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Diagnostic Accuracy of Myocardial Magnetic Resonance Perfusion to Diagnose Ischemic Stenosis With Fractional Flow Reserve as Reference

Systematic Review and Meta-Analysis

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ABSTRACT

OBJECTIVES This paper systematically analyzed the performance of magnetic resonance (MR) perfusion to diagnose coronary artery disease (CAD) with fractional flow reserve (FFR) as the reference standard.

BACKGROUND Myocardial MR perfusion has passed the stage of a research technique and has demonstrated the ability to detect functional or ischemic stenosis of coronary arteries. However, the evidence is limited to single-center studies and small sample sizes.

METHODS We searched PubMed and Embase databases for all published studies that evaluated the accuracy of MR perfusion to diagnose CAD versus FFR. We used an exact binomial rendition of the bivariate mixed-effects regression model with test type as a random-effects covariate to synthesize the available data. Based on Bayes' theorem, the post-test probability was calculated to guide MR perfusion's clinical utility.

RESULTS We identified 14 studies evaluating 1,073 arteries and 650 patients. The pooled sensitivity and specificity were 0.90 (95% confidence interval [CI]: 0.86 to 0.93) and 0.87 (95% CI: 0.82 to 0.90) at the patient level and 0.89 (95% CI: 0.83 to 0.92) and 0.86 (95% CI: 0.77 to 0.92) at the artery and territory levels, respectively. The area under the summary receiver-operating characteristic at the patient level was 0.95 (95% CI: 0.92 to 0.96) and 0.93 (95% CI: 0.91 to 0.95) at the artery and territory levels, respectively. MR perfusion could increase the post-test probability of CAD >80% in patients with a pre-test probability of >37% and can decrease post-test probability of CAD <20% with a pre-test probability of <72%.

CONCLUSIONS With FFR as the reference standard, the diagnostic ability of MR perfusion to detect ischemic CAD is high. (J Am Coll Cardiol Img 2014;7:1098–105) © 2014 by the American College of Cardiology Foundation.

Coronary artery disease (CAD) continues to be a major public health concern in developed and developing countries. Revascularization effectively restores blood flow, but the first step requires an accurate evaluation of myocardial ischemia caused by epicardial coronary artery stenosis (1–3).

Myocardial perfusion imaging by single-photon emission computed tomography has long been applied routinely to evaluate blood supply. In recent years, with the development of magnetic resonance (MR) imaging, myocardial MR perfusion has demonstrated its ability to detect myocardial ischemia (4,5). Compared with single-photon emission computed tomography and other new perfusion modalities, such as positron emission tomography and computed tomography perfusion, MR perfusion offers several advantages, such as no attenuation artifacts, high spatial resolution, and no radiation exposure (6,7). A systematic understanding of the diagnostic

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performance of MR perfusion, therefore, has important practical significance.

Meta-analyses have shown the high accuracy of MR perfusion in diagnosing myocardial ischemia, using quantitative coronary angiography (QCA) as the reference standard (8,9). Although QCA offers a direct visualization of stenotic lumen, it may not reliably detect whether a stenosis leads to ischemia. Given that fractional flow reserve (FFR) is superior to QCA in guiding revascularization (1,2), the purpose of our study was to systematically analyze the diagnostic performance of MR perfusion with FFR as the reference standard.

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METHODS

The meta-analysis was performed using a standard protocol based on the MOOSE (Meta-analysis of Observational Studies in Epidemiology) guidelines (10) and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) statement (11).

DATA SOURCES AND STUDY SELECTION. We searched PubMed and Embase databases for all published studies in the English language evaluating the accuracy of MR perfusion with FFR as the reference standard, by searching the terms "FFR or fractional flow reserve" and "magnetic resonance imaging or MRI." Additionally, references to previous systematic reviews were screened. Two reviewers examined the references independently to exclude duplicate or overlapping data.

