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Combined diagnostic performance of coronary computed tomography angiography and computed tomography derived fractional flow reserve for the evaluation of myocardial ischemia: A meta-analysis

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ABSTRACT

Background: To evaluate the combined diagnostic accuracy of coronary computed tomography angiography (CCTA) and computed tomography derived fractional flow reserve (FFRct) in patients with suspected or known coronary artery disease (CAD).
Methods: PubMed, The Cochrane library, Embase and OpenGray were searched to identify studies comparing diagnostic accuracy of CCTA and FFRct. Diagnostic test measurements of FFRct were either extracted directly from the published papers or calculated from provided information. Bivariate models were conducted to synthesize the diagnostic performance of combined CCTA and FFRct at both "per-vessel" and "per-patient" levels.
Results: 7 articles were included for analysis. The combined diagnostic outcomes from "both positive" strategy, i.e. a subject was considered as "positive" only when both CCTA and FFRct were "positive", demonstrated relative high specificity (per-vessel: 0.91; per-patient: 0.81), high positive likelihood ratio (LR+, per-vessel: 7.93; per-patient: 4.26), high negative likelihood ratio (LR−, per-vessel: 0.30; per patient: 0.24) and high accuracy (per-vessel: 0.91; per-patient: 0.81) while "either positive" strategy, i.e. a subject was considered as "positive" when either CCTA or FFRct was "positive", demonstrated relative high sensitivity (per-vessel: 0.97; per-patient: 0.98), low LR+ (per-vessel: 1.50; per-patient: 1.17), low LR− (per-vessel: 0.07; per-patient: 0.09) and low accuracy (per-vessel: 0.57; per-patient: 0.54).
Conclusion: "Both positive" strategy showed better diagnostic performance to rule in patients with non-significant stenosis compared to "either positive" strategy, as it efficiently reduces the proportion of testing false positive subjects.

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1. Introduction

Invasive fractional flow reserve (FFR), one of several diagnostic methods available in invasive coronary angiography (ICA), is the gold standard for determining functional stenosis in coronary artery disease (CAD) [1]. To avoid the side effects and relative high cost of an invasive procedure [2], several less- or non-invasive imaging tools were developed by combining the anatomical and physiological assessment modalities of CAD. Coronary computed tomography angiography (CCTA) provides excellent diagnostic sensitivity with high negative predictive value for ruling out obstructive CAD. However, CCTA tends to overestimate coronary artery stenosis severity, with the consequence that a high portion of patients who do not show obstructive CAD undergo ICA and downstream treatment, resulting in exposure to additional risks and greater financial burden [3–6]. Recently, several novel technologies based on CCTA imaging have been developed for assessing CAD that simultaneously quantify coronary lesion severity and determine vessel lesion hemodynamic significance. These modalities include

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myocardial computed tomography perfusion (CTP) imaging, transluminal attenuation gradient (TAG) methods and computational analysis of fractional flow reserve (FFRct) [7]. Among these technologies, FFRct exhibits the best performance in diagnosing lesion specific ischemia compared to coronary CCTA stenosis, CTP and TAG [8–11]. Moreover, FFRct is derived from a standard CCTA dataset and requires no additional radiation and/or adenosine stress. Although the diagnostic performance of FFRct has been studied in several prospective trials and systematically reviewed by comparing with CCTA [11–15], there is still a knowledge gap as to the diagnostic performance of the combined FFRct and CCTA in evaluating coronary artery stenosis. In this review, we aim to compare the diagnostic performance of FFRct and CCTA with two different combination strategies from a collection of currently existing reports on FFRct and CCTA studies using invasive FFR as reference standard.

2. Methods

2.1. Search strategy and eligibility criteria

Following the general PRISMA [16] and MOOSE [17] guidelines for meta-analysis, we searched electronic databases including MEDLINE (PubMed), Embase, the Cochrane library and OpenGray up to 31 March 2016 with no restriction on language. The searching terms include "Myocardial fractional flow reserve", "Computed tomography derived fractional flow reserve" and "CT derived fractional flow reserve". In addition, we manually checked all reference lists in the included articles and the relevant review articles.

All retrospective and prospective studies that reported diagnostic accuracy of FFRct and CCTA with invasive FFR as the reference standard, were considered eligible. The studies with time intervals of index and reference tests >6 months were excluded. The final decision on inclusion was reached through consensus of the two screening authors (TXW and QSZ). Review articles, case reports, comments and authors' replies were excluded.

2.2. Data extraction and risk of bias assessment

Original data from the included studies were extracted into pre-defined data extraction forms which consist of 1) study characteristics, 2) patient characteristics and 3) diagnostic performance measurements on FFRct and CCTA with the cut off value of FFR at 0.8.

