Diagnostic performance of wireless fractional flow reserve: a meta-analysis

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Abstract

Introduction: The aim of this study was to evaluate diagnostic performance of wireless fractional flow reserve (FFR) used in patients with coronary artery disease (CAD).
Material and methods: PubMed, Cochrane Library, Embase and Clinical trial.gov databases were searched by computer search and manual retrieval. The search terms included fractional flow reserve, quantitative coronary angiography, computational fluid dynamics and coronary artery disease. The meta-analysis was conducted with Stata12.0. Clinical outcomes included accuracy, sensitivity, specificity, positive likelihood ratio (+LR), negative likelihood ratio (–LR), diagnostic odds ratio (DOR) and area under the receiver operating curve.
Results: Nine studies comprising 2052 vessels were included in the present meta-analysis. The sensitivity, specificity, +LR, –LR, DOC and accuracy were 87% (95% CI: 83–94%), 88% (95% CI: 82–92%), 7.28 (95% CI: 4.78–11.08), 0.14 (95% CI: 0.10–0.21), 50.69 (95% CI: 25.22–101.88) and 0.94 (95% CI: 0.91–0.96) respectively. No significant publication bias was detected.
Conclusions: This meta-analysis suggests that the clinical performance such as accuracy, sensitivity and specificity of wireless FFR is good to detect stenotic lesions with pressure-wire measured FFR as a reference.

Key words: fractional flow reserve, quantitative coronary angiography, computational fluid dynamics, coronary artery disease.

Introduction

Coronary artery disease (CAD) is the world's most common cause of death. Currently, coronary computed tomography angiography (CCTA) is the preferred imaging examination method to evaluate coronary artery disease (CAD) noninvasively, owing to its relatively high sensitivity and negative predictive value for obstructive coronary artery disease [1–3]. However, CCTA mainly assesses the anatomic severity of vessels and is limited in functional severity assessment of coronary stenosis [4]. Fractional flow reserve (FFR) is the gold standard of dynamics of coronary artery lesions [5, 6] and has been widely used among patients who were suspected to have CAD [7–9]. However, in the process of FFR, the ratio of pressure between the two sides of the stenosis was obtained through advancing a pressure wire toward the stenosis during coronary angiography, which is an invasive procedure and is associated with additional risks of adverse events and higher examination costs [10].

AMS

A wireless non-invasive FFR method derived from computational fluid dynamics (CFD) and 3D quantitative coronary angiography (3D-QCA) was invented to assess the hemodynamic effect of coronary stenosis on the basis of their angiographic morphology [11–14]. The wireless FFR method presents high diagnostic value for coronary artery stenosis induced by myocardial ischemia without increasing radiation dosage and provides an ideal noninvasive method for evaluation of lesion dynamics. It was demonstrated that angiography-derived FFR showed good accuracy compared with invasive FFR [15]. This meta-analysis was undertaken to evaluate the diagnostic performance of wireless FFR with pressure wire FFR as a reference among patients with CAD.

Material and methods

Data sources and searches

Databases of PubMed, Cochrane Library, EMBASE, and Clinical Trials.gov were searched until October 2018 with the keywords "Fractional Flow Reserve", "Computational Fluid Dynamic", "angiography" and "Coronary Computed Tomography". References from trials and relevant reviews were manually searched for additional trials.

Study selection

The following inclusion criteria were applied: (1) Patients were suspected or confirmed with coronary artery disease; (2) Patients were assessed by wireless FFR (FFR derived by coronary angiography (FFRangio), FFR derived by coronary CT angiography (FFR_{CT}), quantitative flow ratio (QFR)) and measured invasive FFR; (3) The true positive, false positive, true negative and false negative results were reported; (4) 0.80 of invasive FFR was used as the threshold for lesion significance. Reviews, meta-analyses, observational studies, and small-sample trials ($n < 50$) were excluded. The meta-analysis follows the Standards for Reporting of Diagnostic Accuracy (STARD) [16].

Data extraction and quality assessment

Two authors extracted relevant information from the literature independently. Baseline demographic characteristics such as sample size, age, percentage of male subjects, percentage of diabetes mellitus, percentage of hypertension and study type were extracted from eligible studies. Relevant data of true positives, false positives, true negatives and false negatives were also extracted. The Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the quality of included studies. Risk of bias was evaluated based on four aspects: patient selection, index test, reference standard, flow and timing. Applicability was evaluated based on patient selection, index test and reference standard.

