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ORIGINAL RESEARCH

Agreement of Fractional Flow Reserve Estimated by Computed Tomography With Invasively Measured Fractional Flow Reserve: A Systematic Review and Meta-Analysis

Thomas I. Faulder; Kurundeniya Prematunga, MBBS, MD Radiology; Soniah B. Moloi, BMed; Lauren E. Faulder; Rhondda Jones, PhD; Joseph V. Moxon, PhD

BACKGROUND: Fractional flow reserve (FFR) is the ratio of blood pressure measured distal to a stenosis and pressure proximal to a stenosis. FFR can be estimated noninvasively using computed tomography (CT) although the usefulness of this technique remains controversial. This meta-analysis evaluated the agreement of FFR estimated by CT (FFR-CT) with invasively measured FFR. The study also evaluated the diagnostic accuracy of FFR-CT, defined as the ability of FFR-CT to classify lesions as hemodynamically significant (invasive FFR ≤0.8) or insignificant (invasive FFR >0.8).

METHODS AND RESULTS: Forty-three studies reporting on 7291 blood vessels from 5236 patients were included. A moderate positive linear relationship between FFR-CT and invasively measured FFR was observed (Spearman correlation coefficient: 0.67). Agreement between the 2 measures increased as invasively measured FFR values approached 1. The overall diagnostic accuracy, sensitivity and specificity of FFR-CT were 82.2%, 80.9%, and 83.1%, respectively. Diagnostic accuracy of 90% could be demonstrated for FFR-CT values >0.90 and <0.49. The diagnostic accuracy of off-site tools was 79.4% and the diagnostic accuracy of on-site tools was 84.1%.

CONCLUSIONS: The agreement between FFR-CT and invasive FFR is moderate although agreement is highest in vessels with FFR-CT >0.9. Diagnostic accuracy varies widely with FFR-CT value but is above 90% for FFR-CT values >0.90 and <0.49. Furthermore, on-site and off-site tools have similar performance. Ultimately, FFR-CT may be a useful adjunct to CT coronary angiography as a gatekeeper for invasive coronary angiogram.

Key Words: CT ■ fractional flow reserve-CT coronary angiography ■ diagnostic accuracy ■ fractional flow reserve

Coronary artery disease (CAD) is the most common type of heart disease and affects 1 in 20 adults aged >20 years in the United States.[1] CAD can lead to myocardial ischemia when atherosclerotic plaque narrows the coronary artery and restricts blood flow to the myocardium, thereby increasing the risk of myocardial infarction and acute coronary syndrome.[2] Front-line CAD management aims to limit this risk using lifestyle modifications and medications to slow disease progression.[3] Revascularization (stenting or bypass), however, is considered when optimal medical therapy proves inadequate,[4] although determining which patients require revascularization can be challenging. Computed tomography coronary angiography

Correspondence to: Thomas Faulder and Joseph Moxon, College of Medicine and Dentistry, James Cook University, 1 James Cook Drive, Douglas QLD 4811, Australia. Email: thomas.faulder@my.jcu.edu.au; joseph.moxon@jcu.edu.au

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CLINICAL PERSPECTIVE

What Is New?

- Fractional flow reserve-computed tomography (FFR-CT) can rule out hemodynamically significant coronary artery disease when FFR-CT is >0.90 with 90% accuracy. FFR-CT can also identify hemodynamically significant coronary artery disease when FFR-CT is <0.49 with 90% accuracy.
- On average, FFR-CT values are only 0.01 less than invasive FFR measurements (95% CI, 0.21 to −0.24); clinicians should consider raw FFR-CT values when deciding whether to proceed with invasive angiogram.

What Are the Clinical Implications?

- FFR-CT could be an effective gatekeeper to invasive angiogram, helping avoid complications from invasive procedures.

Nonstandard Abbreviations and Acronyms

CTCA	computed tomography coronary angiography
FFR	fractional flow reserve
FFR-CT	computed tomography fractional flow reserve

(CTCA) is excellent at visualizing the structure of the coronary arteries but the anatomical severity of CAD does not always reflect its functional impact. One method for assessing the functional impact of CAD is to calculate the fractional flow reserve (FFR), defined as the ratio of blood pressures measured distal and proximal to a coronary artery stenosis. FFR is calculated during invasive angiography. After inducing hyperemia with adenosine, a specialized coronary guidewire with built-in pressure sensors near the wire tip is used to measure pressures proximal and distal to the stenosis (see Figure S1).[5] A ratio of 1.0 indicates no difference in blood pressure whereas values ≤0.8 indicate that the stenosis is hemodynamically significant.[6] The management of coronary lesions with FFR values in the "gray zone" from 0.75 to 0.80 is controversial. A recent meta-analysis found that that the incidence of major adverse cardiac events in lesions with gray zone FFR was similar with deferral versus performance of revascularization.[7] The current American Heart Association guidelines recommend the use of FFR to guide the decision to proceed with revascularization in patients with angina and angiographically intermediate stenoses (diameter stenosis severity of 40%–69%).[8] A major limitation of current FFR calculation is the need to invasively measure blood pressure. Invasive FFR carries periprocedural risks of death (1.1 cases per 10 000), stroke (5.9 cases per 10 000), and myocardial infarction (0.2 cases per 10 000).[9] Further limitations of invasive FFR are the time, risks, and costs associated with using a dedicated pressure wire and adenosine to induce hyperemia[5] and inertia to adopt FFR from clinicians who rely on angiography results alone. Recent developments in CT and fluid dynamics computation enable FFR to be estimated noninvasively (FFR-CT) from CTCA, potentially avoiding complications associated with invasive procedures and reducing costs.[10]

CTCA is growing in popularity as a gatekeeper for investigating patients with chest pain. Although CTCA is highly effective at ruling out disease in patients with no known CAD,[11,12] it is poor at predicting which lesions are ischemia causing.[12] One study found that only 49% of CTCA stenoses ≥50% had an FFR ≤0.75 at time of invasive angiography.[13] For this reason, many patients with disease on CTCA do not go on to have invasive angiography if their clinical context does not justify it. The American Heart Association recommends that patients with stenosis ≥50% on CTCA should undergo functional imaging (assessment of hemodynamic consequences of CAD rather than visualization of coronary artery anatomy) before invasive coronary angiogram.[14] Calculating FFR from CTCA could prevent this sequential functional testing.[15]

FFR-CT algorithms have now been developed by multiple companies. A CTCA generates an anatomical image of the coronary arteries, the image is processed into 3-dimensional models of the arteries, and computational fluid dynamics is applied to the 3-dimensional models to quantify the pressure proximal and distal to a lesion so FFR can be calculated.[16] The calculation of FFR-CT is computationally intensive meaning many health care providers outsource this to specialist off-site providers. Other pitfalls of FFR-CT are that abnormal FFR-CT values can be seen in mild stenosis and normal FFR-CT values in severe stenosis.[14] Furthermore, FFR-CT has not been validated in situations such as coronary stents and recent myocardial infarction.[14] Currently only FFR-CT ratios calculated by off-site providers are approved by the US Food and Drug Administration.[15] Despite this, the ability of FFR-CT to inform the decision to revascularize remains controversial.[17] The diagnostic accuracy of FFR-CT is defined as the ability of FFR-CT to classify lesions as hemodynamically significant (invasive FFR ≤0.8) or insignificant (invasive FFR >0.8). Recent meta-analyses suggest that the overall diagnostic accuracy of FFR-CT is higher than CTCA.[18] A 2017 meta-analysis, however, found that the diagnostic accuracy of FFR-CT varies with CAD severity and is low for FFR-CT around 0.8.[19] Directly appraising the relationship of FFR-CT

to invasively measured FFR may provide a better understanding of the validity of the test than diagnostic accuracy.[19] The primary aim of this meta-analysis was to evaluate the agreement of FFR-CT with invasively measured FFR using a large contemporary data set identified through a systematic literature search. Secondary aims were to assess the diagnostic accuracy of FFR-CT in patients with different degrees of CAD severity as evidenced by invasively measured FFR, and to assess whether FFR-CT estimates calculated in-house by treating clinical teams using currently available software are comparable to estimates provided by specialist off-site providers.

