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Research Article

Meta-Analysis of Diagnostic Performance of Contrast-Fractional Flow Reserve versus Quantitative Flow Ratio for Functional Assessment of Coronary Stenoses

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Background. Use of the fractional flow reserve (FFR) technique is recommended to evaluate coronary stenosis severity and guide revascularization. However, its high cost, time to administer, and the side effects of adenosine reduce its clinical utility. Two novel adenosine-free indices, contrast-FFR (cFFR) and quantitative flow ratio (QFR), can simplify the functional evaluation of coronary stenosis. This study aimed to analyze the diagnostic performance of cFFR and QFR using FFR as a reference index. *Methods*. We conducted a systematic review and meta-analysis of observational studies in which cFFR or QFR was compared to FFR. A bivariate model was applied to pool diagnostic parameters. Cochran's Q test and the I^2 index were used to assess heterogeneity and identify the potential source of heterogeneity by metaregression and sensitivity analysis. *Results*. Overall, 2220 and 3000 coronary lesions from 20 studies were evaluated by cFFR and QFR, respectively. The pooled sensitivity and specificity were 0.87 (95% CI: 0.81, 0.91) and 0.92 (95% CI: 0.88, 0.94) for cFFR and 0.87 (95% CI: 0.82, 0.91) and 0.91 (95% CI: 0.87, 0.93) for QFR, respectively. No statistical significance of sensitivity and specificity for cFFR and QFR were observed in the bivariate analysis ($P = 0.8406$ and 0.4397, resp.). The area under summary receiver-operating curve of cFFR and QFR was 0.95 (95% CI: 0.93, 0.97) for cFFR and 0.95 (95% CI: 0.93, 0.97). *Conclusion*. Both cFFR and QFR have good diagnostic performance in detecting functional severity of coronary arteries and showed similar diagnostic parameters.

1. Introduction

Fractional flow reserve (FFR) is the "gold standard" in current clinical practice to evaluate the functional severity of coronary lesions and guide revascularization. There is solid evidence that using FFR leads to better clinical outcomes and economic value; thus it is included in many guidelines and recommended by professional consensus [1]. Despite its effectiveness, several disadvantages of the method have hindered its continued development. For example, the crucial prerequisite for obtaining FFR is to induce hyperemia by the administration of adenosine or other vasodilators but side effects such as hypotension, bradyarrhythmia, respiratory distress, and patient discomfort are very common [2, 3]. In addition, the specialized wire used for measurement of the pressure index increases medical expenses.

The contrast-FFR (cFFR) and quantitative flow ratio (QFR) are two novel adenosine-free indices which show superior diagnostic accuracy to other adenosine-free options, including resting distal coronary pressure to aortic pressure ratio (Pd/Pa) and instantaneous wave-free ratio (iFR). It appears that either of these methods may serve as alternatives to FFR since both observational studies and meta-analyses show emerging evidence of cFFR and QFR as effective alternatives to FFR [4–7].

According to multiple studies, cFFR exhibits extraordinary capacity in pressure wire-dependent functional coronary lesions evaluation [4, 5]. Contrast is widely used in catheter diagnostics since it can induce submaximal hyperemia of coronary microvasculature. Therefore, cFFR obtained by pressure wire after injection of contrast material can be used to evaluate the functional severity of coronary

stenosis [8]. The reported cut-off values of cFFR ranged from 0.82 to 0.85. One study showed that cFFR reached 85.8% diagnostic agreement with FFR, which was higher than that of Pd/Pa and iFR (78.5% and 79.9%, resp.) [4].

QFR is the computed FFR based on 3-dimensional angiographic reconstruction without pharmacologically induced hyperemia and the use of pressure wire which differentiates it from pressure wire-dependent functional coronary lesions evaluation. The FAVOR studies, among others, demonstrated that QFR has a good diagnostic performance to determine the functional severity of coronary stenosis in reference to FFR [9, 10]. Most studies on QFR shared a universal cut-off value, which was consistent with that of FFR at 0.80. QFR is based on accurate calculation of the pressure drop across a coronary stenosis. There are two main methods to obtain this pressure drop: one is to use computational fluid dynamics (CFD) to perform blood flow simulations and the other is to use a mathematical approach by multiplying the resistance times the volumetric flow. There is no difference regarding sensitivity and specificity between the two methods; however, the latter takes less time, does not require dedicated software, and is used in most studies. Finally, recent evidence shows similar diagnostic accuracy between online and offline analyses of QFR [11].

Recent meta-analyses reviewed major studies focusing on the diagnostic accuracy of cFFR or QFR using FFR as a reference [6, 7, 12]. However, there is still no systematic comparison between cFFR and QFR to evaluate their diagnostic performance. Therefore, this study aimed to deepen our understanding of cFFR and QFR utility in assessing coronary stenosis severity.

2. Methods

This meta-analysis was conducted according to the Preferred Reporting Items for Systematic Review and Meta-Analyses (PRISMA) Statement [13]. Institutional review board approval and informed consent were not required for this systematic review and meta-analysis. The study protocol was prospectively registered with PROSPERO (CRD42019138214) and adhered to the PRISMA guidelines.