STUDY ELIGIBILITY. The inclusion criteria for studies were as follows: 1) MR perfusion was used as a diagnostic test for ischemic CAD; 2) FFR served as the standard reference and FFR <0.75 or <0.80 was considered ischemic CAD; and 3) results were reported in absolute numbers of true-positive, false-positive, true-negative, and false-negative results, or sufficiently detailed data were provided to derive these numbers. The exclusion criteria were the study included patients with a history of coronary artery bypass graft surgery or percutaneous coronary intervention and as retrospective studies.

DATA EXTRACTION. The following information was extracted by 2 investigators independently: first author; year of publication; sex; age; body mass index; separate prevalence of multivessel disease, diabetes, and myocardial infarction (MI); type and brand of machine used; perfusion sequence; magnet strength; and true-positive/true-negative/false-positive/false-negative values. Data were recorded separately, whenever available, at the patient and artery/territory levels.

The quality analysis of the study had to conform to QUADAS (Quality Assessment of Diagnostic Accuracy Studies) guidelines (12). Two readers independently evaluated QUADAS items for all included studies; if they disagreed, a third reader adjudicated.

DATA SYNTHESIS AND STATISTICAL ANALYSIS. Interobserver agreement was assessed by the Cohen kappa test, and publication bias was investigated using a regression line, as outlined by Deeks et al. (13), with $p < 0.10$ for the slope coefficient indicating significant asymmetry.

We used an exact binomial rendition of the bivariate mixed-effects regression model with test type as a random-effects covariate to synthesize the available data (14,15). Sensitivity and specificity were calculated along with their 95% confidence intervals (CIs). Based on the parameters estimated by the bivariate model, a hierarchical summary receiver-operating characteristic (sROC) curve was constructed. The area under the sROC curve serves as a global measure of test performance: less predictive ($0.5 \ll$ area under the sROC curve $\ll 0.7$); moderately predictive ($0.7 \ll$ area under the sROC curve $\ll 0.9$); and highly predictive ($0.9 \ll$ area under the sROC curve $\ll 1$) (16).

We used the Cochran Q statistic and measured inconsistency (I^2) (percentage of total variance across studies attributable to heterogeneity rather than chance) for the detection of heterogeneity across studies (17). Possible sources of heterogeneity were pre-defined based on sex, age, prevalence of multivessel disease, prevalence of diabetes, prevalence of MI, magnet strength, and data interpretation. Meta-regression, a collection of statistical procedures (weighted/unweighted linear, logistic regression), was applied to evaluate the potential covariates of heterogeneity. Furthermore, the clinical or patient-relevant utility of MR perfusion was evaluated using the positive/negative likelihood ratio (LR) to calculate the post-test probability based on Bayes' theorem (18).

The sensitivity analysis was conducted by omitting each reference and reanalyzing the data to test whether any studies significantly influenced the final results.

We applied the MIDAS module for STATA, version 12 (StataCorp, College Station, Texas), to perform the analysis and construct the graphs and used SPSS, version 16.0 (SPSS Inc., Chicago, Illinois), to calculate kappa statistics.

ABBREVIATIONS AND ACRONYMS

CAD = coronary artery disease
CI = confidence interval
FFR = fractional flow reserve
LR = likelihood ratio
MI = myocardial infarction
MR = magnetic resonance
QCA = quantitative coronary angiography
sROC = summary receiver-operating characteristic

RESULTS

CHARACTERISTICS OF MR PERFUSION STUDIES. Among the studies that met our inclusion criteria, 2 (19,20) were excluded because they reported populations that potentially overlapped with an earlier study (21). A total of 14 studies were ultimately identified for the literature search and selection algorithm (**Figure 1**, **Table 1**). Eight studies reported data at the patient level, among which 5 studies performed MR perfusion with a magnetic intensity of 1.5-T, 2 with 3.0-T, and 1 with 1.5-T and 3.0-T. Nine studies contained effective information at the artery/territory level, among which 6 studies performed MR perfusion with a magnetic intensity of 1.5-T, 2 with 3.0-T, and 1 with 1.5-T and 3.0-T. Finally, 10 groups of data at the patient level and 10 at the artery/territory level were available for synthesizing data.

METHODOLOGICAL QUALITY. Our inter-rater reliability for assessing quality items was perfect (kappa = 0.89). Online Table 1 summarizes the QUADAS items of each study.

