ARTICLE

Diagnostic performance of angiography-derived fractional flow reserve and CT-derived fractional flow reserve: a systematic review and bayesian network meta-analysis

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Abstract

Objective

Accumulating evidence has demonstrated that fractional flow reserves (FFRs) derived from invasive coronary angiograms (CA-FFRs) and coronary computed tomography angiography-derived FFRs (CT-FFRs) are promising alternatives to wire-based FFRs. However, it remains unclear which method has better diagnostic performance. This systematic review and meta-analysis aimed to compare the diagnostic performances of the two approaches.

Methods

The Cochrane Library, PubMed, Embase, MEDLINE (Ovid), the Chinese China National Knowledge Infrastructure Database (CNKI), VIP, and WanFang databases were searched for relevant studies that included comparisons between CA-FFR and CT-FFR, from their respective database inceptions until January 1, 2023. Studies where both non-invasive FFR (including CA-FFR and CT-FFR) and invasive FFR (as a reference standard) were performed for the diagnosis of ischemic coronary artery disease and were designed as prospective, paired diagnostic studies, were pulled. The diagnostic test accuracy method and Bayesian hierarchical summary receiver operating characteristic (ROC) model for network meta-analysis of diagnostic tests (HSROC-NMADT) were both used to perform a meta-analysis on the data.

Results

Twenty-six studies were included in this network meta-analysis. The results from both the diagnostic test accuracy and HSROC-NMADT methods revealed that the diagnostic accuracy of CA-FFR was higher than that of CT-FFR, in terms of sensitivity (Se; 0.86 vs 0.84), specificity (Sp; 0.90 vs 0.78), positive predictive value (PPV; 0.83 vs. 0.70), and negative predictive value (NPV; 0.91 vs. 0.89) for the detection of myocardial ischemia. A cumulative ranking curve analysis indicated that CA-FFR had a higher diagnostic accuracy than CT-FFR in the context of this study, with a higher area under the ROC curve (AUC; 0.94 vs. 0.87).

Conclusions

Although both of these two commonly used virtual FFR methods showed high levels of diagnostic accuracy, we demonstrated that CA-FFR had a better Se, Sp, PPV, NPV, and AUC than CT-FFR. However, this study provided only indirect comparisons; therefore, larger studies are warranted to directly compare the diagnostic performances of these two approaches.

Keywords

Virtual fractional flow reserve, Coronary computed tomography angiography, Invasive coronary angiogram, Diagnostic performance, Network meta-analysis

1 INTRODUCTION

Current guidelines at the highest level recommend the use of fractional flow reserve (FFR) for the functional assessment of coronary arteries in patients with stable coronary artery disease (SCAD). However, FFR has been difficult to popularize in clinical practice due to its high cost and patient discomfort caused by vasodilators. To address this challenge, interventional cardiologists started to use the instantaneous wave-free ratio (IFR) as an alternative strategy to conventional invasive FFR.[1,2] Although vasodilators are not required for IFR measurements, it is still necessary to operate a pressure guidewire through the lesion. With the rapid development of computer science and artificial intelligence in recent years, engineers have developed several virtual FFR techniques based on the anatomical properties of the coronary arteries that rely entirely on computer algorithms.[3,4] These allow for a faster, cheaper, and safer functional assessment of coronary lesions. Invasive angiogram (ICA)-derived FFRs (CA-FFRs) and coronary computed tomography (CT) angiography (CCTA)-derived FFRs (CT-FFRs) are the two most widely used virtual FFR methods. A recent meta-analysis showed that both CT-FFR and CA-FFR had high levels of sensitivity (Se) and specificity (Sp) for predicting FFRs $\leqslant$ 0.8.[5,6] However, to the best of our knowledge there have been no studies published so far that have determined which of the two has the better diagnostic accuracy. The aim of this network meta-analysis was to compare the diagnostic performances of CT-FFR and CA-FFR.

Diagnostic test accuracy (DTA) assesses one diagnostic indicator at a time, falling short of comparing new criteria with gold standards. A DTA network meta-analysis (DTA-NMA) now enables multiple diagnostic tests to be evaluated concurrently. Another Bayesian method, the hierarchical summary receiver operating characteristic (ROC) model for network meta-analysis of diagnostic tests (HSROC-NMADT), uniquely incorporates test correlations, study heterogeneity, and variable diagnostic test subsets.

In this study, both traditional DTA and the HSROC-NMADT method were used to compare the diagnostic accuracies of CA-FFR and CT-FFR.

2 METHODS

2.1 Search strategy

This meta-analysis was reported in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement.[7] The study protocol was registered with PROSPERO (ID: CRD42022329151) at the onset. We systematically searched the PubMed, Embase, Ovid MEDLINE, and Cochrane Library databases for relevant studies from their respective inceptions to January 1, 2023. We then manually searched the Chinese China National Knowledge Infrastructure Database (CNKI), VIP Database, and WanFang Database as well. The following medical subject headings terms and keywords were used to identify relevant articles:

"fractional flow reserve" or "FFR" or "virtual fractional flow reserve" or "virtual FFR" or "noninvasive fractional flow reserve" or "noninvasive FFR", "diagnostic accuracy" or "diagnostic performance" or "diagnosis accuracy" or "diagnosis test" and "prospective" or "prospectively". Only prospective head-to-head comparison studies were included; other study designs such as retrospective studies were excluded. The references of the pulled studies were also checked for suitable articles. No language restrictions were applied.