2.1. Search Strategy. We searched PubMed, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to collect relevant records to evaluate the diagnostic accuracy of cFFR and QFR with reference to FFR published before June 7, 2019. There was no language restriction on the search. A combination of the National Library of Medicine Medical Subject Headings (MeSH) and Embase subject headings (Emtree) was used with the entry terms "cFFR" OR "QFR" AND "FFR" for a search limited to full-text articles in peer-reviewed journals. Conference abstracts were excluded due to limited data and the potential of bias. When searching with Embase, the publication types were limited to "article" and "article in press" to exclude reviews, editorials, and conference abstracts. The details of the search strategy are shown in Supplementary Materials.

2.2. Selection of Studies. Inclusion criteria were as follows: (1) the accuracy of cFFR or QFR confirmed by FFR as a reference; (2) retrievable true positives, false negatives, false positives, and true negatives to allow construction of a 2×2 contingency table. Studies were excluded if they provided previously reported data or had insufficient data. Electronic records were screened independently by two authors and any discrepancy was resolved by a third investigator.

2.3. Data Extraction and Management. Two investigators conducted data extraction and quality assessment. The following data from the included studies were collected: the first author, publication year, study type, inclusion and exclusion criteria, cut-off values for cFFR/QFR and FFR, diagnostic parameters, general demographics, and characteristics of lesions. Using Review Manager 5.3 (Nordic Cochrane Center, Copenhagen, Denmark) and the Quality Assessment of Diagnostic Accuracy Studies 2 (QUADAS-2) tool, two investigators identified the risk of bias separately and contradictions were judged by a third person. Four key components including patient selection, index test, reference standard, and flow and timing were taken into consideration to judge the risk of bias using a list of 11 signaling questions (with response types: yes, no, or unclear).

2.4. Statistical Analysis. Demographics and other baseline characteristics with continuous distribution were summarized as mean ± standard deviation (SD) or as median (interquartile range). Categorical variables were expressed as number and percentage (%).

True positives, false negatives, false positives, and true negatives were calculated from the reported data as well as sensitivity, specificity, positive, and negative likelihood ratios (LR+ and LR−, resp.), and sample size.

The bivariate mixed-effects regression model was used to pool diagnostic parameters. Cochran's Q test and the I^2 index were calculated to assess potential heterogeneity. Studies with $P < 0.05$ or $I^2 > 50\%$ were regarded as significantly heterogeneous. Metaregression analysis and sensitivity analysis were conducted to identify the source of heterogeneity.

The logit of sensitivity and 1-specificity were used to estimate the Spearman correlation coefficient to investigate the diagnostic threshold effect. Bivariate comparison of sensitivity and specificity between indices (cFFR and QFR) was conducted in the model described by Reitsma et al. [14]. The index was attached to the bivariate model as a covariate to observe the potential diagnostic difference between cFFR and QFR. The logit estimates of sensitivity, specificity, and respective variances were used to delineate a summary receiver-operating characteristic (ROC) curve.

Deek's funnel plot asymmetry test was employed to evaluate publication bias and $P < 0.05$ indicated a significant asymmetry. Statistical analysis was performed using the MIDAS and METAN module for STATA, version 12 (StataCorp, College Station, Texas, USA) with a two-tailed P value and a defined statistical significance of $P < 0.05$.

3. Results

3.1. Characteristics of Included Studies. We screened 279 electronic records (198 for cFFR and 81 for QFR) based on titles and abstracts. Of those, 7 cFFR and 13 QFR studies met the inclusion criteria and were included in the final analysis (Figure 1).

Overall, cFFR was measured in 2220 coronary lesions of 2047 patients and QFR was performed in 3000 coronary lesions of 2588 patients. The mean age of patients was 66.4 (±9.0) years and 3303 (71.3%) of the patients were men. In total, 3246 (70.0%) of the patients were diagnosed with arterial hypertension, 1378 (29.7%) with diabetes mellitus, and 1844 (39.8%) were current or former smokers. Of the total reported patients ($n = 4635$), 27.1% ($n = 1255$) had a previous myocardial infarction. Details from the 20 studies are described in Table 1, while baseline characteristics of the patients and vessels are presented in Tables 2 and 3, respectively. The inclusion and exclusion criteria of the studies are provided in Supplementary Table S1.

In 4 of 7 the cFFR studies, the procedures were performed at a single-center and 3 were multicenter studies. Only 28% of the studies (2 of 7) included centers in Asia. The number of lesions ranged from 34 to 1026 with a median of 104. In 71% of the studies (5 of 7), there was a clear statement regarding a blinded study strategy. To varying degrees, the cut-off values for cFFR were controversial between diagnostic studies, with a range from 0.82 to 0.85, though 0.84 was adopted in more studies (3 of 7). In 7 of 13 QFR studies, data were collected from multiple centers while the others (6 of 13) were single-center studies. Of these studies, nearly 70% of the trials (9 of 13) were conducted in Europe and North America, 3 in Japan, and one in China. The number of included vessels ranged from 49 to 809 (median, 240 vessels). It was clearly stated that a blinded strategy was used in 19 of 20 studies. All QFR studies except one adopted 0.80 as the cut-off value of FFR.