Date analysis

The primary outcome of sensitivity and specificity of wireless FFR in diagnosing hemodynamically significant coronary stenosis was pooled. Secondary outcomes include +LR, -LR, DOR and area under the receiver operating curve, along with the 95% confidence interval (CI) to express the diagnostic performance. Heterogeneity was detected

Records identified through database searching ($n = 594$)

Additional records identified through other sources ($n = 0$)

Records after duplicates removed ($n = 411$)

Records screened ($n = 411$)

Records excluded ($n = 285$)

Full-text articles assessed for eligibility ($n = 126$)

Full-text articles excluded, with reasons ($n = 117$)

Studies included in qualitative synthesis ($n = 9$)

Studies included in quantitative synthesis (meta-analysis) ($n = 9$)

Included
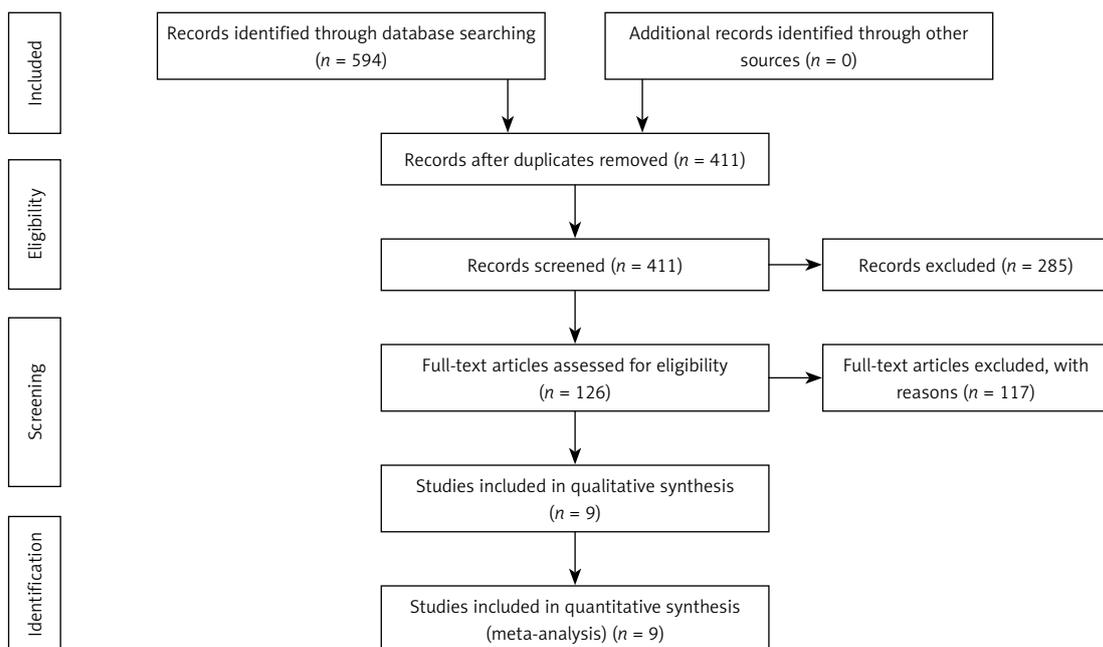
Eligibility

Screening

Identification

Figure 1. Flow chart showing the progress through the stages of the meta-analysis

by bivariate boxplot and publication bias was visually inspected using a funnel plot. All analyses were performed by Stata 11.0 (StataCorp, College Station, TX, USA).

Results

Literature screening and characteristics of included studies

There were 594 articles in total found during the initial search. After removing duplicates and reviewing abstracts, finally 9 studies [14, 15, 17–23] comprising 2052 vessels met all inclusion criteria and were included in the analysis. The whole selection procedure was depicted in Figure 1. The baseline demographic characteristics of the included studies are detailed in Table I. Among the included 9 studies, the angiography-derived FFR calculation was performed using quantitative flow ratio (QFR) in 6 studies, FFR_{angio} was used in 1 study, and FFR_{CT} was used in 2 studies, in which FFR was derived from the computed tomography angiography (Table I). As the included studies were diagnostic test accuracy studies, the Quality Assessment of Diagnostic Accuracy Studies (QUADAS-2) tool was used to assess the study quality. The quality assessment results are presented in Supplementary Figure S1 and Supplementary Figure S2. There was low risk of bias regarding the index test, reference standard and flow and timing. Nevertheless, there existed unclear risk of bias with respect to patient selection due to the absence of consecutive inclusion in 44% (4/9) of the studies. In addition, low risk was observed regarding the index test, reference standard and selection of patients.

