quantitative flow ratio, fractional flow reserve, diabetes mellitus, prior myocardial infarction

ORIGINAL INVESTIGATION

## INTRODUCTION

Coronary pressure-derived fractional flow reserve (FFR) has been widely used in patients with angiographically intermediate stenoses for functional assessment of lesion severity.[1] The FFR-guided percutaneous coronary intervention can reduce unnecessary revascularizations and improve patients' long-term outcomes.[1-4] Nowadays, a novel technology named quantitative flow ratio (QFR) for functional assessment of intermediate coronary stenoses has emerged.[5,6] Recent studies have verified good correlation and agreement between quantitative flow ratio and FFR.[7,8] The advantages of this technology anticipate its clinical applicability, such as wire-free operation, without pharmacologically induced hyperemia, lower median time to QFR computation than FFR, and so on.[8-10] However, scholars have demonstrated that coronary microcirculation dysfunction (CMD) significantly decreased the diagnostic performance of QFR.[11] A lower accuracy of QFR in the diffuse coronary artery disease group compared with those in the focal coronary artery disease group was found.[12] As we all know, patients with diabetes mellitus (DM) have an increased risk of developing CMD and diffuse disease.



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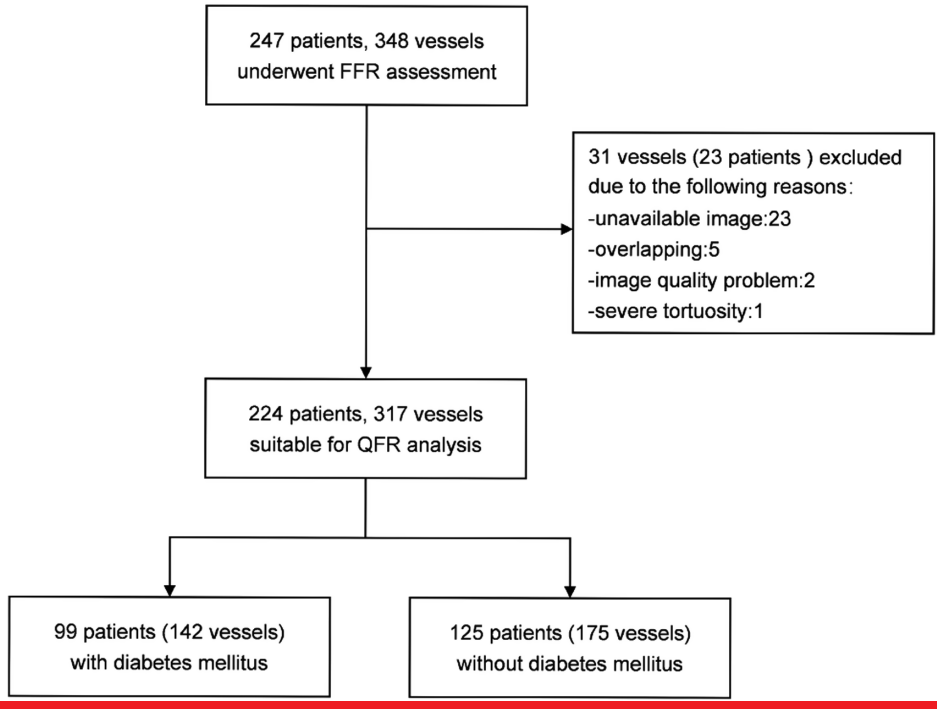


**Figure 1. Study flowchart. FFR, fractional flow reserve; QFR, quantitative flow ratio.**

Poor glycemic control in patients with DM is associated with coronary microangiopathy and appears to influence myocardial blood flow reserve.[13,14] Meanwhile, the risk of microvascular complications and coronary heart disease rises as diabetic duration (DD) increases.[15,16] Hence, the purpose of this study is to estimate the influence of DM, poor glycemic control, and increasing DD on the diagnostic performance of QFR and explore the predictors of discrepancies between QFR and FFR driven by the presence of CMD.

## METHODS

### Study Design

This was a retrospective, single-center, and observational study. This study has been approved by the Medical Ethics Committee. The study protocol was in accordance with the Declaration of Helsinki. Patients who underwent FFR measurement from January 2018 to January 2020 were selected in this study. The exclusion criteria were no availability of the raw image, severe overlap or tortuosity of the target vessel, and poor angiographic image quality. All target vessels assessed with FFR were evaluated with QFR offline by professional technicians blinded to FFR value.