3.2. Diagnostic Performance of cFFR and QFR. As shown in Figure 2, the pooled cFFR yielded a sensitivity of 0.87 (95% CI: 0.81, 0.91) and specificity of 0.92 (95% CI: 0.88, 0.94). The estimate of LR+ and LR− and diagnostic odds ratio were 10.2 (95% CI: 7.8, 13.5), 0.15 (95% CI: 0.10, 0.21), and 70 (95% CI: 51, 96), respectively. The positive predict value (PPV) was 0.88 and negative predict value (NPV) was 0.89. For QFR, the pooled diagnostic parameters were as follows: sensitivity = 0.87 (95% CI: 0.82, 0.91); specificity = 0.91 (95% CI: 0.87, 0.93); LR+ = 9.3 (95% CI: 7.0, 12.4); LR− = 0.14 (95% CI: 0.10, 0.20), and diagnostic odds ratio = 67 (95% CI: 44, 101) (Figure 3). The PPV was 0.84 and NPV reached 0.92. The overall accuracy of cFFR and QFR was 89% and their discordance was 11%. There was no statistical evidence that the expected sensitivity differed between cFFR and QFR ($\chi^2 = 0.04$, $P = 0.8406$) or the specificity ($\chi^2 = 0.60$, $P = 0.4397$). The summary ROC curves of cFFR and QFR are shown in Figure 4. The area under the curve (AUC) was 0.95 (95% CI: 0.93, 0.97) for cFFR and 0.95 (95% CI: 0.93, 0.97) for QFR.

3.3. Heterogeneity Identification and Metaregression Analysis. Analysis of the diagnostic threshold effect was conducted and the resulting Spearman's correlation coefficient was not significant. The correlation coefficient of QFR was 0.162 ($P = 0.596$), while that of cFFR was 0.119 ($P = 0.779$). The proportion of heterogeneity due to the threshold effect was 0.29, denoting no evidence of a threshold effect.

Significant heterogeneity was found between studies for pooled sensitivity ($I^2 = 78.70\%$, $P < 0.01$) and specificity ($I^2 = 59.4\%$, $P < 0.01$) of cFFR and sensitivity ($I^2 = 78.1\%$, $P < 0.01$) and specificity ($I^2 = 78.5\%$, $P < 0.01$) of QFR. Metaregression was performed to identify sources of significant heterogeneity, while study factors including the study quality (whether there are risks of bias evaluated by QUADS-2), number of centers (single or multiple), study design (prospective or retrospective), and baseline characteristics were defined as covariates. No baseline characteristics were identified as contributing to heterogeneity in the cFFR or QFR studies when metaregression was performed (Figures S1 and S2). All 3 study factors contributed to the heterogeneity of the cFFR specificity and the QFR sensitivity and specificity. The study quality and the number of centers had an effect on the heterogeneity for cFFR sensitivity. Sensitivity analysis was performed to identify the robustness of cFFR and QFR studies, which revealed that Johnson's study was the source of heterogeneity of cFFR sensitivity and specificity and Stahi's study was most likely the source of QFR heterogeneity of specificity (Tables S2–S5).

3.4. Quality Assessment and Publication Bias. The methodological quality of the cFFR and QFR studies is summarized in Figures S3 and S4, respectively. The overall quality of cFFR studies varied from moderate to high. Low risk of bias was achieved in 11 studies according to four areas including patient selection, index test, reference standard, and flow and timing in the QFR literature. The unclear risk of bias was obtained in 4 studies in cFFR studies. All studies maintained low concern regarding applicability for patient selection, index test, and reference standard. For the index test, only one study had an unclear risk of bias due to undeclared blinded strategy. The reference standard appeared to be the most important source of bias for reference standards interpreted without knowledge of the results of the index tests. For applicability, all studies except two had low concerns. Sensitivity analysis was performed to identify the robustness of cFFR and QFR studies. As a result, the QFR studies had higher quality than the cFFR studies. As shown in Figures S5 and S6, there is no evident publication bias for cFFR ($P = 0.16$) or QFR ($P = 0.91$) according to Deek's asymmetry test.

4. Discussion

Evidence comparing diagnostic accuracy between cFFR and QFR is absent from the literature. Therefore, this meta-analysis aimed to provide updated evidence. Our findings demonstrate that both cFFR and QFR have good diagnostic performance, when referenced to FFR, with similar pooled sensitivity, specificity, AUC, and overall accuracy.

