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Original Research

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Diagnostic Performance of Angiography-Derived FFR According to the Analysis Factors

You-Jeong Ki, MD, PhD[1], Doyeon Hwang, MD[2], Seokhun Yang, MD[2], Sang-Hoon Na, MD, PhD[2], Joon-Hyung Doh, MD, PhD[3], Chang-Wook Nam, MD, PhD[4], Doo-Youp Kim, MD[5], Byung-Joo Choi, MD[5], Chang-Bae Sohn, MD[5], Hyun-Jong Lee, MD[6], Hyun Kuk Kim, MD, PhD[7], Yongcheol Kim, MD, PhD[8], Eun-Seok Shin, MD, PhD[9], and Bon-Kwon Koo, MD, PhD[2]

[1]Division of Cardiology, Department of Internal Medicine, Uijeongbu Eulji Medical Center, Uijeongbu, Korea
[2]Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, Seoul, Korea
[3]Division of Cardiology, Department of Internal Medicine, Inje University Ilsan Paik Hospital, Goyang, Korea
[4]Division of Cardiology, Department of Internal Medicine, Keimyung University Dongsan Medical Center, Daegu, Korea
[5]Division of Cardiology, Department of Internal Medicine, Ulsan Medical Center, Ulsan Hospital, Ulsan, Korea
[6]Division of Cardiology, Department of Internal Medicine, Bucheon Sejong Hospital, Bucheon, Korea
[7]Department of Internal Medicine and Cardiovascular Center, Chosun University Hospital, Gwangju, Korea
[8]Division of Cardiology, Department of Internal Medicine, Yongin Severance Hospital and Cardiovascular Center, Yonsei University College of Medicine, Yongin, Korea
[9]Division of Cardiology, Department of Internal Medicine, Ulsan University Hospital, University of Ulsan College of Medicine, Ulsan, Korea

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Correspondence to
Bon-Kwon Koo, MD, PhD
Department of Internal Medicine and Cardiovascular Center, Seoul National University Hospital, College of Medicine, Seoul National University, 101, Daehak-ro, Jongno-gu, Seoul 03080, Korea.
Email: bkkoo@snu.ac.kr

ORCID iDs
You-Jeong Ki
https://orcid.org/0000-0003-0102-2810
Doyeon Hwang
https://orcid.org/0000-0002-0215-5319
Seokhun Yang
https://orcid.org/0000-0003-2078-3930
Sang-Hoon Na
https://orcid.org/0000-0002-1289-7965
Joon-Hyung Doh
https://orcid.org/0000-0001-7966-9564
Chang-Wook Nam
https://orcid.org/0000-0002-3370-5774

AUTHOR'S SUMMARY

The diagnostic performance of angiography-derived fractional flow reserve (FFR) according to the analysis factors was investigated. In 285 vessels from 239 patients, quantitative flow ratio (QFR) accuracy was influenced by a composite score of angiographic factor, system factor, lesion factor, and subjective difficulty factor. The higher the composite score, the lower the diagnostic performance of QFR in predicting FFR ≤0.80. However, that trend was not observed with angiographic severity assessed by 3-dimensional-quantitative coronary analysis. While QFR generally showed good diagnostic performance with FFR, its diagnostic accuracy decreases with increasing lesion complexity, system factors, analysis difficulty and lower angiographic image quality.

ABSTRACT

Background and Objectives: Quantitative flow ratio (QFR) is a method for estimating fractional flow reserve (FFR) without the use of an invasive pressure wire or hyperemic agent. However, the reasons for variation in QFR accuracy across studies and the factors associated with its accuracy remain unclear. The aim of this study was to investigate the diagnostic performance of QFR under different clinical and analysis conditions.
Methods: This multicenter trial prospectively enrolled patients undergoing coronary angiography with an indication for invasive FFR. The composite score for the QFR analysis factors was calculated based on the presence or absence of the angiographic factor, system factor, lesion factor, and subjective difficulty factor. The diagnostic performance of the QFR

Chang-Bae Sohn
https://orcid.org/0000-0001-7403-3778
Hyun-Jong Lee
https://orcid.org/0000-0003-1260-0778
Hyun Kuk Kim
https://orcid.org/0000-0002-4554-041X
Yongcheol Kim
https://orcid.org/0000-0001-5568-4161
Eun-Seok Shin
https://orcid.org/0000-0002-9169-6968
Bon-Kwon Koo
https://orcid.org/0000-0002-8188-3348

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Conflict of Interest
Dr. Bon-Kwon Koo received an Institutional Research Grants from NK&D Co., LTD, Abbott Vascular, Boston Scientific Corporation and Philips.

Data Sharing Statement
The data generated in this study is available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Na SH, Doh JH, Nam CW, Kim HK, Shin ES, Koo BK; Data curation: Ki YJ, Hwang D, Yang S, Na SH, Doh JH, Nam CW, Kim DY, Choi BJ, Sohn CB, Lee HJ, Kim HK, Kim Y, Shin ES, Koo BK; Formal analysis: Ki YJ, Yang S; Investigation: Ki YJ, Hwang D, Doh JH, Nam CW, Koo BK; Methodology: Ki YJ, Hwang D, Yang S, Doh JH, Kim DY, Choi BJ, Kim HK, Kim Y; Project administration: Na SH, Nam CW, Koo BK; Supervision: Hwang D, Na SH, Nam CW, Choi BJ, Sohn CB, Lee HJ, Kim Y, Shin ES, Koo BK; Validation: Na SH, Choi BJ, Lee HJ, Kim Y, Shin ES; Visualization: Yang S, Na SH, Kim DY, Sohn CB; Writing - original draft: Ki YJ, Koo BK; Writing - review & editing: Ki YJ, Koo BK.