To evaluate the impact of DM on the diagnostic performance of QFR, patients were classified into 2 groups: the DM group and the non-DM group (Figure 1). The American Diabetes Association has declared that hemoglobin A1c (HbA1c) level test is the primary tool for assessing glycemic control.[17] Multiple trials have suggested that patients with HbA1c $\geq$ 7% or DD $\geq$ 10 years were associated with a high risk of microvascular complications.[16,18,19] Therefore, patients with DM were further grouped according to HbA1c level and DD: (i) HbA1c $\geq$ 7% group and HbA1c < 7% group; (ii) DD $\geq$ 10 years group and DD < 10 years group.

Clinical data were retrospectively analyzed. The diagnosis of DM was based on plasma glucose criteria, either the fasting plasma glucose value or the 2-hour plasma glucose value during a 75-g oral glucose tolerance test or HbA1c criteria according to American Diabetes Association.[20] HbA1c level was tested during hospitalization and DD was recorded in the medical history in the patients' electronic cases. In the analysis of baseline clinical characteristics, chronic kidney disease was defined as patients with glomerular filtration rate < 60 mL/min. There were no patients with heart failure with preserved ejection fraction in our subjects. Heart failure was determined by symptoms, physical signs and the result of echocardiography (left ventricular ejection fraction <50%). Left ventricular ejection fraction was determined during hospitalization.

Fractional flow reserve was performed according to the severity of coronary artery stenosis mentioned previously.[2,3] The FFR value was obtained by using a pressure wire

## HIGHLIGHTS

- Good correlation and agreement between quantitative flow ratio (QFR) and fractional flow reserve (FFR) were found in both the diabetes mellitus group and the non-diabetes mellitus group.
- The independent predictor of the classification discrepancy between QFR and FFR was prior myocardial infarction.
- The diagnostic performance of QFR is not affected by diabetes mellitus, poor glycemic control, and increasing diabetic duration.

(Certus wire, St. Jude Medical, St. Paul, Minn, USA) during maximal hyperemia and was defined as the ratio of coronary pressure distal to the coronary lesion to the aortic pressure. Maximum hyperemia was induced in all cases by intravenous adenosine triphosphate infusion at the concentration of 140 μg/kg/min. Quantitative flow ratio analysis was performed by using AngioPlus (Angioplus galley, Pulse, China, Figure 2). The QFR computation parameters include QFR value, diameter stenosis, area stenosis, lesion length, and minimal lumen diameter.

### Statistical Analysis

Continuous variables were expressed as mean ± SD or median with interquartile range and were respectively compared with the independent sample Student's *t*-test and Mann–Whitney *U*-test. Normality in the distribution was verified by the Kolmogorov–Smirnov test. Categorical variables were expressed as numbers and percentages, compared with the Student's *t*-test chi-square or Fisher exact test as appropriate. The correlation and agreement between QFR and FFR were, respectively, assessed by the Pearson correlation coefficient and Bland–Altman plot. Both QFR and FFR values were classified by the threshold ≤ 0.80 and classification discrepancy was obtained. Independent predictors of classification discrepancy between QFR and FFR were identified by performing a logistic regression analysis. The diagnostic performance of QFR was compared with the area under the receiver-operating characteristic curves (AUC), which was obtained by the DeLong method. Classification agreement, sensitivity, specificity, positive predictive value, negative predictive value, positive likelihood ratio, and negative likelihood ratio of QFR were calculated and added the 95% confidence intervals (CIs). Statistical Package for the Social Sciences 26.0 (IBM Inc., Armonk, NY, USA) and MedCalc 19.5.6 (MedCalc Software, Ostend, Belgium) were used for statistical analysis. A *P*-value < .05 was considered statistically significant.