METHODS

Search Criteria

This review is reported in line with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. A systematic review was conducted to identify studies that evaluate the agreement or concordance between FFR-CT and invasive FFR values. Medline, Emcare, CINAHL, and SCOPUS databases were searched using a search strategy developed in collaboration with a specialist librarian (refer to Data S1).

To be eligible for inclusion, articles had to compare FFR-CT to invasive FFR, present per-vessel data in scatterplots to enable data extraction and use a method for calculating FFR-CT provided by a known supplier (see Table S1). In cases of ambiguity, study authors were contacted to request data and clarify discrepancies. Studies using experimental algorithms developed in house to predict FFR-CT were excluded. If 2 studies analyzed patients from the same study, the larger data set was used. Editorials, reviews, and articles written in languages other than English were not included.

The review protocol has been registered with the Prospective Register of Systematic Reviews database (CRD42023449147). Initial data searches were conducted on June 15, 2023. A final literature search was conducted in July 2023. No ethics approval was needed because this was a reanalysis of unidentifiable previously published data.

Data Extraction and Quality Assessment

Two authors (T.I.F and L.E.F.) independently extracted data from, and assessed the quality of, the included studies. Discrepancies were reviewed at a consensus meeting. Table and Table S1 detail all variables extracted from the studies.[20–62] Key variables included whether FFR-CT was calculated on site or off site, patient demographics and characteristics of blood vessels. Data are available on request from the authors.

The quality and potential bias of the included studies were assessed using a modified Joanna Briggs Institute Checklist for Diagnostic Test Accuracy Studies (Table S2).[63] Individual scores were calculated based on the number of "yes" answers. Studies were allocated a maximum score of 7. Scores ≤3 were considered to denote poor-quality studies, studies with a score of 4 or 5 were considered moderate quality and high-quality studies achieved scores of 6 or 7. No articles were excluded based on their quality assessment score.

Statistical Analysis

Methods presented by Cook et al.[19] were adapted to extract data detailing the relationship of FFR-CT and FFR values from published scatterplots. Scatterplot images were imported into the Matlab software (MathWorks Inc, v 9.14) and the XY coordinates of all presented data points were extracted by a single author (T.I.F.) using the GRABIT add-on.[64] The interobserver reproducibility of the data extraction method was assessed by comparing the independently extracted X and Y values for data points from 5 studies using Spearman correlation and Bland–Altman plots. This revealed close agreement between the 2 observers suggesting that applied methods were reproducible (Spearman's rank correlation rho for both X and Y coordinates was 1 [Figure S2]).

Extracted data were used in 2 ways, first to assess trends on a per-study level and second in a pooled per-vessel analysis. The per-study performance of FFR-CT was assessed using forest plots to enable comparison to previous meta-analyses. Anticipating high interstudy heterogeneity, these analyses adopted a random effects approach. Publication bias was assessed using funnel plots and interstudy heterogeneity measured with I^2 values. CIs for the correlation coefficient and diagnostic accuracy were calculated using a bootstrap with 1000 resamples whereas CIs were calculated for sensitivity and specificity using the binom.wilson() function in the binom package. SE was calculated for sensitivity and specificity as $\sqrt{\frac{p(1-p)}{n}}$.[65]

The per-vessel relationship used all data points to assess the relationship between FFR-CT and invasively measured FFR. Spearman's correlation and Bland–Altman analysis were initially used to ensure compatibility of findings to that of previous reports. The relationship between FFR-CT and invasively measured FFR was further investigated using beta regression as this was deemed to model the observed data more appropriately. Beta regression is appropriate for continuous variables between 0 and 1 such as proportions, rates, and percentages. FFR-CT is a ratio bounded between 0 and 1 and beta regression can accommodate the bounded nature of the data.[66]

Table. Key Data Extracted From Included Studies

Study	On or off site	Number of patients	Number of arteries	Age, y	Sex, male	Hypertension	Diabetes	Smoking¶	Hyperlipidemia
Zhao et al.[20]	On	305	348	59.2±9.7	210	187	93	144	198
Chua et al.[21]	Off	109	219	63.2±9.8	78	88	29	54	87
Xue et al.[22]	On	484	618	61.6±9	346	286	116	163‡**	141
Ammon et al.[23]	On	69	100	63±10	51	55	11	28	49
Zhang et al.[24]	Off	63	63*	74 (69.8–78.0)	101	80	29	NR	NR
Renker et al.[25]	On	330**	502	63 (56–69)	248	216	72	117‡	196
Michail et al.[26]	Off	39	60	76.2±6.7	28	27	21	16	26
Cami et al.[27]	Off	NR	182	60.7±10	876	950	237	742	920
Jiang et al.[28]	On	442	544	61.2±9.1	309	249	97	147§	120
Omori et al.[29]	Off	253	365	71 (64–75)	170	177	69	127	161
Xu et al.[30]	On	437	570	61 (56–67)	311	251	95	146‡	118
Ihdayhid et al.[31]	On	48	86	61.8±10.2	36	38	14	23	42
Kato et al.[32]	On	38	44	67.4±9.6	24	22	18	8	31
Matsumura et al.[33]	Off	93	139	72.0±8.2	60	51	33	10‡	61
Ko et al.[34]	Off	49	91	61.9±9.8	39	39	15	26	44
Kurata et al.[35]	On	74	91	70.2±10.3	56	57	28	23	40
Modi et al.[36]	Off	NR	19	64.7±12.0	17	12	6	5	15
Driessen et al.[37]	Off	157	505†	58.1±8.7	132	96	33	99	83
Ghekiere et al.[38]	Off	37	39	NR	NR	NR	NR	NR	NR
Ihdayhid et al.[39]	On	46	84	61.7±10.0	35	36	14	23	40
Rother et al.[40]	On	71	91	65±9	55	55	11	NR	45
Donnelly et al.[41]	On	44	60	64.6±8.9	NR	30	8	11§	33
Xia et al.[42]	Off	129	156	58.6±9.2	86	80	39	48‡	58
Ko et al.[43]	On	30	58	60.0±8.5	39	22	9	18	24
Gaur et al.[44]	Off	60	124	61±10	50	21	6	39‡	17
Yang et al.[45]	On	72	138	62.7±8.9	64	29	23	33‡	19
Norgaard et al.[46]	Off	37	37	59±9	111	82	24	43‡	73
Tesche et al.[47]	On	37	37	61±11	25	24	15	13§	16
Kruk et al.[48]	On	90	96	63.4±8.2	29	79	13	38	81
Norgaard et al.[49]	Off	214	333	64±10	132	146	49	37‡	168
Wang et al.[50]	On	32	32	58±12	21	21	13	10§	14
Renker et al.[51]	On	53	67	61.2±12.0	34	31	18	8‡	31
Kim et al.[52]	Off	44	48	65.0±9.1	35	36	13	NR	28
Nakazato et al.[53]	Off	82	150	63±8	60	56	16	12‡	65
Min et al.[54]	Off	60	66	64±8	46	41	15	14‡	37
Boussoussou et al.[55]	Off	38	38*	61.6±9.0	30	29	8	9	6
Van Hammersvelt et al.[56]	On	57	77	58.5±9.2	42	49	12	19‡	47
Gao et al.[57]	On	317	366	59.4±9.7	217	196	98	153	201
Guan et al.[58]	On	110	139	67.2±8.9	71	61	20	NR	16
Jiang et al.[59]	On	146	190	66 (58–74)	91	60	19	NR	12
Wang et al.[60]	Off	63	71	68.8±8.6	32	33	31	27	27
Koo et al.[61]	Off	103	159	62.7±8.5	74	67	26	24‡	67
Wen et al.[62]	On	73	89	57.8±10.2	57	35	7	34‡	24