was assessed for each composite score using FFR ≤0.80 as the reference.
Results: A total of 285 vessels from 239 patients were analyzed. The median FFR and QFR values were 0.83 (interquartile range [IQR], 0.78–0.88) and 0.83 (IQR, 0.76–0.89), respectively. Using FFR ≤0.80 as a reference, QFR showed an overall diagnostic accuracy of 81.4%. Higher composite scores were associated with lower diagnostic performance of QFR in predicting FFR ≤0.80 (p-for-trend=0.010). The diagnostic accuracy of QFR ranged from 94.1% in vessels with low composite scores to 73.7% in those with high composite scores.
Conclusions: The diagnostic accuracy of QFR decreases with increasing lesion complexity, system factors, lower angiographic image quality, and analysis difficulty. These findings suggest that specific lesion, system, and imaging-related factors can significantly impact the reliability of QFR in clinical practice.

Trial Registration: ClinicalTrials.gov Identifier: NCT06305572

Keywords: Coronary angiography; Coronary artery disease; Percutaneous coronary intervention; Physiology

INTRODUCTION

Fractional flow reserve (FFR) is an invasive physiological index used to define coronary stenosis that causes ischemia.[1-4] Although FFR is highly recommended in current guidelines, it is underused in real-world practice due to the several reasons, including drug-induced hyperemia, prolonged procedure time, and the need for an invasive pressure guidewire.[5]

Angiography-derived FFR, including quantitative flow ratio (QFR), is a method for calculating FFR without using a coronary pressure wire and pharmacological hyperemic agents. Previous studies have shown the excellent diagnostic performance of angiography-derived FFR, with area under the receiver-operating characteristic curves (AUCs) ranging from 0.92 to 0.96 when compared to FFR.[6-11] A recent randomized controlled trial reported that a QFR-guided percutaneous coronary intervention (PCI) strategy showed better clinical outcomes compared with angiography-guided PCI.[12] However, a study that anonymously compared different angiography-derived FFR systems found that the AUC values ranged from 0.73 to 0.75,[13] which is much lower than those from the previous validation studies.[6-11] In addition, FAVOR III Europe trial failed to demonstrate non-inferiority of the QFR-guided revascularization strategy to the standard FFR-guided strategy, a finding that raises questions about the utility of angiography-derived FFR.[14]

However, it is not well known why the diagnostic performance of angiography-derived FFR varies between studies and what factors are associated with the accuracy of QFR. The aim of this study was to investigate the diagnostic performance of QFR according to different lesion, system, and image quality factors.

METHODS

Ethical statement

Information about the trial objectives, design, and population was registered on ClinicalTrial.gov (NCT06305572). This study complied with the provisions of the Declaration of Helsinki

2013. The study protocol was approved by the Institutional Review Board (IRB) of each participating site (Seoul National University Hospital IRB approved number: 1903-013-1014), and all patients provided written informed consent.

Data source and study subjects

This study was a prospective, multicenter, observational study designed to assess the diagnostic performance of QFR in identifying physiologically significant coronary artery disease (CAD), using FFR as the reference standard. Patients suspected of having CAD who were undergoing diagnostic coronary angiography (CAG) with an indication for invasive FFR were included. Clinical exclusion criteria included cardiogenic shock, reduced ejection fraction (≤40%), and suboptimal angiographic image quality for QFR analysis (**Supplementary Figure 1**). If the clinical presentation was acute coronary syndrome, only non-culprit lesions were included.

Coronary angiography and fractional flow reserve

CAG was performed using standard techniques. All coronary physiological measurements were performed after diagnostic angiography using a standardized protocol as previously described.[15] Hyperemia was induced by intravenous infusion of adenosine (140 μg/kg/min) or intracoronary nicorandil (2 mg). During hyperemia, FFR was determined by dividing the mean distal coronary artery pressure by the aortic pressure. After the measurement of the FFR value, the pressure wire pullback angiogram was recorded.

Quantitative flow ratio analysis

QFR was analyzed in an independent core laboratory (Uijeongbu Eulji Medical Center) using the software package QAngio XA 3D 2.1 (Medis Medical Imaging Systems, Leiden, The Netherlands). End-diastolic frames of 2 matched images separated by >25° and with an acquisition time difference ≤120 minutes were selected and used for the reconstruction of a 3-dimensional (3D) model. The arterial contour was automatically detected, and manual correction was performed if necessary. The 3D-quantitative coronary analysis (QCA) included lesion length, percent diameter stenosis (%DS), percent area stenosis (%AS), and minimal lumen diameter. The following 3 QFR calculations were performed based on different mean hyperemic flow velocities: 1) Fixed QFR: a fixed empirical hyperemic flow velocity was used for computation; 2) Contrast QFR: contrast QFR was calculated from modeled hyperemic flow velocity based on the thrombolysis in myocardial infarction (TIMI) frame count. The frame counting step requires the user to manually select the start frame and the end frame; 3) Auto QFR: automatic QFR is an easier way of calculating a QFR that uses a patient-specific TIMI frame count, but with automatically specified start and end frames. Contrast QFR was used to compare the accuracy of QFR according to composite score or to compare it to the accuracy of %DS assessed by 3D-QCA. A contrast QFR ≤0.80 was considered functionally significant.[8][11][12]