Clinical results

Specificity and sensitivity

The diagnostic result of wire FFR was used as a reference in calculation of the specificity and sensitivity of wireless FFR. The pooled sensitivity of the wireless FFR in stenotic lesion detection was 87% (95% CI: 83%-94%) and pooled specificity was 88% (95% CI: 82–92%), as shown in Figure 2.

Positive and negative likelihood ratio

Positive likelihood refers to the ratio of the true positive rate to the false positive rate, with the gold standard as a reference. Negative likelihood ratio refers to the ratio of the false negative rate to the true negative rate, with the gold standard as a reference. The diagnostic result by pressure wire FFR was the gold standard. Pooled positive likelihood (+LR) was 7.28 (95% CI: 4.78–11.08) and negative likelihood ratio (–LR) was 0.14 (95% CI: 0.10–0.21) (Figure 3).

Table I. Baseline demographic characteristics of the included studies

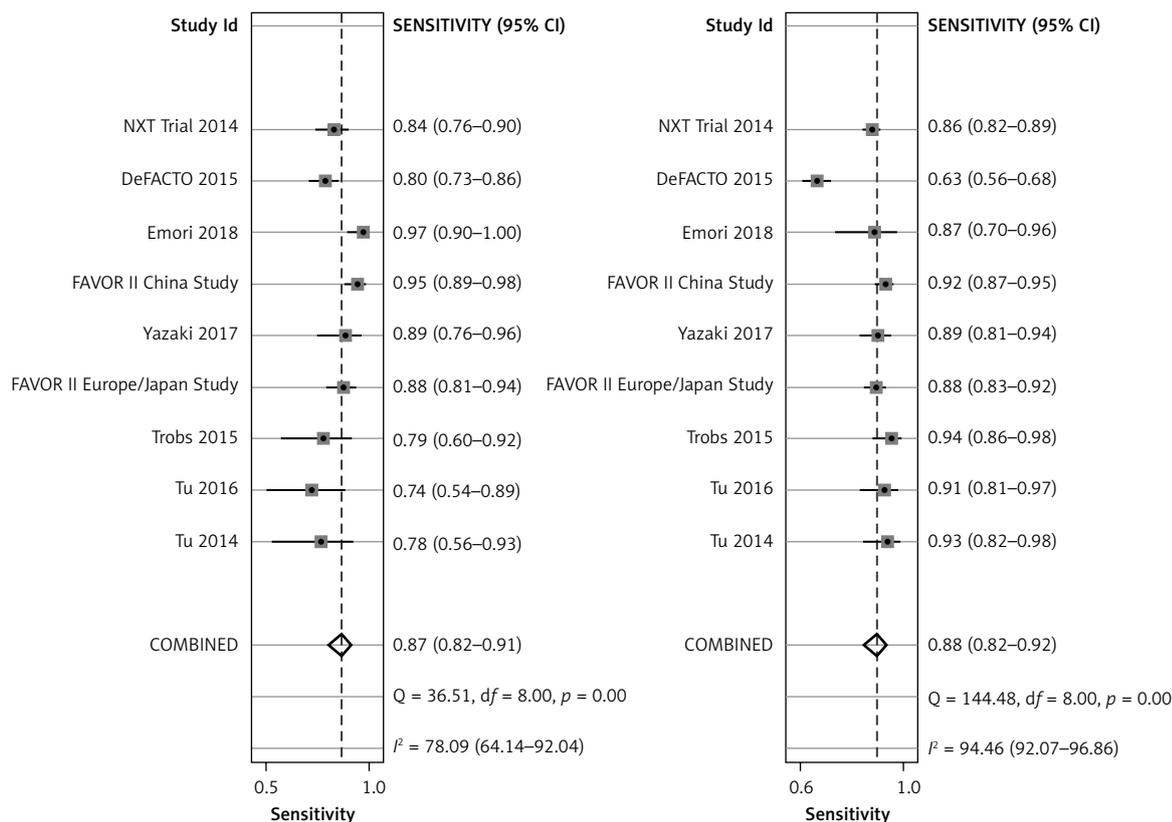| Study	Number of patients	Number of lesions	Age	Male (%)	Current smoker (%)	Diabetes mellitus (%)	Hypertension (%)	Study type	Reference standard	Threshold	Technology
Tu 2014	68	77	62.0 ±9.0	69.1	23.5	29.4	69.1	observational study	IV FFR	FFR ≤ 0.8	QFR
Tu 2016	73	84	65.8 ±8.9	83.5	43.8	27.4	43.8	prospective, observational, multicenter	IV FFR	FFR ≤ 0.8	QFR
Tröbs 2015	73	100	67 ±11	66	15	23	88	retrospectively analyzed study	IV FFR	FFR ≤ 0.8	FFRangio
FAVOR II Europe/Japan Study	272	317	67 ±10	72	57	29	74	prospective, observational, multicenter	IV FFR	FFR ≤ 0.8	QFR
Yazaki 2017	142	151	72.5 ±9.5	70.4	23.2	28.9	71.1	retrospective, single-center, observational study	IV FFR	FFR ≤ 0.8	QFR
FAVOR II China Study	308	332	61.3 ±10.4	73.7	28.2	86	60.1	prospective, multicenter trial	IV FFR	FFR ≤ 0.8	QFR
Emori 2018	100	100	70 ±10	71	21	48	73	retrospective, single-center study	IV FFR	FFR ≤ 0.8	QFR
DeFACTO 2015	252	407	62.9 ±8.7	70.6	17.5	21.2	71.2	prospective, multicenter	IV FFR	FFR ≤ 0.8	FFRCT
NXT Trial 2014	251	484	64 ±10	64	18	23	69	prospective, multicenter study	IV FFR	FFR ≤0.8	FFRCT