2.2 Study selection

Several assessments were performed, followed by the removal of duplicate articles after the initial screening. The titles and abstracts of relevant publications were further screened for suitability before full article retrieval. Meeting abstracts, editorials, and reviews were also excluded. In this study, CT-FFR was defined as the calculation of virtual FFR based on CCTA images and CA-FFR was defined as a virtual FFR derived from a computational analysis of coronary angiography images. We included studies where: 1) the type of virtual FFR was either CT-FFR or CA-FFR; 2) invasive FFR was used as the gold standard comparison; 3) the enrollment of all patients in the study was

prospective; and 4) indicators such as true positive (TP), true negative (TN), false positive (FP), false negative (FN) were available. In cases where TP, TN, FP, or FN were not reported, they were calculated from the known variables. We excluded any studies for which we were unable to obtain all of these parameters. Three investigators (ZXC, JYZ, and YJC) independently reviewed all retrieved studies, and differences were resolved through discussion.

2.3 Data extraction and quality assessment

Study data, including the first author's name, sample size, clinical baseline characteristics, vascular lesion characteristics, types of algorithms and software, Se, Sp, cutoff value and others were independently extracted by three investigators (JYZ, ZXC, CL). The study quality was independently evaluated by two cardiologists (JYZ and ZXC) according to the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) criteria.[8]

2.4 Statistical analysis

The diagnostic accuracy measures included in this study were commonly used indicators, such as Se and Sp. The analysis was conducted on a per-vessel basis. DTA studies can include different subsets of index tests, and the reference standard used may be imperfect. In the past, most DTA meta-analyses were only able to assess one measurement of diagnostic performance at a time. In practice, there may be many measurements available for the target condition. For clinical decision-making, interest is often in the comparative accuracies of index tests (i.e., how does the accuracy of a new test compare to that of existing test[s] or current practice?).

More recently, DTA-NMA has been introduced to compare the accuracies of multiple index tests. It borrows strength from indirect evidence, which can improve statistical accuracy and reduce bias when comparing test accuracy. DTA-NMA concurrently models the accuracies of different index tests and (1) results in diagnostic accuracy

estimates with higher levels of precision; (2) allows inferences to be drawn regarding differences in levels of accuracy between tests that could not be compared head-to-head previously; and (3) ranks the performances of multiple tests according to their diagnostic accuracy, at varying test thresholds (if applicable), using all of the available evidence.

Several models designed for DTA-NMA,[9-18] along with two hierarchical meta-regression methods,[9,11] facilitate comparative meta-analyses. DTA-NMA models—mostly Bayesian—offer an advantage by considering within-study test correlations when primary studies use within-participant designs. The choice of DTA-NMA model depends on data specifics—including test thresholds, reference standards, and study designs. The HSROC-NMADT method requires a joint classification data format, accommodating imperfect reference standards and multiple thresholds through a Bayesian approach. It handles test correlations and study heterogeneity, allowing flexibility in the choice of summary statistics. HSROC-NMADT treats all studies as if they used a crossover design, where all patients underwent both index and gold standard tests. In cases where a study's reference test is not a gold standard, it is treated as an index test. If a test was not evaluated, its results were handled as missing data in a missing data framework.

2.4.1 Meta-analysis of diagnostic test accuracy

Pooled Se, Sp, positive predictive value (PPV), negative predictive value (NPV), and diagnostic odds ratio (DOR) were calculated for each virtual FFR test. The pooled DOR is a single indicator of test performance that pools the diagnostic measures of a diagnostic test. It is defined as the ratio of the odds of the TP relative to the odds of the FP. We used the bivariate random-effects model for our analysis, along with pooling of the diagnostic performance measures across the studies, as well as comparisons between different index tests. The bivariate model estimates pairs of logit-transformed Se and Sp from studies, incorporating any correlations that might exist between Sp measurements from different studies.[9,19] Forest plots were created to display the point

estimate and 95% confidence intervals (CIs) for the selected statistics. We developed a hierarchical summary receiver operating curve (HSROC) and calculated the area under the curve (AUC) to examine the diagnostic accuracy of each virtual FFR test. Heterogeneity among the outcomes of the included studies in this meta-analysis was evaluated using Cochran's Q test and the I^2 statistic. Significant heterogeneity was indicated by $p < 0.10$ in Cochran's Q tests and a ratio of > 50% in the I^2 statistic.

We included enough studies (n > 10) to conduct meta-regression analyses to search for sources of heterogeneity in the relative DORs (RDORs) of CA-FFR and CT-FFR. Pre-specified subgroup analyses were conducted according to whether severe distorted calcified lesions were included, whether strict inclusion criteria of target vessel stenosis were used, and whether each study was investigator-initiated.

Statistical analyses were performed using Stata 16.0, RevMan 5.3 (The Cochrane Collaboration), and Meta-Disc softwares. The statistical significance level was set at $p < 0.05$.

2.4.2 Network meta-analysis

Our network meta-analysis (NMA) was performed using the HSROC-NMADT method.[10] For assessing the diagnostic values of the methods, analyses were performed to estimate the odds ratios (ORs) of the detection of recurrence and 95% CIs for Se, Sp, PPV, and NPV values in the included manuscripts.

