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CARDIAC

Computed tomography angiography-derived fractional flow reserve (CT-FFR) for the detection of myocardial ischemia with invasive fractional flow reserve as reference: systematic review and meta-analysis

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Abstract

Objectives A method named computed tomography angiography-derived fractional flow reserve (FFR_{CT}) is an alternative method for detecting hemodynamically significant coronary stenosis. We carried out a meta-analysis to derive reliable assessment of the diagnostic performances of FFR_{CT} and compare the diagnostic accuracy with CCTA using FFR as reference.

Methods We searched PubMed, EMBASE, The Cochrane Library, and Web of science for relevant articles published from January 2008 until May 2019 using the following search terms: FFR_{CT}, noninvasive FFR, non-invasive FFR, noninvasive fractional flow reserve, non-invasive fractional flow reserve, and CCTA. Pooled estimates of sensitivity and specificity with the corresponding 95% confidence intervals (CIs) and the summary receiver operating characteristic curve (sROC) were determined.

Results Sixteen studies published between 2011 and 2019 were included with a total of 1852 patients and 2731 vessels. The pooled sensitivity and specificity for FFR_{CT} at the per-patient level was 89% (95% CI, 85–92%) and 71% (95% CI, 61–80%), respectively, while on the per-vessel basis was 85% (95% CI, 82–88%) and 82% (95% CI, 75–87%), respectively. No apparent difference in the sensitivity at per-patient and per-vessel level between FFR_{CT} and CCTA was observed (0.89 versus 0.93 at per-patient; 0.85 versus 0.88 at per-vessel). However, the specificity of FFR_{CT} was higher than CCTA (0.71 versus 0.32 at per-patient analysis; 0.82 versus 0.46 at per-vessel analysis).

Conclusions FFR_{CT} obtained a high diagnostic performance and is a viable alternative to FFR for detecting coronary ischemic lesions.

Key Points

- *Noninvasive FFR_{CT} has higher specificity for anatomical and physiological assessment of coronary artery stenosis compared with CCTA.*
- *Noninvasive FFR_{CT} is a viable alternative to invasive FFR for the detection and exclusion of coronary lesions that cause ischemia.*

Keywords Hemodynamics · Computed tomography angiography · Myocardial ischemia · Stenosis · Coronary artery disease

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Abbreviations

AUC	Area under the SROC
CAD	Coronary artery disease
CCTA	Coronary computed tomography angiography
CIs	Confidence intervals
CMR	Cardiovascular magnetic resonance
CTP	Computed tomography perfusion
FFR	Fractional flow reserve
FFRCT	Computed tomography angiography-derived fractional flow reserve
FN	False negative

FP	False positive
I^2	Inconsistency index
ICA	Invasive coronary angiography
LR−	Negative likelihood ratio
LR+	Positive likelihood ratio
NPV	Negative predictive value
PPV	Positive predictive value
SPECT	Single-photon emission computed tomography
SROC	Summary receiver operating characteristic curve
TN	True negative
TP	True positive

Introduction

Coronary artery disease (CAD) is responsible for 17% of all death worldwide [1]. The prevalence of CAD is still increasing worldwide making CAD the most common cause of cardiovascular disease mortality [2]. Fractional flow reserve (FFR), a pressure wire-based index that is used during coronary angiography to assess the potential coronary stenosis, is considered as the reference standard for evaluating the severity of stenosis in CAD and one of the key parameters for revascularization therapy [3, 4]. Compared with the strategy directed by angiography, FFR guided blood transport reconstruction is capable of improving event-free survival in a cost-saving and long-lived way [5, 6]. However, as an invasive method, the implementation of FFR needs expensive devices and has potential procedure-related complications such as non-fatal myocardial infarction, cerebrovascular accidents, and even death, which should not be ignored by clinicians. Coronary computed tomography angiography (CCTA) as a non-invasive method for detecting CAD is widely used in patients with a low-to-intermediate pre-test risk [7]. Unfortunately, coronary stenosis assessed by CCTA is often overestimated, and only a few proportions of severe stenosis identified by CCTA could explain myocardial ischemia [8, 9]. Recently, computed tomography angiography-derived fractional flow reserve (FFR_{CT}) has been recommended for evaluating functional severity by utilizing computational fluid dynamics to calculate coronary blood pressure [10]. This method can calculate the blood flow and pressure field of the coronary artery according to the anatomical image data without invasive operation or hyperemia process [11, 12]. In addition, FFR_{CT} has showed high diagnostic performance in the presence of coronary artery calcification [13]. However, the diagnostic accuracy of FFR_{CT} in the assessment of lesion-specific myocardial ischemia is not yet clear. The purpose of this meta-analysis is to determine the diagnostic performance of FFR_{CT} to assess the functional significance of coronary stenosis in patients with suspected or known CAD using invasive FFR as the reference standard.

Methods

Data sources and searches

The analysis was performed according to the PRISMA guidelines [14]. We have performed a computerized literature search of the PubMed, EMBASE, The Cochrane Library, and Web of science for relevant articles published from January 2008 until May 2019 using the following keyword search terms: FFR_{CT}, noninvasive FFR, non-invasive FFR, noninvasive fractional flow reserve, non-invasive fractional flow reserve, and CCTA. No restrictions were applied to the language.

Study selection

We included a study if (1) study population comprised ≥ 30 patients with suspected or known CAD clinically; (2) data were presented at patient- and/or vessel-level; (3) invasive FFR was performed for coronary lesions in all patients; (4) the FFR threshold to diagnose ischemia was ≤ 0.80; (5) either the absolute number of true positives (TP), false positives (FP), false negatives (FN), and true negatives (TN), or sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) could be retrieved from the published full text.

Studies were excluded based on the following criteria: (1) studies were not on humans (studies in vitro or animal systems); (2) studies did not report the diagnostic results associated with the determination of the results of interest (FFR ≤ 0.80); (3) the literature related to reviews, prognostic studies, comments, and case reports.

The title and abstract were examined and the full text of potentially qualified studies was double-checked by two independent reviewers (BY Z and SL W). A third reviewer (MJ L) was consulted to resolve any uncertainty regarding eligibility if there was a discrepancy.

Data extraction and quality assessment

Two reviewers (BY Z and SL W) independently extracted the data. Disagreements were resolved through discussion, and a third reviewer (MJ L) was involved to achieve a consensus when necessary. The quality of included studies was assessed using the standards for reporting of diagnostic accuracy (STARD) tool. The tool is structured as a list of 30 questions, each should be answered "yes," "no," or "unclear," as previously described in detail by Bossuyt et al [15].

Data synthesis and analysis

The diagnostic performance analysis was carried out both at the per-patient and per-vessel levels. The major calculated

outcome data were sensitivity and specificity. The pooled corresponding 95% CIs of sensitivity and specificity were also calculated.