DATA SYNTHESIS AND STATISTICAL ANALYSIS. The pooled sensitivity and specificity were 0.87 (95% CI: 0.84 to 0.91) and 0.87 (95% CI: 0.83 to 0.90), respectively, at the patient level. Between-study differences in the diagnostic performance of MR perfusion were found for sensitivity ($Q = 16.41$; $I^2 = 45.2\%$; $p = 0.06$), but no significant heterogeneity was detected for specificity ($Q = 6.04$; $I^2 = 0.40\%$; $p = 0.43$). Because we noticed that the sensitivity of Bernhardt et al. (22) with 1.5-T was significantly different from other studies, we omitted these data and reanalyzed the remaining information to test whether the data caused this phenomenon. The heterogeneity decreased greatly with sensitivity ($Q = 4.19$; $I^2 = 0.00\%$; $p = 0.76$) and specificity ($Q = 4.72$; $I^2 = 0.00\%$; $p = 0.69$). The pooled sensitivity and specificity were 0.90 (95% CI: 0.86 to 0.93) and 0.87 (95% CI: 0.82 to 0.90), respectively, at the patient level (**Figure 2**).

Overall, 1,073 arteries and 650 patients were analyzed. The results showed that 26.75% of the arteries (287 of 1,073; range 16.28% to 41.33%) and 45.69% of patients (297 of 650; range 25.29% to 73.27%) had hemodynamic CAD. No publication bias could be detected at the patient and artery/territory levels ($p = 0.18$ and $p = 0.90$, respectively).

Using the pre-specified potential factors of heterogeneity as covariates in the meta-regression with the random-effects model, we found that the prevalence of multivessel disease ($p < 0.001$) and MI ($p < 0.001$) were significant predictors, but other factors did not influence the diagnostic accuracy, including age ($p = 0.76$), sex ($p = 0.22$), magnet strength ($p = 0.57$), quantitative or semiquantitative data interpretation ($p = 0.87$), threshold of FFR to define an ischemic stenosis ($p = 0.33$), and the prevalence of diabetes ($p = 0.88$).

At the artery/territory level, the pooled sensitivity and specificity were 0.89 (95% CI: 0.83 to 0.92) and 0.86 (95% CI: 0.77 to 0.92), respectively. Slight heterogeneity was found for sensitivity ($Q = 9.79$; $I^2 = 18.29\%$; $p = 0.28$), whereas the heterogeneity was significant for specificity ($Q = 59.46$; $I^2 = 86.55\%$; $p < 0.001$). Online Figure 1 demonstrated the high area under the sROC curve at both the patient and artery/territory levels (0.95 [95% CI: 0.92 to 0.96] and 0.93 [95% CI: 0.91 to 0.95], respectively).

The per-patient analysis revealed a positive LR of 6.70 (95% CI: 5.06 to 8.87) and a negative LR of 0.12 (95% CI: 0.08 to 0.16) for MR perfusion. Based on Bayes' theorem, **Figure 3** illustrates the relationship between pre-test and post-test probability of CAD, which indicated that MR perfusion could increase the post-test probability of CAD >80% in patients with a pre-test probability of >37% and can decrease post-test probability of CAD <20% with a pre-test probability of <72%.