## RESULTS

A total of 247 patients (348 vessels) underwent FFR assessment from January 2018 to January 2020. Twenty-three (9%) patients (31 (9%) vessels) were excluded due to unavailable image (vessel number (n) = 23), overlapping (n = 5), image quality problem (n = 2), and severe tortuosity (n = 1). A total of 224 (91%) patients (317 (91%) vessels) were finally enrolled. Ninety-nine (44%) patients (142 (45%) vessels) were in the DM group (all type 2 DM) and 125 (56%) patients (175 (55%) vessels) were in the non-DM group; 63 (64%) patients (87 (61%) vessels) were in HbA1c ≥ 7% group and 36 (36%) patients (55 (39%) vessels) were in HbA1c < 7% group; 58 (59%) patients (81 (57%) vessels) were in DD ≥ 10 years group and 41 (41%) patients (61 (43%) vessels) were in DD < 10 years group (Tables 1 and 2).

The mean age was 65.1 ± 9.2 years (62% men). A total of 180 (57%) vessels were left anterior descending arteries. Body mass index, dyslipidemia, triglyceride, and high-density lipoprotein cholesterol were significantly different between the DM group and the non-DM group. No significant differences were found between groups with or without DM regarding vessel characteristics (Tables 1 and 2).

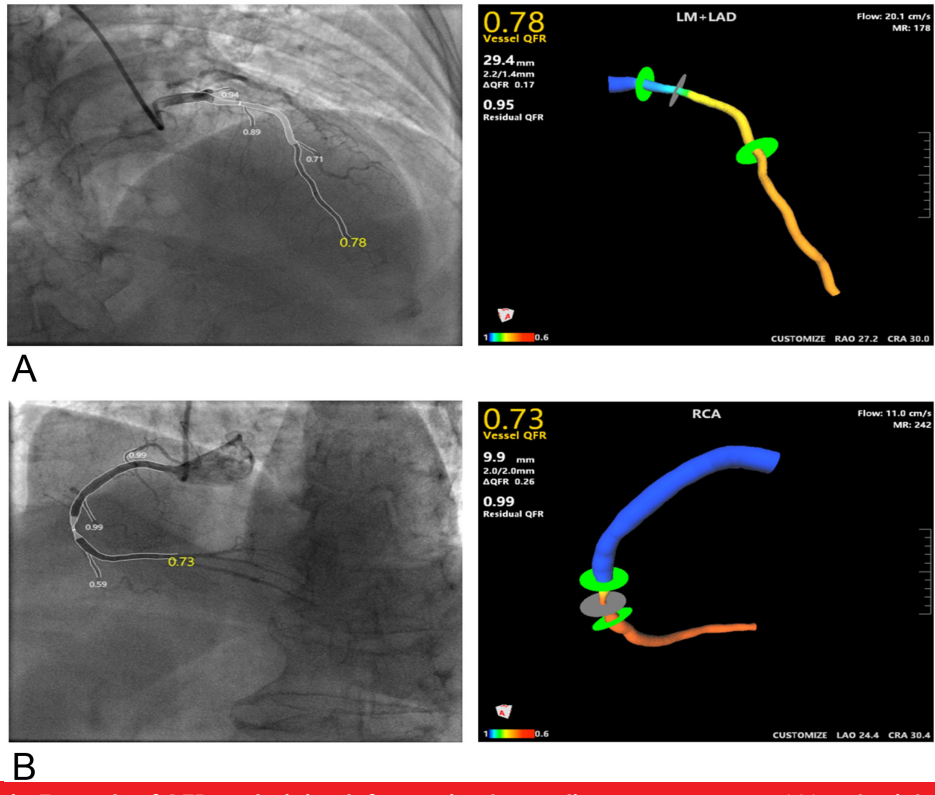


**Figure 2. QFR analysis. Example of QFR analysis in a left anterior descending coronary artery (A) and a right coronary artery (B). QFR, quantitative flow ratio.**