Definitions of the quantitative flow ratio analysis factors

This study examined 4 factors associated with QFR analysis: the angiographic factor, the system factor, the lesion factor, and the subjective difficulty factor. The frequencies of these QFR analysis factors and their components comprising each factor are illustrated in **Figure 1**. Angiographic factor consists of 3 components: CAG quality, appropriate CAG angle, and TIMI frame count. CAG image quality was defined as acceptable if the identification of the coronary artery wall was easy and reliable. Appropriate CAG angles were defined as using 2 cranial angulations in the left anterior descending artery, a maximum right anterior

oblique angle of ≥30° in the left circumflex artery, and including caudal angulation in the right coronary artery. The accuracy of QFR according to the angiogram angle selected for analysis in each vessel is presented in **Supplementary Figure 2**. The appropriate number of TIMI frame counts was defined as when the difference between the start and end frames is between ≥4 and ≤8, using the interquartile range (IQR). Vessels were defined to have an angiographic factor if they did not meet any of 3 components. System factor consists of 2 components: electrocardiogram (ECG) gating and the usage of the correspondence function. Vessels were defined to have a system factor if they did not meet both components. Lesion factors included lesion length (<30 mm), pullback pressure gradient (PPG) index (>0.78),[16][17] and single lesion. A lesion factor was considered positive if any of 3 components were not met. QFR analysis included the following user-interactive steps. 1) selection of end-diastole frames with good contrast filling; 2) selection of anatomical landmarks in both images; 3) review of the automated lumen edge detection, including manual correction of contours if indicated; 4) selection of one of 3 algorithms for reference vessel function. The subjective difficulty of the analysis was categorized per vessel using a score based on the difficulty of these user-interaction steps (2 indicates that the difficulty of the analysis is easy; 1 acceptable; 0 difficult). A score of ≤1 was considered positive for the subjective difficulty factor. Based on the presence or absence of the angiographic factor, the system factor, the lesion factor and the subjective difficulty factor, the composite score for the QFR analysis factors was calculated as the sum of the 4 factors (**Figure 2**).

Statistical analysis

For the sample size calculation, the accuracy of QFR was estimated as 83% based on previous studies,[6][11][18] and with target goal as 75%. The target goal was chosen to be higher than the upper limit of the diagnostic accuracy of QCA based on previous studies.[6][8] Assuming a 15% expected loss in analysis due to QFR failure and a 10% dropout rate, 280 patients needed to be enrolled (power=0.80, 2-sided alpha=0.05).

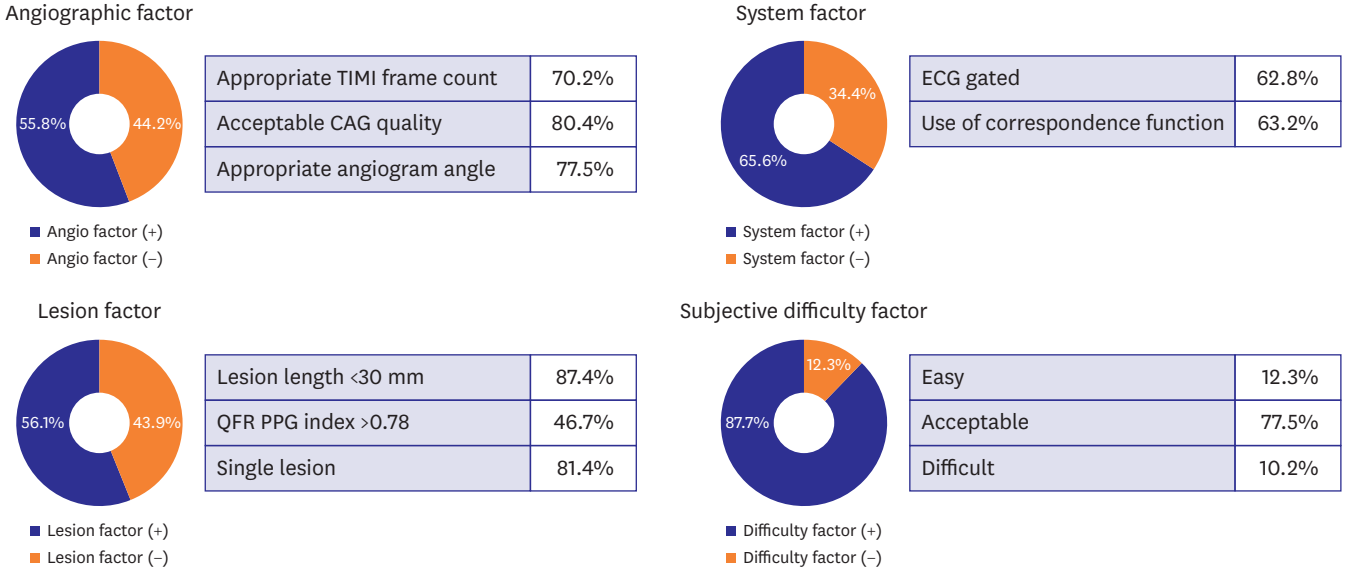

Figure 1. The QFR analysis factors for the calculation of the composite score and the frequency of each factor component. Composite score of QFR analysis factors included angiographic factor, system factor, lesion factor, and subjective difficulty factor. The pie graph shows the frequency of each factor and the table shows the frequency of each component.
CAG = coronary angiogram; ECG = electrocardiogram; PPG = pullback pressure gradient; QFR = quantitative flow ratio.