*Copied from patients with computed tomography fractional flow reserve (FFR) vs invasive FFR.
†Only 157 were expected for analysis because the scatterplot provided only per-patient analysis and not per-vessel analysis.
‡Current smoker.
§Unspecified whether current or former smoker.
¶Current or former smoker.
**Not available in all patients.

Furthermore, Cook et al. found significant heterogeneity of variance of FFR-CT from invasive FFR making linear regression inappropriate.[19] The goodness of fit of the beta-regression model was assessed using Cook's distance plots, residuals versus indices of observations, half-normal plots of residuals, and predicted versus observed plots.

The accuracy of FFR-CT in diagnosing hemodynamically significant stenoses was assessed using receiver operator characteristic (ROC) curves applied to the whole data set. CIs for the areas under the curve (AUC) were calculated using the ci.auc() function in the pROC package using the bootstrap method with 1000 bootstrap replicates. Diagnostic accuracy across different FFR values was further assessed by applying local regression curves. The diagnostic accuracy of FFR-CT values generated by off- and on-site providers was compared using the roc.test function in the pROC R package [67] (bootstrapped 1000 times).

All data analyses were conducted using the R statistical software package (version 2023.06.1+524).

RESULTS

Characteristics and Quality of Included Studies

The systematic literature search identified 43 studies that were eligible for inclusion in this review (Figure 1). Collectively, these papers provided data of the relationship between invasive- and CT-measured FFR as measured in 7291 arteries from 5236 patients (Table 1). Of the 43 studies, 20 (46.5%) presented data generated by off-site providers and the remaining 23 studies used in-house tools to calculate FFR-CT (see Table S1).

Only 36 of the 43 studies presented demographic details of the assessed population (Table 1). Available data suggest that all studies included older adults with a high prevalence of the most commonly reported cardiovascular risk factors (smoking, diabetes, hypertension, hypercholesterolemia, and high body mass index). 70% of patients were male, 36% of patients were past or current smokers, 25% of patients had diabetes, 63% had hypertension, and 50% of patients had hyperlipidemia. The mean and median body mass index were in the 25 to 30 range (detailed in Table S1 and Data S2).

Of the 43 studies, 8 studies analyzed blood vessels with luminal stenosis between 30% and 90%, 5 studies analyzed blood vessels with luminal stenosis ≥50%, and 4 studies analyzed blood vessels with luminal stenosis between 10% and 90%. In the remaining 26 studies, a variety of luminal stenosis thresholds were used (refer to Table S1). In the 30 studies that described the site of the vessel, 2673 (63%) were left anterior descending, 744 (18%) were left circumflex, and 809 (19%) were right coronary artery.

Thirty-five studies recruited patients with suspected or known CAD, 2 studies recruited patients with recent ST-segment–elevation myocardial infarction (STEMI) and 2 studies recruited patients with aortic stenosis. The patient selection was not explained in the remaining 4 studies (see Table S1). There was also variability in the model of CT scanner used between the studies. Twelve studies used CT scanners with a minimum of 64 detector rows, 16 studies used CT scanners with a minimum of 128 detector rows, 3 studies used CT scanners with a minimum of 256 detector rows, 7 studies used CT scanners with a minimum of 320 detector rows, and 3 studies used CT scanners with a minimum of 384 detector rows. Two studies did not specify the CT scanner used. Twenty-six studies were published between 2011 and 2019 and 17 studies from 2020 to 2023.

Of the included studies, 11 were considered to be high quality, 24 of moderate quality, and 8 low quality (refer to Table S2). Fifteen of the 18 HeartFlow and 7 of 12 Siemens studies were at risk of bias as disclosures revealed close relationships (either employment, grant support, or other financial interests) between the study authors and the manufacturers of the software used to calculate FFR-CT (refer to Table S3). Inspection of the funnel plot suggested that smaller studies may have had a bias toward reporting higher diagnostic accuracies than larger studies. Alternatively, smaller studies reporting lower diagnostic accuracy may not have been published. The t-value of the funnel plot of diagnostic accuracies was 1.07 suggesting against systemic bias overall (Figure S3).

Primary Outcome Assessment: The Agreement of FFR-CT With Invasively Measured FFR

Data extracted from the included studies were used to assess the agreement of FFR-CT with invasively measured FFR on a per-vessel level. FFR-CT and corresponding FFR values were expected for 7291 arteries but only 5883 data points (80.7%) could be extracted from presented graphs due to overlap of data points. The median FFR value of these data points was 0.831 (interquartile range 0.740–0.902). The median FFR-CT value was 0.824 (interquartile range 0.731–0.896). Among the 5883 data points, 2408 were determined to be hemodynamically significant (FFR ≤0.8) by invasive FFR (40.9%) and 2537 were determined hemodynamically significant (FFR ≤0.8) by FFR-CT (43.1%).

Assessment at the study level suggested an overall correlation coefficient of 0.70 (95% CI, 0.67–0.72) of FFR-CT with FFR and moderate interstudy heterogeneity was observed (Figure 2A, I^2: 64.6%). Assessment of the correlation on a per-vessel level confirmed a moderate positive correlation of FFR-CT with invasive FFR (Figure 2B, Spearman correlation coefficient 0.67). The overall limits of agreement were −0.23 to