According to whether there is statistical heterogeneity exist, random effect or fixed effect model was used to collect data using weighted averages based on the sample size of each study at a per-patient and per-vessel level [16]. Data with heterogeneity were pooled using a random effect model (DerSimonian-Laird model), while data without heterogeneity were pooled using a fixed effect model (Mantel-Haenszel model). Potential heterogeneity, which means variation between studies, was defined as an I^2 statistic value of more than 50% [17]. The summary receiver operating characteristic curve (SROC) was fitted using estimates of sensitivity and specificity from the studies included in the meta-analysis and the pooled area under the curve (AUC) was also calculated [18]. Theoretically, AUCs between 0.75 and 0.92 represent a good degree of diagnostic accuracy, while AUCs of 0.93–0.96 are considered much better [19].

Publication bias was assessed visually using a scatter plot of the inverse of the square root of the effective sample size (1/ESS1/2) versus the diagnostic log 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 1/ESS1/2, and weighting by ESS. A $p < 0.05$ for the slope coefficient indicates significant asymmetry [20].

The sensitivity analysis was conducted by leaving out each reference and reanalyzing the data to test if there are any studies significantly influenced the results.

To compare test performance, probability modifying plots of pre-test and post-test probabilities were synthesized. Furthermore, the clinical or patient relevant utility of CCTA and FFR_{CT} was evaluated using the positive/negative likelihood ratio (LR) to calculate the post-test probability based on Bayes' theorem [21]. When heterogeneity exits, meta-regress analysis will be performed to identify possible sources of heterogeneity. The analysis was performed by using Stata14.0 (Cochrane collaboration) and Meta-Disc1.4.

Results

Literature search

The initial search obtained 248 potentially related publications. After exclusions based on title, abstract, and text, 16 studies were finally included in the present meta-analysis [22–37]. The detailed progress of study selection is described in the flow chart in Fig. 1.

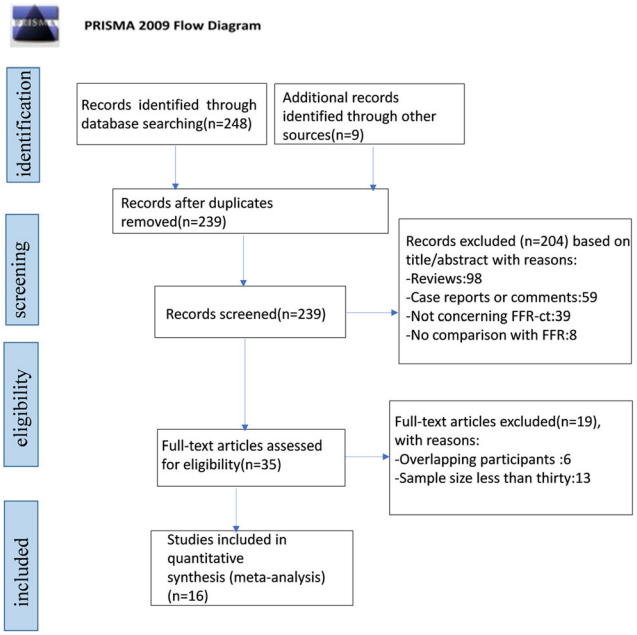

Fig. 1 Flow chart of search and selection of eligible studies. Twelve studies were ultimately identified. Abbreviations: n, number of studies; FFR_{CT}, fractional flow reserve derived from computed tomography

Characteristics of the included studies

A total of 1852 patients and 2731 vessels were analyzed. Studies were published between 2011 and 2019. The sample size of each study ranged from 32 to 254 patients (32 to 484 vessels). Study populations were typical patients undergoing evaluation for suspected or known CAD. Baseline characteristics such as the study design, body mass index, number of participants, and vessels are listed in Table 1 and relevant parameters during the experiment such as stressor for FFR and administration of β-blockers are listed in Table 2; characteristics about intervention history, FFR threshold, equipment parameters, and high dangerous elements are displayed in Table 3.

Data synthesis

For a per-patient basis, seven studies reporting the relevant values for evaluating diagnostic performance of FFR_{CT} were included in the analysis [24–27, 34–36]. The sensitivity and specificity of FFR_{CT} at patient-level ranged from 76 to 94% and 54 to 84% with a pooled sensitivity and specificity of 89% (95% CI 85–92%) and 71% (95% CI 61–80%) using a random effect model (Fig. 2), respectively.

For a per-vessel basis, 13 studies reporting the necessary values for evaluating diagnostic performance of FFR_{CT} were included in the analysis [23–30, 32–36], while 12 studies reported the necessary values for evaluating diagnostic performance of CCTA [22–24, 26–31, 33–35]. The sensitivity of FFR_{CT} for the included studies ranged from 76 to 100% and

Table 1 Basic characteristics of included studies

First author (ref. #), year	Journal	Age, years	Male, *n* (%)	Body mass index, kg/m^2	Study populations	Number of all patient, *n*	Number of evaluable patients, *n*	Number of vessels, *n*
Koo et al [24], 2011	JACC: Cardiovascular imaging	62.7 ± 8.5	74 (72)	25.8 ± 3.5	Suspected or known CAD	103	103	159
Min (A) et al [25], 2012	JAMA	62.9 ± 8.7	178 (71)	ND	Suspected or known CAD	285	252	407
Nørgaard et al [26], 2014	JACC	64.0 ± 10.0	162 (64)	26.0 ± 3.0	Suspected stable CAD	365	254	484
Renker et al [27], 2014	The American Journal of Cardiology	61.2 ± 12.0	34 (64)	28.9 ± 6.5	Suspected or known CAD	53	53	67
Wang R et al [28], 2015	European Journal of Radiology	58.0 ± 12.0	21 (66)	29.7 ± 6.6	Suspected or known CAD	67	32	32
Coenen et al [29], 2015	Radiology	61.4 ± 9.2	82 (77)	27.2 ± 4.0	Suspected or known CAD	122	106	189
Min (B) et al [30], 2012	The American Journal of Cardiology	64.0 ± 8.0	46 (81)	ND	Suspected or known CAD	103	103	159
Wong et al [31], 2013	JACC	62.7 ± 8.7	35 (65)	ND	Suspected or known CAD	67	54	78
Tesche et al [32], 2016	Journal of Cardiovascular Computed Tomography	61.0 ± 11.0	25 (68)	29.4 ± 6.4	Suspected or known CAD	53	37	37
Ko (A) et al [22], 2014	European Society of Radiology	63.6 ± 10.4	66 (76)	27.9 ± 5.3	Suspected or known CAD	125	115	230
Ko (B) et al [33], 2017	JACC: Cardiovascular imaging	60.0 ± 8.5	21 (70)	28.5 ± 4.6	Suspected or known CAD	42	30	85
Kruk et al [34], 2016	JACC: Cardiovascular imaging	63.4 ± 8.2	29 (32)	28.5	Suspected or known CAD	98	90	96
Chung et al [35], 2017	American Journal of Cardiology	60.7 ± 9.3	93 (80)	24.7 ± 3.6	Suspected or known CAD	140	117	218
Sand et al [37], 2018	JACC: Cardiovascular imaging	64 ± 11	84 (59)	27 ± 4	Symptomatic patients with intermediate range coronary artery disease	1628	143	ND
Röthe et al [36], 2018	Journal of Cardiovascular Computed Tomography	65 ± 9	55 (78)	27 ± 3	Suspected CAD	148	71	91
Wardzia et al [23], 2019	Journal of Cardiovascular Computed Tomography	64.47 (8.64)	59 (65.3)	64.47 (8.64)	Intermediate pre-test probability of CAD	98	90	96