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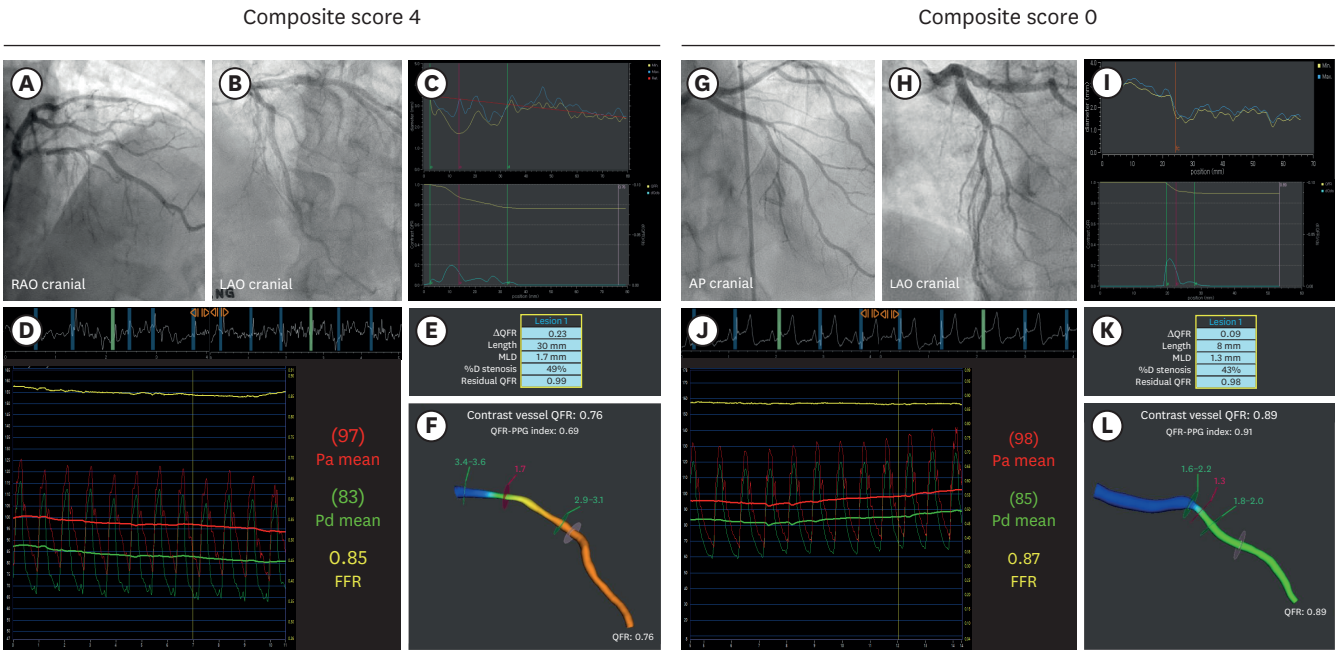

Figure 2. Case examples. (A, B) The CAGs were of bad analysis quality (angiographic score 1). (C, D) The correspondence function was not used in the analysis (system score 1). (E, F) The culprit lesion was 30 mm in length, and the PPG index was 0.69 (lesion score 1). Subjective difficulty of the analysis was acceptable (subjective difficulty score 1). The QFR value was 0.76 and the FFR value was 0.85. (G, H) The CAGs were of good quality, taken at the appropriate angles with a thrombolysis in myocardial infarction frame of 5 (angiographic score 0). (I, J) The analysis used the electrocardiogram gated function and correspondence function (system score 0). (K, L) The vessel had a single lesion with a length of 7 mm and a PPG index of 0.91 (lesion score 0). Subjective difficulty of the analysis was easy (subjective difficulty score 0). The QFR value was 0.89 and the FFR value was 0.87.
CAG = coronary angiography; FFR = fractional flow reserve; PPG = pullback pressure gradient; QFR = quantitative flow ratio.

All analyses were performed on a per-vessel basis. For continuous variables, data are expressed as mean ± standard deviation if normally distributed, or as median with IQR if non-normally distributed, and as percentages for categorical variables. Normality was assessed using the Shapiro-Wilk test. The χ^2 test or Fisher's exact test was used for categorical variables, and the Student's t-test was used for continuous variables to compare between groups. The relationship and agreement between QFR and FFR were assessed by Spearman's correlation coefficient and Bland-Altman plot, respectively. A receiver operating characteristic curve analysis was conducted to evaluate the AUC of QFR for predicting FFR ≤0.80. The DeLong method was used to perform a comparison of the AUC between groups. Diagnostic performance was reported per-vessel as accuracy, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) in comparison with FFR. Diagnostic performance was also compared between subgroups stratified by composite score of QFR analysis factors. The χ^2 test for trend was used to assess trends in proportions. A generalized estimating equation was used to adjust for intra-subject variability among vessels from the same patient. A 2-sided $p<0.05$ was considered significant. Analyses were performed using SPSS version 23.0 (IBM SPSS Statistics, Chicago, IL, USA) and R version 4.3.1 (R Foundation for Statistical Computing, Vienna, Austria).

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RESULTS

Baseline characteristics

From March 2019 to April 2022, 280 patients were enrolled, and 239 patients with 285 vessels were analyzed in this study after exclusions based on predefined criteria (**Supplementary Figure 1**). Baseline patient and lesion characteristics are summarized in **Table 1**. The mean age of the patients was 64.8 years, 77.4% were male, and 34.7% had diabetes mellitus. The interrogated vessels had a %DS of 47.2%±9.7%. The median FFR and QFR values were 0.83 (IQR, 0.78–0.88) and 0.83 (IQR, 0.76–0.89), respectively. The proportion of functionally significant vessels was 35.1% for FFR and 40.4% for QFR, respectively. The distribution of FFR and QFR values is illustrated in **Figure 3**.

Diagnostic performance of quantitative flow ratio and 3-dimensional quantitative coronary angiography

The accuracy of contrast QFR in detecting an FFR ≤0.80 in all analyzed vessels was 81.4%, which was numerically higher than fixed QFR (78.2%) and auto QFR (77.6%) (**Supplementary Figure 3**). The sensitivity, specificity, PPV, and NPV of contrast QFR were 81.0%, 81.6%, 70.4%, and 88.8%, respectively. Contrast QFR showed a good correlation (Spearman's correlation coefficient: 0.709; p<0.001) and agreement with FFR (**Supplementary Figure 4**). A higher AUC was observed for contrast QFR, fixed QFR, and auto QFR in comparison to 3D-QCA %DS and %AS for detecting FFR ≤0.80 (p for AUC comparison between all QFR values and %DS or %AS derived from 3D-QCA <0.001, **Supplementary Figure 5**).