**Table 1. Baseline Clinical Characteristics**

| Variables | Total (n = 224) | DM Group (n = 99) | Non-DM Group (n = 125) | *P* |
|---|---|---|---|---|
| Age (years) | 65.1 ± 9.2 | 65.1 ± 8.9 | 65.1 ± 9.4 | .73 |
| Male | 138 (62) | 63 (64) | 75 (60) | .58 |
| BMI (kg/m$^2$) | 25.9 ± 2.9 | 26.41 ± 2.8 | 25.50 ± 3.0 | .02 |
| Hypertension | 167 (75) | 80 (81) | 87 (70) | .06 |
| Dyslipidemia | 127 (57) | 65 (66) | 62 (50) | .02 |
| HbA1c ≥ 7% | 63 (28) | 63 (64) | - | - |
| DD ≥ 10 years | 58 (26) | 58 (59) | - | - |
| CHOL (mmol/L) | 3.78 (3.32-4.61) | 3.75 (3.30-4.55) | 3.83 (3.42-4.78) | .28 |
| TG (mmol/L) | 1.32 (0.97-1.82) | 1.61 (1.00-2.18) | 1.20 (0.95-1.68) | .01 |
| HDL-C (mmol/L) | 1.07 (0.91-1.23) | 1.00 (0.87-1.16) | 1.14 (0.93-1.29) | .01 |
| LDL-C (mmol/L) | 2.08 (1.74-2.68) | 2.05 (1.67-2.65) | 2.11 (1.79-2.72) | .36 |
| Smoking (current or past) | 109 (49) | 50 (51) | 59 (47) | .62 |
| Chronic kidney disease | 12 (5) | 5 (5) | 7 (6) | .82 |
| Family history of CAD | 60 (27) | 26 (26) | 34 (27) | .88 |
| Prior PCI | 39 (17) | 21 (21) | 18 (14) | .18 |
| Prior myocardial infarction | 15 (7) | 7 (7) | 8 (6) | .84 |
| Prior CABG | 0 (0) | 0 (0) | 1 (1) | .37 |
| Heart failure | 6 (3) | 1 (1) | 5 (4) | .16 |

Data presented as n (%), mean ± SD or median (interquartile range). *P* value for comparison between groups. Significance level was .05. BMI, body mass index; CABG, coronary artery bypass surgery; CAD, coronary artery disease; CHOL, cholesterol; DD, diabetic duration; DM, diabetes mellitus; HbA1c, hemoglobin A1c; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; PCI, percutaneous coronary interventions; TG, triglyceride.

**Table 2. Baseline Vessel and Procedural Characteristics**

| Variables | Total (n = 317) | DM Group (n = 142) | Non-DM Group (n = 175) | *P* |
|---|---|---|---|---|
| HbA1c ≥ 7% | 87 (27) | 87 (61) | - | - |
| DD ≥ 10 years | 81 (26) | 81 (57) | - | - |
| Left anterior descending | 180 (57) | 75 (53) | 105 (60) | .20 |
| Left circumflex | 48 (15) | 21 (15) | 27 (15) | .87 |
| Right coronary artery | 58 (18) | 29 (20) | 29 (17) | .38 |
| Coronary side branch | 31 (10) | 17 (12) | 14 (8) | .24 |
| QFR | 0.82 ± 0.09 | 0.82 ± 0.10 | 0.82 ± 0.09 | .42 |
| QFR ≤ 0.8 | 115 (36) | 48 (34) | 67 (38) | .41 |
| FFR | 0.82 ± 0.09 | 0.81 ± 0.09 | 0.82 ± 0.08 | .11 |
| FFR ≤ 0.8 | 121 (38) | 56 (39) | 65 (37) | .68 |
| Diameter stenosis (%) | 45 ± 9 | 44 ± 9 | 45 ± 10 | .58 |
| Area stenosis (%) | 68 ± 10 | 68 ± 10 | 68 ± 11 | .71 |
| Lesion length (mm) | 26.4 (16.4-39.2) | 26.0 (16.1-38.3) | 26.4 (16.9-39.9) | .64 |
| Minimal lumen diameter (mm) | 1.4 (1.1-1.7) | 1.4 (1.1-1.6) | 1.5 (1.2-1.7) | .11 |

Data presented as n (%), mean ± SD or median (interquartile range). *P*-value for comparison between groups. Significance level was .05.DD, diabetic duration; DM, diabetes mellitus; FFR, fractional flow reserve; HbA1c, hemoglobin A1c; QFR, quantitative flow ratio.