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Figure 2. Individual studies and summary point estimates for sensitivity and specificity

Diagnostic odds ratio and summary receiver operator curves

Diagnostic odds ratio (DOR) refers to the ratio of +LR to −LR, indicating the accuracy of the diagnostic test. The higher DOR is, the more accurate is the diagnostic test. The receiver operating characteristics (ROC) curve graphically presented the association between sensitivity and specificity. The closer the area under the ROC is to 1.0, the more accurate the diagnostic test will be. Summary receiver operator curve (SROC) refers to using one ROC curve to show the association between specificity and sensitivity obtained by a series of studies in a meta-analysis. The pooled DOR in our analysis was 50.69 (95% CI: 25.22–101.88), as shown in Figure 4. The SROC revealed an area under the curve (AUC) of 0.94 (95% CI: 0.91–0.96), as shown in Figure 5.

Sensitivity and publication bias analysis

Sensitivity analysis was conducted with bivariate boxplot (Supplementary Figure S3). The sensitivity analysis result showed that the study DeFACTO 2015 is a major source of heterogeneity. According to the result of publication bias analysis performed with Deeks' funnel plot (p = 0.39), there was no significant publication bias, as shown in Supplementary Figure S4.

Discussion

In the last 20 years, FFR has gradually been recognized as standard functional assessment metrics, especially for critical lesions (diameter stenosis 30–70%) [24]. The DEFER study and FAME study confirmed that percutaneous coronary intervention guided by FFR can reduce medical costs and unnecessary re-revascularization [25, 26]. Usage of FFR for patients who have already been selected to perform PCI can reduce the number of stents needed to implant and improve the relative clinical effect [27–29]. However, its invasiveness and high cost limited its wide application. Seeking a non-invasive, economic, accurate alternative is necessary.