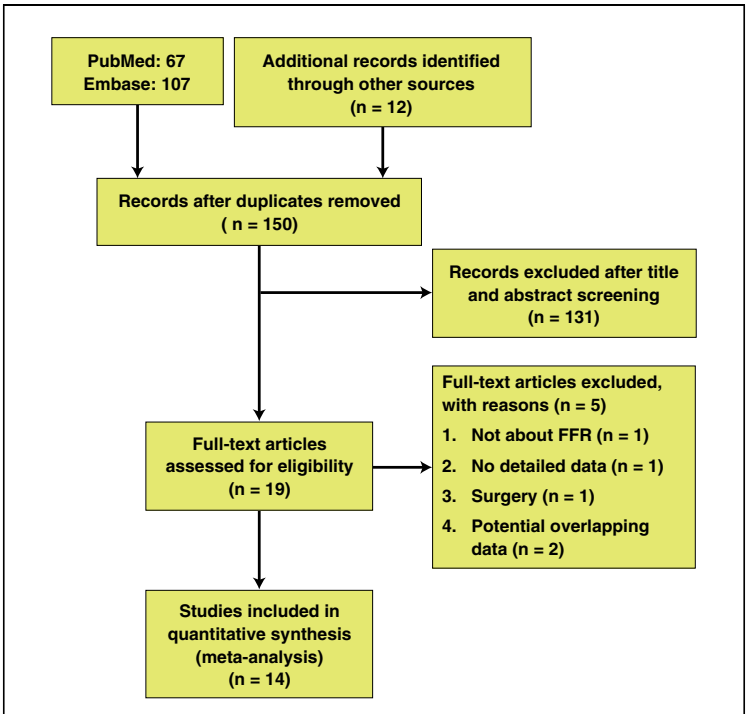

FIGURE 1 Literature Search and Selection Algorithm

Fourteen studies were ultimately identified. FFR = fractional flow reserve.

A sensitivity analysis, conducted at both the patient and artery/territory levels to investigate the influence of each individual study on the overall meta-analysis summary estimate, demonstrated that no study influenced the pooled sensitivity and specificity >0.02 (Online Figure 2).

DISCUSSION

Myocardial perfusion is critical to the supply of oxygen and substrates for contractile function (23). Generally, low myocardial perfusion can be caused by epicardial coronary artery stenosis as well as abnormal coronary microcirculation (24). Accurate measurement of ischemic stenoses of the epicardial coronary arteries is essential for reasonable revascularization.

In previous meta-analyses with QCA as the reference standard, MR perfusion offered comparatively high accuracy for CAD detection, with a sensitivity of 0.89 (8) and 0.91 (9), and a specificity of 0.76 (8) and 0.81 (9). The present analysis indicates that with FFR as the standard reference, the specificity (0.87) of MR perfusion increases, whereas the sensitivity (0.90) is similar. The improved specificity may stem from a lower rate of false-positive reports of arteries with no functional flow limitation despite appearing stenotic on QCA (25,26).

In this study, we estimated the relationship between pre-test and post-test probability of CAD based on Bayes' theorem to guide the clinical utility of MR perfusion. The result indicates that for patients with a low pre-test probability of CAD, MR perfusion could be applied as an exclusionary test. Although noninvasive MR perfusion may avoid potential iatrogenic complications and unnecessary costs (26), MR perfusion requires that the endocardial and epicardial borders of the left ventricular wall be detected or traced for each image frame of a perfusion study, a time-consuming step for quantitative analysis (27). In addition to the symptoms caused by vasodilator stress agents (e.g., adenosine) during stress MR perfusion, MR perfusion may not be a preferred noninvasive test for patients with a low pre-test probability of CAD (27). For patients with a high pre-test probability of CAD, MR perfusion may be applied as a confirmatory test. Nevertheless, these patients are generally recommended for invasive testing regardless of the presence of troublesome symptoms or clinical findings (28,29). Consequently, MR perfusion appears most clinically useful in patients with an intermediate pre-test probability of CAD, as both a positive and negative test can provide a relatively acceptable post-test probability of CAD.