According to a previously described protocol, a prior distribution (prior probability) was first selected.[20,21] Second, the likelihood was calculated from the data and a Bayesian hierarchical model was created within the NMA. Third, prior distribution and likelihood were entered as inputs to a Markov Chain Monte Carlo (MCMC) simulation, and a distribution that best converged the posterior distribution was set. The probability of stable distribution and the area under the posterior distribution function were determined using the MCMC simulation. Finally, statistical reasoning for the treatment effect was performed using the determined posterior distribution. For the MCMC simulation, we selected a random-effects model that had

three chains, 5,000 burn-ins, 50,000 iterations, and an interval of 5, to sufficiently remove the effects of initial values. For our consistency test, we performed node-splitting assessments to determine the association between the direct and indirect evidence.

To assist in the interpretation of diagnostic performance, the surface under the cumulative ranking curve (SUCRA) was used to calculate the probability of each test, to reveal the most effective diagnostic method based on a Bayesian approach using probability values. A higher SUCRA value therefore indicated a better ranking for the given intervention.[10,20] R version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria) and Stata 16.0 software were used for the NMA analysis.

2.4.3 Publication bias

Publication bias was assessed visually using a scatterplot of the inverse of the square root of the effective sample size vs the diagnostic natural logarithm of the odds ratio (lnDOR), which exhibits a symmetrical funnel shape when publication bias is absent. Formal testing for publication bias was conducted using a regression of lnDOR against the inverse of the square root of the effective sample size, with weighting done via ESS. A p value < 0.05 for the slope coefficient was taken to indicate significant asymmetry.[22]

3 RESULTS

3.1 Study selection

We identified 875 publications. Of these, 133 were found to be duplicates. Twenty-six of the remaining studies met our inclusion criteria. Details of the search strategy are shown in Fig.1.

3.2 Study characteristics and quality assessment

We included 26 studies (3,804 patients, 5,124 vessels), of whom 16 directly compared the diagnostic accuracies of CT-FFR to the invasive FFR gold standard, and 10 directly compared CA-FFR to the same gold standard. All of the included studies were diagnostic trials that used a matched design. Details regarding the listed studies are

reported in Table 1-5. The participants ranged in number from 19–308, and the number of target vessels ranged from 35–484. The studies were published between November 2011 and October 1, 2022. One study[23] respectively compared both CA-FFR and CT-FFR techniques to the gold standard, but did not perform a direct comparison between the two. We therefore grouped their two datasets into different groups and considered them two separate studies for the purposes of our statistical analysis.

The results of the QUADAS-2 scale analysis of the included studies are shown in Fig. 2. Most of the studies were judged to have low risks of bias. Concerns regarding applicability were low for most of the evaluated studies.

3.3 Meta-analysis of diagnostic test accuracy

All of the included studies provided data that permitted the extraction of TP, FP, TN, and FN, according to the reference standard used (Fig. 3a,b). Reference standard FFR is an invasive hemodynamic index of blood flow reserve fraction based on pressure guidewires. It is the ratio of the maximum perfusion that a diseased coronary vessel can provide to the maximum perfusion that the vessel could theoretically provide in the absence of stenosis.

In 10 of the studies (1,731 patients, 2,039 vessels) that used ICA-derived FFR—most of which set its threshold to 0.8 (Table 3)—Se varied between 0.67–1.00, while Sp varied between 0.82–0.96 (Fig. 3a). The meta-analytic estimates were 0.86 (95% CI: 0.81, 0.90) for Se and 0.90 (95% CI: 0.86, 0.93) for Sp (Table 6). This meant that there were very few false positives but several false negatives for CA-FFR; therefore, the test was more useful for ruling-in the disease when positive.

Similarly, in 16 of the studies (1,739 participants, 2,751 vessels) that used CT-FFR (also most often at a threshold of almost 0.8 [Table 3]), a high Se was achieved (0.75–0.97) but Sp varied between 0.62–0.87 (Fig. 3b). The meta-analytic estimates were 0.84 (95% CI: 0.81, 0.86) for Se and 0.78 (95% CI: 0.73, 0.82) for Sp (Table 6).

In terms of the HSROC analysis, the overall curve for CA-FFR was closer to the upper left corner, implying that its overall diagnostic efficacy may be higher than that

of CT-FFR (Fig. 4). In terms of the AUC analysis, CA-FFR (0.94; 95% CI: 0.92, 0.96) had a larger AUC area than CT-FFR (0.87; 95% CI: 0.84, 0.90), which again suggests that CA-FFR may have a better diagnostic efficacy (Table 6).

3.4 Network meta-analysis result

All 26 studies were included in the NMA.[23–47] The diagnostic values of CT-FFR, CA-FFR, and invasive FFR for diagnosing hemodynamically significant coronary artery disease are shown within network plots in Fig. 5, which graphically depict the networks of eligible comparisons. The results of this NMA revealed that the diagnostic accuracy of the CA-FFR test was higher than that of the CT-FFR test, with better Se (0.86 vs 0.84), Sp (0.90 vs 0.78), PPV (0.83 vs 0.70), and NPV (0.91 vs 0.89) values for the detection of myocardial ischemia (Table 7).

In terms of the cumulative ranking curve, the integration curve for CA-FFR concentrated more toward the upper-left, while the curve for CT-FFR tended toward the lower-right. This indicated that CA-FFR had a higher diagnostic accuracy than CT-FFR in the context of this study (Fig. 6).

