

Diagnostic performance of noninvasive fractional flow reserve derived from coronary computed tomography angiography in ischemia-causing coronary stenosis: a meta-analysis

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Abstract

Purpose Fractional flow reserve based on coronary computed tomographic angiography (CCTA; FFR_{CT}) can evaluate functional severity in coronary artery disease (CAD). This study investigated the diagnostic value of FFR_{CT} for determining CAD severity.

Materials and methods Medline, Cochrane, EMBASE, and Google Scholar databases were searched until June 16, 2016 using the following search terms: fractional flow reserve, coronary computed tomography angiography, myocardial ischemia. Randomized controlled trials, two-arm prospective studies, and retrospective studies were included in the analysis.

Results Twenty-one studies were included with a total of 2216 subjects and 2798 vessels. FFR_{CT}, sensitivity per-vessel and per-patient were $\geq 82\%$ and specificity was $\geq 73\%$ for diagnosis of ischemia. FFR_{CT} had better diagnostic accuracy and discrimination than CCTA.

Conclusion This study indicates that FFR_{CT} may be a good tool for screening and diagnosing of myocardial ischemia in patients with CAD.

Keywords Fractional flow reserve · Coronary computed tomography angiography · Myocardial ischemia · Stenosis · Coronary artery disease

Introduction

Invasive coronary angiography and non-invasive coronary computed tomographic angiography (CCTA) are established methods for detecting coronary artery disease (CAD) [1–3]. The main use of CCTA is in the diagnosis or exclusion of obstructive CAD [4]. For this use, CCTA has high sensitivity (>90%) and high negative predictive value (>98%) [4]. Overall, clinical situations where CCTA is considered of benefit to perform is when CAD is suspected in patients at intermediate risk who have undergone stress tests that are not conclusive or in whom a stress test cannot be performed [4]. CCTA is a safe technique and can be useful in clinical management of patients [5]. Improvement in scanners, image acquisition, and reconstruction has allowed CCTA to consistently be performed in a radiation range of 1–5 mSV [6]. Despite recent advancements, CCTA remains strictly an anatomic test, and, hence, similar to conventional invasive angiography, it lacks the necessary information to guide revascularization decisions, which requires objective evidence of ischemia [6].

However, both conventional invasive angiography and CCTA are limited. Invasive coronary angiography is limited by that fact that the correlation between angiographic and physiological stenosis is poor [7, 8]. A limitation of CCTA is that in the presence of CAD, it can overestimate the severity of stenosis compared with invasive coronary angiography [3]. In addition, CAD functional severity only weakly correlates with CCTA severity. This latter limitation is of particular importance in that determination of functional severity is a key factor used in decision-making with regard to the management of CAD [3].

Fractional flow reserve (FFR), which assesses the ratio of flow across a stenosis to putative flow in the absence of stenosis, is considered the reference standard for evaluating

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the severity of stenosis in CAD and is one of the key parameters for revascularization therapy [9–11]. FFR, as measured by conventional invasive angiography, is considered the gold standard for discriminating lesion-specific ischemia [6]. Prior studies have shown that an FFR ratio of 0.80 identifies patients with coronary lesions who will benefit from coronary revascularization [10, 12]. FFR is limited by its invasiveness and costs, and, hence, it is not commonly used in clinical practice for coronary revascularization decision-making [6].

Recently, a method that utilizes computational fluid dynamics to calculate coronary blood flow, pressure, and FFR based on routinely acquired CCTA at rest (FFR_{CT}) has been introduced for evaluating functional severity [13–15]. FFR_{CT} combines functional and anatomical information to facilitate determination of appropriate treatments, and has the benefit of being non-invasive [1]. FFR_{CT} may be a useful diagnostic tool for distinguishing patients who will benefit from revascularization therapy from those who will not [1]. The diagnostic performance of FFR_{CT} has been tested in three prospective multicenter trials [1, 14, 15]. All three trials found FFR_{CT} was superior compared with invasive FFR [1, 14, 15]. FFR_{CT} has also demonstrated high diagnostic performance in the presence of coronary calcification [6]. However, the diagnostic accuracy of FFR_{CT} in the evaluation of lesion-specific myocardial ischemia is not clear, particularly in patients with intermediate coronary stenosis. No current guidelines provide recommendations regarding the use of FFR_{CT} testing and interpretation [6]. The purpose of this meta-analysis was to further evaluate the diagnostic value of FFR_{CT} compared with invasive FFR for diagnosing myocardial ischemia in patients with CAD. The study also compared the diagnostic accuracy of FFR_{CT} with CCTA.

Materials and methods

Search strategy

This analysis was performed in accordance with the PRISMA guidelines. Medline, Cochrane, EMBASE, and Google Scholar databases were searched until June 16, 2016 using the following search terms: fractional flow reserve, coronary computed tomography angiography, myocardial ischemia. Randomized controlled trials (RCTs), two-arm prospective studies, and retrospective studies were included in the analysis. Eligible studies evaluated adult patients with suspected coronary artery disease who underwent clinically indicated invasive coronary angiography or CCTA, and reported quantitatively outcomes of interest. Letters, comments, editorials, case reports, proceedings, and personal communications were excluded. Potential references were hand-searched by two independent reviewers

to evaluate if they met the inclusion/exclusion criteria. A third reviewer was consulted, when necessary, to resolve any uncertainty regarding eligibility.

Data extraction and quality assessment

The following information/data was extracted from the included studies: the name of the first author, year of publication, study design, number of participants and vessels, participants' age and gender, previous CAD, comorbidities, smoking history, and the major outcomes.

The quality of the included studies was evaluated using Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) [16].

Outcome measures

The outcomes were sensitivity, specificity, positive and negative predictive values of FFR for diagnosis of ischemia, and areas under the curve (AUCs) of per-patient and per-vessel performance of FFR_{CT} ≤ 0.80 and computed tomography (CT) stenosis ≥ 50% compared with invasive FFR for diagnosing ischemia.