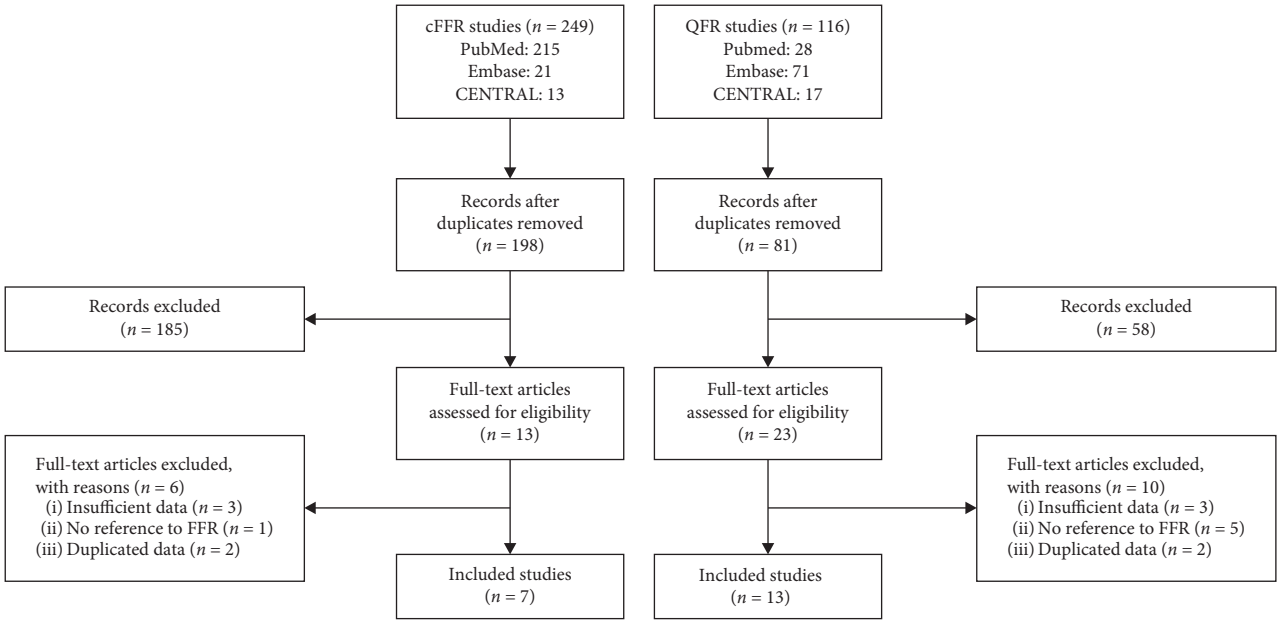

Figure 1: Flow-diagram of search and selection strategy.

Table 1: Study characteristics.

Included studies, author (reference number)	Year	No. of lesions	Type of study	FFR cut-off	cFFR/QFR cut-off
cFFR					
Johnson et al. [4]	2016	763	Multicenter, prospective	0.80	0.83
Topcu et al. [15]	2016	34	Single-center, prospective	0.80	0.85
MEMENTO-FFR [5]	2016	1026	Multicenter, retrospective	0.80	0.85
Kanaji et al. [16]	2016	80	Single-center, prospective	0.80	0.84
Shiode et al. [17]	2017	109	Single-center, prospective	0.80	0.82
Van Wyk et al. [18]	2017	100	Single-center, prospective	0.80	0.84
Cerrato et al. [19]	2018	108	Multicenter, prospective	0.80	0.84
QFR					
FAVOR pilot [9]	2016	84	Multicenter, prospective	0.80	0.80
Yazaki et al. [20]	2017	151	Single-center, retrospective	0.80	0.80
FAVOR II China [10]	2017	328	Multicenter, prospective	0.80	0.80
Spitaleri et al. [21]	2018	49	Single-center, prospective	0.80	0.80
Emori et al. [22]	2018	100	Single-center, retrospective	0.80	0.80
Ties et al. [23]	2018	101	Single-center, retrospective	0.80	0.80
Emori et al. [24]	2018	150	Single-center, retrospective	0.800	0.80
WIFI II [25]	2018	240	Multicenter, prospective	0.80	0.80
Mejia-Renteria et al. [26]	2018	300	Multicenter, prospective	0.80	0.80
Kołtowski et al. [27]	2018	306	Single-center, retrospective	0.80	0.79
FAVOR II Eur-Japan [28]	2018	317	Multicenter, prospective	0.80	0.80
Hwang et al. [29]	2019	358	Multicenter, prospective	0.80	0.80
Stähli et al. [30]	2019	516	Single-center, prospective	0.80	0.80

Three previous meta-analyses assessed the diagnostic parameters of QFR for detecting significant coronary stenosis. The reliability of the analysis may have been affected by the lack of current studies and the inclusion of a conference abstract [7, 11, 12]. Another meta-analysis included 4 well-designed multicenter prospective studies, in which the QFR calculation followed a strict procedure and finished by well-trained operators, but the study sample was relatively small. It may be that the diagnostic performance of QFR in clinical practice is difficult to ascertain because it relies on clinical staff for accuracy and there are different protocols in each setting [12].

In the present analysis, significant heterogeneity was found in cFFR and QFR sensitivity and specificity. The sensitivity and specificity of the CONTRAST study differed from those of the rest of the cFFR studies and the results did not overlap the overall 95% CI. The CONTRAST study was a multicenter prospective trial to investigate cFFR, iFR, and Pd/Pa agreement with binary FFR ≤ 0.80 [4]. The study included 763 patients undergoing routine FFR assessment

Table 2: Baseline patient characteristics.