3.5 Subgroup analyses

We investigated the effects of various factors on the diagnostic accuracies of CA-FFR and CT-FFR. The result of our meta-regression showed that the chosen factors were highly correlated and had no statistical significance ($p > 0.05$). In our subgroup analysis, the following factors were evaluated: whether severe distorted calcified lesions were included, whether strict inclusion criteria of target vessel stenosis were used, and whether the study was investigator-initiated. None of these factors affected the diagnostic accuracy of CA-FFR (Supplementary Fig. 1a). However, whether strict inclusion criteria for target vessel stenosis were used significantly affected the diagnostic accuracy of CT-FFR ($p = 0.002$, Supplementary Fig. 1b).

3.6 Publication bias

The funnel plot asymmetry test developed by Deek was used to evaluate publication bias. The plot had a form that resembled a symmetrical funnel, and the Deek's funnel

plot asymmetry test had a p value of 0.05. This indicated that there was no significant publication bias (Fig. 7).

4. DISCUSSION

To the best of our knowledge, this is the first network meta-analysis aimed at comparing the performance of CA-FFR and CT-FFR for the diagnosis of hemodynamically significant coronary artery disease using the HSROC-NMADT method. All of the studies included were determined to be of good quality. The main finding of this study was that CA-FFR had better diagnostic accuracy than CT-FFR in terms of Se (0.86 vs 0.84), Sp (0.90 vs 0.78), PPV (0.83 vs 0.70), NPV (0.91 vs 0.89), and AUC, using a Bayesian meta-analysis method.

The advantage of CA-FFR over CT-FFR was reflected particularly in terms of Sp and PPV. This suggests that the former has a significantly lower rate of misdiagnosis and better identifies authentic myocardial ischemia than the latter. On the other hand, CT-FFR, although relatively poor in terms of Sp, did not differ much in terms of Se and NPV when compared with CA-FFR. As a completely noninvasive virtual FFR technique, CT-FFR, with its high Se, may therefore represent an effective tool for screening ischemic heart disease in the future.

The virtual FFR technique is based on computational fluid dynamics (CFD).[46] Thus, the imaging quality, which determines the accuracy of the reconstructed vessel anatomy, is crucial to its accuracy. Compared to ICA, the spatial resolution of CCTA is relatively low. Calcification and motion artifacts can further affect the image quality and thus impair the accuracy of CT-FFR.[48] The Determination of Fractional flow reserve by Anatomic Computed Tomographic angiOgraphy (DeFACTO) study[49] clearly showed that the quality of CCTA images can greatly affect the accuracy of CT-FFR, particularly when patients have high heart rates or arrhythmias. The next-generation HeartFlow 2.0 and CT-FFR softwares developed by other manufacturers have tried to improve upon image acquisition quality control and 3D reconstruction

algorithms. The spatial resolution remains the major challenge of CCTA, however, that limits the accuracy of 3D reconstructions of vessel anatomy.[4]

Artifacts represent another important factor that affects the imaging quality of CCTA, and thus the accuracy of CT-FFR. It has been well established that severe calcification reduces the diagnostic accuracy of CCTA, and thus the diagnostic efficacy of CT-FFR.[50,51] It is likely that this inaccuracy stems from a partial volume effect of CCTA, which means that the presence of a calcified lesion leads to an overestimation of the overall CT value in the adjacent region and, consequently, the degree of luminal stenosis.[52,53]

For CA-FFR, the most important factor affecting the imaging quality may be quite different. The spatial resolution of ICA is typically high enough to ensure accurate 3D reconstruction of vessel anatomy. Furthermore, the imaging quality of ICA is less affected by coronary calcification. A post-hoc analysis of the accuracy of FFRs derived from coronary angiographies (FFRangios) vs standard FFRs (FAST-FFRs)[54] showed that the presence or absence of calcified lesions did not significantly affect the diagnostic accuracy of CA-FFR (Se: 0.87 vs 0.95, $p > 0.05$; Sp: 0.93 vs 0.91, $p > 0.05$). However, most CA-FFR algorithms are based on two different projection angles to generate the 3D structure of the vessel. In cases with distorted vessels or eccentric lesions, it may be difficult to accurately display the severity of the lesion with only two projection angles. This can significantly affect the accuracy of the CA-FFR calculation.

The inclusion criteria of the target vessel can also greatly affect the diagnostic accuracy of virtual FFR. In a systematic review done by Cook et al.[55], the overall accuracy of CT-FFR for diagnosing myocardial ischemia was 82%. For lesions with borderline FFR values (0.7–0.8), the accuracy of CT-FFR dropped significantly, to only 46%. Interestingly, several studies on CA-FFR have demonstrated that its diagnostic accuracy does not decrease significantly in patients with borderline FFR values.[41,43,47] For example, the Functional Assessment by Various Flow Reconstructions (FAVOR) pilot study included 84 vessels with intermediate stenosis, and the diagnostic accuracy

of quantitative flow ratio (QFR) for them ranged from 80–87% for different kinds of calculations—which is much better than the reduced diagnostic accuracy of CT-FFR mentioned above.[47] In the subgroup analysis of intermediate lesions from the FAVOR II China study,[41] QFR had a diagnostic accuracy of 92.3% for intermediate lesions. These results may suggest that CA-FFR could represent a better option than CT-FFR in patients with very borderline FFR values. In our study, subgroup analyses showed a similar trend. Whether strict inclusion criteria of target vessel stenosis were used significantly affected the diagnostic accuracy of CT-FFR, but not CA-FFR. However, most of the studies included in our NMA used less strict inclusion criteria—usually at 30–90% of the stenosis diameter. Future studies focusing on difficult borderline lesions (widely regarded as those around 70% of the stenosis diameter should be welcomed.