CT-FFR computed tomography angiography-derived fractional flow reserve, *FFR* fractional flow reserve, *CCTA* coronary computed tomography angiography, *N* number, *D* not defined

Table 2 Relevant parameters during the experiment

First author (ref. #), year	Study design	Time period between FFR and CT-FFR	Stressor for FFR	Coronary artery model	Administration of β-blockers	Pre-examination administration of nitrates	Creatinine, mg/dl	Level of analysis for CT-FFR	Level of analysis for CCTA	CT-FFR evaluation
Koo et al [24], 2011	Prospective, consecutive	2.3 (0~26) days	Adenosine	18-segment model	54 (96.4)	41 (64.1)	0.97 ± 0.18	Patient, vessel	Patient, vessel	Remote center
Min (A) et al [25], 2012	Prospective, consecutive	15.5 (5~33) days	Adenosine	18-segment model	ND	ND	ND	Patient, vessel	Patient	Remote center
Nørgaard et al [26], 2014	Prospective, consecutive	18 (1~55) days	Adenosine	18-segment model	198 (78)	253 (99.6)	0.9 ± 0.2	Patient, vessel	Patient, vessel	Remote center
Renker et al [27], 2014	Retrospective	< 3 months	Adenosine	18-segment model	30 (53)	ND	ND	Patient, vessel	Patient, vessel	On-site
Wang R et al [28], 2015	Retrospective	< 3 months	Adenosine	19-segment model	ND	ND	ND	Vessel	Vessel	On-site
Coenen et al. [29], 2015	Retrospective	50 days	Adenosine	20-segment model	ND	ND	ND	Vessel	Vessel	On-site
Min (B) et al [30], 2012	ND	ND	Adenosine	18-segment model	ND	ND	1.0 ± 0.2	Vessel	Vessel	On-site
Wong et al [31], 2013	ND	< 2 months	Adenosine	19-segment model	50 (92)	ND	ND	ND	Vessel	On-site
Tesche et al [32], 2016	Retrospective	< 3 months	Adenosine	18-segment model	ND	ND	ND	Vessel	ND	On-site
Ko (A) et al [22], 2014	ND	< 6 months	Adenosine	19-segment model	66 (78)	ND	ND	ND	Vessel	ND
Ko(B) et al [33], 2017	Prospective, consecutive	ND	Adenosine	18-segment model	27 (90)	30 (100)	ND	Vessel	Vessel	Remote center
Kruk et al [34], 2016	Prospective	< 6 months	Adenosine	ND	ND	90 (100)	ND	Patient, vessel	Patient, vessel	On-site
Chung et al [35], 2017	Retrospective	ND	Adenosine	ND	27 (23)	18 (15)	0.92 ± 0.19	Patient, vessel	Patient, vessel	On-site
Sand et al [37], 2018	Prospective	ND	Adenosine	17-segment model	37 (26)	143 (100)	ND	Vessel	Vessel	Remote center
Röthe et al [36], 2018	Retrospective	ND	Adenosine	ND	ND	ND	ND	Patient, vessel	Patient, vessel	On-site
Wardzia et al [23], 2019	Prospective	< 6 months	Adenosine	ND	ND	90 (100)	ND	Vessel	Vessel	On-site

CT-FFR computed tomography angiography-derived fractional flow reserve, *FFR* fractional flow reserve, *CCTA* coronary computed tomography angiography, *N* number, *D* not defined

Table 3 Intervention history, threshold, equipment parameter, and high dangerous element

First author (ref. #), year	Prior revascularization, *n* (%)	Prior myocardial infarction, *n* (%)	FFR threshold to diagnose ischemia	Coronary stenosis in CCTA/ICA	Tube voltage, mV	Tube current, mA	Radiation dose, mSv	Diabetes mellitus, *n* (%)	Hypertension, *n* (%)	Hyperlipidemia, *n* (%)	Current smoker, *n* (%)	Heart rate, beats/min
Koo et al [24], 2011	16 (16)	17 (17)	< 0.80	CCTA with ≥ 50% stenosis	100 or 120	400 to 650	3~15	26 (26)	67 (65)	67 (65)	24 (36)	63.9 ± 8.5
Min (A) et al [25], 2012	16 (6.3)	15 (6)	< 0.80	ICA with stenosis of 30 to 90%	ND	ND	6.4 (4.4~15.0)	53(21.2)	179 (71.2)	201 (79.8)	44 (17.5)	ND
Nørgaard et al [26], 2014	0 (0)	5 (2)	< 0.80	CCTA with stenosis of 30 to 90%	100 or 120	ND	3.0 ± 2.2 for prospective acquisition; 14.3 ± 7 for retrospective acquisition	58 (23)	174 (69)	200 (79)	46 (18)	63 ± 10
Renker et al [27], 2014	9 (16)	ND	< 0.80	ICA with stenosis of 30 to 90%	80 to 120	350 to 650	ND	18 (32)	31 (54)	31 (54)	8 (14)	70.2 ± 12.6
Wang R et al [28], 2015	0	0	< 0.80	CCTA stenosis ≥ 50%	100 or 120	320–412	7.7 ± 1.0	13 (40)	21 (65)	ND	10 (31)	ND
Coenen et al [29], 2015	0	0	≤ 0.80	CCTA stenosis ≥ 50%	ND	ND	7.6	20 (19)	63 (59)	ND	26 (25)	66 ± 13
Min (B) et al [30], 2012	8 (14)	14 (38)	≤ 0.80	40 to 69% by QCA	ND	ND	3 to 15	37 (64)	41 (71)	37 (64)	15 (27)	61.7 ± 9
Wong et al [31], 2013	ND	ND	≤ 0.80	CCTA stenosis ≥ 50%	100,120	300 to 500	5.7 ± 5.2	9 (17)	38 (70)	ND	9 (17)	55.3 ± 7.1
Tesche et al [32], 2016	ND	ND	≤ 0.80	CCTA stenosis ≥ 50%	100–120	320–412	6.6 ± 0.8	15 (41)	24 (65)	ND	ND	69 ± 12.1
Ko (A) et al [22], 2014	0	9.6 (11)	≤ 0.80	CCTA stenosis ≥ 50%	120	300–500	4.5 ± 3.1	18.2 (21)	72.1 (83)	70.4 (81)	18.2 (21)	56 ± 8
Ko (B) et al [33], 2017	ND	ND	≤ 0.80	CCTA stenosis ≥ 50%	100 or 120	340–820	4.9 ± 2.2	9 (30)	22 (73)	24 (80)	8 (27)	52.5 ± 6.8
Kruk et al [34], 2016	ND	ND	≤ 0.80	CCTA stenosis ≥ 50%	80 to 120	ND	7.3	13 (14.4)	79 (87.8)	81 (90)	18 (20.2)	61
Chung et al [35], 2017	0	1 (0.8)	≤ 0.80	CT stenosis ≥ 50%	100	320	ND	24 (21)	63 (54)	46 (39)	31 (27)	71.5 ± 11.5
Sand et al [37], 2018	ND	ND	≤ 0.80	CT stenosis ≥ 50%	ND	ND	3.3 (2.2–5.6)	17 (12)	89 (62)	75 (52)	94 (66)	55 ± 7
Röthe et al [36], 2018	11 (16)	10 (14)	≤ 0.80	CT stenosis ≥ 50%	70 to 120	ND	ND	11 (16)	55 (78)	45 (63)	25 (35)	ND
Wardzia et al [23], 2019	ND	ND	≤ 0.80	CT stenosis ≥ 50%	80 to 120	ND	ND	14.3 (16)	87.8 (98)	89.8 (99)	38.8 (43)	ND