TABLE 1 Characteristics of Included Studies

First Author (Ref. #), Year	No. of Enrolled Patients	No. of Excluded Patients	Prevalence of CAD, %	Age, yrs	M/F	Threshold of FFR	Scanner Brand (Magnet Strength)	Perfusion Sequence	Data Interpretation	Prevalence		
										Multivessel Disease	MI	Diabetes
Ebersberger et al. (5), 2013	120	4	29	63.0 ± 14.0	71/45	0.80	Philips (3.0- T)	Fast-field echo pulse	Semiquantitative	0.38	0	0.26
Groothuis et al. (43), 2013	210	18	25	56.0 ± 10.0	96/96	0.75	Siemens (1.5-T)	Steady-state free precession gradient echo	Semiquantitative	–	0	0.12
Bernhardt et al. (22), 2012	37	3	38	62.0 ± 10.9	26/8	0.80	Philips (1.5-T, 3.0-T)	Steady-state free precession	Semiquantitative	–	–	0.15
Huber et al. (44), 2012	31	0	–	–	27/4	0.75	Siemens (1.5-T)	Saturation recovery-turbo FLASH	Quantitative	0.32	0	0.23
Jogiya et al. (26), 2012	55	2	58	63.5 ± 10.8	41/12	0.75	Philips (3.0-T)	3D spoiled turbo gradient echo pulse	Quantitative	0.19	–	0.30
Bettencourt et al. (21), 2013	139	36	39	62.0 ± 8.0	68/35	0.80	Siemens (1.5-T)	Gradient echo pulse	Quantitative	0.24	0	0.39
Manka et al. (45), 2012	120	0	52	63.7 ± 11.9	90/30	0.75	Philips (1.5-T)	3D saturation recovery gradient echo pulse	Semiquantitative	0.13	0.28	0.26
Walcher et al. (46), 2012	42	6	42	63.1 ± 9.9	27/9	0.80	Philips (1.5-T)	Steady-state free precession sequences	Semiquantitative	–	0	0.14
Kirschbaum et al. (47), 2011	50	0	–	64.0 ± 10.0	38/12	0.80	GE (1.5-T)	Not specified	Quantitative	–	0	0.18
Lockie et al. (48), 2011	42	0	–	57.4 ± 9.6	33/9	0.75	Philips (3.0-T)	Saturation recovery gradient echo	Semiquantitative	–	0	0.19
Watkins et al. (25), 2009	103	2	73	60.0 ± 9.0	75/26	0.75	Siemens (1.5-T)	Turbo FLASH	Semiquantitative	0.89	0	0.16
Costa et al. (33), 2007	37	7	–	65.0 ± 11.0	16/14	0.75	Siemens (1.5-T)	Saturation recovery gradient echo	Quantitative	0.70	0	0.23
Rieber et al. (4), 2006	50	7	–	65.5 ± 8.1	38/15	0.75	Siemens (1.5-T)	Saturation recovery turbo FLASH	Semiquantitative	0.39	0.19	0.23
Kühl et al. (49), 2007	30	2	–	63.0 ± 11.0	17/11	0.75	Philips (1.5-T)	Single-shot turbo gradient echo	Semiquantitative	–	0	0.25

Values are n or mean ± SD.
3D = 3-dimensional; CAD = coronary artery disease; FLASH = fast imaging using low angle shot; FFR = fractional flow reserve; MI = myocardial infarction; M/F = male/female; MR = magnetic resonance.