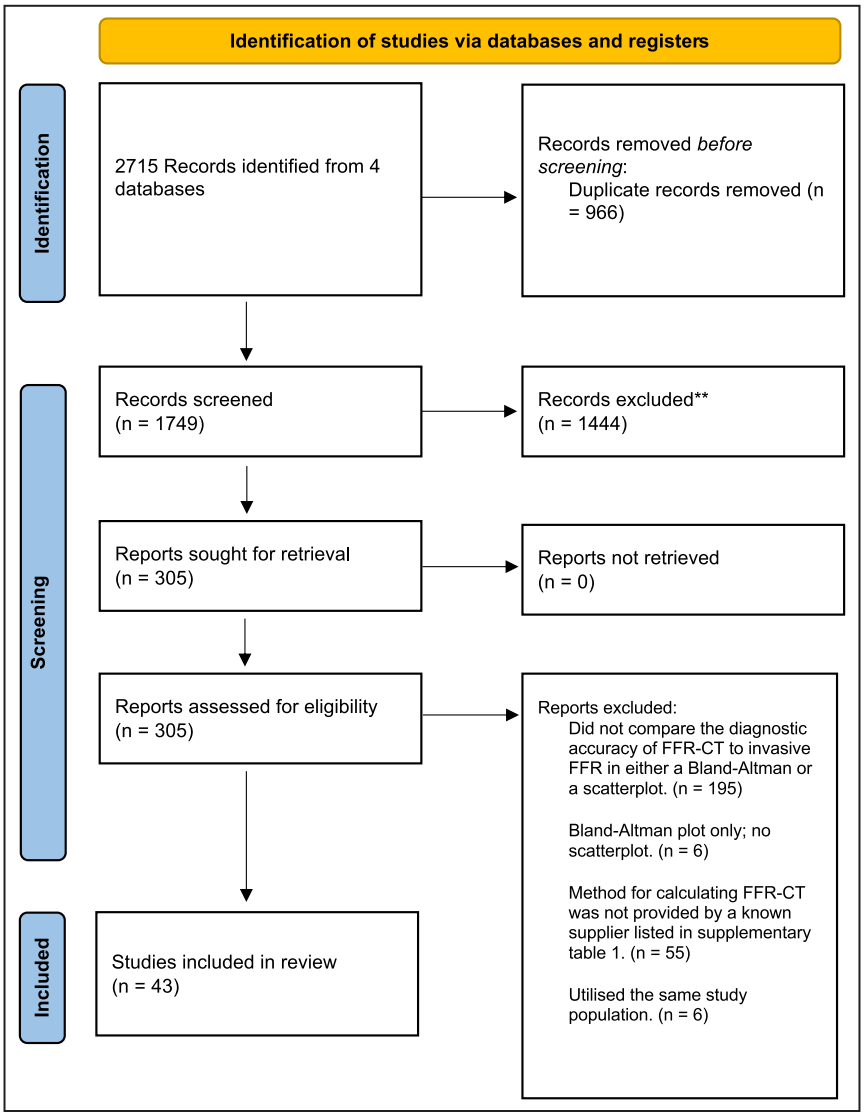

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses diagram.
CT indicates computed tomography; and FFR, fractional flow reserve.

0.21 (Figure 2C). Agreement between the 2 measures increased as invasively measured FFR values approached 1 and appeared poorer at lower FFR values suggesting that the relationship was nonlinear (Figure S4). Beta regression was therefore applied supporting a moderate positive relationship between FFR-CT and invasively measured FFR (pseudo R squared 0.308, Figure 2B).

Secondary Outcome Assessment: Diagnostic Accuracy of FFR-CT

On a per-study level, the overall diagnostic accuracy of FFR-CT was 0.83 (95% CI, 0.81–0.85, I^2 64.1%) as shown in Figure 3A. Forest plots showing sensitivity and specificity for each study are shown in Figures S5 and S6. Diagnostic accuracy did not appear to be affected by year of study or number of CT scanner slices (Figures S7–S9). The diagnostic accuracy was observed to be lower in the 2 studies that specifically assessed patients with recent MI at 70% (95% CI, 63%–78%) versus 83% (95% CI, 80%–84%) when assessing all studies. In contrast, the 2 studies investigating patients with aortic stenosis reported similar accuracies to those seen in studies assessing a heterogenous mix of patients (Figure S7).

On a per-vessel level, ROC curve analysis assessing all available data demonstrated that FFR-CT had moderate diagnostic accuracy (AUC 0.87, diagnostic accuracy 82.2%, sensitivity 80.9%, specificity 83.1%, positive predictive value 76.8%, and negative predictive value 86.3%; Figure 3B, Table S4 and Figure S10). Marked differences in the diagnostic accuracy of FFR-CT was observed for different FFR-CT values (Figure 4). Of note,

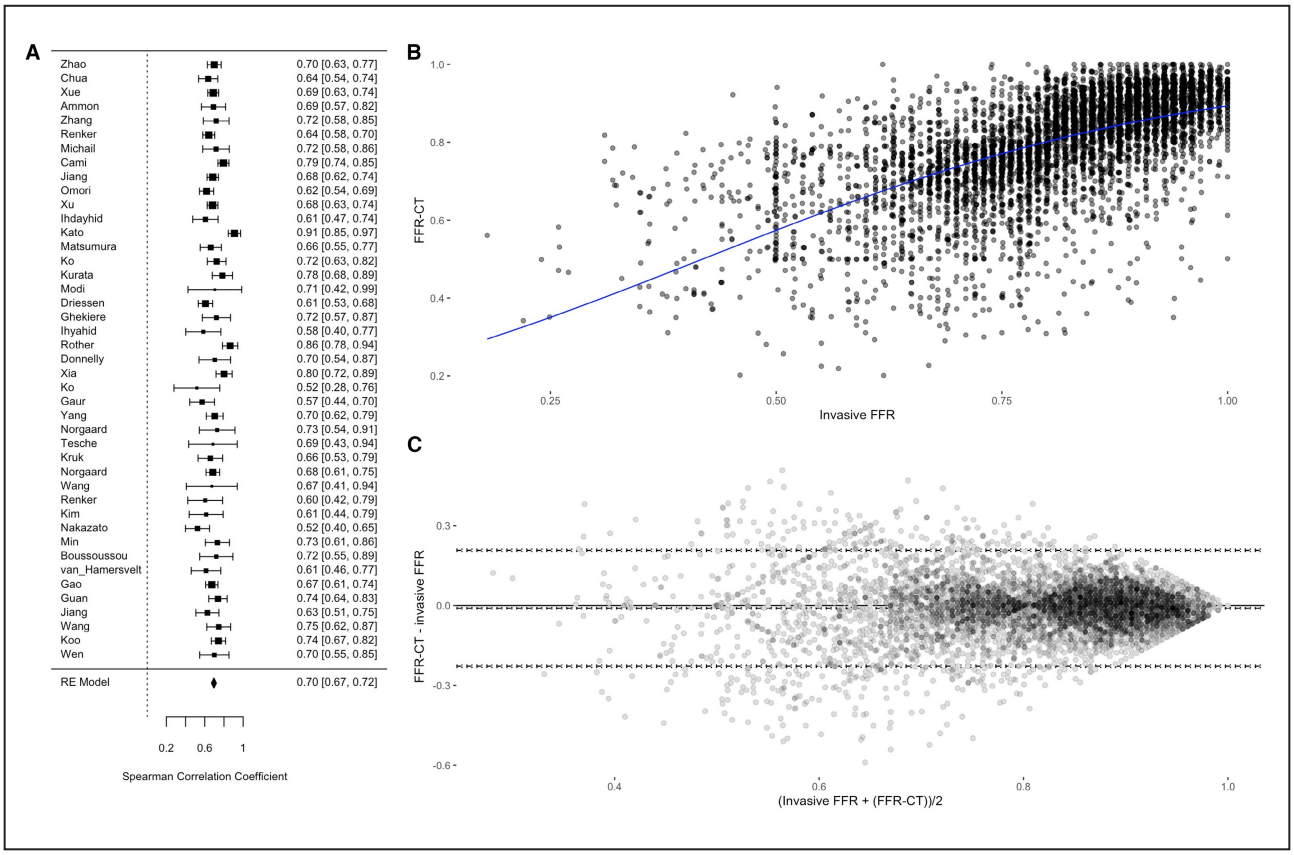

Figure 2. Agreement between FFR-CT and invasive FFR on a per-study and per-vessel level.
A, Forest plot depicting the correlation between FFR-CT and invasive FFR for each of the 43 included studies. The I^2 value was 64.6%. **B**, Scatterplot comparing all FFR-CT (*y* axis) to invasive FFR (*x* axis). The blue curve was generated by the beta regression model. The gray zone represents the CIs. The Spearman correlation coefficient was 0.67 and the pseudo R squared value was 0.308. **C**, Bland–Altman graph plotting difference between FFR-CT and invasive FFR on the *y* axis against average of the 2 measurements for all data points. Dashed lines represent upper (0.21) and lower (−0.23) limits of agreement and average difference (−0.01). CT indicates computed tomography; and FFR, fractional flow reserve.

diagnostic accuracy of FFR-CT was lowest (67%) for individuals with FFR-CT values of 0.70 to 0.80.