Our study mainly focused on the diagnostic performance of virtual FFRs. The long-term clinical outcomes related to the results of these tests are what is most important for clinical decision-making. Currently, several randomized controlled trials have already investigated the prognostic benefits of virtual FFR in clinical decision-making. In the Quantitative Flow Ratio Guided and Angiography Guided Percutaneous Intervention in Patients with Coronary Artery Disease (FAVOR III China) study, 3,847 patients with 50–90% stenosis by visual assessment were randomly assigned to a QFR-guided percutaneous coronary intervention (PCI) strategy or a standard angiography-guided strategy. After a one-year follow-up, the QFR-guided PCI group had significantly better clinical outcomes, mainly driven by fewer myocardial infarctions and ischemia-driven revascularizations, compared to the standard angiography-guided group.[56] The Assessing Diagnostic Value of Non-invasive CT-FFR in Coronary Care (ADVANCE) study prospectively enrolled 5,083 patients with suspected coronary artery disease who underwent CT-FFR. The one-year follow-up results showed that CT-FFR examination reduced the revascularization rate and, more importantly, improved the prognosis.[57] Another important factor that influenced the clinical use of

virtual FFR was convenience. CT-FFR is based on non-invasive CCTA; therefore, it has greater potential in rapid screening to reduce invasive tests and total cost.

In addition to the two most prominent virtual FFR techniques—CT-FFR and CA-FFR—there are other options based on intravascular imaging, such as optical coherence tomography (OCT)-based FFR (OFR) and intravascular ultrasound (IVUS) based-FFR (ultrasonic flow ratio; UFR).[58,59] OCT and IVUS also represent excellent imaging tools for the calculation of virtual FFR because: (1) both OCT and IVUS have excellent spatial resolution; (2) the pull-back images of OCT and IVUS are naturally suitable for 3D reconstruction. Several pilot studies have demonstrated that both OFR and UFR have excellent diagnostic performance when compared with conventional virtual FFR techniques. However, both OCT and IVUS are invasive tests that require expensive devices and consumables. As a result, OFR and UFR hold no significant advantages over standard wire-based FFR in most clinical scenarios. Because of their limited clinical use and a general lack of large sample studies evaluating these techniques, OFR and UFR were not included in this meta-analysis.

Overall, virtual FFR is still a rapidly developing technique. Current evidence has shown that virtual FFR technology has good accuracy in defining clinically relevant ischemia. This study used an indirect comparison approach to show that CA-FFR has relatively better diagnostic accuracy. However, more prospective studies designed to directly compare the two diagnostic methods are eagerly anticipated. An ongoing study evaluating the diagnostic accuracy of CCTA-derived vs angiography-derived quantitative flow ratio (the CAREER study; NCT04665817) will hopefully provide more direct evidence. The continued optimization of virtual FFR technology will likely have a profound impact on the diagnosis and treatment strategy of coronary heart disease in the future.

This network meta-analysis had several key limitations worth noting. First, patient and lesion selection varied among the different studies, which therefore may have introduced some heterogeneity. Second, the diagnostic accuracy of CA-FFR vs CT-FFR was compared indirectly, using a network meta-analysis method. Future prospective studies with large sample sizes are warranted to confirm our findings. Third,

the categorization of CA-FFR can include QFR, FFRangio, NiFFR, and other techniques as well. We did not undertake a rigorous differentiation of the definitions used in the various studies we included. The use of different analysis software, as well as online vs offline analysis, can also introduce variations in the results. In the future, larger-scale studies are needed to address these issues separately. Furthermore, considering the availability of data, this network meta-analysis only included data at the per-vessel level; therefore, per-patient level analyses are also warranted in the future.

Our network meta-analysis showed that both CA-FFR and CT-FFR had high diagnostic accuracy. However, CA-FFR had better Se, Sp, PPV, NPV, and AUC than CT-FFR, when analyzed using a Bayesian meta-analysis approach. More head-to-head studies directly comparing these two non-invasive FFR methods should be conducted to provide a more accurate answer to this question in the future.

AUTHORS' CONTRIBUTIONS

JYZ, ZXC, and CL independently performed the searches and screening of the titles and abstracts. The statistical analysis was performed by ZXC, JYZ, and YJC. JYZ and ZJC wrote the manuscript. YH conceived, instructed, reviewed, and revised the manuscript. All authors read and approved the final version of the manuscript.

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CONFLICT OF INTEREST

The authors reported no conflict of interest.

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Table 1 Characteristics of the included studies