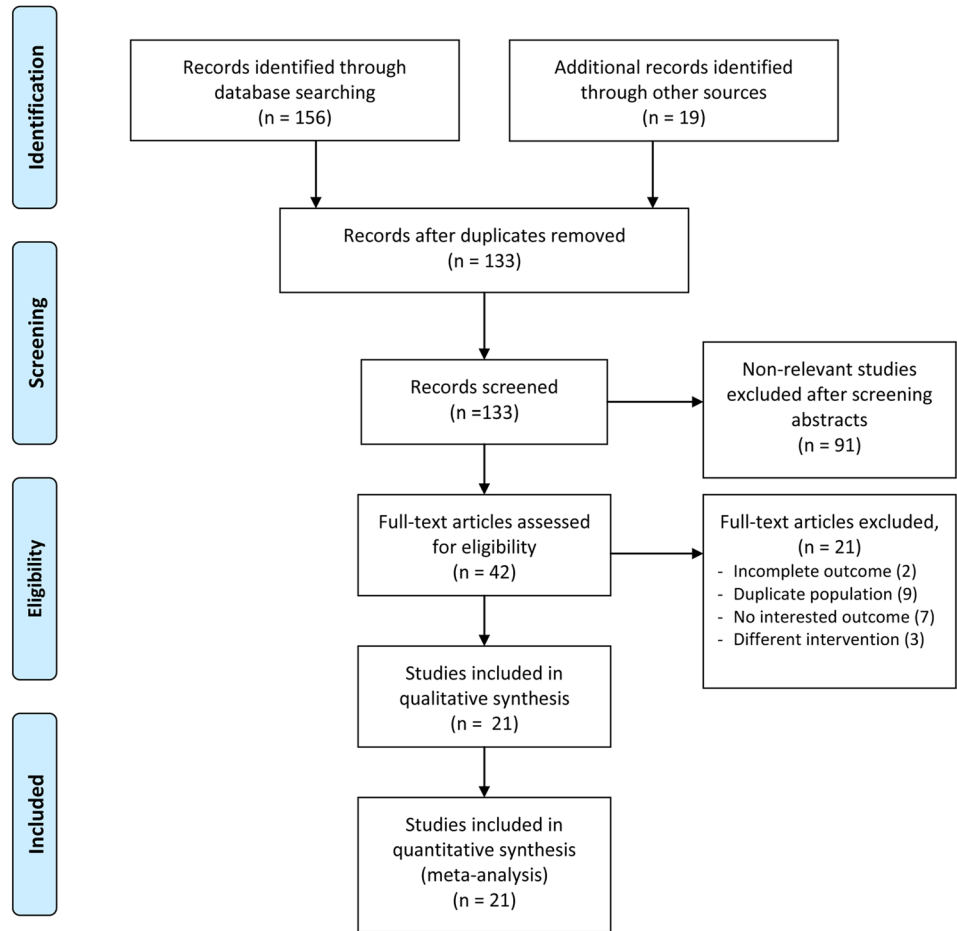
Statistical analysis

Accuracy data were used to construct 2 × 2 tables of non-invasive FFR from CCTA for diagnosis of ischemia. The true-positive, false-positive, true-negative, and false-negative values were abstracted and recorded. Ischemia was defined by an FFR_{CT} ≤ 0.80 or a CCTA with stenosis ≥ 50%. Diagnostic performance of FFR_{CT} and CCTA stenosis was assessed with invasive FFR as the reference standard. Pooled measures for diagnostic performance, such as sensitivity (true positive/true-positive + false negative), specificity (true negative/true-negative + false positive), diagnostic odds ratios (diagnostic ORs) with their corresponding 95% confidence intervals (95% CIs), and area under the receiver-operating characteristic (AUC ROC) curves were calculated. The sensitivity and specificity “per-vessel” was based on the number of vessel diagnosed, and “per-patient” was based on the number of patients evaluated. The diagnostic ORs combine sensitivity and specificity into one measure for diagnostic performance. A diagnostic OR of 1 means the test has no ability to discriminate. In the context of this study, higher diagnostic OR represents better diagnostic accuracy of FFR_{CT} for determining ischemia. Inverse variance weights were used for pooling and significant heterogeneity, which was expected because of the emerging nature of this field, was addressed by the application of random effects (DerSimonian–Laird approach) modeling. All statistical assessments were two-sided and a *P* value < 0.05 was considered

Fig. 1 Prisma 2009 flow diagram



PRISMA 2009 Flow Diagram



to indicate statistical significance. All analyses were performed using Meta-Disc version 1.4 [17].

Results

Of the 175 studies initially identified, 133 were excluded for being duplicates or irrelevant (Fig. 1). Forty-two underwent full text review of which 21 were excluded for not reporting complete outcomes, reporting data on duplicate study populations, not reporting outcomes of interest, or investigating other types of interventions.

Twenty-one studies were included in the analysis with a total of 2216 subjects and 2798 vessels [1, 2, 14, 15, 18–34]. The number of patients in the studies ranged from 37 to 475 and the number of vessels in the studies ranged from 37 to 484 (Table 1). The age range of patients was similar across studies with the mean age being about 60 years.

The majority of patients were male. In general, over half the patients across the studies had hypertension (range 37–81%) and less than a third had diabetes (range 10–68%). The incidence of dyslipidemia varied among the studies (range 19–95%). The percentage of patients who smoked was from 14 to 46% (Table 1). Less than a quarter of the patients had prior myocardial infarction (range 2–19%) or percutaneous coronary intervention (range 3–23%; Table 2). The cut-off threshold for both invasive FFR and FFR_{CT} ranged from 0.75 to 0.80, and the cut-off threshold for CCTA ranged from 50 to 65% (Table 2).