Mean QFR and FFR were 0.82 ± 0.09 and 0.82 ± 0.09, respectively, and showed no significant difference in the DM group and the non-DM group (QFR in DM and non-DM groups: 0.82 ± 0.10 vs. 0.82 ± 0.09, $P = .42$; FFR in DM and non-DM groups: 0.81 ± 0.09 vs. 0.82 ± 0.08, $P = .11$). Both QFR and FFR values were classified by the threshold ≤ 0.80, and their proportions showed no difference in the DM group and the non-DM group (QFR ≤ 0.80: 34% vs. 38%, $P = .41$; FFR ≤ 0.80: 39% vs. 37%, $P = .68$). Good correlation and agreement between QFR and FFR were found in both groups (DM group: $r = 0.834$, $P < .001$; mean difference: 0.007 ± 0.108; non-DM group: $r = 0.835$, $P < 0.001$; mean difference: 0.005 ± 0.102; Figure 3). Univariable and multivariable analyses of independent predictors in classification discrepancy between QFR and FFR (using the cutoff ≤ 0.80) were performed and presented in Figure 4. Prior myocardial infarction (MI) rather than DM showed a statistically significant association with increased classification discrepancy between QFR and FFR (odds ratio (OR) 3.16 (95% CI: 1.29-7.75), $P = .01$).

The AUCs were not significantly different between DM and non-DM groups, HbA1c ≥ 7% and < 7% groups, DD ≥ 10 years and < 10 years groups (AUC: DM group vs. non-DM group: 0.90 (95% CI 0.84-0.94) vs. 0.92 (95% CI 0.87-0.96), $P = .54$; HbA1c ≥ 7% group vs. HbA1c < 7% group: 0.89 (95% CI 0.81-0.95) vs. 0.92 (95% CI 0.81-0.97), $P = .65$; DD ≥ 10 years group vs. DD < 10 years group: 0.88 (95% CI 0.79-0.94) vs. 0.89 (95% CI 0.79-0.96), $P = .83$; respectively, Figure 5). The classification agreement, sensitivity, and specificity of QFR in DM group were 82%, 70%, and 90%, respectively (Table 3).

## DISCUSSION

We retrospectively studied the influence of DM on the diagnostic performance of QFR and explored the predictors of discrepancies between QFR and FFR. The following results were found: (i) the distribution of QFR value showed no difference in DM and non-DM groups; (ii) there were a good correlation and agreement between QFR and FFR in the DM group; (iii) the classification discrepancy between QFR and FFR was affected by prior MI rather than DM; (iv) DM, poor glycemic control, and increasing DD did not decrease the diagnostic performance of QFR.

The FFR has been generally used for the functional evaluation of coronary stenosis for decades. A value of FFR ≤ 0.8 is taken as the cutoff value to identify functionally significant stenosis, which indicates the potential of stenosis to induce myocardial ischemia. Despite that, its adoption in clinical practice remains limited, probably due to the requirements