Risk of bias was independently assessed by QSZ and SLM using the Quality Assessment of Diagnostic Accuracy Studies, Version 2 (QUADAS-2) [18] comprising four key domains: patient selection, index test, reference standard, and flow and timing. Each domain was assessed for risk of bias, and the first three were also evaluated for applicability. Signaling questions were included to inform judgments regarding risk of bias: a domain would be rated "high risk of bias" if the response to a nested signaling question was "No". Any disagreement in quality assessment was resolved via consensus.

2.3. Statistical methods

The analysis of diagnostic performance was carried out at both per-vessel and per-patient levels. Two strategies on the joint use of FFRct and CCTA, i.e. "either positive" and "both positive", were evaluated. "Either positive" meant that the subjects were diagnosed as "coronary artery stenosis" by either positive result from CCTA ≥50% or FFRct < (or <=) 0.8, whereas "both positive" strategy meant that the subject was diagnosed as "coronary artery stenosis" only when both tests showed positive results. Diagnostic test measurements; sensitivity and specificity; positive likelihood ratio (LR+) and negative likelihood ratio (LR−); diagnostic odds ratio (DOR), area under curve (AUC) and their 95% confidence intervals were extracted directly from the publications or calculated indirectly from the information given with software Reviewer Manager 5.3. Pooled estimates were determined using a bivariate model in which pairs of sensitivity and specificity estimates were analyzed jointly to account for possible correlation between studies. To compare test performance, probability modifying plots of pre-test and post-test probabilities were synthesized at both "per-vessel" and "per-patient" levels.

Study heterogeneity was assessed by a bivariate meta-regression model. The following variables identified a priori were included as covariates in meta-regression analysis: study design (prospective or retrospective), site of FFRct (on-site or off-site) and proportion of excluded subjects (less or >30% over all eligible subjects). Deek's funnel plots for assessing publication bias [19] were produced by plotting the natural logarithm of the DOR (LnDOR) against the inversed root square of effective sample size for FFRct and

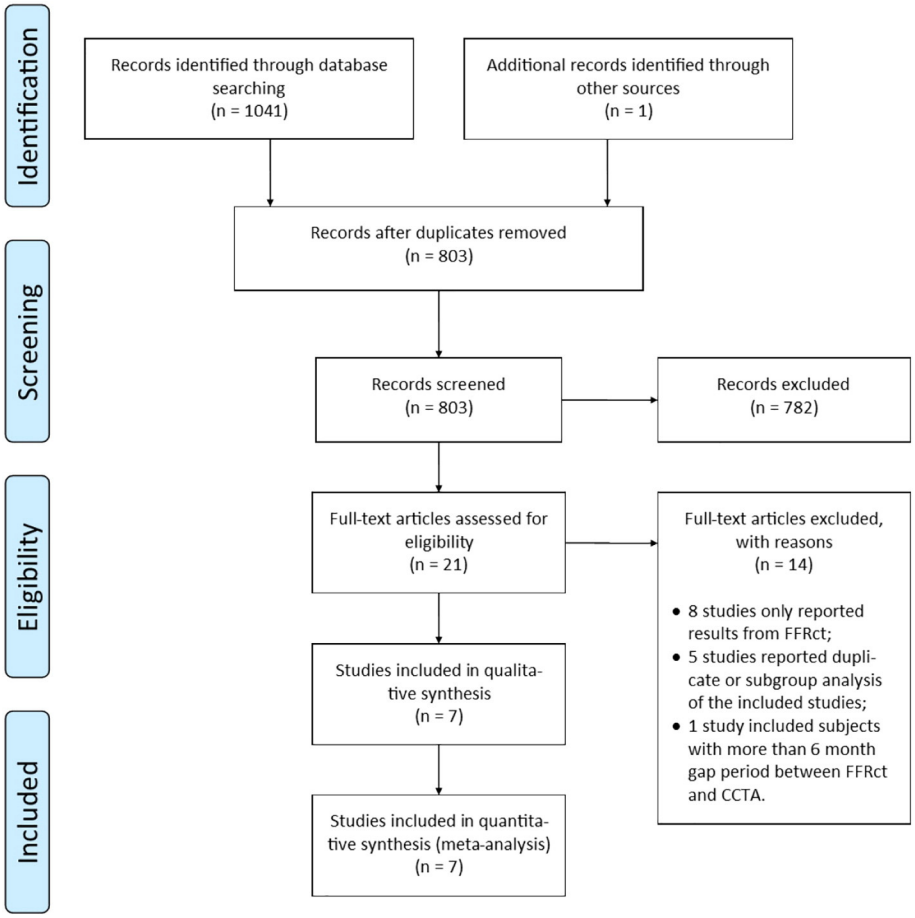

Fig. 1. PRISMA flowchart of study selection.

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