FFR fractional flow reserve, *CCTA* coronary computed tomography angiography, *ICA* invasive coronary angiography, *ND* not defined

specificity ranged from 73 to 96% with a pooled sensitivity of 85% (95% CI 82–88%) using a fixed-effects model and pooled specificity of 82% (95% CI 75–87%) using a random-effects model (Fig. 3).

Compared with CCTA alone, noninvasive FFR_{CT} was more specific and discriminative for detecting hemodynamic coronary stenosis when invasive FFR was used as a reference standard (Table 4). The pooled sensitivity of FFR_{CT} and CCTA were quite similar (0.89 versus 0.93 at per-patient, $p = 0.44$; 0.85 versus 0.88 at per-vessel, $p = 0.87$). However, the specificity of FFR_{CT} was higher than that of CCTA (0.71 versus 0.32 at per-patient analysis, $p < 0.001$; 0.82 versus 0.46 at per-vessel analysis, $p < 0.001$).

The AUCs of FFR_{CT} at the per-patient level and the per-vessel level were 0.90 and 0.91, respectively, which are higher than those of CCTA (0.76 at per-patient level and 0.73 at per-vessel level) (Fig. 4).

Quality of the included studies

Our inter-rater reliability for assessing quality items was perfect (kappa = 0.89). Quality assessment using the Standards for Reporting of Diagnostic Accuracy (STARD) tool (Suppl. material 1) showed that 16 studies were recorded as "NOT" in item #20 and item #23. One study was recorded as "NOT" in item #17. All studies get "Yes" in the other items, indicating the included studies have high quality.

Publication bias

The publication bias was assessed using Deek's funnel plot asymmetry test. Each of the four plots resembled a symmetrical funnel shape. The p value for Deek's funnel plot asymmetry test was 0.05. Therefore, there is no significant publication bias exist (Fig. 5).

Meta-regress analysis

Heterogeneity between studies were assessed using the inconsistency index (I^2). Meta-regress analysis was applied when $I^2 \geq 50\%$. Multivariable meta-regress analysis at the per-patient and per-vessel level showed that study design, sample size, age, gender, proportion of diabetes, proportion of smoking, hypertension, hyperlipidemia, heart rate, CT scanner type, and time period between FFR_{CT} and FFR were not the sources of heterogeneity.

Sensitivity analysis and probability modifying plots

The sensitivity analysis, in order to investigate the influence of each individual study on the overall meta-analysis summary estimate conducted at both the patient and vessel levels, demonstrated that no study significantly influenced the pooled sensitivity and specificity (Suppl. material 2).

Probability modifying plots were plotted with pre-test versus post-test probabilities (Fig. 6). At both per-vessel and per-patient levels, when the disease was estimated to be pre-test positive, the higher value of post-test probability was obtained with FFR_{CT} strategy than CCTA. It indicated that FFR_{CT} showed better performance on identifying true positive patients. On the other hand, when pre-test estimate was negative, FFR_{CT} and CCTA produced similar value of post-test probability, indicating similar performance on identifying true negative patients.

To be precise, the per-patient analysis revealed a positive LR of 3.08 and a negative LR of 0.16, when the per-vessel analysis revealed a positive LR of 4.64 and a negative LR of 0.18 for FFR_{CT}. As for CCTA, the per-patient analysis revealed a positive LR of 1.37 and a negative LR of 0.23, when the per-vessel analysis revealed a positive LR of 1.64 and a negative LR of 0.26. Based on Bayes' theorem, at per-patient level, FFR_{CT} could increase the post-test probability of CAD > 64% with a pre-test probability of > 37% (CCTA is > 45%) and can decrease post-test probability of CAD < 30% with a pre-test probability of < 73% (CCTA is < 38%). At per-vessel level, FFR_{CT} could increase the post-test probability of CAD > 73% with a pre-test probability of > 37% (CCTA is > 49%) and can decrease post-test probability of CAD < 33% with a pre-test probability of < 73% (CCTA is < 41%).

Discussion

We found that a noninvasive form of FFR derived from CCTA (FFR_{CT}) exhibited high diagnostic accuracy for the detection of hemodynamic relevance of stenoses in patients with known or suspected CAD by using invasive FFR as a standard reference. These findings remained consistent regardless of whether it was examined at a per-patient or per-vessel level when FFR cutoff value of 0.8 was used as reference standard.