Accuracy of quantitative flow ratio according to composite score

The frequency of QFR analysis factors and their components are illustrated in **Figure 1**. The diagnostic performance of QFR according to each factor is shown in **Supplementary Table 1**. There were no differences in lesion characteristics according to the composite score (**Table 2**).

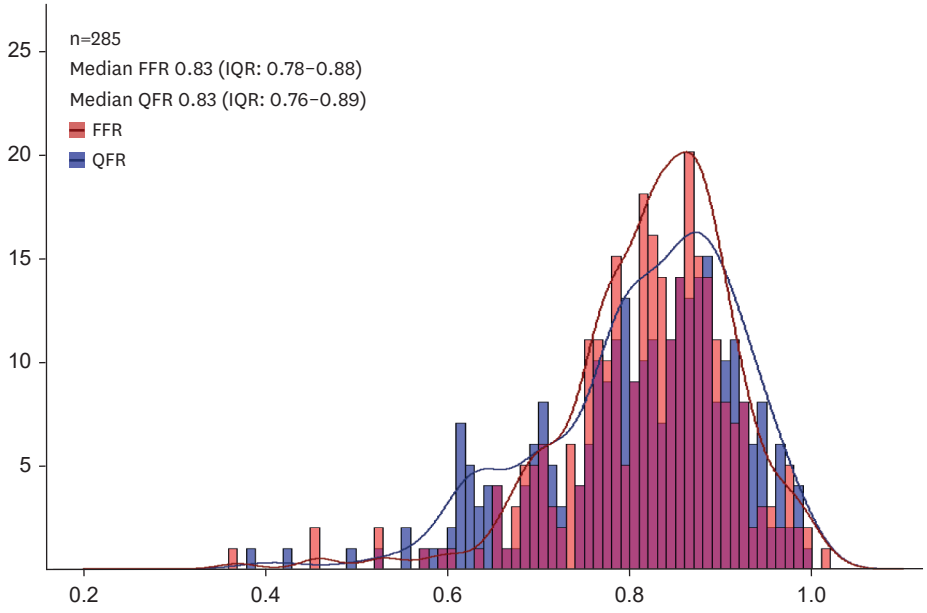

Figure 3. Distribution of FFR and QFR values. The median values for FFR and QFR are 0.83, with IQR of 0.78–0.88 for FFR and 0.76–0.89 for QFR.
FFR = fractional flow reserve; IQR = interquartile range; QFR = quantitative flow ratio.

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Table 1. Baseline patient and lesion characteristics

	Total
Patients	(n=239)
Age (years)	64.8±8.8
Male	185 (77.4)
Body mass index (kg/m²)	24.8±3.0
Acute coronary syndrome	46 (19.2)
Diabetes mellitus	83 (34.7)
Hypertension	155 (64.9)
Hypercholesterolemia	205 (85.8)
Prior MI	2 (0.8)
Prior PCI	17 (7.1)
LV ejection fraction (%)	61.4±5.8
Vessels	(n=285)
Target vessel	
Left anterior descending artery	191 (67.0)
Left circumflex artery	36 (12.6)
Right coronary artery	58 (20.4)
FFR data	
FFR	0.83 (0.78–0.88)
FFR ≤0.80	100 (35.1)
QFR vessel data	
Fixed QFR	0.83 (0.75–0.89)
Auto QFR	0.82 (0.74–0.89)
Contrast QFR	0.83 (0.76–0.89)
Contrast QFR ≤0.80	115 (40.4)
PPG index	0.78 (0.67–0.85)
3D-QCA parameters	
Lesion length (mm)	19.0±9.9
Diameter stenosis (%)	47.2±9.7
Area stenosis (%)	64.2±11.9

Data presented as mean ± standard deviation, number (%) or median (interquartile range).
3D = 3-dimensional; FFR = fractional flow reserve; LV = left ventricle; MI = myocardial infarction; PCI = percutaneous coronary intervention; PPG = pullback pressure gradient; QCA = quantitative coronary angiography; QFR = quantitative flow ratio.

Table 2. Baseline lesion characteristics according to composite score

	Total (n=285)	Composite score 4 (n=57)	Composite score 3 (n=110)	Composite score 2 (n=84)	Composite score 0–1 (n=34)	p value
Target vessel						0.264
Left anterior descending artery	191 (67.0)	38 (66.7)	76 (69.1)	55 (65.5)	22 (64.7)	
Left circumflex artery	36 (12.6)	4 (7.0)	16 (14.5)	14 (16.7)	2 (5.9)	
Right coronary artery	58 (20.4)	15 (26.3)	18 (16.4)	15 (17.9)	10 (29.4)	
PCI	77 (27.0)	13 (22.8)	30 (27.3)	25 (29.8)	9 (26.5)	0.839
FFR data						
FFR	0.83 (0.78–0.88)	0.81 (0.78–0.86)	0.83 (0.77–0.89)	0.86 (0.78–0.90)	0.84 (0.79–0.89)	0.370
FFR ≤0.80	100 (35.1)	25 (43.9)	43 (39.1)	23 (27.4)	9 (26.5)	0.112
QFR vessel data						
Fixed QFR	0.83 (0.75–0.89)	0.83 (0.74–0.88)	0.83 (0.75–0.89)	0.85 (0.78–0.88)	0.86 (0.80–0.92)	0.430
Auto QFR	0.82 (0.74–0.89)	0.80 (0.70–0.87)	0.82 (0.72–0.91)	0.83 (0.76–0.89)	0.85 (0.78–0.91)	0.373
Contrast QFR	0.83 (0.76–0.89)	0.82 (0.76–0.88)	0.82 (0.73–0.91)	0.85 (0.78–0.90)	0.86 (0.78–0.90)	0.555
Contrast QFR ≤0.80	115 (40.4)	26 (45.6)	50 (45.5)	28 (33.3)	11 (32.4)	0.215
3D-QCA parameters						
Diameter stenosis (%)	47.2±9.7	45.9±7.9	47.1±10.0	47.9±9.7	47.4±11.5	0.679
Area stenosis (%)	64.2±11.9	63.2±10.3	63.5±12.7	65.7±11.1	64.3±13.9	0.565