Diagnostic accuracy of 80% could be demonstrated only for FFR-CT values >0.85 and <0.64. Diagnostic accuracy of 90% could be demonstrated for FFR-CT values >0.90 and <0.49 (Figure 4).

Of the 5883 vessels in which FFR-CT was compared with invasive FFR, 1047 (17.8%) were misclassified by FFR-CT (Table S4 and Figure S10). FFR-CT labeled 459 stenoses as insignificant (FFR-CT >0.8) that were deemed hemodynamically significant by invasive FFR (FFR ≤0.8). These 459 stenoses had a median FFR of 0.75 (interquartile range 0.10). FFR-CT also labeled 588 blood vessels as hemodynamically significant (FFR-CT ≤0.8) that were insignificant by invasive FFR (FFR >0.8). These 588 stenoses had a median FFR of 0.86 (interquartile range 0.07). Furthermore, 1374 vessels in this study had an FFR-CT >0.9. Of these, 1283 had invasive FFR >0.8 and 91 had invasive FFR ≤0.8 (see Figure S11). Therefore, if vessels with FFR-CT >0.9 had not proceeded to invasive angiogram, then 1437 of 5833 vessels could have avoided further investigation, of which 91 (or 6.6%) would have been hemodynamically significant. The 91 vessels deemed nonhemodynamically significant by FFR-CT that were reclassified as hemodynamically significant by invasive FFR had a median FFR value of 0.76 (Q1 0.70 to Q3 0.79). Therefore, for FFR-CT values >0.9, there is a 90% chance that invasive angiogram can be safely deferred. Although there is a 10% chance the lesion will be hemodynamically significant, the majority of these lesions will have invasive FFR between 0.70 and 0.79.

Secondary Outcome Assessment: Agreement of Off-Site and On-Site FFR-CT Estimates With Invasive FFR

Data extracted from 20 studies were used to evaluate the agreement of FFR-CT provided by off-site providers with invasive FFR (including 2401 data points, Table S1). The overall limits of agreement for off-site tools were −0.22 to 0.20 (Figure 5D). Compared with

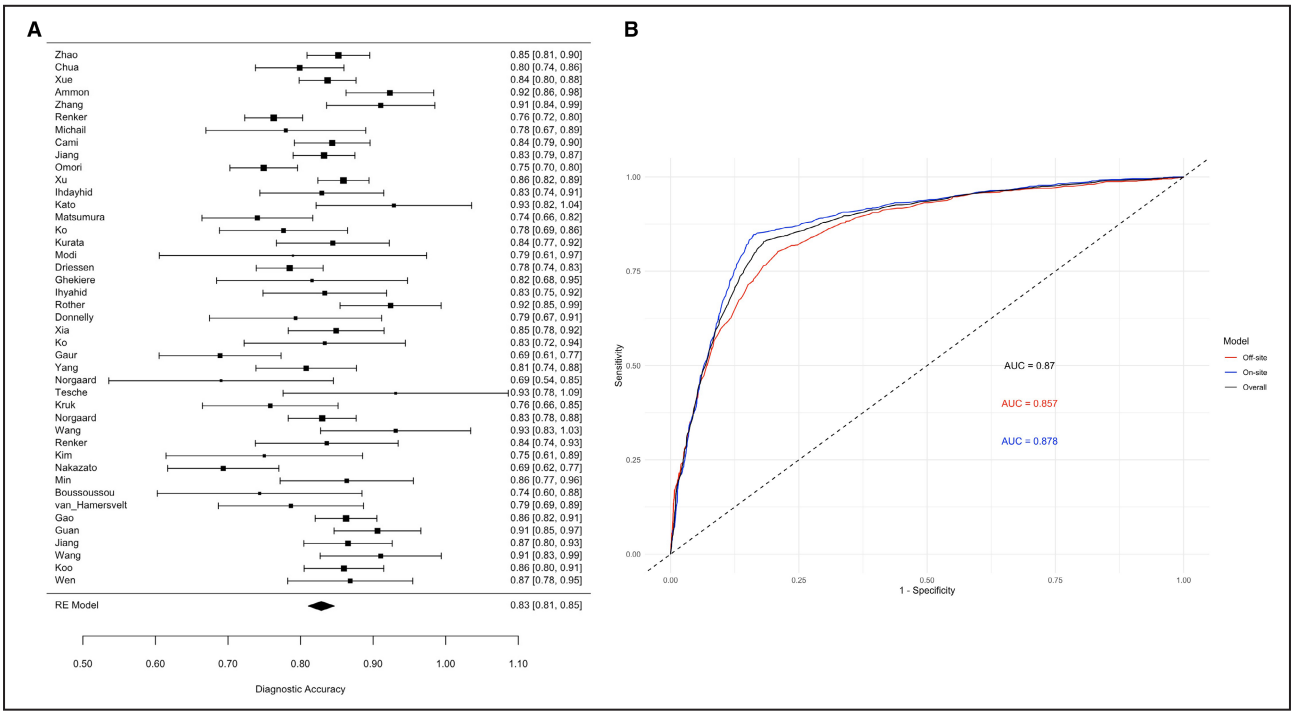

Figure 3. Diagnostic accuracy of FFR-CT on a per-study and per-vessel level.
A, Forest plot for the diagnostic accuracy of FFR-CT from each of the 43 studies. The I^2 value was 64.1%. **B**, Receiver operator characteristic curve depicting the diagnostic accuracy of FFR-CT using invasive FFR ≤0.8 as a positive result for off-site FFR-CT tools (red), on-site FFR-CT tools (blue), and all FFR-CT tools (black). AUC indicates area under the curve; CT, computed tomography; and FFR, fractional flow reserve.

invasive FFR, off-site FFR-CT had AUC 0.86, diagnostic accuracy 79.3%, sensitivity 77.1%, specificity 80.9%, positive predictive value 72.6%, and negative predictive value 84.2% (Table S5 and Figure 3B).

Similarly, data extracted from 23 studies were used to evaluate the agreement of FFR-CT provided by on-site suppliers with invasive FFR (including 3482 data points, Table S1). The overall limits of agreement were −0.24 to 0.21 (refer to Figure 5). Compared with invasive FFR, on-site FFR-CT had AUC 0.88, diagnostic accuracy 84.1%, sensitivity 83.4%, specificity 84.7%, positive predictive value 80%, and negative predictive value 88% (refer to Table S6 and Figure 3B).

Statistical comparison revealed that predictions made by on-site providers were more accurate than off-site providers in the included studies. A bootstrap test for the 2 ROC curves with 1000 resamples found that the difference in AUC was statistically significant (*P* value: 0.033). The 95% CIs for the diagnostic accuracy of off-site and on-site tools were 0.84 to 0.87 and 0.87 to 0.89 respectively.