Sensitivity, specificity, diagnostic odd ratios (ORs), and area under the receiver-operating characteristic curve (AUC) for FFR_{CT}

A total of eight studies [1, 2, 14, 15, 18, 25, 29, 31] were included in the meta-analysis of diagnostic performance

Table 1 Summary of basic characteristics of selected studies for meta-analysis

First author (year)	Study design	No. of patients	No. of vessels	Age (years)	Male (%)	Populations	History of chronic diseases			Smoking
							HT	DM	DL	
Dai (2016)	Prospective	40	40	63.7	33	Moderate lesions (50–70%) in a single artery	57.5%	35%	77.5%	18%
Osawa (2016)	Prospective	53	75	71.4	68	Suspected or known CAD	81%	68%	68%	17%
Tesche (2016)	Retrospective	37	37	61	68	Suspected or known CAD	65%	41%	43%	35%
Neglia (2015)	Prospective	475	na	60	61	Suspected CAD	61%	24%	56%	25%
Coenen (2014)	Prospective	106	189	61.4	77	Suspected or known CAD	59%	19%	59%	25%
Kim (2014)	Prospective	44	48	65	80	Suspected CAD	81%	29%	63%	na
Ko BS (2014)	Prospective	115	48	64	66	Suspected or known CAD	72%	18%	70%	14%
Nørgaard (2014)	Prospective	254	484	64	64	Suspected CAD	69%	23%	23%	18%
Opolski (2014)	Prospective	61	71	63	64	Known CAD (single coronary artery lesions of intermediate severity)	79%	10%	95%	25%
Renker (2014)	Retrospective	53	67	61.2	64	Suspected or known CAD	54%	32%	54%	14%
Rossi (2014)	Prospective	80	210	60	79	Suspected CAD (stable chest pain)	60%	20%	66%	33%
Stuijzand (2014)	Prospective	85	253	57.3	60	Suspected CAD	37%	16%	38%	45%
Voros (2014)	Prospective	85	85	61.3	62	Suspected CAD	78%	21%	91%	na
Choo (2013)	Prospective	37	81	61.7	76	Suspected CAD	57%	24%	19%	38%
Schaap (2013)	Prospective	98	225	62	68	Suspected CAD	63%	12%	60%	26%
Wong (2013)	Prospective	54	78	62.7	65	Suspected or known CAD	70%	17%	70%	17%
Choi (2012)	Retrospective	63	97	63.1	70	Known CAD ($\geq 50\%$ diameter stenosis)	62%	33%	64%	46%
Min (2012)	Prospective	252	406	62.9	71	Suspected or known CAD	71%	21%	80%	18%
Koo (2011)	Prospective	103	159	62.7	72	Suspected or known CAD	65%	26%	65%	36%
Kristensen (2010)	Prospective	42	56	61	76	Known CAD (coronary artery lesions of intermediate severity)	na	na	na	na
Meijboom (2008)	Retrospective	79	89	60	81	Known CAD (appearance of a coronary narrowing)	na	na	na	na

DM diabetes mellitus, HT hypertension, DL dyslipidemia

Table 2 Intervention history and cut-off points

First author (year)	Previous myocardial infarction	Percutaneous coronary intervention	GABG	Cut-off threshold		
				Reference standard (invasive FFR)	FFR _{CT}	CCTA (%)
Dai (2016)	na	na	Excluded	0.8	0.76	
Osawa (2016)	na	Excluded	Excluded	0.8		50
Tesche (2016)	0	Excluded	Excluded	0.8	0.8	
Neglia (2015)	na	17%	3%	0.8		50
Coenen (2014)	13%	10%	Excluded	0.8	0.8	50
Kim (2014)	10%	na	0%	0.8	0.8	
Ko BS (2014)	10%	na	na	0.8		50
Nørgaard (2014)	2%	na	Excluded	0.8	0.8	50
Opolski (2014)	15%	23%	Excluded	0.8		
Renker (2014)	na	16%	0%	0.8	0.8	50
Rossi (2014)	na	na	na	0.75		50
Stuijzand (2014)	Excluded	Excluded	Excluded	0.8		50
Voros (2014)	na	na	na	0.75		62
Choo (2013)	5%	Excluded	Excluded	0.75		50
Schaap (2013)	na	Excluded	Excluded	0.8	0.8	50
Wong (2013)	9%	9%	Excluded	0.8		50
Choi (2012)	3%	3%	na	0.8		50
Min (2012)	6%	6%	0%	0.8	0.8	50
Koo (2011)	17%	16%	0%	0.8	0.8	50
Kristensen (2010)	19%	na	na	0.75		56
Meijboom (2008)	13%	37%	4%	0.8	0.75	50

GABG coronary artery bypass grafting, FFR fractional flow reserve, CCTA coronary computed tomographic angiography

of FFR_{CT} for ischemia on a per vessel basis (Fig. 2). Thirteen studies were excluded from the analysis as they did not report true-positive, false-positive, true-negative, and false-negative values. The range of sensitivities among the studies was from 74 to 100% and the pooled sensitivity was 0.82 (95% CI 0.79–0.86; Fig. 2a). The range of specificities varied from 63 to 96% and the pooled specificity was 0.79 (95% CI 0.76–0.82; Fig. 2b). For all studies, the pooled diagnostic OR was 25.18 (95% CI 11.82–53.66; Fig. 2c) and the areas under the summary ROC curves were 0.8957 (with a standard error of 0.017; Fig. 2d).

Only four studies reported diagnostic performance of FFR_{CT} for ischemia on a per-patient basis, and were included in the analysis [1, 14, 15, 29] (Fig. 3). The range of sensitivities among the studies was from 86 to 94% and the pooled sensitivity was 0.90 (95% CI 0.86–0.93; Fig. 3a). The range of specificities among the studies was from 54 to 91% and the pooled specificity was 0.73 (95% CI 0.68–0.77; Fig. 3b). In addition, the pooled diagnostic OR was 31.41 (95% CI 10.94–90.19; Fig. 3c) and the areas under the summary ROC curves were 0.9574 (with a standard error of 0.025; Fig. 3d).