Data presented as mean ± standard deviation, number (%) or median (interquartile range).
3D = 3-dimensional; FFR = fractional flow reserve; PCI = percutaneous coronary intervention; QCA = quantitative coronary angiography; QFR = quantitative flow ratio.

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Table 3. Diagnostic performance of quantitative flow ratio in determining myocardial ischemia in each analysis condition

	TP	TN	FP	FN	Sensitivity	Specificity	Accuracy	PPV	NPV	AUC	p value*
Total (n=285)	81	151	34	19	81 (72.3–88.6)	81.6 (75.8–87.4)	81.4 (76.5–86.3)	70.4 (62.1–79.6)	88.8 (83.8–93.3)	0.887 (0.845–0.930)	
Composite score 4 (n=57)	18	24	8	7	72 (53.9–88.5)	75 (60.0–89.3)	73.7 (61.4–84.2)	69.2 (51.4–85.7)	77.4 (62.1–90.6)	0.811 (0.694–0.927)	Reference
Composite score 3 (n=110)	35	52	15	8	81.4 (69.2–92.7)	77.6 (66.7–87.9)	79.1 (71.8–87.3)	70 (56.9–82.6)	86.7 (77.4–94.3)	0.874 (0.805–0.943)	0.365
Composite score 2 (n=84)	19	52	9	4	82.6 (65.0–95.7)	85.2 (76.3–94.0)	84.5 (76.2–91.7)	67.9 (50.0–85.0)	92.9 (86.0–98.3)	0.915 (0.839–0.991)	0.146
Composite score 0–1 (n=34)	9	23	2	0	100 (66.4–100.0)	92 (78.6–100.0)	94.1 (85.3–100.0)	81.8 (55.6–100.0)	100 (85.2–100.0)	0.991 (0.970–1.000)	0.004

AUC = area under the curve; FN = false negative; FP = false positive; NPV = negative predictive value; PPV = positive predictive value; TN = true negative; TP = true positive.
*The p value comparing the AUC of each group. The AUC result of composite score 4 was used as a reference value for analysis.

Figure 4 and **Table 3** show the diagnostic performance of QFR according to the composite score. The diagnostic accuracy of QFR ranged from 94.1% in vessels with a low composite score to 73.7% in those with a high composite score. The higher the composite score, the lower the accuracy, sensitivity, specificity, and AUC of QFR in predicting FFR ≤0.80. The trend of change in the diagnostic accuracy of 3D-QCA %DS by composite score was not significant, but the change in QFR was significantly different (p for trend in QFR accuracy=0.010, **Figure 4**). When divided by each composite score, the AUC was larger for QFR compared to 3D-QCA %DS for predicting FFR ≤0.80 across all score groups (**Figure 5**). In vessels with composite scores of 2 to 4, the AUC value of contrast QFR was significantly higher than that of 3D-QCA %DS. In vessels with composite score of 0 to 1, there was a trend towards a higher AUC for QFR compared to 3D-QCA %DS.

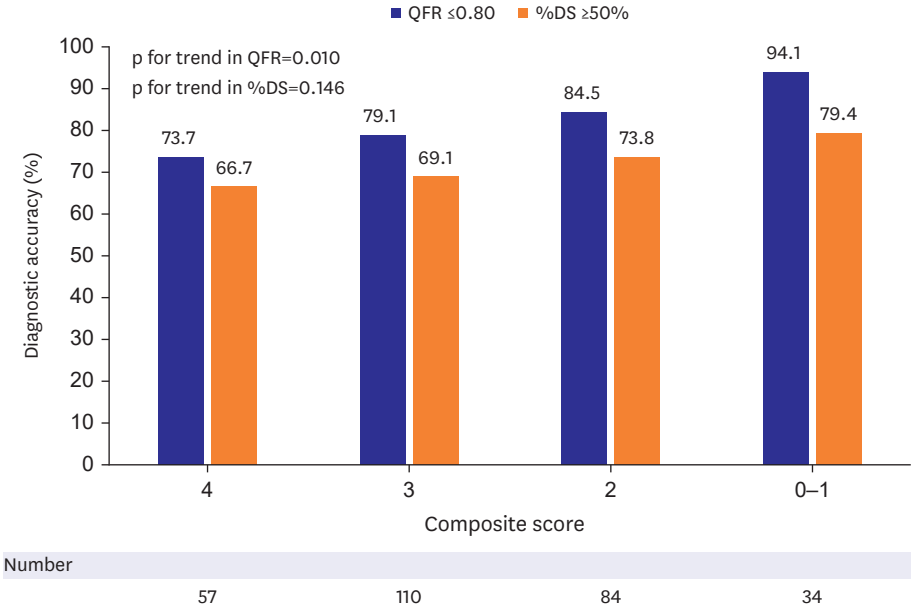

Figure 4. Diagnostic accuracy of QFR and angiographic %DS according to the composite score. The figure illustrates the accuracy of QFR and 3-dimensional-quantitative coronary analysis %DS and in predicting fractional flow reserve ≤0.80 according to composite score.
DS = diameter stenosis; QFR = quantitative flow ratio.