The high sensitivities indicated that FFR_{CT} and CCTA have the ability to measure the proportion of actual myocardial ischemia [38]. CCTA is a validated method for the patients with low or mild pre-test probability and the long-term prognostic value was confirmed [39]. However, the limitation of CCTA remains the only anatomical assessment of coronary stenoses in the absence of evaluation of their functional hemodynamic significance, while functional hemodynamic for those stenoses graded as an intermediate at the anatomical assessment are rather important [40]. FFR_{CT}, which found to be better for the noninvasive screening of CAD patients with diameter stenosis than CCTA [41], can noninvasively obtain pressure and blood flow information by using vessel specific fractional flow reserve data derived from CCTA. The calculation of FFR requires the knowledge of the pressure profile

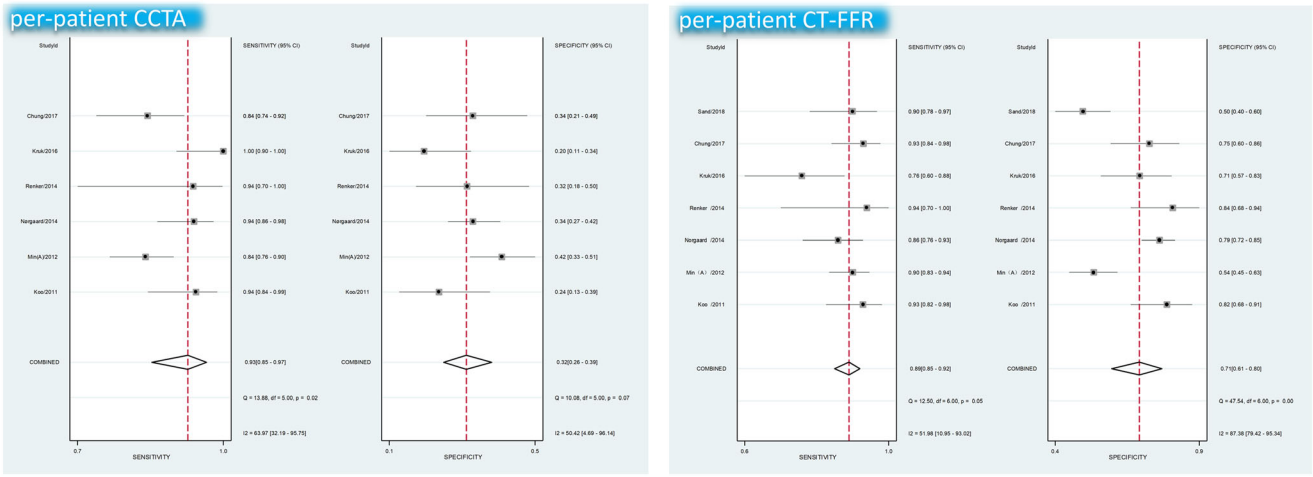

Fig. 2 Forest plots illustrating detailed sensitivity and specificity at per-patient level. Diagnostic performance of CCTA for diagnosis of ischemia: pooled sensitivity is 93% (95% CI 85–97%) and pooled specificity is 32% (95% CI 26–39%); diagnostic performance of FFR_{CT} for diagnosis of ischemia: pooled sensitivity is 89% (95% CI 85–92%) and pooled specificity is 71% (95% CI 61–80%)

inside a coronary artery before and after the stenosis. This makes FFR_{CT} exhibits more accuracy than CCTA in detecting coronary ischemic lesions. Besides, as mentioned above, the low specificity of CCTA indicated that only a minority severe stenosis identified by CCTA have been confirmed to cause ischemia. The higher specificity of FFR_{CT} overcomes the shortcoming of CCTA that tends to overestimate coronary stenosis. FFR_{CT} served as a combined anatomic and functional assessment can accurately identify patients who have lesion-causing ischemia. In addition, FFR_{CT} has higher AUC versus that of CCTA, which means a superior degree of diagnostic accuracy. FFR_{CT} was a feasible and safe alternative to invasive coronary angiography (ICA), which enables estimation of FFR value without the need of additional invasive procedure, extra administration of medication, radiation exposure, or modification of acquisition protocols. It can provide information both on the anatomic and functional significance of a coronary lesion in a relatively safe and economical manner and make a cost–benefit balance in terms of clinical management and patient's care. The accuracy and computational time of FFR_{CT} crucially depends on highly accurate image input data, which in turn depends on CCTA protocol variations [42]. FFR_{CT} acted as a new noninvasive method could be an alternative to ICA in helping guide patient

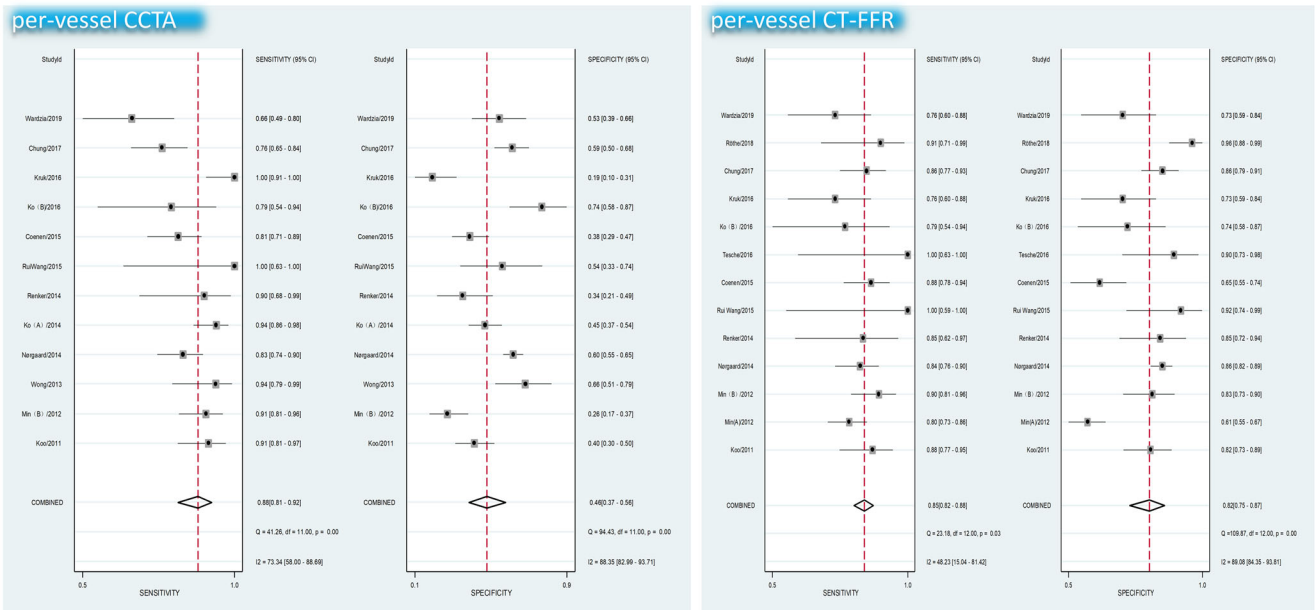

Fig. 3 Forest plots illustrating detailed sensitivity and specificity at per-vessel level. Diagnostic performance of CCTA for diagnosis of ischemia at a per-vessel level: pooled sensitivity is 88% (95% CI 81–92%) and pooled specificity is 46% (95% CI 37–56%); diagnostic performance of FFR_{CT} for diagnosis of ischemia: pooled sensitivity is 85% (95% CI 82–88%) and pooled specificity is 82% (95% CI 75–87%)