Included studies	No. of patients	Age (y) ± SD	Male (%)	Diabetes (%)	Smoking (%)	Hypertension (%)	Dislipidemia (%)	Prior MI (%)
cFFR								
Johnson et al. [4]	763	66 ± 10	72	29	48	71	67	26
Topcu et al. [15]	28	63.4 ± 12.8	79	18	61	39	—	46
MEMENTO-FFR [5]	926	68	68	33	40	82	64	26
Kanaji et al. [16]	75	66.6 ± 10.3	79.3	40.8	69.2	63.8	45	—
Shiode et al. [17]	93	70.4 ± 8.7	73.1	35.0	24.0	73.0	54	10
Van Wyk et al. [18]	76	65.6	75	15.8	9.2	51.3	76.3	—
Cerrato et al. [19]	86	66.7 ± 9.9	80.2	34.9	47.7	80.2	55.8	60.5
QFR								
FAVOR pilot [9]	73	65.8 ± 8.9	83.5	27.4	—	43.8	—	31.5
Yazaki et al. [20]	142	72.5 ± 9.5	70.4	28.9	23.2	—	62	40.8
FAVOR II China [10]	308	61.3 ± 10.4	73.4	27.9	87	60.1	45.1	15.6
Spitaleri et al. [21]	45	62 ± 11	36	4	19	29	47	8.3
Emori et al. [22]	100	70 ± 10	71	48	21	73	58	22
Ties et al. [23]	96	63.9 ± 10.3	60.4	25.0	52.8	70.8	72.9	46.2
Emori et al. [24]	150	69.5 ± 9	77.3	46.7	26.7	83.3	61	25
WIFI II [25]	191	61 ± 8	67	10	59	70	—	40
Mejia-Renteria et al. [26]	242	64.2 ± 10.3	76	38	23	66	58	19
Kołtowski et al. [27]	268	66.3 ± 9.98	72	28	10.4	75.7	54.5	47.8
FAVOR II Eur-Japan [28]	272	67 ± 10	72	29	57	74	68	4
Hwang et al. [29]	265	60.6 ± 13.3	76.9	33.0	*17.8	50.4	59.1	6.1
Stähli et al. [30]	436	71.5	67.9	22.5	34	87.8	79.1	32.8

*Current smoker; MI: myocardial infarction.

Table 3: Baseline angiographic characteristics.

Included studies	No. of lesions	LAD (%)	LCX (%)	RCA (%)
cFFR				
Johnson et al. [4]	763	60	18	18
Topcu et al. [15]	34	62	24	14
MEMENTO-FFR [5]	1026	—	—	—
Kanaji et al. [16]	80	64.2	13.3	22.5
Shiode et al. [17]	109	83	3	23
Van Wyk et al. [18]	100	61	17	15
Cerrato et al. [19]	108	16.7	15.7	—
QFR				
FAVOR pilot [9]	84	54.8	14.3	22.6
Yazaki et al. [20]	151	63.6	16.6	17.2
FAVOR II China [10]	328	55.7	14.8	26.2
Spitaleri et al. [21]	49	—	—	—
Emori et al. [22]	100	63	23	14
Ties et al. [23]	101	—	—	—
Emori et al. [24]	150	64.7	11.3	24.0
WIFI II [25]	240	51	11	18
Mejia-Renteria et al. [26]	300	59.0	12.3	16.3
Kołtowski et al. [27]	306	56.9	10.1	26.5
FAVOR II Europe-Japan [28]	317	50	16	22
Hwang et al. [29]	358	62.3	19.0	18.7
Stähli et al. [30]	516	55.6	13.0	23.1

LAD: left anterior descending artery; LCX: left circumflex artery; RCA: right coronary artery.

for standard indications and all patients received FFR, cFFR, iFR, and Pd/Pa. All pressure tracings were standardized and centrally reviewed by a core laboratory. The other cFFR studies were of moderate quality due to their single-center design, small sample size, nonconsecutive population, and lack of a rigorous blinding method, which may be the source