DISCUSSION

The primary aim of this study was to evaluate the agreement between FFR-CT and invasive FFR. Based on an analysis of 5883 data points extracted from 43 independent studies, there was a moderate correlation between FFR-CT and invasive FFR. There was significantly greater scatter between FFR-CT and invasive FFR for lower FFR-CT values and there was a small bias toward overestimating functional disease severity by FFR-CT.

A secondary aim was to evaluate the ability of FFR-CT to correctly classify lesions as hemodynamically significant. The overall diagnostic accuracy, sensitivity, and specificity of FFR-CT were 82.2%, 80.9%, and 83.1% respectively. These values differ from those reported by a prior meta-analysis of 23 studies including 2178 patients and 3029 vessels that found sensitivity and specificity of 88% and 79% for FFR-CT.[68] These differences may reflect that Luo et al. assessed accuracy by compiling diagnostic accuracy percentages from the included studies rather than extracting FFR-CT and invasive FFR measurements from all studies. Additionally, the current study included data from 43 studies whereas Luo et al. included only 23. Assessing diagnostic accuracy, however, may be misleading because the diagnostic accuracy of FFR-CT varies with FFR-CT values. Cook et al. found that the diagnostic accuracy of FFR-CT could be as low as 50% between 0.7 and 0.8 and as high as 98% for FFR-CT values <0.4 or very close to 1.[19] This meta-analysis found that the diagnostic accuracy of FFR-CT ranged

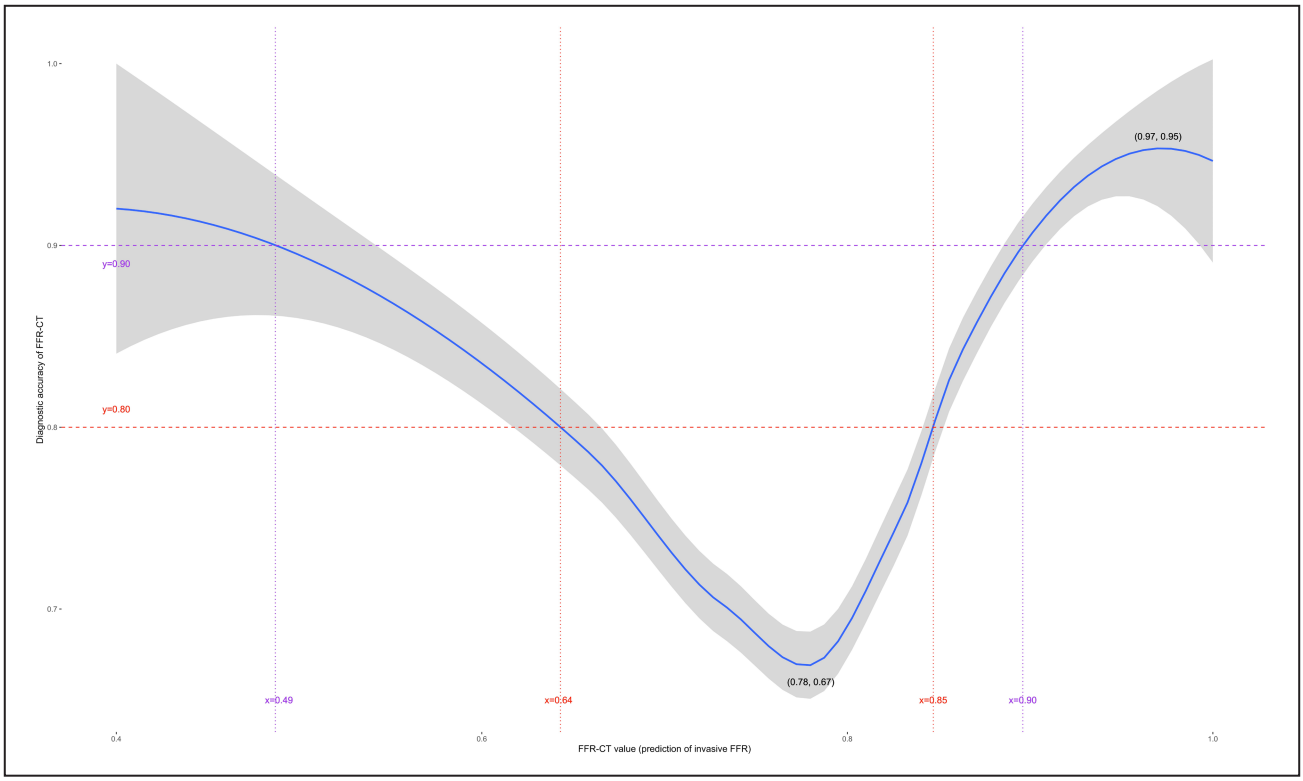

Figure 4. Diagnostic accuracy curve for FFR-CT between 0.4 and 1.0.
The blue line represents the diagnostic accuracy of FFR-CT, defined as the ability of FFR-CT to classify lesions as hemodynamically significant (invasive FFR ≤0.8) or insignificant (invasive FFR >0.8). The gray area represents 95% CIs. The diagnostic accuracy is >80% for FFR-CT <0.64 or >0.85 (red), and the diagnostic accuracy is >90% for FFR-CT >0.90 or <0.49 (purple). The diagnostic accuracy is poorest for FFR-CT 0.78 at 67%, and highest for FFR-CT 0.97 at 95%. CT indicates computed tomography; and FFR, fractional flow reserve.

from 67% for FFR-CT of 0.78 to 95% for FFR-CT of 0.97. Therefore, the diagnostic accuracy of FFR-CT in this meta-analysis is more consistent than reported by Cook et al. Assessing diagnostic accuracy for different ranges of FFR-CT values is of limited value, however, because diagnostic accuracy can be interpreted only in the context of the actual FFR-CT value and FFR-CT is a continuous variable from 0 to 1 that confers more information than diagnostic category alone. Our data suggest caution in interpreting FFR-CT values in "the gray zone" of 0.75 to 0.80. This meta-analysis found that across the 5883 data points included, FFR-CT values are on average 0.01 lower than the corresponding invasive FFR value (Figure 2C). Thus, lesions with an FFR-CT of 0.81 but invasive FFR of 0.79 would be falsely considered nonhemodynamically significant if relying on imaging-based diagnosis alone despite the 2 values being very close to each other.