Study	Imaging modality	Population	Patients, n	Number of vessels, n (%)	Age, years	Male, n (%)
Babakhani 2021[38]	CA-FFR (QFR)	who had positive noninvasive diagnostic modalities	245	250	60.1 ± 9.3	155 (63)
Tanigaki 2019[23]	CA-FFR (QFR)	stable coronary artery disease	152	233	69.0 ± 9.0	98 (64)
Tu 2021[39]	CA-FFR (QFR)	suspected or known CAD	306	330	61.3 ± 10.4	227 (74)
Tu 2016[47]	CA-FFR (QFR)	stable angina pectoris	73	84	65.8 ± 8.9	61 (84)
Westra 2018[40]	CA-FFR (QFR)	suspected CAD	172	255	61.0 ± 8.0	116 (67)
Xu 2017[41]	CA-FFR (QFR)	suspected or known CAD	308	332	61.3 ± 10.4	227 (74)
Morris 2013[42]	CA-FFR	stable angina pectoris	19	35	64 (45-81)	12 (63)
Westra 2015[43]	CA-FFR (QFR)	stable angina or acute myocardial infarction	272	317	67.0 ± 10.0	196 (72)
Pellicano 2017[44]	CA-FFR	stable angina	184	203	65.9 ± 9.5	123 (67)
Masdjedi 2022[45]	CA-FFR	with an indication to perform invasive pre-PCI FFR assessment	334	334	66.0 ± 12.0	244 (73)
Fukuoka 2022[24]	CT-FFR	Suspected or known CAD	77	132	70.0 ± 9.0	54 (70)
Omori 2021[25]	CT-FFR	Suspected CAD	253	365	71 (64-75)	170 (67)
Zhang 2021[26]	CT-FFR	Suspected or known CAD	108	169	60.0 ± 9.0	81 (75)
Ko 2019[27]	CT-FFR	Symptomatic patients with no known CAD	51	96	61.9 ± 9.8	39 (77)
Tanigaki 2019[23]	CT-FFR	stable coronary artery disease	152	233	69 ± 9	98 (64)

Wang 2019[28]	CT-FFR	Patient underwent non-invasive CT with documented FFR	63	71	68.8 ± 8.6	32 (50)
Wardzia 2019[29]	CT-FFR	Intermediate pre-test probability of CAD	90	96	64.5 (8.6)	59 (65)
Donnelly 2018[30]	CT-FFR	With symptoms of stable chest pain	44	60	64.6 ± 8.9	29 (66)
Ihdayhid 2018[31]	CT-FFR	Suspected CAD	46	82	61.7 ± 10.0	35 (76)
Ko 2017[32]	CT-FFR	Suspected or known CAD	30	85	60.0 ± 8.5	21 (70)
Yang 2017[33]	CT-FFR	Suspected CAD	72	138	62.7 ± 8.9	64 (89)
Kruk 2016[34]	CT-FFR	Suspected CAD	90	96	63.4 ± 8.2	29 (32)
Norgaard 2014[35]	CT-FFR	Suspected stable CAD	254	484	64.0 ± 10.0	162 (64)
Min (1) 2012[60]	CT-FFR	Suspected or known CAD	252	407	62.9 ± 8.7	178 (71)
Min (2) 2012[36]	CT-FFR	Suspected or known CAD	60	66	63.5 ± 8.1	46 (81)
Koo 2011[37]	CT-FFR	Suspected or known CAD	103	159	62.7 ± 8.5	74 (72)

Abbreviation: CA-FFR, angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve.

Values are mean ± SD or median (range) or n (%)

Table 2 Patient characteristics of included studies

Study	Imaging modality	Body mass index, kg/m^2	Prior MI, n (%)	Diabetes mellitus, n (%)	Hypertension, n (%)	Hyperlipidemia, n (%)	Current smoker, n (%)
Babakhani 2021[38]	CA-FFR	NA	NA	83 (34)	145 (59)	158 (64)	94 (38)
Tanigaki 2019[23]	CA-FFR (QFR)	NA	NA	46 (30)	99 (65)	80 (53)	59 (39)
Tu 2021[39]	CA-FFR (QFR)	25.2 ± 3.3	48 (16)	86(28)	185 (60)	139 (45)	87 (28)
Tu 2016[47]	CA-FFR (QFR)	26.3 ± 6.3	23 (32)	17 (27)	32 (44)	NA	NA
Westra 2018[40]	CA-FFR (QFR)	27.0 ± 4.0	NA	18 (10)	121 (70)	NA	NA
Xu 2017[41]	CA-FFR (QFR)	25.2 ± 3.3	48 (16)	86 (28)	185 (60)	139 (45)	87 (28)
Morris 2013[42]	CA-FFR	29.0	1 (5)	1 (5)	16 (84)	19 (100)	4 (21)
Westra 2015[43]	CA-FFR (QFR)	27.0 ± 5.0	NA	78 (29)	201 (74)	186 (68)	156 (57)
Pellicano 2017[44]	CA-FFR	NA	35 (19)	59 (32)	124 (67)	164 (89)	32 (17)
Masdjedi 2022[45]	CA-FFR	27.0 ± 4.0	NA	90 (27)	240 (72)	220 (66)	56 (17)
Fukuoka 2022[24]	CT-FFR	25.0 ± 7.0	NA	23 (30)	54 (70)	44 (57)	45 (58)
Omori 2021[25]	CT-FFR	24.0 (22.0-26.0)	NA	69 (27)	177 (70)	161(63.6)	47(18.6)