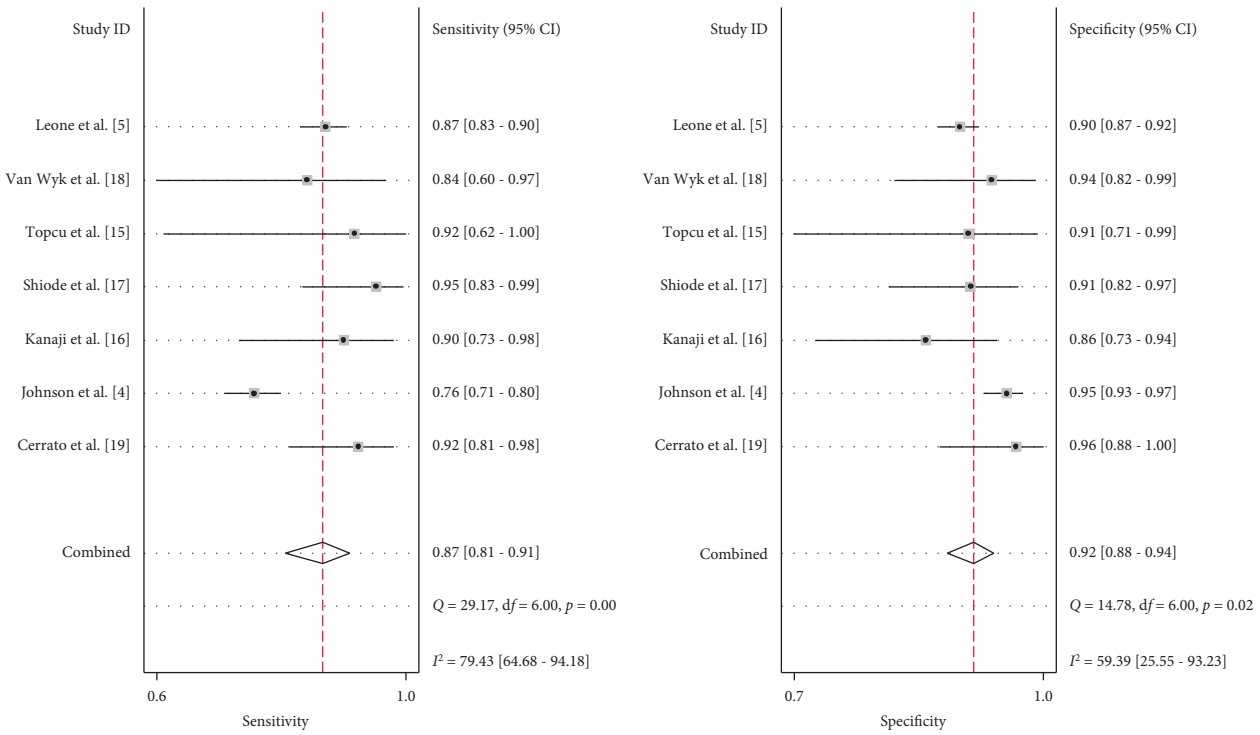

Figure 2: Forest plots for sensitivity and specificity of cFFR. CI: confidence intervals.

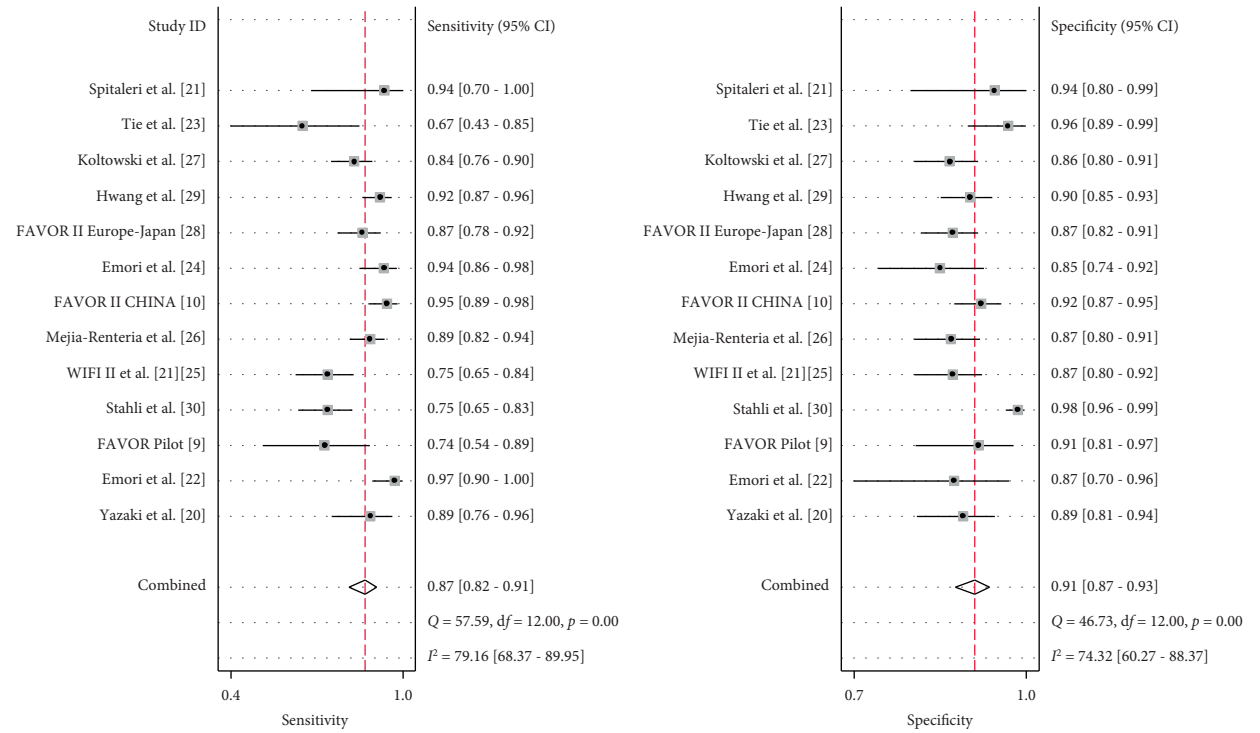

Figure 3: Forest plots for sensitivity and specificity of QFR. CI: confidence intervals.

of potential bias. Exclusion of the CONTRAST study remarkably improved the heterogeneity. Considering the level of heterogeneity between CONTRAST and other studies, it is evident that more well-designed trials are necessary to verify the diagnostic performance of cFFR.