Sensitivity, specificity, diagnostic odd ratios (ORs), and area under the receiver-operating characteristic curve (AUC) for CCTA stenosis

Sixteen studies reported true-positive, false-positive, true-negative, and false-negative values and were included in the meta-analysis of diagnostic performance of CCTA for ischemia on a per-vessel basis (Fig. 4) [1, 2, 14, 19–24, 26, 27, 29, 30, 32–34]. The range of sensitivities among the studies varied from 53 to 95% and the pooled sensitivity was 0.87 (95% CI 0.85–0.89; Fig. 4a). The range of specificities among the studies was from 34 to 88% and the pooled specificity was 0.63 (95% CI 0.60–0.65; Fig. 4b). For all studies, the pooled diagnostic OR was 12.25 (95% CI 7.84–19.14; Fig. 4c) and the areas under the summary ROC curves were 0.8543 (with a standard error of 0.030; Fig. 4d).

For a per-patient basis, eight studies reported the necessary values for evaluating diagnostic performance of CCTA and were included in the analysis [1, 14, 15, 20, 23, 28, 29, 34] (Fig. 5). The range of sensitivities among the studies varied from 83 to 100% and the pooled sensitivity was 0.91 (95% CI 0.88–0.93; Fig. 5a). The range

Fig. 2 Diagnostic performance of FFR_{CT} for diagnosis of ischemia on a per-vessel level

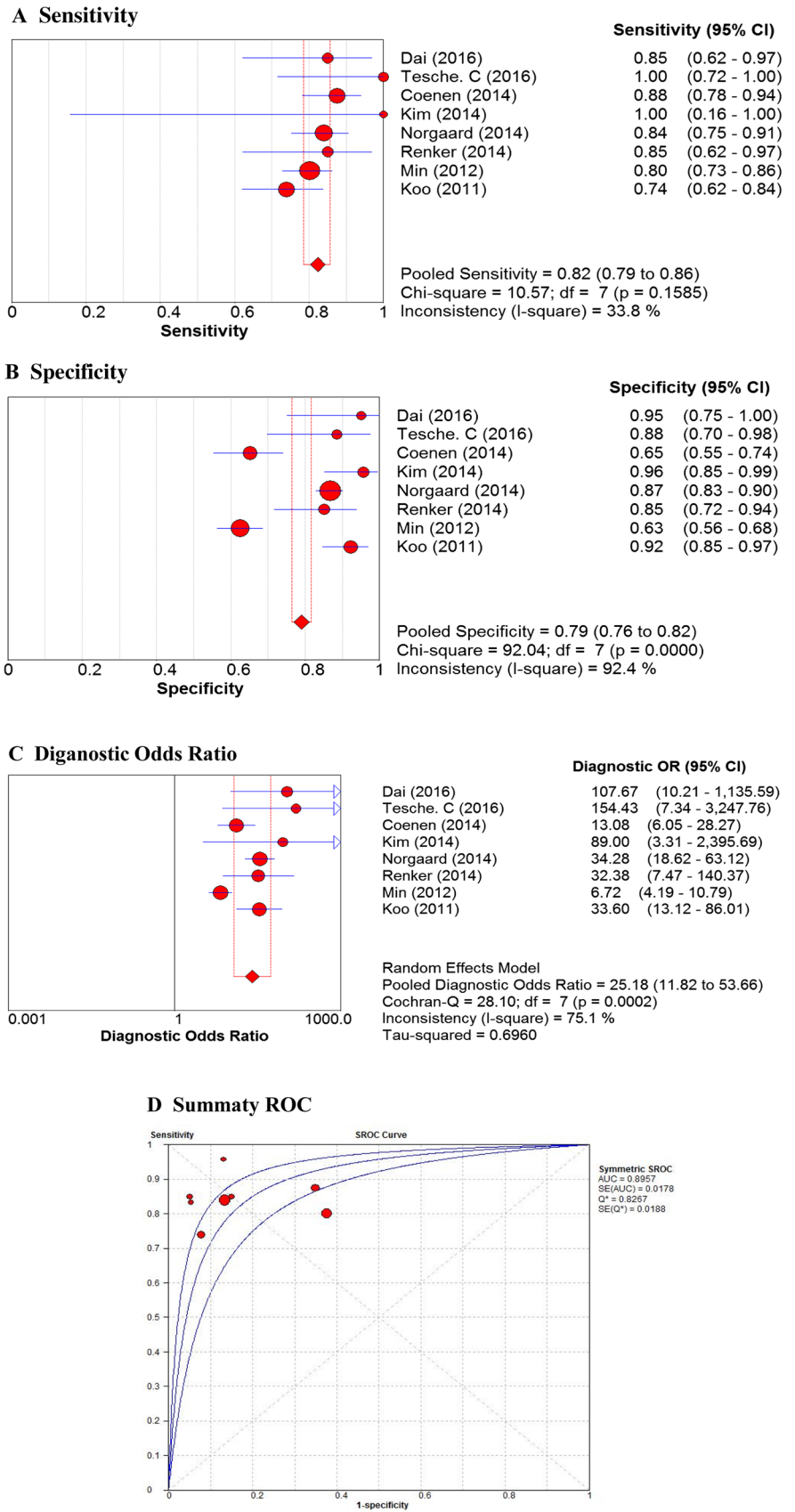
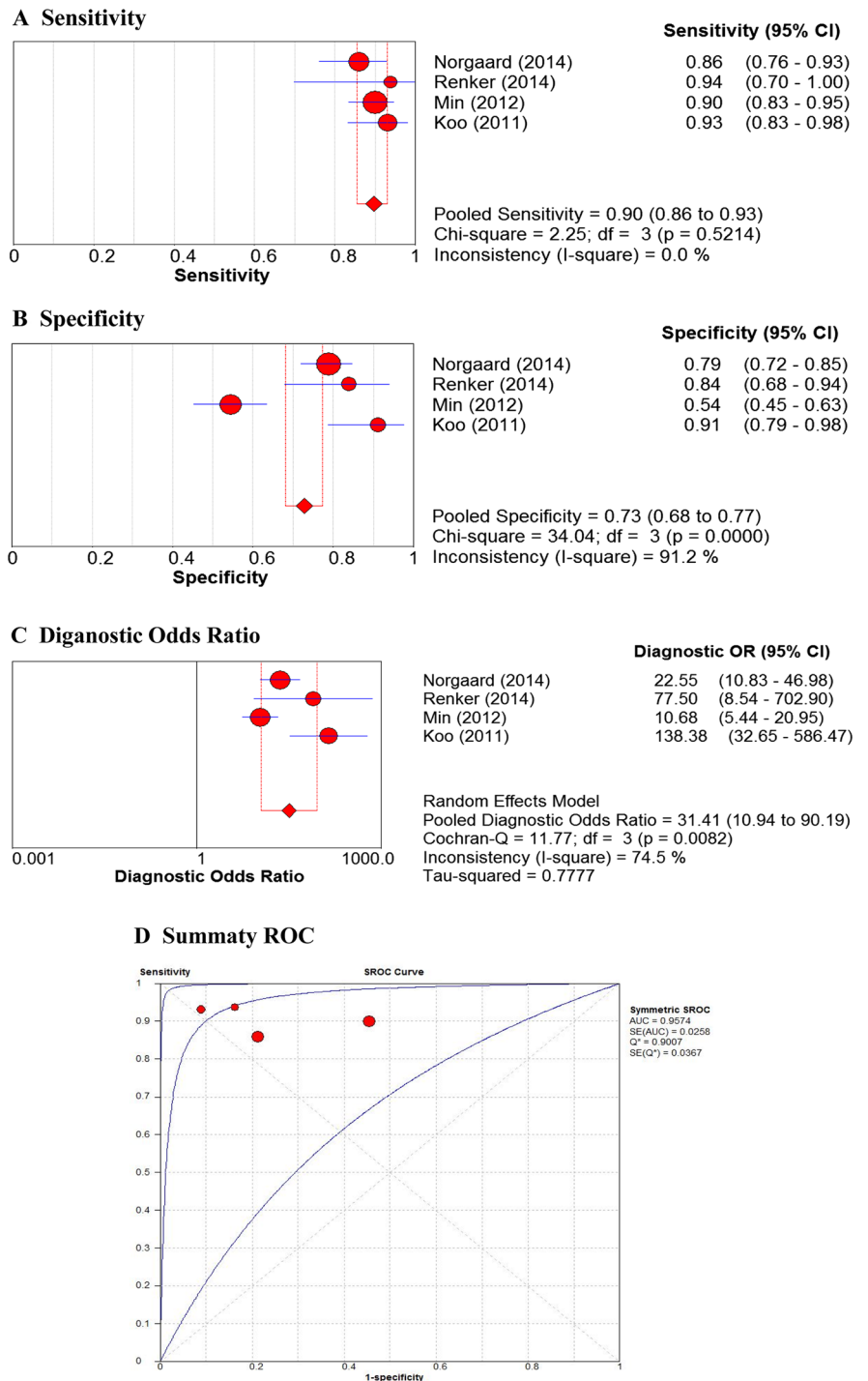