Findings regarding the diagnostic accuracy of FFR-CT in patients with recent STEMI should be interpreted with caution. The lower diagnostic accuracy of FFR-CT in this cohort (70% versus 83% in patients undergoing investigation for suspected or known CAD) from this meta-analysis may reflect the physiological alterations induced by the MI. FFR-CT assumes a normal vasodilatory response[69] but a reduced vasodilator response in the microvasculature has been observed up to 6 months following myocardial infarction, possibly reducing FFR-CT accuracy.[44,70] Furthermore, the performance of hyperemic physiology assessment (invasive FFR) is poorer in coronary arteries with total or partial occlusion in the acute phase meaning the benchmark of invasive FFR may be unreliable.[71] It would be more appropriate to compare FFR-CT to invasive FFR in selective patients with STEMI after a fixed time interval.[55]

Findings regarding the diagnostic accuracy of FFR-CT in patients with severe aortic stenosis also require careful interpretation. The slightly higher diagnostic accuracy of FFR-CT in this cohort (84% versus 83% in patients undergoing investigation for suspected or known CAD) was not statistically significant. The 2 studies investigating patients with aortic stenosis had very small sample sizes of 63 (Zhang) and 60 (Michail) patients. Furthermore, the 2 studies had different methodologies. More studies are therefore needed to determine whether FFR-CT is feasible for the investigation of CAD in patients with aortic stenosis. This is especially important considering 25% to 50% of patients with severe aortic stenosis have concomitant CAD.[72]

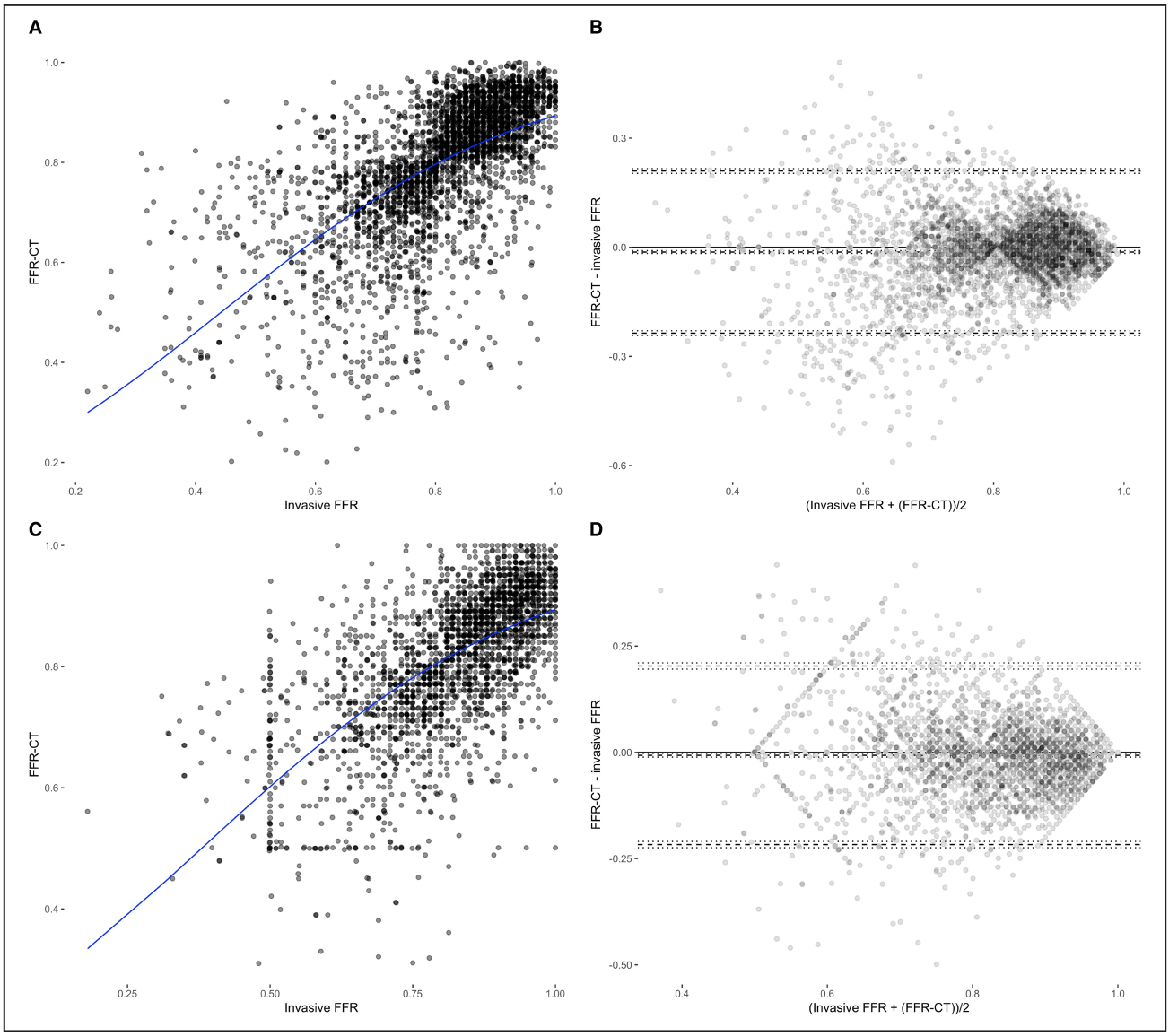

Figure 5. Agreement between FFR-CT generated using on-site and off-site tools and invasive FFR.
A, Scatterplot comparing FFR-CT generated using on-site tools (*y* axis) to invasive FFR (*x* axis). The blue curve was generated by the beta regression model. The gray zone represents the CIs. **B**, Bland–Altman graph plotting the difference between FFR-CT generated by on-site tools and invasive FFR on the *y* axis against the average of the 2 measurements on the *x* axis for all invasive FFR values. Dashed lines represent upper (0.21) and lower (−0.24) limits of agreement and average difference (−0.01). **C**, Scatterplot comparing FFR-CT generated using off-site tools (*y* axis) to invasive FFR (*x* axis). The blue curve was generated by the beta regression model. The gray zone represents the CIs. **D**, Bland–Altman graph plotting the difference between FFR-CT generated using off-site tools and invasive FFR on the *y* axis against the average of the 2 measurements on the *x* axis for all invasive FFR values. Dashed lines represent upper (0.20) and lower (−0.22) limits of agreement and average difference (−0.01). CT indicates computed tomography; and FFR, fractional flow reserve.

The meta-analysis also found negligible change in the diagnostic accuracy over time or with increased number of CT slices.

The final aim of the meta-analysis was assessing the agreement of off-site and on-site tools for estimating FFR-CT with invasive FFR. This meta-analysis found sensitivities and specificities of 0.83 versus 0.77 and 0.85 versus 0.81 for on-site and off-site tools respectively (Tables S5 and S6). These findings are consistent with a 2019 meta-analysis of 18 studies that found sensitivity of 0.84 versus 0.85 and specificity of 0.80 versus 0.73 for on-site and off-site studies respectively suggesting the results are reproducible.[73]

Findings of this review must be considered in light of inherent strengths and weaknesses. Strengths included performing a systematic literature search encompassing 43 studies and robust methods for data extraction. Additionally, this meta-analysis is the first to focus on agreement between FFR-CT and invasive FFR considering Cook et al. primarily evaluated

diagnostic accuracy. Furthermore, this study applied beta regression instead of linear regression to the scatterplots as this was deemed more appropriate to account for data distribution (bounded between 0 and 1) and anticipated heteroscedasticity as noted by Cook et al.[19] than linear measures of association employed by other studies (eg, correlation coefficients). Direct comparison between the findings of the current study and Cook et al. may therefore be inappropriate.

Limitations relate to the quality of available data. As described in the quality assessment, studies evaluated FFR-CT at different sites (left anterior descending, left circumflex, or right coronary artery) with varying degrees of severity (for example, 10%–90% stenosis or 40%–70% stenosis). Differences in diagnostic accuracy reported between studies may reflect sampling of different vessels that could not be assessed due to lack of linkage between invasive FFR and FFR-CT pairings with specific blood vessels in the scatterplots. Additionally, the inability to link observed FFR and FFR-CT to subject-specific covariates prevented assessment of accuracy based on patient factors. Future studies—particularly individual patient level meta-analysis where these covariates can be assessed—are needed to further the field. Furthermore, the lack of retesting of FFR-CT and invasive FFR in the individual studies means there may have been some degree of error in the measurements obtained, further limiting assessments of the accuracy of FFR-CT. Unlike previous meta-analyses, this study corrected for the impact of sampling bias by linking diagnostic accuracy to FFR-CT values. Additionally, the data include only vessels with successful invasive and FFR-CT, whereas variable numbers of vessels were excluded due to failed FFR measurements in the original studies.