Table 4 Outcome summary at all level

	Studies	Total (n)	TP	FP	FN	TN	Sensitivity (95% CI)	Specificity (95% CI)	PLR (95% CI)	NLR (95% CI)	DOR (95% CI)	NPV (95% CI)	PPV (95% CI)	AUC
Per-patient analysis														
CT-FFR	7	1013	387	183	49	395	0.93 (0.85–0.97)	0.71 (0.61–0.80)	3.08 (2.21–4.28)	0.16 (0.11–0.22)	18.29 (10.17–32.91)	0.78 (0.73–0.83)	0.68 (0.64–0.72)	0.90
CCTA	7	868	347	319	41	161	0.88 (0.85–0.97)	0.32 (0.26–0.39)	1.37 (1.26–1.48)	0.23 (0.12–0.43)	4.77 (3.28–6.92)	0.73 (0.69–0.77)	0.55 (0.53–0.57)	0.76
Per-vessel analysis														
CT-FFR	13	2100	603	293	112	1092	0.85 (0.82–0.88)	0.82 (0.75–0.87)	4.64 (3.33–6.47)	0.18 (0.14–0.23)	23.52 (13.58–40.73)	0.76 (0.72–0.80)	0.74 (0.70–0.77)	0.91
CCTA	12	1865	550	618	93	604	0.88 (0.81–0.92)	0.46 (0.37–0.56)	1.16 (1.41–1.91)	0.26 (0.18–0.39)	5.72 (3.80–8.63)	0.71 (0.67–0.76)	0.58 (0.55–0.61)	0.73

CT-FFR computed tomography angiography-derived fractional flow reserve, *CCTA* coronary computed tomography angiography

care [43]. In conclusion, our findings suggest that FFR_{CT} may be a good diagnostic tool for screening of hemodynamic relevance of stenoses in patients with known or suspected CAD.

Recently, five analyses have discussed the potential effectiveness of the utilization of FFR_{CT} to guide clinical decision-making [44–48]. Their studies demonstrated similar results that FFR_{CT} significantly improves specificity without noticeably altering the sensitivity of CCTA with invasive FFR as a reference standard for the detection of hemodynamically relevant stenosis. Cook et al [44] performed a systematic review including 908 vessels from 536 patients in 5 studies. They reported that the overall per-vessel diagnostic accuracy of FFR-CT was 81.9% (95% CI, 79.4–84.4%) in association of FFR_{CT} with invasive FFR in different levels. In Baumann et al's [45] meta-analysis, a total of 765 patients and 1306 vessels were included. They found that FFR_{CT} significantly improves specificity without noticeably altering the sensitivity of CCTA (sensitivity 83.7% vs 84.6%, specificity74.7% vs 49.7% on per-lesion basis; sensitivity 89.2% vs 70.2%, specificity 90.2 % vs 35.4% on per-patient basis) with invasive FFR as a reference standard. And the intermediate stenosis subgroup exhibited the same result which indicated FFR_{CT} may become particularly relevant for the difficult evaluation of intermediate stenosis to guide the indication for revascularization. Celeng et al [46] included studies that compared the diagnostic performance of coronary computed tomography angiography (CCTA), CT myocardial perfusion (CTP), fractional flow reserve CT (FFR_{CT}), the transluminal attenuation gradient (TAG), and their combined use with CCTA. After analyzing 1069 patients of 18 articles, they found that FFR_{CT} demonstrated a substantial improvement in the identification of hemodynamically significant CAD compared with CCTA. At vessel and patient level, pooled specificity of FFR_{CT} was 0.78 and 0.76 respectively which was substantially higher than that of CCTA (0.61, 0.48). The SROCs also showed good diagnostic performance for FFR_{CT} compared with CCTA. In our meta-analysis, we updated relevant literature published in 2017–2019 and performed a similar analysis but much higher specificity and diagnosis accuracy of FFR_{CT} because of the larger sample size (1852 vs 1069) and the higher quality literatures included in our meta-analysis. Gonzalez JA and his colleagues [47] compared the pooled diagnostic performance of FFR_{CT} with conventional CCTA by using FFR as the gold standard. Eighteen studies with a total 1535 patients were included in the meta-analysis. The sensitivity and specificity of CCTA at the patient level is 0.92 (0.88–0.98) and 0.43 (0.38–0.47), respectively. Comparing with CCTA, their findings suggested that FFR_{CT} had similar sensitivity value (90% vs. 92%), while higher specificity (72% vs. 43%). However, the inclusion criteria of the previous studies covered relatively wide range including some studies with low quality were included, which may result in lacking of credible reliability. The total number of vessels in the analysis of per-vessel level was not mentioned in their study, thus resulting in