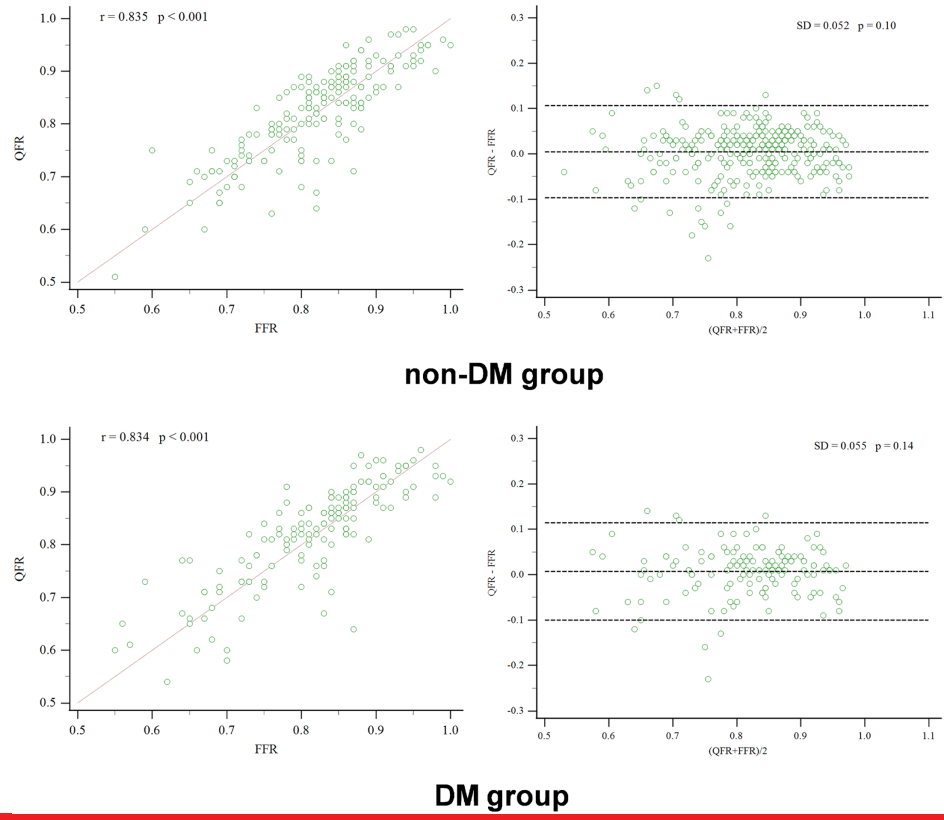


**Figure 3. Correlation and agreement between QFR and FFR. Good correlation and agreement of QFR and FFR were observed in both groups. DM, diabetes mellitus; FFR, fractional flow reserve; QFR, quantitative flow ratio.**

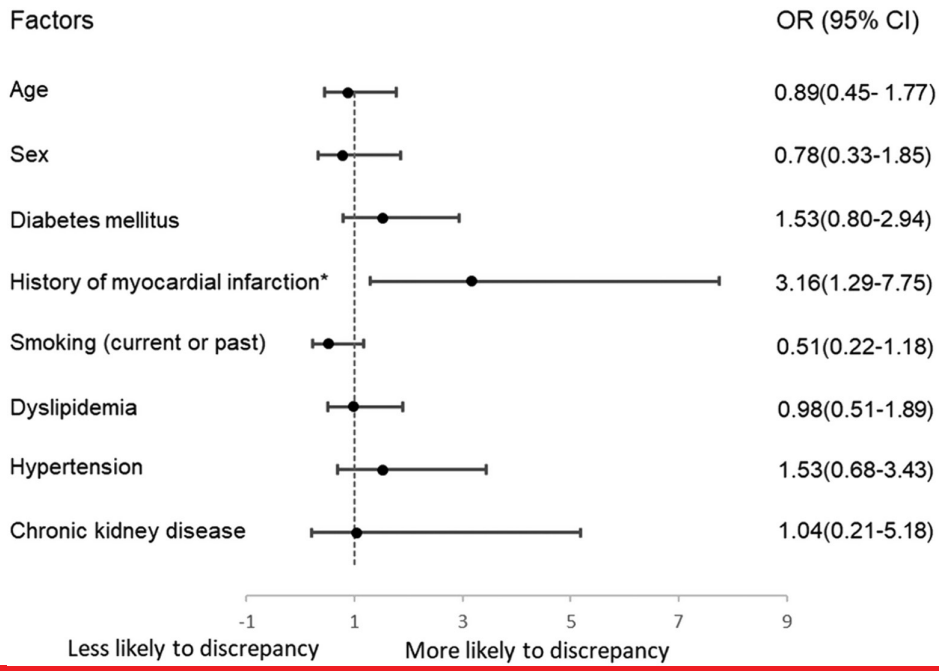


**Figure 4. Independent predictors of QFR–FFR classification discrepancy. Classification discrepancy was obtained using the cutoff ≤ 0.80 for both methods. Variables associated with coronary microcirculation dysfunction are shown on the left. Each dot represents the point estimate of the effect of that variable in the model, whereas the line shows the 95% confidence interval. Group with *P*-value < .05 are marked with an asterisk. FFR, fractional flow reserve; QFR, quantitative flow ratio.**