This meta-analysis showed that the diagnostic performance of wireless FFR has high sensitivity and specificity with pressure wire FFR as a reference in stable coronary artery disease patients. The pooled diagnostic accuracy of wireless FFR was high, with an AUC of 0.94 (95% CI: 0.66–0.94), and the high sensitivity and specificity confirm its good diagnostic performance. The high +LR (7.28 (95% CI: 4.78–11.08)), low −LR (0.14 (95% CI: 0.10–0.21)) and high DOR (50.69 (95% CI: 25.22–101.88)) provide strong evidence of the usefulness of wireless FFR in clinical practice. A recent published meta-analysis including 1842 vessels showed a pooled sensitivity of 89%, specificity of
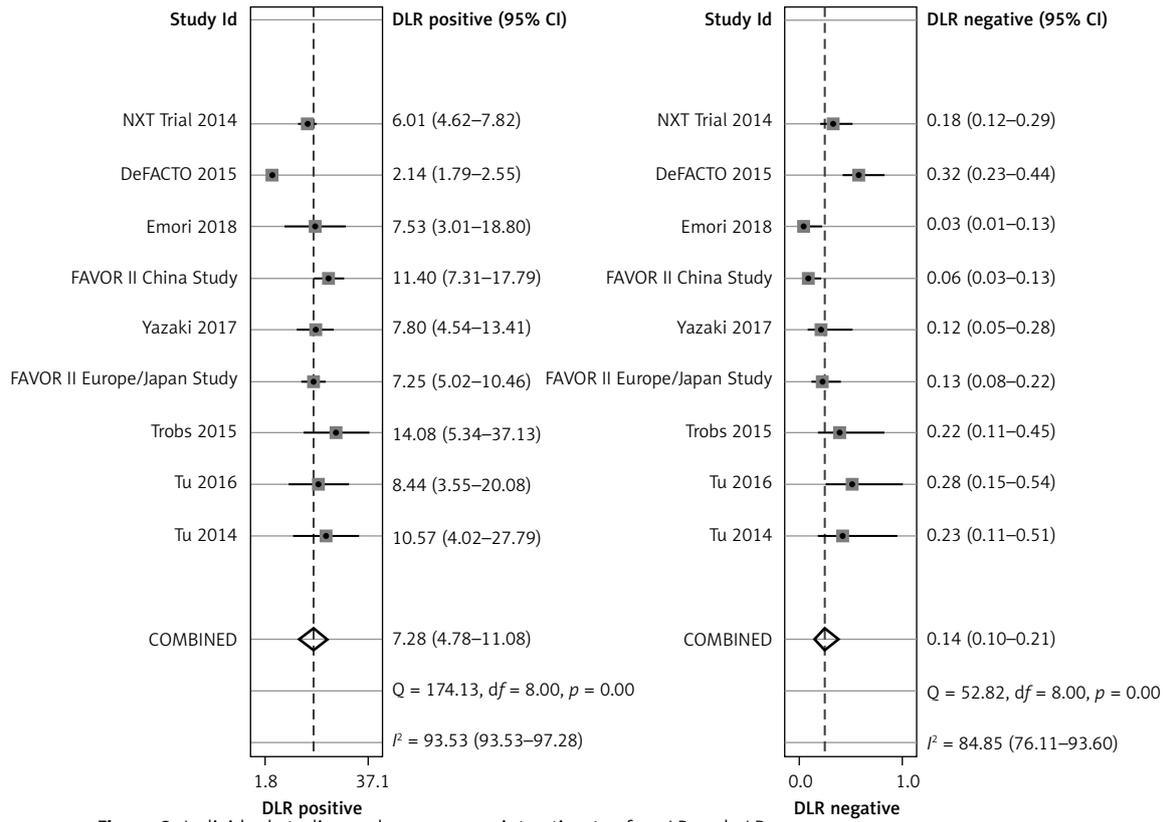
Study Id		DLR positive (95% CI)
NXT Trial 2014		6.01 (4.62–7.82)
DeFACTO 2015		2.14 (1.79–2.55)
Emori 2018		7.53 (3.01–18.80)
FAVOR II China Study		11.40 (7.31–17.79)
Yazaki 2017		7.80 (4.54–13.41)
FAVOR II Europe/Japan Study		7.25 (5.02–10.46)
Trobs 2015		14.08 (5.34–37.13)
Tu 2016		8.44 (3.55–20.08)
Tu 2014		10.57 (4.02–27.79)
COMBINED		7.28 (4.78–11.08)
		Q = 174.13, df = 8.00, p = 0.00
		I² = 93.53 (93.53–97.28)

1.8   37.1
DLR positive

Study Id		DLR negative (95% CI)
NXT Trial 2014		0.18 (0.12–0.29)
DeFACTO 2015		0.32 (0.23–0.44)
Emori 2018		0.03 (0.01–0.13)
FAVOR II China Study		0.06 (0.03–0.13)
Yazaki 2017		0.12 (0.05–0.28)
FAVOR II Europe/Japan Study		0.13 (0.08–0.22)
Trobs 2015		0.22 (0.11–0.45)
Tu 2016		0.28 (0.15–0.54)
Tu 2014		0.23 (0.11–0.51)
COMBINED		0.14 (0.10–0.21)
		Q = 52.82, df = 8.00, p = 0.00
		I² = 84.85 (76.11–93.60)