Although studies focused on QFR and cFFR commenced around the same time, QFR attracted more extensive interest. As a result, there are more QFR clinical trials available to analyze (13 vs. 7) and most QFR studies had a higher quality than the cFFR studies. Regardless, the heterogeneity

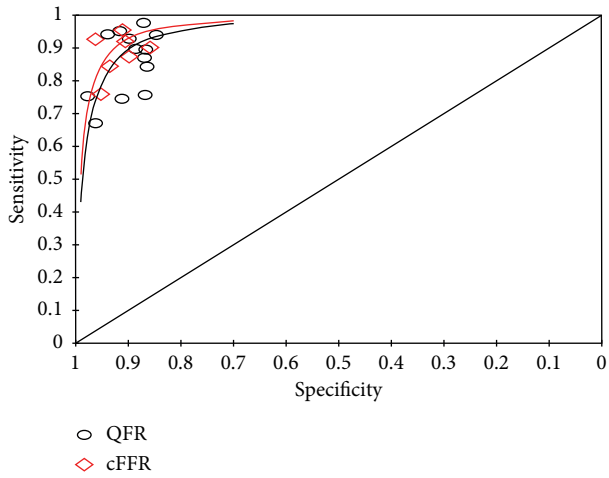

Figure 4: Summary receiver-operating characteristic curve for cFFR and QFR.

of sensitivity and specificity for QFR studies were still significant. In metaregression, we identified some factors influencing heterogeneity, but the limited number of studies made it unreliable to undertake subgroup analysis. By reviewing the current meta-analysis of cFFR and QFR, we found that heterogeneity of the correlation values of cFFR ($I^2 = 81.00\%$) [6] and sensitivity and specificity of QFR (I^2 ranged from 70.1% to 72.07% and 24.1% to 60.1%, resp.) [7, 12] both are high. However, despite the large heterogeneity, we found that our research reported consistent results with previous studies, which reported that the sensitivity and specificity of cFFR were 88% and 93%, while the reported sensitivity of QFR ranged from 84% to 89%, with the specificity being 88% [6, 7, 12]. At the same time, observational studies and a meta-analysis have shown that the diagnostic accuracy of cFFR and QFR was better than that of iFR, suggesting that both may have similar diagnostic accuracy. Therefore, our results should be reasonable and informative.

Compared to adenosine, the contrast medium used in cFFR is more accessible and is associated with fewer side effects [5]. In 1959, an animal experiment first reported that contrast material induced significant coronary hyperemia [31]. Further human study demonstrated that contrast material could reach approximately 60% of the maximal flow velocity as compared to adenosine, which produced a difference of only 6% in terms of FFR [32]. The possible mechanism is that osmolality triggers the potassium channel of the vascular endothelial cell, which is independent of the nitric oxide pathway [33]. According to this, Lenone conducted a multicenter RINASCI study to test the diagnostic performance of cFFR using FFR as a reference. This began an era of interest in cFFR since the study showed that cFFR was significantly correlated to FFR, indicating excellent accuracy. Thereafter, a few single- and multicenter studies revealed similar results [34]. Most cFFR studies investigated the diagnostic accuracy of Pd/Pa and a few cFFR studies compared the diagnostic accuracy of iFR to cFFR at the same time. The results were consistent between studies which showed that cFFR provided superior diagnostic accuracy to iFR and Pd/Pa and was confirmed by a meta-analysis [4, 5, 6, 16].

Although many limitations and concerns about coronary angiography (CAG) persist, a 3D reconstruction model of the target vessel and the contrast-flow velocity can be obtained from CAG images, which allow us to compute QFR by software online or offline without the need for pressure wires. This procedure takes less time than FFR (median time, 5 min vs. 7 min) and needs no other operation except for acquiring 2 diagnostic angiographic projections at least 25° apart [28]. There are 3 different flow simulation models available: fixed-flow QFR (fQFR), contrast-flow QFR (cQFR), and adenosine-flow QFR (aQFR). Of these, cQFR allows for better discrimination between functionally significant and nonsignificant stenosis than fQFR and avoids pharmacologic hyperemia compared to aQFR. Therefore, it is the major index in most QFR studies including the present meta-analysis [9]. The FAVOR II China study was the first clinical trial with adequate statistical power to examine the diagnostic performance of QFR and along with further trials demonstrated good diagnostic accuracy and clinical feasibility. Studies that directly compare QFR to iFR or Pd/Pa are absent or few, but meta-analysis revealed that QFR has higher sensitivity and specificity than iFR [7]. Since it has the advantage of not needing pressure wire or adenosine and there is a reduction in procedure time, QFR appears as a safe and cost-reducing diagnostic method applicable for the larger population to simplify the process of physiological evaluation of coronary stenosis.