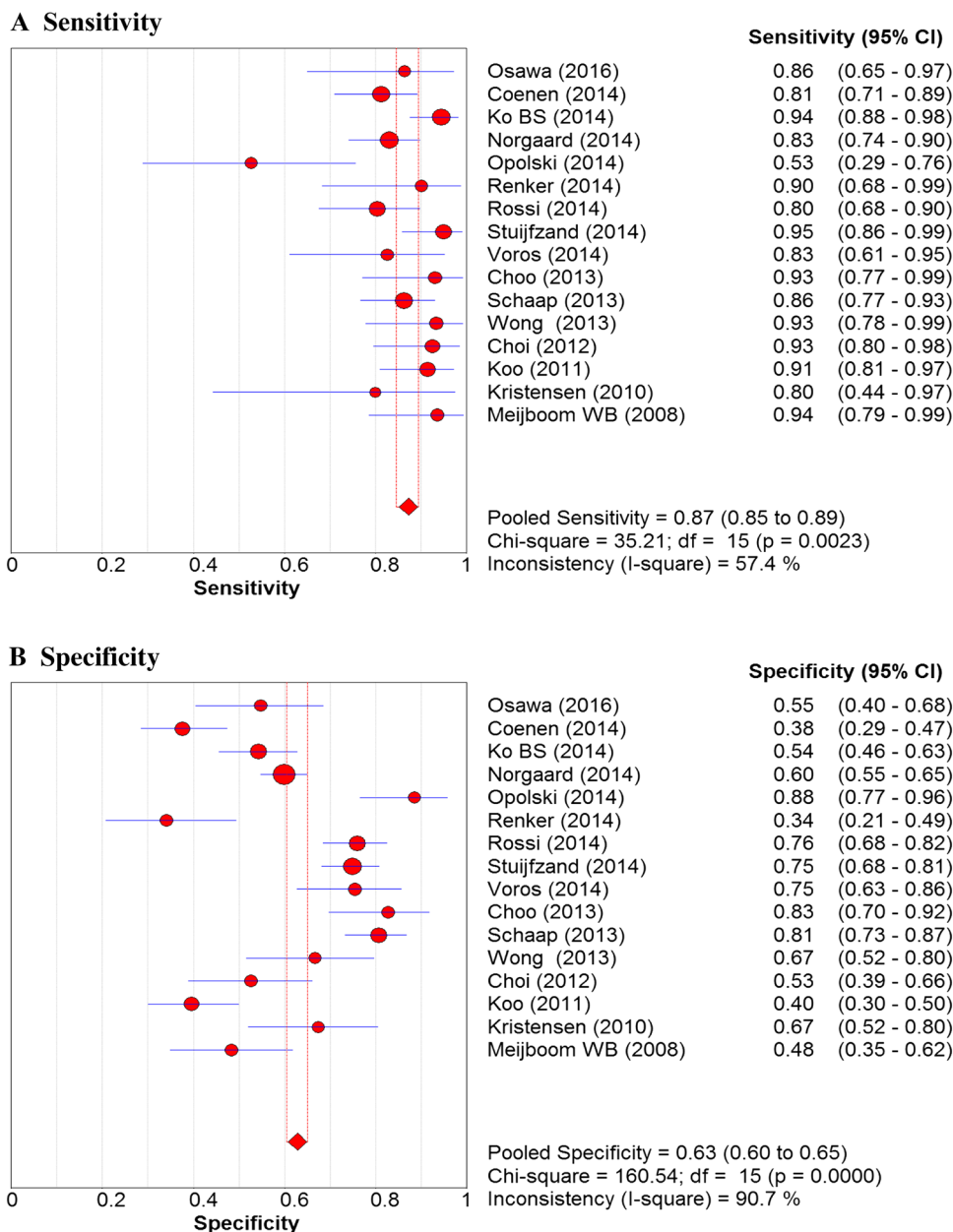
Fig. 3 Diagnostic performance of FFR_{CT} for diagnosis of ischemia on a per-patient level