Another limitation in the quality of the included studies was the potential risk of perceived reporting bias because most studies evaluated the diagnostic accuracy of tools developed by companies they were sponsored by. This may lead to overestimation of diagnostic accuracy.

In the absence of vessel-level data, analyses in the current review relied on data extracted from graphs presented in the included studies. Although data extraction methodologies were shown to be highly reproducible, some data points were missed due to overlapping data. Most overlapping data points that were missed occurred where the agreement between invasive FFR and FFR-CT was highest, which may lead to underestimation of diagnostic accuracy. Despite this, 80.7% of data points could be extracted and the current analysis represents the largest data set assessing diagnostic accuracy of FFR-CT to date. Furthermore, the sensitivity, specificity, and diagnostic accuracy reported in this study are similar to values generated from other meta-analyses, suggesting that the results were reproducible.[19,68,73] Extracting individual data points from the primary studies was necessary to evaluate the agreement between invasive FFR and FFR-CT.

A further limitation is that the findings of this review predominantly arise from investigation of vessels in older, male-dominated populations. The ability to extrapolate these results to other populations is unclear although a previous meta-analysis reported similar diagnostic accuracy of FFR-CT on a per-patient and per-vessel basis (AUCs of 0.90 and 0.91 respectively).[18] These findings suggest that per-patient and per-vessel results may be comparable. Furthermore, this meta-analysis included some studies in patient cohorts in which the use of FFR-CT is not well established yet such as those with acute myocardial infarction. FFR-CT may be more or less accurate in these specific populations. For example, the performance of hyperemic physiology assessment (invasive FFR) is poorer in coronary arteries with total or subtotal occlusion, meaning FFR-CT could be more accurate in patients with acute myocardial infarction than in patients with chronic cardiac syndromes. Most papers (36 of 43), however, performed FFR-CT and invasive FFR where clinically indicated in patients with suspected or known CAD and only 2 studies compared FFR-CT to invasive FFR in patients with STEMI. Additionally, this meta-analysis included a wide variety of CT technologies from various providers. CT scanners ranged from 64 detector row scanners to 384 detector row scanners (listed in Table S1).

Finally, this study described the diagnostic performance of specific on-site tools (see Table 1). The diagnostic accuracy of other on-site tools for calculating FFR-CT remains unclear. A study evaluating experimental techniques for calculating FFR-CT would have been subject to significant publication bias as inaccurate tools are less likely to have been published. Future meta-analyses should focus on comparing FFR-CT to other noninvasive imaging techniques such as CT perfusion that have been proposed to rule out hemodynamically significant disease. Additionally, more research is required to validate the use of FFR-CT in patients with recent STEMI and severe aortic stenosis. The cost-effectiveness of FFR-CT also needs further investigation. A study by Kimura et al.[10] suggested FFR-CT was cost effective for selecting patients for percutaneous coronary intervention compared with invasive coronary angiography but further health economic studies are needed to validate the value of using FFR-CT in routine clinical practice.

Ultimately, deciding which patients need to undergo invasive coronary angiogram after CTCA is a multifactorial decision. FFR-CT readings could be an important component of this decision. FFR and FFR-CT were compared in 5883 blood vessels in this meta-analysis; 1374—or 23.4%—of these blood vessels had FFR-CT

≥0.901. Of the 1374 blood vessels, 1283 (93.4%) had invasive FFR ≥0.80 at the time of invasive angiography. American Heart Association guidelines suggest that percutaneous coronary intervention should not be performed in these patients.[74] The remaining 91 (6.6%) blood vessels had a median invasive FFR of 0.76. Evidence from other meta-analyses suggests that deferral of revascularization in these "gray zone" vessels may have been safe.[7] Together, these results suggest that deferral of invasive coronary angiogram for patients with FFR-CT >0.90 may be considered. In contrast, FFR-CT values <0.49 strongly suggest the need for revascularization as analyses demonstrated that 100% of lesions with FFR-CT <0.500 were confirmed to be hemodynamically significant by FFR during invasive coronary angiogram (Figure S12).

FFR-CT values from 0.49 to 0.90 still demonstrate a high level of agreement with invasively measured FFR. Clinicians should recognize that the invasive FFR is likely to be very close to the FFR-CT (with an average difference of 0.01 [95% CI, 0.21 to −0.24]) and use this knowledge to help decide whether to proceed with functional imaging or invasive angiography.

FFR-CT is effective at ruling out hemodynamically significant CAD when FFR-CT is >0.90. Therefore FFR-CT could be an important adjunct to CTCA as a gatekeeper to invasive angiography. This could be of pivotal importance in avoiding complications from invasive procedures, avoiding unnecessary interventions, and driving cost savings for health care systems.[10] As FFR-CT continues to improve with CTCA hardware and machine learning software, virtual percutaneous coronary intervention and projection selection based on FFR-CT may eventually become possible. FFR-CT may have a role in gatekeeping invasive FFR. FFR-CT technology, however, cannot yet replace invasive FFR in guiding revascularization decisions.

CONCLUSIONS

The level of agreement between FFR-CT and invasive FFR is higher in healthy vessels than severely diseased vessels. Data demonstrate that FFR-CT is effective in ruling out hemodynamically significant lesions if FFR-CT is >0.90. If FFR-CT is >0.9, there is a 90% chance that invasive angiogram can be safely deferred. Although there is a 10% chance the lesion will be hemodynamically significant, the majority of these lesions will have invasive FFR between 0.70 and 0.79. It is essential to consider actual FFR-CT values instead of diagnostic classification as ischemic or nonischemic, because diagnostic accuracy varies widely with FFR-CT. On average across all data points, FFR-CT values were 0.01 lower than corresponding invasive FFR values. Findings also suggest a small but statistically significant difference in the reliability of FFR-CT estimations provided by off-site providers and those calculated in house using commercially available tools. Collectively, these results suggest that FFR-CT may potentially be a useful adjunct tool to identify hemodynamically significant lesions. FFR-CT can rule in hemodynamically significant CAD if FFR-CT is <0.49 and rule out hemodynamically significant CAD if FFR-CT is >0.90. However, the lower diagnostic accuracy of FFR-CT between 0.49 and 0.90 may justify further investigation for patients with FFR-CT values in this range.

ARTICLE INFORMATION

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Affiliations

College of Medicine and Dentistry, James Cook University, Townsville, QLD, Australia (T.I.F., J.V.M.); Department of Medical Imaging (K.P.) and Department of Cardiology (S.B.M.), Townsville University Hospital, Townsville, QLD, Australia; College of Medicine and Dentistry, University of Adelaide, Adelaide, SA, Australia (L.E.F.); The Australian Institute of Tropical Health and Medicine (J.V.M.), Graduate Research School (R.J.); and Tropical Australian Academic Health Centre (R.J.), James Cook University, Townsville, QLD, Australia.

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Supplemental Material

Data S1–S2
Tables S1–S6
Figures S1–S12

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