Our results indicated that both cFFR and QFR are promising tools to guide coronary revascularization. The present findings regarding higher NPV in QFR imply that a negative QFR result is more reliable in excluding the hemodynamic significance of a coronary lesion. Therefore, a hybrid strategy to assess revascularization treatment that only measures FFR in QFR "gray zone" lesions will reduce the use of adenosine on the premise of sufficient diagnostic accuracy. However, evidence comparing the clinical outcomes of cFFR- or QFR- with FFR-guided strategy is needed to widely use this strategy in the clinical setting. To this end, 2 large randomized controlled trials investigating clinical outcomes of QFR-based diagnostic strategy compared to FFR- and CAG-guided strategy are in the recruiting process and initial results are expected to be available in 2020. This includes the FAVOR III Europe-Japan Study (ClinicalTrials.gov Identifier: NCT03729739) and FAVOR III China study (ClinicalTrials.gov Identifier: NCT03656848), which will deepen our understanding of QFR-guided strategy on clinical outcomes [35, 36], yet a related cFFR study is still missing.

There are still obstacles before cFFR and QFR are recommended for clinical practice. For cFFR, it is impossible to evaluate serial or diffused lesions through pull-back because of the short duration (13 sec) of hyperemia induced by contrast [37]. Additionally, the exact volume and type of contrast material to evaluate cFFR is controversial and varies between cFFR studies, usually 5–6 ml for right coronary arteries and 8–10 ml for left coronary arteries. Subgroup

analysis of MEMENTO-FFR and CONTRAST studies showed that the overall accuracy of cFFR was not significantly affected by contrast volume and osmolality [5, 38]. However, Spagnoli et al. found that the hyperemia condition increased with contrast volumes from 6 to 10 ml. Discordant conclusions from different studies imply that further research is needed to elucidate the effect of contrast volume on hyperemia [37]. Lastly, the risk of contrast-induced nephropathy from cFFR is unknown, but the volume of contrast medium is usually 5–12 ml in previous studies which should have little effect on renal function. QFR also has its limitations. Accurate QFR calculation is a semiautomatic frame count method based on high-quality angiography, which is subjective and inconvenient [9]. Any factor influencing the quality of the angiography and determination of vessel outlines will lessen the diagnostic accuracy of QFR. In several observational studies comparing QFR and FFR, common clinical conditions were excluded from the analysis (such as presence of complex lesions, bifurcations, and medical history of recent myocardial infarction or coronary artery bypass grafting); thus it is difficult to estimate the functional significance in these settings [10]. Recently, a novel automatic method of QFR computation provides good diagnostic accuracy in determining the functional significance of coronary stenosis, which may accelerate the application of QFR in daily practice [39].

4.1. Limitations. There are a few limitations of our study to consider. First, there were fewer available cFFR studies than QFR studies (7 vs. 13) and there were no studies comparing cFFR and QFR directly. Therefore, further study is needed to compare diagnostic performance. Secondly, high-quality cFFR studies were relatively rare and cut-off values of cFFR to determine the functional severity of coronary stenosis differed between studies, which made it difficult to accurately compare cFFR sensitivity and specificity. Lastly, significant heterogeneity existed in our study despite the negative metaregression of population characteristics; thus well-designed prospective clinical trials are needed to understand cFFR- and QFR-guided assessments in complex clinical settings.

5. Conclusion

The diagnostic performance of QFR and cFFR using FFR as a reference had similar sensitivity, specificity, and AUC. Both emerged as safe, simple, and cost-saving alternatives to FFR for determining the functional severity of coronary stenosis. Considering that it does not utilize a pressure wire and has accumulated more study data, QFR is more competitive than cFFR. However, it should be noted that our conclusion should be seen in the context of the observed heterogeneity. Clinical trials are warranted to confirm these data in a clinical setting.

Abbreviations

AUC: Area under the curve
CFD: Computational fluid dynamics
cFFR: contrast-fractional flow reserve
DOR: Diagnostic odds ratio
FFR: Fractional flow reserve
LR: Likelihood ratios
NPV: Negative predict value
PPV: Positive predict value
QFR: Quantitative flow ratio
SD: Standard deviation.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors have no conflicts of interest to declare.

Authors' Contributions

Ruitao Zhang and Jianwei Zhang contributed equally to this paper. Lijun Guo conceived and designed the study, judged the contradictions of the other two authors, and interpreted the results. Ruitao Zhang and Jianwei Zhang contributed equally to this work. Ruitao Zhang and Jianwei Zhang performed study search, data extraction, and quality assessment separately. Jianwei Zhang performed data analysis. Ruitao Zhang drafted the manuscript. All the authors read and approved the final version of the manuscript.

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Supplementary Materials

(1) Search strategy for PubMed, Embase, and CENTRAL. (2) Table S1: inclusion and exclusion criteria of included studies. (3) Tables S2–S5: sensitivity analysis of cFFR and QFR. (4) Figures S1–S2: metaregression analysis of cFFR and QFR. (5) Figures S3–S4: methodological quality of included studies for cFFR and QFR. (4) Figures S5-S6: Deek's funnel plot for cFFR and QFR studies. (*Supplementary Materials*)

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