Zhang 2021[26]	CT-FFR	26.1 ± 4.8	NA	30 (28)	69 (64)	76 (70)	16 (15)
Ko 2019[27]	CT-FFR	NA	NA	15 (29)	39 (77)	44 (86)	NA
Tanigaki 2019[23]	CT-FFR	NA	NA	46 (30)	99 (65)	80 (53)	59 (39)
Wang 2019[28]	CT-FFR	25.3 ± 3.4	NA	31 (49)	33 (52)	27 (43)	27 (43)
Wardzia 2019[29]	CT-FFR	64.5 (8.6)	NA	14.3 (16)	88 (98)	90 (99)	39 (43)
Donnelly 2018[30]	CT-FFR	29.0 (26.0-31.0)	NA	8 (18)	30 (68)	33 (75)	11 (25)
Ihdayhid 2018[31]	CT-FFR	NA	NA	14 (30)	36 (77)	40 (87)	8 (17)
Ko 2017[32]	CT-FFR	28.5 ± 4.6	NA	9 (30)	22 (73)	24 (80)	8 (27)
Yang 2017[33]	CT-FFR	25.4 ± 3.5	NA	23 (32)	29 (40)	19 (26)	33 (46)
Kruk 2016[34]	CT-FFR	28.5 (26.5-30.1)	NA	13 (14.4)	79 (88)	81 (90)	18 (20)
Norgaard 2014[35]	CT-FFR	26.0 ± 3.0	5 (2)	58 (23)	174 (69)	200 (79)	46 (18)
Min (1) 2012[60]	CT-FFR	NA	15 (6)	53 (21)	179 (71)	201 (80)	44 (18)
Min (2) 2012[36]	CT-FFR	NA	8 (14)	15 (27)	41 (71)	37 (64)	14 (38)
Koo 2011[37]	CT-FFR	25.8 ± 3.5	17 (17)	26 (26)	67 (65)	67 (65)	24 (36)

Abbreviation: CA-FFR, angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve; QFR, quantitative flow ratio.

Values are mean ± standard deviation or median (range) or n (%)

Table 3 Test characteristics of included studies

Study	Index test	Test program	FFR threshold
Babakhani 2021[38]	CA-FFR	C Angio Software	0.81
Tanigaki 2019[23]	CA-FFR (QFR)	contrast-flow QFR	0.8
Tu 2021[39]	CA-FFR (QFR)	AngioPlus Core	0.8
Tu 2016[47]	CA-FFR (QFR)	QAngio XA 3D prototype	0.8
Westra 2018[40]	CA-FFR (QFR)	QAngio XA 3-dimensional (3D) 1.1 software package	0.8
Xu 2017[41]	CA-FFR (QFR)	An angiogram vendor integrated QCA software or by a QCA workstation	0.8
Morris 2013[42]	CA-FFR	Philips 3D workstation based upon Graphical Interface for Medical Image Analysis and Simulation software	0.8
Westra 2015[43]	CA-FFR (QFR)	CE-marked software; QAngio XA3D/QFR solution	0.8
Pellicano 2017[44]	CA-FFR	FFRangio (developed by CathWorks, Ltd)	0.8
Masdjedi 2022[45]	CA-FFR	QAngio ®XA 3D prototype	0.8
Fukuoka 2022[24]	CT-FFR	Heartflow	0.8
Omori 2021[25]	CT-FFR	HeartFlow	0.8
Zhang 2021[26]	CT-FFR	Dedicated QAngio CT software	0.8
Ko 2019[27]	CT-FFR	Heartflow	0.8

Tanigaki 2019[23]	CT-FFR	Heartflow	0.8
Wang 2019[28]	CT-FFR	DEEPVESSEL-FFR	0.81
Wardzia 2019[29]	CT-FFR	cFFR v2.1, Siemens based on machine learning algorithms	0.8
Donnelly 2018[30]	CT-FFR	research prototype on-site CT-FFR simulation algorithm	0.8
Ihdayhid 2018[31]	CT-FFR	Toshiba Medical Systems Corp	0.8
Ko 2017[32]	CT-FFR	Heartflow	0.8
Yang 2017[33]	CT-FFR	Heartflow	0.8
Kruk 2016[34]	CT-FFR	Heartflow	0.8
Norgaard 2014[35]	CT-FFR	Heartflow	0.8
Min (1) 2012[60]	CT-FFR	Heartflow	0.8
Min (2) 2012[36]	CT-FFR	Heartflow	0.8
Koo 2011[37]	CT-FFR	Heartflow	0.8

Abbreviation: CA-FFR, angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve; QFR, quantitative flow ratio; QCA, quantitative coronary angiography.

Table 4 Vascular baseline in CA-FFR

Study	Imaging modality	Included range of the lesions	Calcified vessels	Tortuous vessels	Atrial fibrillation or tachyarrhythmias	Severe heart failure	Online	3D reconstruction
Babakhani 2021[38]	CA-FFR	30-90	NA	NA	NA	NA	0	1
Tanigaki 2019[23]	CA-FFR (QFR)	30-70	NA	NA	NA	NA	1	1

Tu 2021[39]	CA-FFR (QFR)	30-90	NA	NA	Excluded	Excluded	1	0
Tu 2016[47]	CA-FFR (QFR)	30-80	NA	NA	NA	NA	0	1
Westra 2018[40]	CA-FFR (QFR)	30-90	NA	NA	NA	NA	0	1
Xu 2017[41]	CA-FFR (QFR)	30-90	61 (18.4%)	47 (14.2%)	Excluded	Excluded	1	1
Morris 2013[42]	CA-FFR	>30	NA	4 (11.4%)	Excluded	NA	0	1
Westra 2015[43]	CA-FFR (QFR)	30-90	41 (13%)	34 (11%)	Excluded	NA	1	1
Pellicano 2017[44]	CA-FFR	50-90	NA	NA	NA	NA	0	1
Masdjedi 2022[45]	CA-FFR	30-70	48 (14%)	27 (8%)	NA	NA	0	1

Abbreviation: CA-FFR, angiography-derived fractional flow reserve; QFR, quantitative flow ratio; NA, not available.