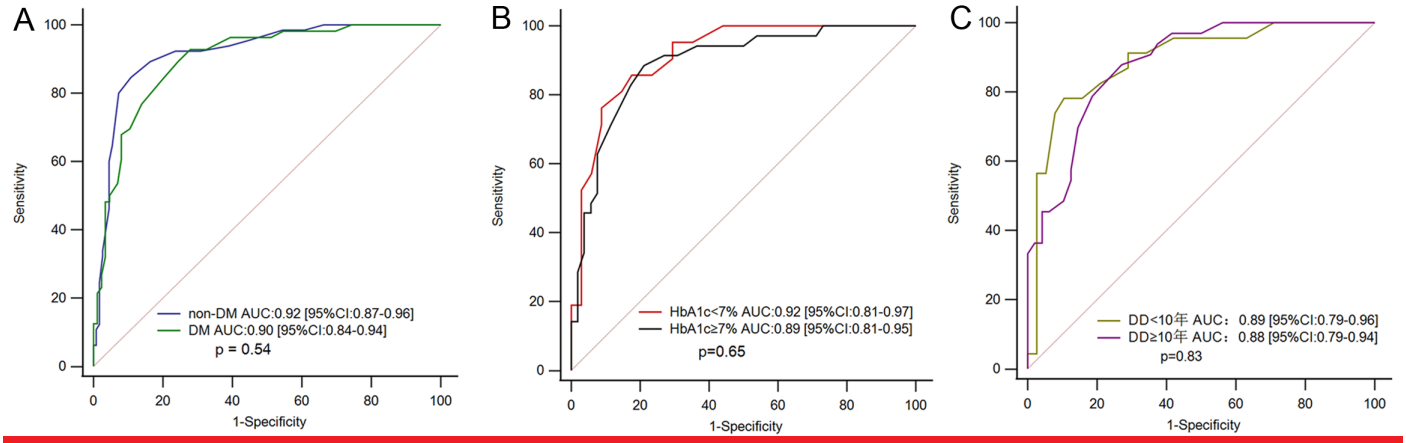


**Figure 5. Comparison of the per-vessel receiver-operating characteristic curves for QFR. AUC represents the diagnostic performance of QFR, using FFR as a gold standard. The per-vessel receiver-operating characteristic curves for QFR in the DM group and non-DM group (A), HbA1c < 7% group and HbA1c ≥ 7% group (B), DD < 10 years group and DD ≥ 10 years group (C). No significant differences in the abovementioned groups were found. AUC, area under the receiver-operating characteristic curve; DD, diabetic duration; DM, diabetes mellitus; FFR, fractional flow reserve; HbA1c, hemoglobin A1c; non-DM, non-diabetes mellitus; QFR, quantitative flow ratio.**

for invasive operations, costly pressure wires, and hyperemic agents. The QFR has recently emerged as a novel approach that can evaluate the functional significance of intermediate stenosis without pressure wires and hyperemic agents. A good correlation and agreement between QFR and FFR were found in our trial, which is consistent with recent studies.[6,7,9] Increasing conclusive findings confirmed a wider adoption of QFR in physiological assessment in patients undergoing coronary angiography.[21-23]

However, it is unknown whether QFR is applicable to specific populations. Mejía-Rentería et al[11] have reported that CMD decreased the diagnostic performance of QFR and that the presence of CMD is a major driver of misclassification between QFR and FFR.[11] Besides, a diffuse disease common in diabetic patients may also influence the diagnostic accuracy of QFR.[12] Therefore, we studied the influence of DM on the application of QFR and simultaneously explored the clinical relevance of discrepancies between QFR and FFR driven by the presence of CMD. As shown in the results, prior MI was a major factor of classification discrepancy between QFR and FFR (OR 3.16 (95% CI: 1.29-7.75), $P = .01$). Mejía-Rentería et al[11] performed a multivariable analysis which identified acute coronary syndromes as one of the significant independent predictors of misclassification between QFR and FFR. Emori et al[24] found that the accuracy of QFR is influenced in the prior-MI-related coronary arteries compared with non-prior-MI-related coronary arteries. We speculated that the presence of collateral circulation in patients with prior MI changes the pressure of vessels and may be associated with CMD, which influences the results of QFR.[25] Studies exploring the relationship between prior MI and QFR need to be further developed.

At the same time, we compared the diagnostic performance of QFR in DM and non-DM groups, HbA1c ≥ 7% and < 7% groups, DD ≥ 10 years and < 10 years groups, respectively. It was shown that no significant differences in the AUC of QFR were found in each group. The author's interpretations of the results are as follows. First of all, it is not a small