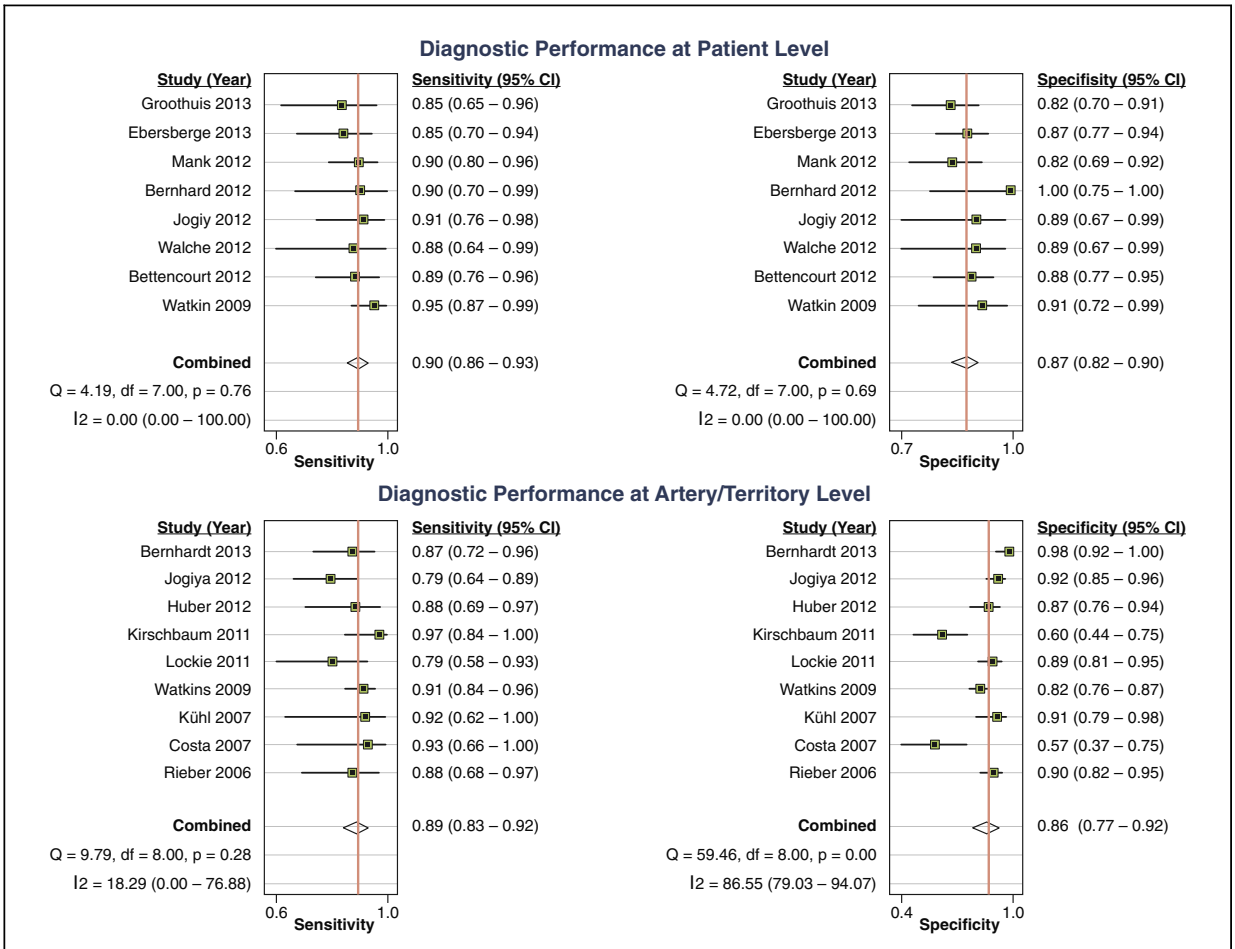

FIGURE 2 Forest Plots Illustrating Detailed Sensitivity and Specificity

The pooled sensitivity and specificity were 0.90 (95% confidence interval [CI]: 0.86 to 0.93) and 0.87 (95% CI: 0.82 to 0.90), respectively, at the patient level and 0.89 (95% CI: 0.83 to 0.92) and 0.86 (95% CI: 0.77 to 0.92), respectively, at the artery/territory level.

The results also support the guideline recommendation that MR perfusion is appropriate for detecting CAD in symptomatic patients with uninterpretable electrocardiograms who have an intermediate pretest probability of CAD (30).

Several factors influencing the diagnostic performance of FFR should be explained. FFR is an effective tool for detecting functional stenosis of the epicardial artery and FFR-guided revascularization is superior to QCA-guided treatment (1,2,31). However, for patients with microvascular disease, FFR may underestimate the degree of ischemia because the pressure distal to the stenosis is generally affected (32). MR perfusion also detects ischemia in the myocardium; the decreased perfusion area presented in MR perfusion, however, may be induced by obstructive epicardial CAD or by abnormal microvascular disease (24). Although MR perfusion may provide more information on coronary microcirculation than FFR, the areas with a hypointense signal in patients with microvascular dysfunction are frequently regarded as false positives because the hemodynamic changes caused by the epicardial coronary arteries could not be detected. More attention, therefore, should be paid when explaining the MR perfusion imaging in patients with potential microvascular disease (33).