of specificities among the studies varied from 24 to 92% and the pooled specificity was 0.61 (95% CI 0.58–0.65; Fig. 5b). The pooled diagnostic OR was 15.91 (95% CI 4.95–51.09; Fig. 5c) and the area under the summary ROC curves was 0.9087 (with a standard error of 0.060; Fig. 5d).

In summary, this analysis found that noninvasive FFR_{CT} was associated with improved diagnostic specificity and discrimination compared with CCTA alone for the diagnosis of ischemia when invasive FFR was served as the referent standard (diagnostic OR, 25.18 vs. 12.25 for per-vessel basis and diagnostic OR, 31.41 vs. 15.91 for per-patient basis).

Fig. 4 Diagnostic performance of CCTA for diagnosis of ischemia on a per-vessel level



Quality assessment

The included studies were evaluated using QUADAS-2 criteria. All studies had low risk of bias with regard to patient selection, index test, reference standard and flow and timing (Table 3). The risk of bias was low for applicability. These findings indicate the studies were of good quality.

Discussion

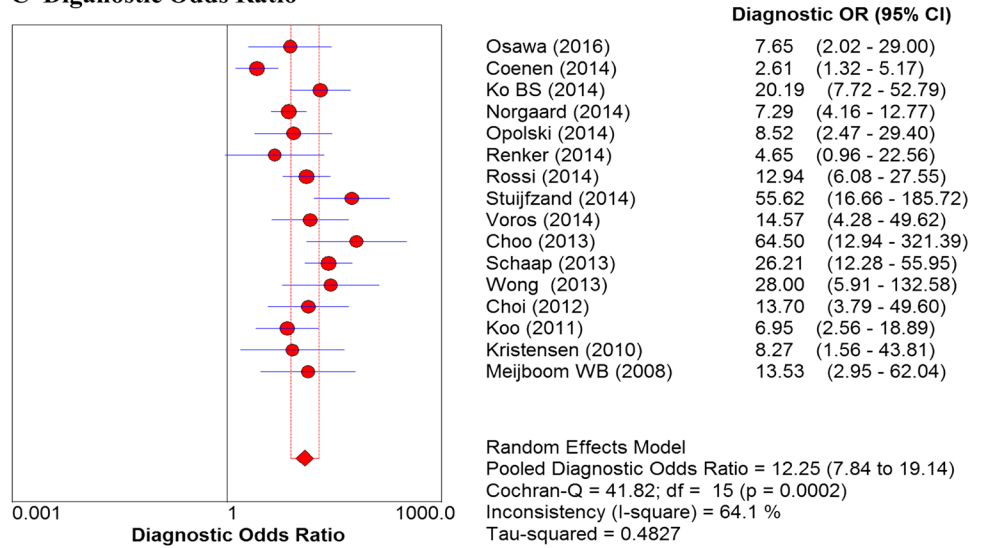
The aim of this analysis was to investigate the diagnostic value of noninvasive FFR_{CT} and CCTA compared with invasive FFR for the diagnosis of myocardial ischemia in

patients with CAD. No apparent difference in the pooled sensitivity per vessel and per patients between FFR_{CT} and CCTA was observed. However, the pooled specificity of FFR_{CT} per vessel (0.79) and per patients (0.73) was relatively higher than the pooled specificity per vessel (0.63) and per patients (0.61) of CCTA. Therefore, noninvasive FFR_{CT} was associated with improved diagnostic specificity and discrimination compared with CCTA alone for the diagnosis of ischemia when FFR served as the reference standard (diagnostic OR 25.18 vs. 12.25 for per vessel basis, diagnostic OR 31.41 vs. 15.91 for per patient basis).