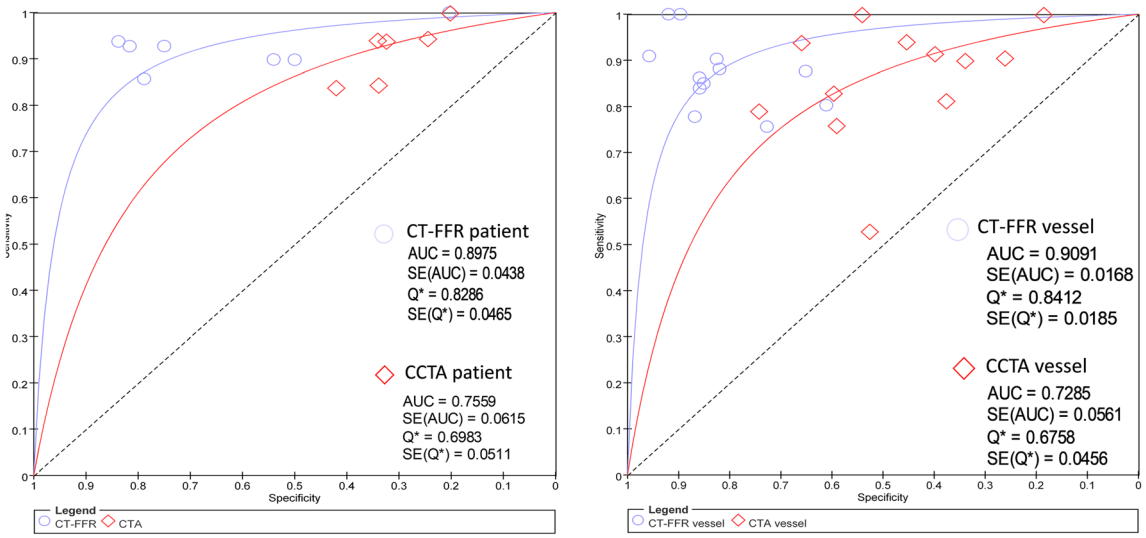

Fig. 4 Summary receiver operating characteristic (ROC) curve, plotting the true positive rate (sensitivity) against the false-positive rate (1—specificity) of FFR_{CT} and CCTA at vessel level and patient level. Each symbol represents an individual study in the meta-analysis, with the size of the symbol proportional to the sample size of the study. The Q* statistic represents the point where sensitivity and specificity are equal. AUC indicates area under the summary receiver operating characteristic curve. The AUCs (area under the SROC) of FFR_{CT} at the per-patient level and the per-vessel level were 0.90 and 0.91, which are 0.76 at per-patient level and 0.73 at per-vessel level of CCTA

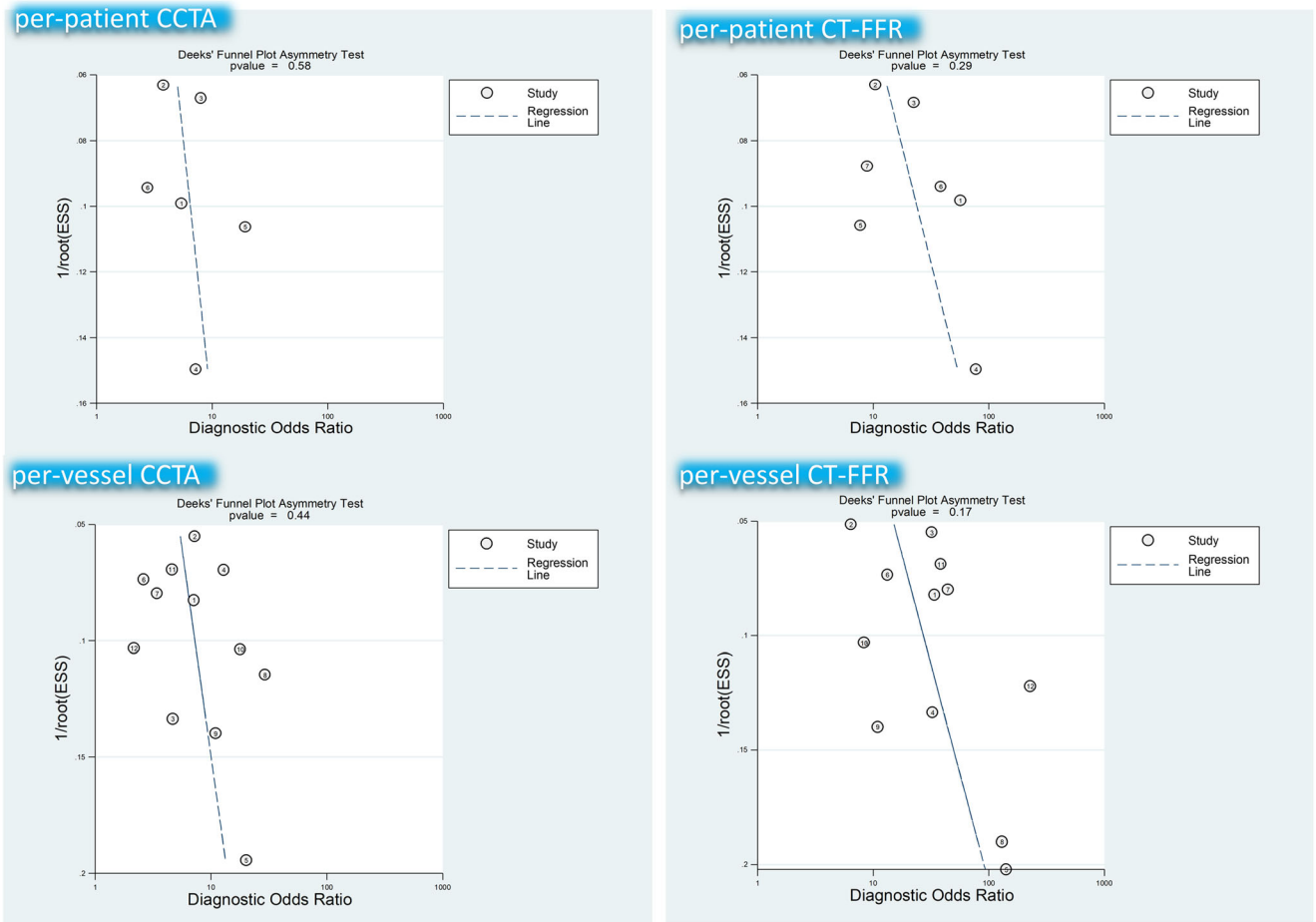

Fig. 5 Funnel plots for studies at per-vessel level and at per-patient level. All funnel plots resembled a symmetrical funnel shape, indicating publication bias was unlikely