0.0   1.0
DLR negative

Figure 3. Individual studies and summary point estimates for +LR and –LR

Study Id		DIAGNOSTIC SCORE (95% CI)
NXT Trial 2014		3.48 (1.59–3.48)
DeFACTO 2015		1.91 (0.79–1.91)
Emori 2018		5.42 (2.02–5.42)
FAVOR II China Study		5.27 (2.38–5.27)
Yazaki 2017		4.15 (1.68–4.15)
FAVOR II Europe/Japan Study		4.01 (1.81–4.01)
Trobs 2015		4.16 (1.55–4.16)
Tu 2016		3.39 (1.18–3.39)
Tu 2014		3.81 (1.32–3.81)
COMBINED		3.93 (3.23–4.62)
		Q = 89.39, df = 8.00, p = 0.00
		I² = 91.05 (86.59–95.51)

0.8   5.4
Diagnostic score

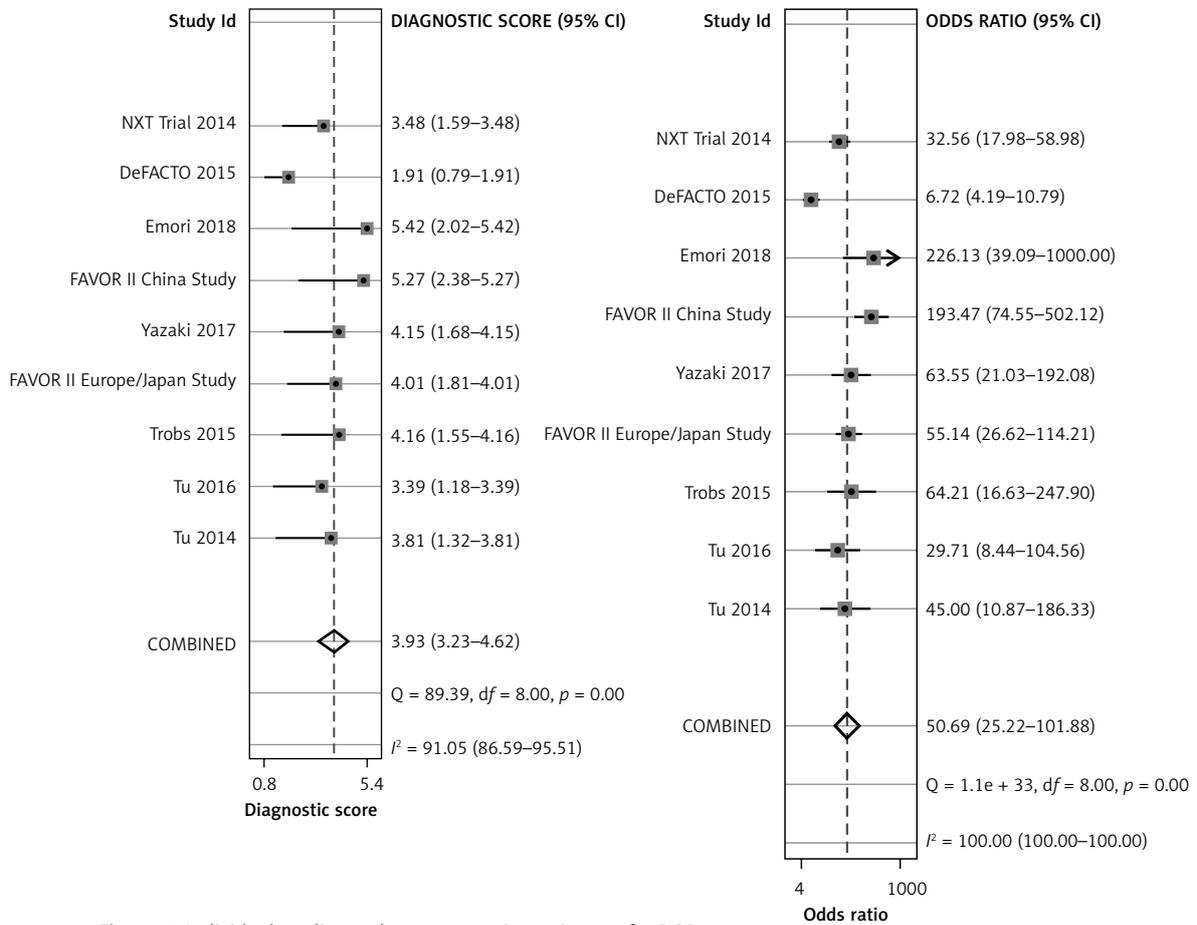| Study Id		ODDS RATIO (95% CI)
NXT Trial 2014		32.56 (17.98–58.98)
DeFACTO 2015		6.72 (4.19–10.79)
Emori 2018		226.13 (39.09–1000.00)
FAVOR II China Study		193.47 (74.55–502.12)
Yazaki 2017		63.55 (21.03–192.08)
FAVOR II Europe/Japan Study		55.14 (26.62–114.21)
Trobs 2015		64.21 (16.63–247.90)
Tu 2016		29.71 (8.44–104.56)
Tu 2014		45.00 (10.87–186.33)
COMBINED		50.69 (25.22–101.88)
		Q = 1.1e + 33, df = 8.00, p = 0.00
		I² = 100.00 (100.00–100.00)