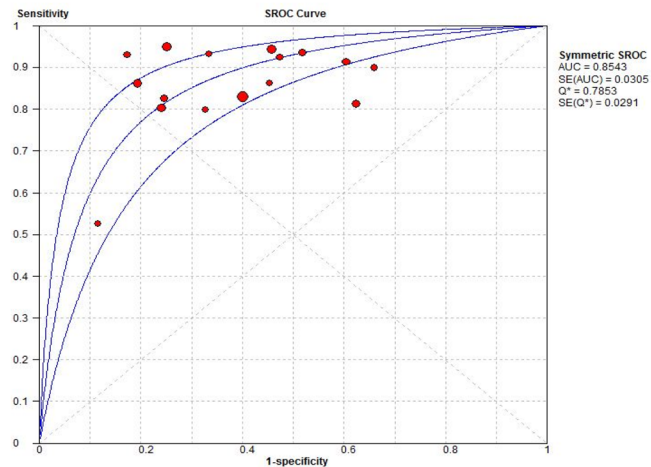
One prior meta-analysis assessed the diagnostic performance of FFR_{CT} compared with FFR [35]. Their analysis included 706 patients and 1165 vessels of lesions. The

Fig. 4 continued

C Diagnostic Odds Ratio



D Summary ROC



pooled sensitivity and specificity at the per-patient level were 90 and 72%, respectively, and at the per-vessel level, were 83 and 78%, which are quite similar to the values we found, and support the findings that FFR_{CT} has high diagnostic accuracy compared with invasively measured FFR for the detection of ischemia-causing stenosis in stable patients with known or suspected CAD.

Another prior meta-analysis compared the diagnostic performance of CCTA, computed tomography perfusion (CTP), and FFR_{CT} for evaluating the functional significance of coronary stenosis in patients with suspected or known CAD using FFR as the gold standard technique [36]. The meta-analysis included 18 studies with a total of 1535 patients. They found that CCTA had a high sensitivity and negative predictive value (92 and 87%, respectively) for ruling out stenosis as defined by FFR on a per-patient basis. CTP and FFR_{CT} had similar sensitivities (94

and 90%, respectively) and negative predictive values (92 and 90%) on a per-patient basis. Their findings indicate that sensitivity and negative predictive value are not improved with CTP or FFR_{CT} compared with CCTA. However, CTP and FFR_{CT} had higher estimates for specificity (77 and 72%, respectively) and positive predictive value on a per-patient analysis compared with CCTA. This is similar to our analysis which indicated FFR_{CT} has similar sensitivity but higher specificity compared with CCTA alone.

Two other meta-analyses evaluated pooled data from three prospective, international, multicenter studies that evaluated the diagnostic performance of FFR_{CT} using invasive FFR as a reference standard [37, 38]. Together, the three included studies had a total of 609 patients and 1050 vessels. The two meta-analyses found the pooled sensitivity was 89%, specificity 71%, the positive predictive value 70%, and negative predictive value 90% at the per-patient level and were 83, 78,

Fig. 5 Diagnostic performance of CCTA for diagnosis of ischemia on a per-patient level