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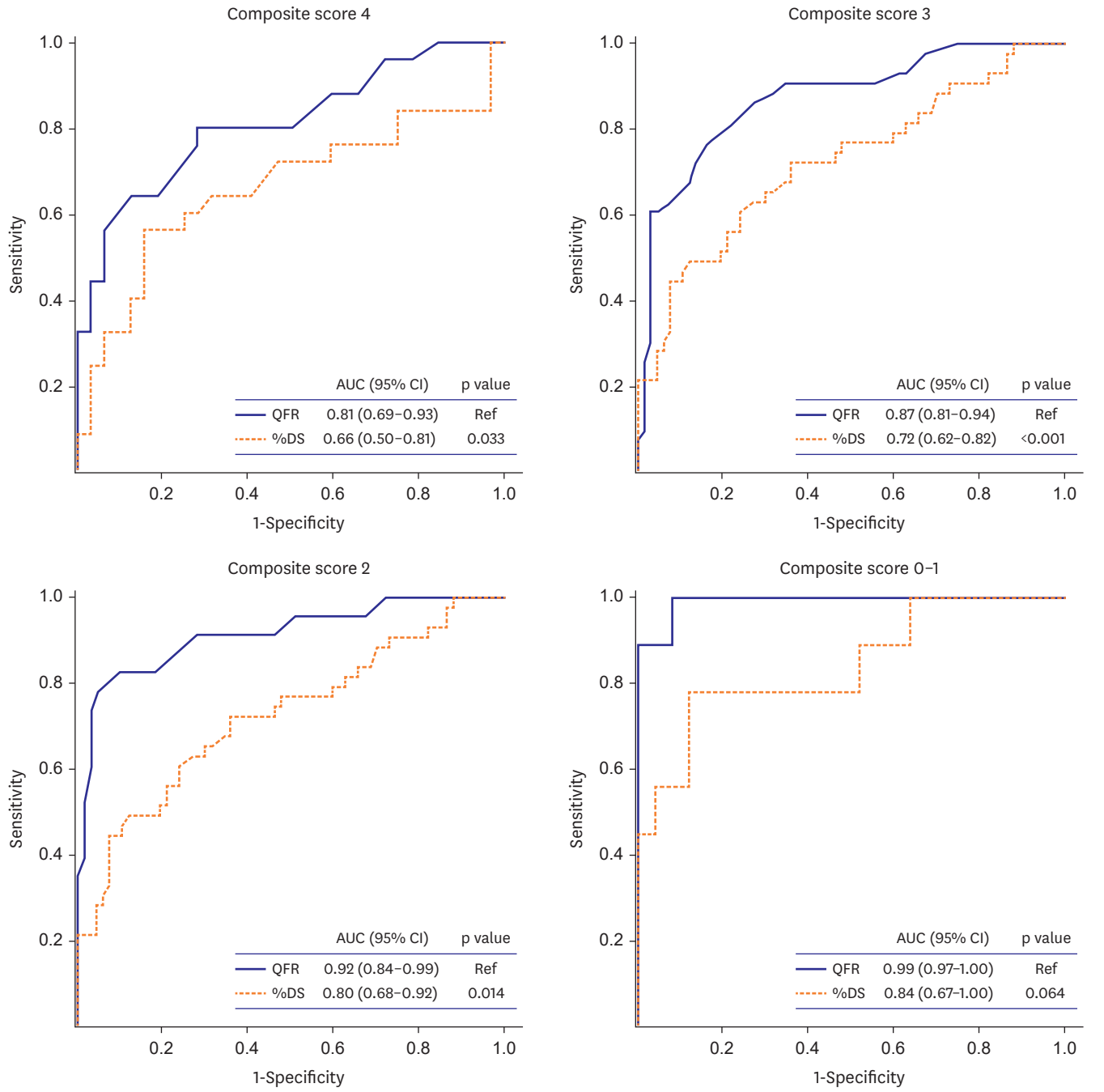

Figure 5. Discrimination abilities of QFR, and angiographic %DS for predicting FFR ≤0.80 according to the composite score. The AUC for predicting FFR ≤0.80 was larger for QFR compared to angiographic %DS assessed by 3-dimensional-quantitative coronary analysis when divided by each composite score.
AUC = area under the receiver-operating characteristic curve; CI = confidence interval; DS = diameter stenosis; FFR = fractional flow reserve; QFR = quantitative flow ratio; ROC = receiver operating characteristic.

DISCUSSION

This study assessed the diagnostic performance of the QFR for predicting FFR ≤0.80 under different analysis conditions and evaluated their influence on the accuracy of the QFR.
The main findings of the current study are as follows: 1) QFR showed good overall diagnostic

performance and was highly correlated with FFR. 2) The accuracy of QFR was influenced by the composite of the angiographic factor, system factor, lesion factor, and subjective difficulty factor. The presence of the 4 factors led to a significant variation in the diagnostic accuracy of QFR, ranging from 94.1% in vessels with low composite scores to 73.7% in those with high composite scores. 3) The higher the composite score, calculated based on the presence of these 4 factors, the lower the diagnostic performance of QFR for predicting FFR ≤0.80. However, that trend was not observed with angiographic lesion severity assessed by 3D-QCA.