Table 5 Vascular baseline in CT-FFR

Study	Imaging modality	Included range of the lesions	Calcified vessels	Tortuous vessels	Atrial fibrillation or tachyarrhythmias	Severe heart failure
Fukuoka 2022[24]	CT-FFR	NA	excluded	excluded	NA	NA
Omori 2021[25]	CT-FFR	50-90	NA	NA	NA	NA
Zhang 2021[26]	CT-FFR	NA	NA	NA	excluded	excluded
Ko 2019[27]	CT-FFR	10-90	NA	NA	excluded	NA
Tanigaki 2019[23]	CT-FFR	30-70	NA	NA	NA	NA
Wang 2019[28]	CT-FFR	30-90	NA	NA	excluded	NA
Wardzia 2019[29]	CT-FFR	50-90	NA	NA	excluded	NA
Donnelly 2018[30]	CT-FFR	30-70	NA	NA	NA	NA
Ihdayhid 2018[31]	CT-FFR	10-90	NA	NA	excluded	NA
Ko 2017[32]	CT-FFR	NA	NA	NA	excluded	NA
Yang 2017[33]	CT-FFR	NA	excluded	excluded	NA	NA
Kruk 2016[34]	CT-FFR	50-90	NA	NA	excluded	NA
Norgaard 2014[35]	CT-FFR	30-90	NA	NA	NA	NA
Min (1) 2012[60]	CT-FFR	40-70	NA	NA	NA	NA
Min (2) 2012[36]	CT-FFR	NA	NA	NA	excluded	NA
Koo 2011[37]	CT-FFR	NA	NA	NA	excluded	excluded

Abbreviation: CT-FFR, computer tomography-derived fractional flow reserve; NA, not available.

Table 6 Main findings of the diagnostic test accuracy method

Indicator	**CA-FFR (95% CI)**	**CT-FFR (95% CI)**
Sensitivity	0.86 (0.81 - 0.90)	0.84 (0.81 - 0.86)
Specificity	0.90 (0.86 - 0.93)	0.78 (0.73 - 0.82)
Pos	8.60 (6.10 - 12.10)	3.80 (3.10 - 4.50)
Neg	0.16 (0.11 - 0.22)	0.21 (0.18 - 0.25)
DOR	55.0 (33.0 - 99.0)	18.0 (13.0 - 24.0)
AUC	0.94 (0.92 - 0.96)	0.87 (0.84 - 0.90)

CI, confidence interval; Pos, positive likelihood ratio; Neg, negative likelihood ratio; DOR, diagnostic odds ratio; AUC, area under the receiver operating characteristic curve; CA-FFR, angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve.

Table 7 Main findings of the HSROC-NMADT method

Indicator	CA-FFR, Mean (SD)	CT-FFR, Mean (SD)
Sensitivity	0.86 (0.028)	0.84 (0.019)
Specificity	0.90 (0.021)	0.78 (0.023)
PPV	0.83 (0.030)	0.70 (0.025)
NPV	0.91 (0.017)	0.89 (0.015)
Pos	8.55 (1.840)	3.80 (0.410)
Neg	0.16 (0.030)	0.21 (0.025)

HSROC-NMADT, Bayesian hierarchical summary receiver operating characteristic model for network meta-analysis of diagnostic tests; SD, standard deviation; PPV, positive predictive value; NPV, negative predictive value; Pos, positive likelihood ratio; Neg, negative likelihood ratio; CA-FFR, angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve.

Figure Legends

Fig.1 PRISMA flow diagram of the study selection. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement; iFR, Instantaneous Wave-free Ratio; Pd/Pa, distal coronary pressure-to-aortic pressure ratio; MPI, myocardial perfusion imaging; SPECT, single photon emission computed tomography; PET, positron emission tomography; CMR, cardiac magnetic resonance imaging; FFR, fractional flow reserve.

Fig.2 Quality assessment of included studies by QUADAS-2 Revised Criteria. QUADAS, Quality assessment of Diagnostic Accuracy Studies. Stacked bars represent the proportion of studies with a low risk of bias, unclear risk of bias, or high risk of bias with regard to patient selection, utilized reference standard, and imaging modality (index test).

Fig.3a Pooled sensitivity and specificity of CA-FFR using the DTA method. CA-FFR, invasive angiogram derived fractional flow reserve; DTA, diagnostic test accuracy.

Fig.3b. Pooled sensitivity and specificity of CT-FFR using the DTA method. CT-FFR, coronary computed tomography angiography derived fractional flow reserve; DTA, diagnostic test accuracy.

Fig.4 Summary receiver operating characteristic curve, plotting the true positive rate (sensitivity) against the false-positive rate (1-specificity) of CT-FFR and CA-FFR. CA-FFR, angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve

Fig.5 Evidence network plot of diagnostic value of CT-FFR, CA-FFR and the gold standard invasive FFR for the detection of hemodynamically significant coronary artery disease. The thickness of the line segment represents the number of relevant studies. FFR, fractional flow reserve; CA-FFR, coronary angiography-derived fractional flow reserve; CT-FFR, computer tomography-derived fractional flow reserve.

Fig.6 The cumulative ranking curve using HSROC-NMADT method. HSROC-NMADT, Bayesian hierarchical summary receiver operating characteristic model for network meta-analysis of diagnostic tests.

Fig.7 The funnel plot for included studies. The funnel plot resembled a symmetrical funnel shape, indicating publication bias was unlikely