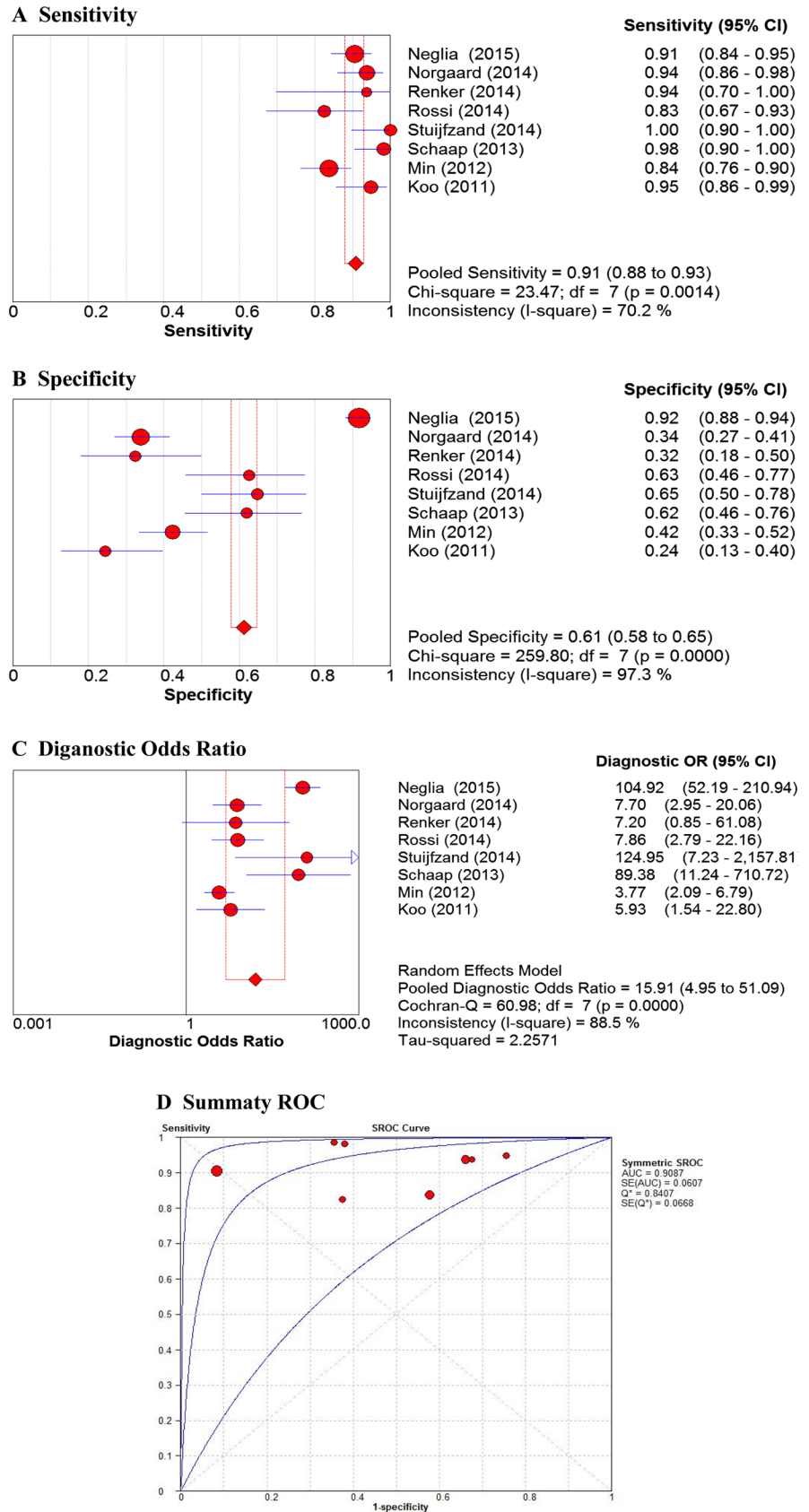


Table 3 Quality assessment

First author	Year	Concerns regarding applicability (low/high/unclear)													
		Risk of bias (low/high/unclear)		Patient selection		Index test		Reference standard		Flow and timing		Patient selection		Index test	
		Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Were the index test results interpreted without knowledge of the results of the reference standard?	If a threshold was used, was it pre-specified?	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without knowledge of the results of the index test?	Was there an appropriate interval between index test(s) and reference standard?	Did all patients receive a reference standard?	Did all patients receive the same reference standard?	Were all patients included in the analysis?	Were there concerns that the included patients do not match the review question?	Were there concerns that the index test, its conduct, or interpretation differs from the review question?	Were there concerns that the target condition as defined by the reference standard does not match the review question?
Dai	2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Osawa	2016	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Tesche	2016	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Low	Low	Low
Neglia	2015	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Low	Low	Low
Coenen	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Kim	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Ko BS	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Norgaard	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Opolski	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Renker	2014	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Rossi	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Stuijffzand	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Voros	2014	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Choo	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Schaap	2013	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Choi	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Min	2012	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Koo	2011	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	No	Low	Low	Low
Kris-tensen	2010	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low
Meijboom	2008	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Low	Low	Low

61, and 92%, respectively, at the per-vessel level. Both meta-analyses also found FFR_{CT} demonstrated significantly better accuracy compared with CCTA in detecting lesion-specific ischemia. FFR_{CT} remained highly specific and sensitive in patients with intermediate coronary stenosis with respect to ischemia diagnosis [37]. The meta-analysis of Li et al. found the diagnostic OR at the per-patient level was 21.2 and at the per-vessel level was 19.2. Consistent with our findings, these two meta-analyses conclude the FFR_{CT} is a viable alternative to invasive FFR [37, 38].

Another meta-analysis evaluated the diagnostic performance of multiple methods, including single-photon emission computed tomography (SPECT), stress echocardiography (SE), invasive coronary angiography (ICA), CCTA, FFR_{CT} , and cardiac magnetic resonance imaging (MRI) [39]. They found MRI had a high performance for diagnosing hemodynamically significant CAD both for per patient and per vessel when compared with FFR as the reference standard, and also that FFR_{CT} yielded high diagnostic sensitivity (90% per patient and 83% per vessel) and specificity (71% per patient and 78% per vessel). FFR_{CT} diagnostic performance was overall greater than that of CCTA (per-patient sensitivity and specificity were 90 and 39%, respectively, and per-vessel, they were 91 and 58%). FFR_{CT} also had greater diagnosis performance compared with ICA and SPECT.

In general, our study and the prior meta-analyses summarized above indicate that FFR_{CT} has diagnostic benefit compared with invasive FFR in evaluating stenosis in patients with CAD and may have greater benefit than CCTA, particularly in differentiating a true positive from a false positive. This conclusion is supported by the other studies that found FFR_{CT} provided increased diagnostic performance compared with CCTA alone, using invasive FFR as a reference, in discriminating hemodynamically significant coronary stenosis [40–42]. Compared with prior meta-analysis, our meta-analysis included a larger sample size comparing the diagnostic performance of FFR_{CT} and CCTA and incorporated recent clinical studies.

Although FFR_{CT} shows good diagnostic performance, there are currently several limitations to this technology. Significant CT imaging artifacts, such as low contrast, motion, and blooming due to coronary calcification may negatively impact the performance of CCTA and, consequently, FFR_{CT} [6]. Currently, FFR_{CT} testing and analysis can take significant time (2–6 h) due to limitations of computer software and the fact that computer processing is typically done offsite [6]. The fact the analysis is slow and done offsite has limited its use, although new computational approaches are being developed to change this current situation [6]. In addition, studies are necessary to compare the cost-effectiveness of FFR_{CT} with other diagnostic modalities.

There were several limitations to the study that should be considered when interpreting the results. The patient populations were heterogeneous and only a limited number of vessels were evaluated by FFR_{CT} , which may have affected the results particularly since FFR_{CT} is specific for detecting epicardial vascular lesions. In addition, the definition of significant functional stenosis differed across the studies, ranging from 30 to 95%. Moreover, some studies did not evaluate lesions that were less than 50% or greater than 75%. Different cutoffs for performing a procedure were also used among the studies. The findings were also limited by the methods (hardware and software) used to obtain images for FFR_{CT} analysis which differed across studies. These differences may have impacted the quality of images obtained which would have influenced interpretation of the findings, and consequently, final diagnostic performance. Higher-quality images may have necessitated higher radiation and contrast doses; however, the ability of studies to do this was limited by the potential of an increased risks of adverse effects in certain patient populations, such as those of reproductive age or with renal failure. The quality of images was also limited by the body mass index (BMI) and the heart rate of patients, which may have resulted in sampling bias. The findings of this analysis were limited by the small number of studies included in each meta-analysis. These small numbers also precluded us from evaluating if publication bias may have influenced our results.

Conclusion

In conclusion, our findings suggest that FFR_{CT} may be a good diagnostic tool for screening for myocardial ischemia in patients with CAD. Additional studies are required to further explore these findings.

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Compliance with ethical standards

Conflict of interest The authors declare no conflicts of interest.

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