Additionally, artifacts, such as susceptibility artifacts, off-resonance artifacts, and dark-rim artifacts (27,34,35), may influence MR perfusion accuracy. Playing images in cine mode effectively differentiates image artifacts and true perfusion defects (36). Apart from the perfusion imaging, regional function (wall thickening or strain imaging) analysis as well

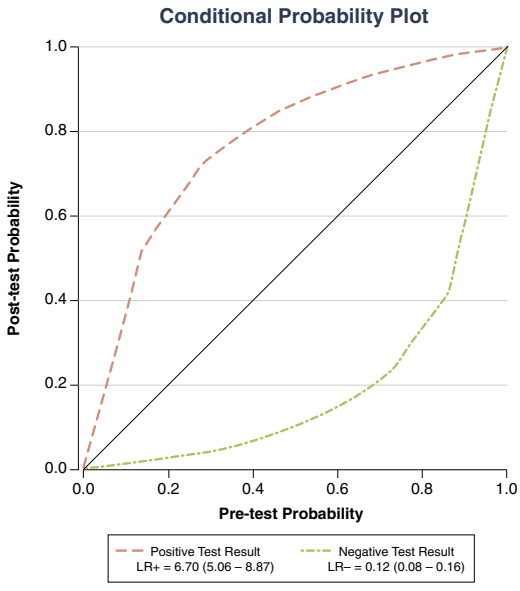

FIGURE 3 Relationship Between Pre- and Post-Test Probability of CAD

Magnetic resonance perfusion could increase the post-test probability of coronary artery disease (CAD) >80% in patients with a pre-test probability of >37% and can decrease the post-test probability of CAD <20% if the pre-test probability is <72%. LR = likelihood ratio.

as delayed-gadolinium enhancement, which have shown high accuracy in detecting obstructive CAD and are generally performed simultaneously with MR perfusion, may provide incremental information of CAD (9,27,35). However, no data have shown that a multicomponent examination for MR perfusion improves overall accuracy to distinguish ischemic stenosis. Although many technical factors, such as MR pulse sequence, magnet strength, and data interpretation, might influence the pooled results theoretically, no statistical significance could be found, which guarantees the pooled results of the present study.

Multivessel disease causes most CAD (37). Discriminating functional stenosis at the artery/territory level is therefore critical for determining the need for revascularization. Our results indicate diagnostic performance at the artery/territory level is even higher than at the patient level. However, the between-study differences also increase greatly. It is worth emphasizing that although the model was believed to be appropriate for assigning individual segments to specific coronary artery territories (38), as guidelines recommend, there is still variability in the coronary blood supply to myocardial segments (39,40), which may be the reason for the higher heterogeneity. Further studies with the additional analysis of adjacent segments may help improve the clinical value of MR perfusion (39,40).

STUDY LIMITATIONS. First, we did not compare the accuracy of MR perfusion with another myocardial perfusion modality. Second, although numerous efforts were made to contact the investigators for additional data, not all of the included studies provided comprehensive data on the patient and artery/territory levels. Third, studies including patients who had undergone a previous percutaneous coronary intervention or coronary artery bypass graft were excluded for limited references. However, to decide whether further treatment is required, clinical evaluation using MR perfusion may be necessary for those patients (41,42). Further multicenter studies are required to illustrate this issue more clearly. Finally, it should be noted that the acceptable accuracy of MR perfusion is based on FFR-guided revascularization. Although revascularization for epicardial artery disease has become increasingly applied to relieve symptoms and improve patient prognosis (1,2,31), recent studies show that augmented vascular resistance may occur in the coronary microcirculation (24). The reference standard should be whether MR perfusion is helpful for ischemia detection. This may vary depending on whether the purpose is to detect epicardial artery functional stenosis for revascularization, for which FFR would be the ultimate option, or to evaluate ischemia in the myocardium for systemic treatment, for which the gold standard may be long-term follow-up. Because of the limitations of both our review and the evidence base, further studies at different sites with long-term follow-up as the reference standard are needed to address the potential of MR perfusion for use in triage to positively alter management and outcomes in patients with suspected CAD.

CONCLUSIONS

With FFR as the reference standard, the diagnostic ability of MR perfusion to detect ischemic CAD is high.

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APPENDIX For a supplemental table and figures, please see the online version of this article.