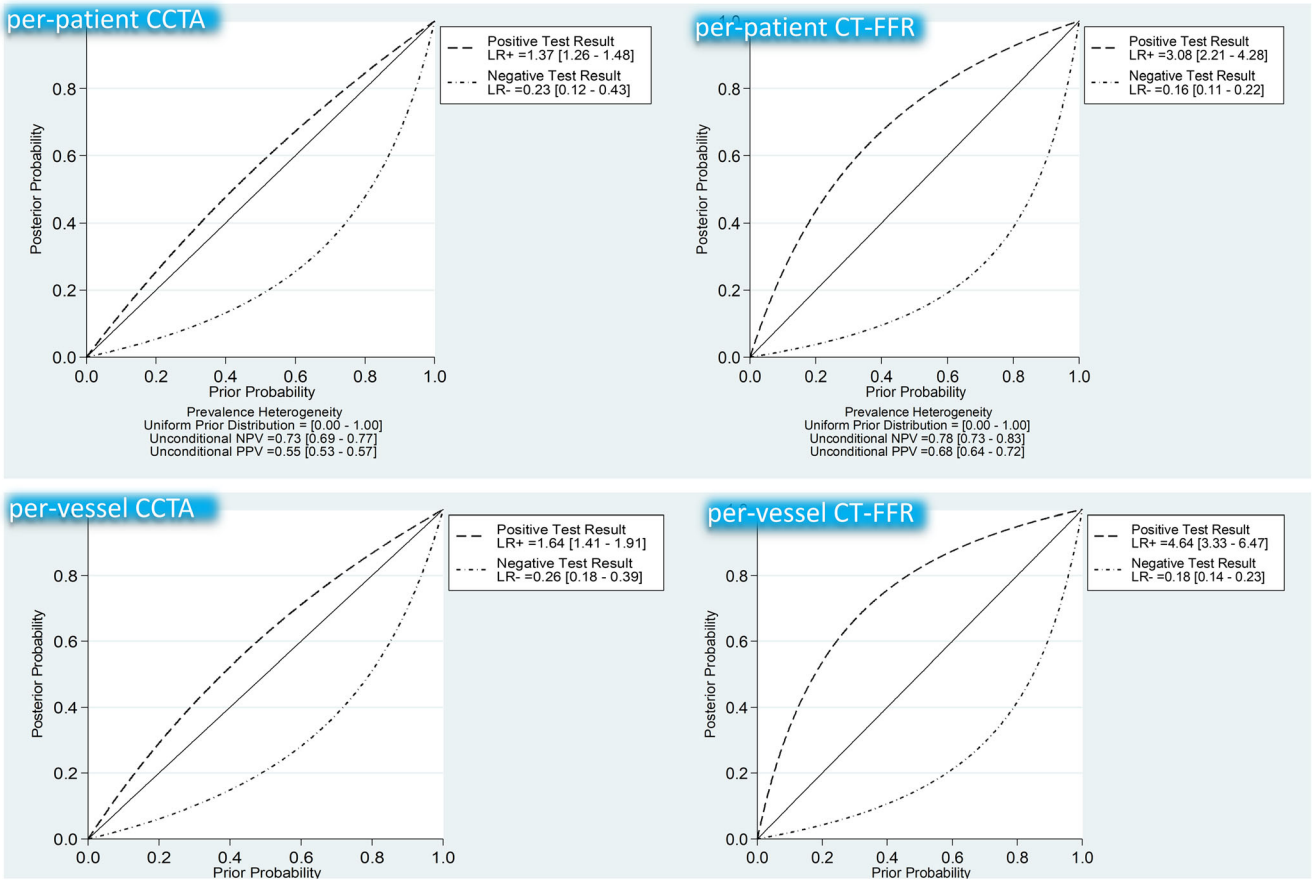

Fig. 6 Probability modifying plots at per-vessel level and at per-patient level. FFR_{CT} could increase the post-test probability of CAD > 64% with a pre-test probability of > 37%, while CCTA is > 45%, and can decrease post-test probability of CAD < 30% with a pre-test probability of < 73%, while CCTA is < 38% at per-patient level. And at per-vessel level, FFR_{CT} could increase the post-test probability of CAD > 73% with a pre-test probability of > 37%, while CCTA > 49%, and can decrease post-test probability of CAD < 33% with a pre-test probability of < 73%, while CCTA < 41%

the lack of data integrity. In addition, the summary receiver operating characteristic curve (sROC) and the area under curve (AUC) was not performed in previous studies [47]. Regress analysis was not analyzed even though the results have heterogeneity [47], which hinders the conduciveness to find sources of heterogeneity. In a study with 2216 patients and 2798 vessels, Deng et al [48] reported the pooled sensitivity and specificity of FFR_{CT} at the per-patient level were 90% and 73%, respectively, while at the per-vessel level were 82% and 79%, respectively. Although the inclusion criteria of our study were not all the same, the pooled specificity and sensitivity were similar, which aggrandizes more universalism and stringency to our finding. However, insufficient document feature extraction of their study may add difficulty to heterogeneity analysis. We used STARD as quality assessment tool, which is much more detailed than QUADAS and can assess literatures more rigorously.

Comparing with FFR_{CT}, all other noninvasive methods used to detect hemodynamic relevance of stenoses including computed tomography perfusion (CTP), single-photon emission computed tomography (SPECT), and perfusion cardiovascular magnetic resonance (perfusion-CMR) have disadvantages to some extent. Firstly, CTP, especially dynamic CTP, has the risk of radiation exposure [49], which is potentially a problem in patients with high BMI and fast heart rates. Secondly, although belonging to noninvasive examination, SPECT has high ionization radiation but lower spatial resolution, poor attenuation correction, and limited usage of tracers [50]. Thirdly, perfusion-CMR imaging does not suffer from attenuation artifacts compared to nuclear techniques and provides the highest spatial resolution. But CMR stress perfusion is time consuming and MR compatible monitor is required which is the shortcoming of this technique [51].

Limitations

Several points regarding limitations of this analysis are worth mentioning. Firstly, the evidence considered in this review exhibited methodological limitations. (1) The heterogeneity existed in our meta-analysis, but we cannot explore the source, making it harder to transpose the findings to the clinical

setting and make a definitive conclusion. (2) All of our involved studies used clinically relevant cutoff of 0.80; however, in some studies [52], a cutoff of 0.75 was used to assess the prognostic value of FFR for revascularization. Due to lack of trials, our study could not determine the diagnostic accuracy of $FFR_{CT} < 0.75$. Besides, a 50% stenosis threshold by CCTA is associated with high sensitivity but poor specificity for hemodynamically significant coronary artery disease [53]. Maybe a 70% threshold performs better in this situation. These remains future experiments to explore a suitable threshold. Secondly, there are some technological limitations hindering the clinical application of FFR_{CT}. The image quality may be reduced by various factors including image noise, motion artifacts, and beam-hardening artifacts from metallic devices or from coronary calcifications. And the diagnostic performance of FFR_{CT} may be affected by the adherence of physiological and protocol-dependent factors such as heart rate control, blood pressure, contrast enhancement methods, and the use of pre-scan nitroglycerin [54]. More importantly, although FFR_{CT}-testing processing times resulting from software are expected to be improved, current FFR_{CT} evaluation also demands a considerable amount of time (2–6 h) and some discrepancy between modeling FFR_{CT} and directly measured FFR is expected to be present due to the need for post-processing and the slow analysis procedure [13]. Recently, the evaluation of virtual functional assessment index (vFAI) measured from CCTA-based coronary anatomical models [55] has been allowed to determine the hemodynamic relevance of a given coronary lesion with a few minutes long computation time. It can also be used as an adjunct technique to diagnose hemodynamic abnormalities.

Conclusions

In summary, the present data shows that noninvasive FFR_{CT} derived from standard CCTA image data exhibited high diagnostic performance in patients with known or suspected CAD for the detection of hemodynamically significant coronary stenosis. However, it still requires more data to explain how to bring this new technology into the real clinical practice to guide the decision-making in the coming years.

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Compliance with ethical standards

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Statistics and biometry No complex statistical methods were necessary for this paper.

Informed consent Written informed consent was waived by the Institutional Review Board.

Ethical approval Institutional Review Board approval was obtained.

Methodology
- retrospective
- diagnostic or prognostic study
- multicenter study

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