Angiography-derived FFR is a method for evaluating FFR without using a coronary pressure wire and pharmacologic hyperemic agent.[6] In validation studies, angiography-derived FFRs from different vendors showed an AUC value of 0.92 to 0.96.[6-11] However, in a study that anonymously compared different angiography-derived FFR systems, the AUC values were in the range of 0.73 to 0.75.[13] In our study with a core laboratory analysis, QFR showed an AUC of 0.89 (95% confidence interval, 0.85–0.93), which is lower than that of previous validation studies,[6-11] but still better than that in the anonymous comparison study.[13] The variation in diagnostic performance among different studies may be due to differences in lesion and patient characteristics, and operators. The FAVOR III Europe trial challenged QFR by showing that the QFR-guided revascularization strategy failed to demonstrate non-inferiority to the standard FFR-guided strategy.[14] One contributing factor was the lower median QFR values compared to median FFR values, which resulted in a higher proportion of patients in the QFR group undergoing revascularization. Similarly, in our study, QFR identified a higher proportion of functionally significant lesions compared to FFR (40.4% vs. 35.1%), reflecting a relative 15% excess. This is in line with the 21% excess observed in FAVOR III Europe, suggesting that QFR may systematically classify more lesions as significant. These findings highlight the potential for overtreatment when revascularization decisions rely solely on QFR. Notably, the study's training protocol for QFR analysis was relatively lenient. QFR observers were required to complete the vendor's training and certification process as well as study-specific training. The study-specific training involved the analysis of at least 30 cases and submission of 3 batches of 5 analyzed cases each for feedback, approval, and additional training if required. In addition, case-by-case feedback focusing on the quality of QFR analysis was provided by the trial core laboratory, but this may not have been sufficient to ensure optimal QFR proficiency. These results do not necessarily indicate the inefficacy of angiography-based FFR methods but suggest potential variability in QFR accuracy influenced by several factors.

Our study investigated the influence of several analysis factors on the diagnostic performance of QFR. Most angiography-derived FFR systems require 3D coronary reconstruction to reduce the effect of vessel tortuosity and lesion asymmetry, and to construct a patient-specific coronary geometry.[19-22] Therefore, several elements, including the quality of the angiogram, the specific angiographic view, the ECG-gated function, and the use of the correspondence point, influence 3D coronary reconstruction and are important factors for accurate FFR estimation.[11][23] Moreover, TIMI frame counts that are too low or too high may affect the accuracy of QFR, as they make it difficult to estimate an accurate FFR value and may be associated with microvascular dysfunction.[13][24] This study observed that QFR accuracy tended to be higher in vessels with short lesions (<30 mm), high QFR PPG index (>0.78) and a single lesion, suggesting that QFR could be less accurate in diffuse or multiple lesions.[25] Furthermore, similar to previous study,[23] we found that the accuracy of the QFR decreased as the subjective difficulty of the user interaction step increased. In the future, fully automated artificial intelligence analysis may improve the accuracy of angiography-derived FFR by standardizing analysis methods and simplifying the steps that affect accuracy.

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When the diagnostic performance was assessed according to the composite score of the angiographic factor, system factor, lesion factor and subjective difficulty factor, the diagnostic performance of QFR for predicting FFR ≤0.80 decreased as the composite score increased. The accuracy of QFR varied from 73.7% to 94.1%, and the AUC ranged from 0.81 to 0.99. Although angiographic %DS assessed by 3D-QCA was less influenced by these factors, its performance in predicting low FFR was lower than that of QFR. These results suggest that diagnostic accuracy can differ according to several lesion factors, system factors, and angiographic image quality. We used an equal-weight scoring system for the 4 QFR analysis factors due to limited evidence on their relative impact. Subgroup analyses showed that only the subjective difficulty factor significantly affected diagnostic performance, while other factors did not show consistent differences (**Supplementary Table 1**). Given sample size constraints, vessels were grouped by total composite score. However, as analysis conditions and influencing factors may vary across angiography-derived FFR systems and evolve with software updates, future studies should refine factor weighting and consider system-specific variability. Physicians need to understand the importance of these elements, along with analysis skills, when applying angiography-derived FFR in daily practice.

Our study has some limitations. Firstly, the study population is relatively small. Although the final number of analyzable patients (n=239) met the minimum sample size requirement, a post hoc power analysis based on the observed QFR accuracy of 81.4% yielded approximately 52%, indicating a modest reduction in statistical power. However, the target accuracy of 75% used in the initial calculation was conservatively chosen based on prior QCA performance,[6)8)] while the actual QCA accuracy in our cohort was lower at 71.2%, suggesting that the clinical relevance of the QFR findings remains valid. Secondly, 4 different analysis factors were used in our study. Additional factors, including the operators' skill, may also influence the diagnostic performance of angiography-derived FFR. All analyses were performed in the core laboratory, and no external validation was performed in this study. Finally, since this study used QFR, the applicability of the results to other angiography-derived FFRs needs to be further investigated.

In conclusion, QFR generally showed good agreement and diagnostic performance compared to FFR. However, the diagnostic accuracy of QFR decreases with increasing lesion complexity, system-related issues, lower angiographic image quality, and analysis difficulty. These results should be considered when using angiography-derived FFR in clinical practice.

SUPPLEMENTARY MATERIALS

Supplementary Table 1
Diagnostic performance of quantitative flow ratio in determining myocardial ischemia in each analysis condition

Supplementary Figure 1
Study flow.

Supplementary Figure 2
Fractional flow reserve-quantitate flow ratio concordance rates according to the diagnostic angle of the coronary angiography.

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Supplementary Figure 3

Comparison of diagnostic performance of QFR indices and angiographic %DS for predicting fractional flow reserve ≤0.80.

Supplementary Figure 4

Correlation and agreement between QFR and FFR.

Supplementary Figure 5

Receiver operating characteristic curves of angiographic %DS, %AS and QFR indices for predicting fractional flow reserve ≤0.80.

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