4   1000
Odds ratio

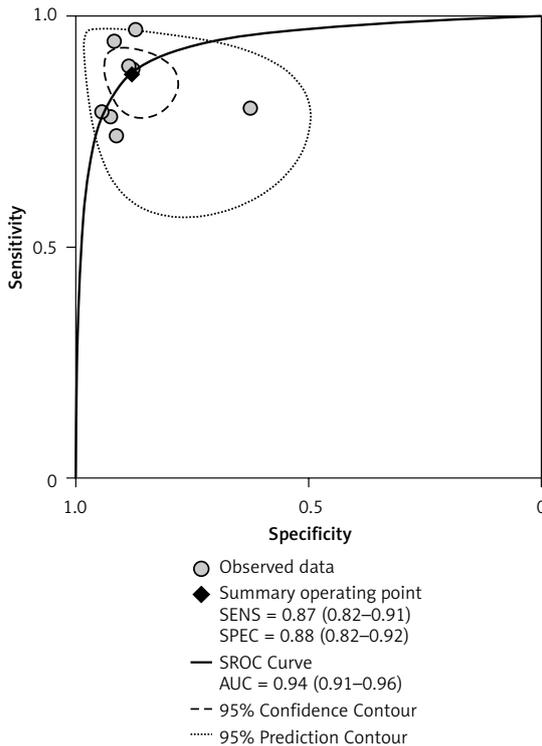**Figure 4.** Individual studies and summary point estimates for DOR

Figure 5. Summary receiver operator curves (SROC)

90%, positive likelihood ratio of 9.3, negative likelihood ratio of 0.13, and summary area under ROC of 0.84 [30]. Our analysis result was consistent with this meta-analysis, suggesting that wireless FFR might be good to detect hemodynamically significant lesions.

Compared with pressure wire measured FFR, wireless FFR can reduce the risk of adverse events related to the invasive pressure wire application, such as vessel dissection and myocardial infarction [31, 32]. At the same time, wireless FFR can reduce the hospitalization costs by avoiding the use of pressure wire and the related adverse events.

The advantages of our analysis include the following: this is one of very few meta-analyses evaluating the accuracy of wireless FFR with invasive FFR as a reference; most updated clinical trials were included in our analysis; FFR_{CT}, a new type of wireless FFR in which FFR was derived from the computed tomography angiography (CTA) was included; a threshold of 0.80 by pressure wire measurement of FFR was made.

Nevertheless, there were some limitations of our meta-analysis. Firstly, most of the included studies used wireless FFR in simple lesions; thus there is a lack of application in complex lesions such as CABG and calcified lesions. Secondly, different software of the wireless FFR used in different clinical trials may lead to heterogeneity between studies. Thirdly, we could not obtain data of individual patients to address some unresolved

problems to make further analysis, such as the clinical performance in the uncertainty zone. In future, more rigorous, large-sample, high quality international trials are needed; several angiography-based methods have been developed to derive FFR [12, 15, 33–34], so subgroup analysis based on various methods could be performed.

In conclusion, this meta-analysis indicates that the clinical performance such as accuracy, sensitivity and specificity of wireless FFR is good to detect stenotic lesions with pressure-wire measured FFR as a reference.

Conflict of interests

The authors declare no conflict of interest.

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