**Table 3. Per-Vessel Analysis in Diagnostic Performance of QFR**

| Variables | DM Group (n = 142) | Non-DM Group (n = 175) | HbA1C ≥ 7% Group (n = 87) | HbA1C < 7% Group (n = 55) | DD ≥ 10 Years Group (n = 81) | DD < 10 Years Group (n = 61) |
|---|---|---|---|---|---|---|
| Classification agreement | 116 (82) | 153 (87) | 70 (80) | 46 (84) | 64 (79) | 52 (85) |
| AUC | 0.90 (0.84-0.94) | 0.92 (0.87-0.96) | 0.89 (0.81-0.95) | 0.92 (0.81-0.97) | 0.88 (0.79-0.94) | 0.89 (0.79-0.96) |
| Sensitivity | 70 (56-81) | 85 (74-92) | 66 (48-81) | 81 (58-95) | 67 (48-82) | 78 (56-93) |
| Specificity | 90 (81-95) | 89 (82-94) | 94 (84-99) | 88 (73-97) | 92 (80-98) | 92 (79-98) |
| PPV | 81 (69-89) | 82 (73-89) | 89 (71-96) | 81 (62-92) | 85 (68-94) | 86 (67-95) |
| NPV | 82 (75-87) | 91 (85-95) | 80 (72-87) | 88 (76-95) | 80 (71-87) | 88 (76-94) |
| +LR | 6.7 (3.5-12.7) | 7.8 (4.8-13.4) | 11.4 (3.7-35.1) | 6.9 (2.7-17.7) | 8.0 (3.0-21.1) | 9.9 (3.3-30.0) |
| −LR | 0.3 (0.2-0.5) | 0.2 (0.1-0.3) | 0.4 (0.2-0.6) | 0.2 (0.1-0.5) | 0.4 (0.2-0.6) | 0.2 (0.1-0.5) |

Data presented as n (%) for classification agreement, n (95% CI) for +LR and −LR, and % (95% CI) for all other parameters. AUC, area under the receiver-operating characteristic curve; DD, diabetic duration; DM, diabetes mellitus; HbA1c, hemoglobin A1c; +LR, positive likelihood ratio; −LR, negative likelihood ratio; NPV, negative predictive value; PPV, positive predictive value.

percentage of patients with good glycemic control and DD < 10 years in our baseline clinical characteristics comparison. Sara et al[26] have suggested that the influence of poor glycemic control on coronary microvasculature is found only in female diabetics. Second, scholars have demonstrated that insulin resistance is associated with coronary microvasculature abnormalities in nondiabetics.[27] These clinical characteristics related to insulin resistance and CMD may disturb the influence of DM on the diagnostic performance of QFR. Moreover, Mejía-Rentería et al[11] have shown no significant difference in DM proportion in patients with CMD compared with patients without CMD (40% vs. 37%, $P = .78$) in baseline clinical characteristics comparison.[11] Third, Scarsini et al[28] have confirmed good diagnostic accuracy of QFR in diffuse disease, which is conducive to understanding the existing results. Last but not least, although the difference is not statistically significant, we found relatively low sensitivity and low positive likelihood ratio in inter-group comparisons, which are likely attributed to the small sample size. Researches with expanding sample size need to be further carried out. Together, the present findings indicate that DM did not decrease the diagnostic performance of QFR.

Smit et al[29] also found that the diagnostic performance of QFR was no significant difference in patients with or without DM, which is in line with our findings. But they did not explain the classification discrepancy between QFR and FFR. And the effects of poor glycemic control and increasing DD on QFR have not been elaborated.

Our study assessed the influence of DM on the diagnostic performance of QFR from 3 diabetic aspects and the existing results suggested that QFR is applicable to diabetic patients, which provides the theoretical basis for the clinical application of QFR.

### Study Limitations

First, QFR is an angiography-based technology. Its results depend on image quality and optimal projections. In our study, angiographic images were retrospectively collected, which probably influences the reliability of QFR analysis. Second, the influence of patients' other diseased vessels on QFR analysis for target vessels is unknown. It is necessary to develop the research in this respect. Third, more reliable results may be obtained if the sample size is expanded.

## CONCLUSION

The clinical application of QFR is not limited to diabetic patients according to the present results. The independent predictor of the classification discrepancy between QFR and FFR was prior MI rather than DM. The relationship between prior MI and QFR needs to be further developed.

**Ethics Committee Approval:** This study has been approved by the Medical Ethics Committee of Beijing Friendship Hospital, Capital Medical University, and the study protocol was in accordance with the Declaration of Helsinki. Ethics Committee decision date: November 01, 2021, decision number: 2021-P2-329-01.

**Peer-review:** Externally peer-reviewed.

**Author Contributions:** C.H.: conception, design. D.T.: medical writing, provision of study materials, conception, design. Z.L.: medical writing. G.X., M.L. and B.Y.: provision of study materials. Final approval of the manuscript to be published: all authors. The authors are grateful to Zhao Guoliang for data collection.

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