

Diagnostic Performance of CMR, SPECT, and PET Imagings for the Detection of Cardiac Amyloidosis: A Meta-Analysis

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Research Article

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Abstract

Background: Noninvasive myocardial imaging modalities, such as cardiac magnetic resonance (CMR), single photon emission computed tomography (SPECT), and Positron emission tomography (PET), are well-established and extensively used to detect cardiac amyloid (CA). The purpose of this study is to directly compare CMR, SPECT, and PET scans in the diagnosis of CA, and to provide evidence for further scientific research and clinical decision-making.

Methods: PubMed, Embase, and Cochrane Library were searched. Studies used CMR, SPECT and/or PET for the diagnosis of CA were included. Pooled sensitivity, specificity, positive and negative likelihood ratio (LR), diagnostic odds ratio (DOR), their respective 95% confidence intervals (CIs) and the area under the summary receiver operating characteristic (SROC) curve (AUC) were calculated. Quality assessment of included studies was conducted.

Results: A total of 31 articles were identified for inclusion in this meta-analysis. The pooled sensitivities of CMR, SPECT and PET was 0.84, 0.98 and 0.78, respectively. Their respective overall specificities were 0.87, 0.92 and 0.83. Subgroup analysis demonstrated that ^{99m}Tc -HMDP manifested the highest sensitivity (0.99). ^{99m}Tc -PYP had the highest specificity (0.95). The AUC values of ^{99m}Tc -DPD, ^{99m}Tc -PYP, ^{99m}Tc -HMDP were 0.89, 0.99, and 0.99, respectively. PET scan with ^{11}C -PIB demonstrated a pooled sensitivity of 0.91 and specificity of 0.97 with an AUC value of 0.98.

Conclusion: Our meta-analysis reveals that SEPCT scans present better diagnostic performance for the identification of CA as compared with other two modalities.

Background

Cardiac amyloidosis (CA) is a myocardial disease characterized by abnormal extracellular deposition of amyloid fibrils, which gives rise to a progressive structural and functional damage to the cardiac tissue [1, 2]. CA is the main cause of death and occurrence in systemic amyloidosis [3]. On the basis of the underlying nosologies, two subtypes (systemic light chain (AL) amyloidosis and transthyretin (ATTR) amyloidosis) account for most cases of cardiac amyloid. The two types of amyloidosis possess different clinical presentations and prognosis [4, 5].

The diagnostic approaches of cardiac amyloidosis include clinical symptoms, laboratory tests, non-invasive imaging, and histopathological diagnosis [6]. Unfortunately, this disease is commonly asymptomatic over a period of time from the beginning and the symptoms are usually nonspecific, and therefore its diagnosis is often delayed [2]. Currently, the confirmation of CA still relies on endomyocardial biopsy [7]. Nevertheless, endomyocardial biopsy is an invasive modality which can lead to unwanted complications. Echocardiography is widely employed for the diagnosis of CA in patients with suspected amyloidosis in clinical settings, however, it does not differentiate ATTR from AL CA [8]. It is reported that the diagnostic accuracy of echocardiography in combination with electrocardiogram (ECG) findings is only 60% [9]. Cardiac magnetic resonance (CMR) imaging is a mature and advanced imaging approach to describe the morphological characteristics and function of the heart and determine the characteristics of cardiac tissue, however, it may be in lack of specificity in distinguishing the potential causes of different types of CA [5, 10, 11]. Molecular imaging is another type of noninvasive modality for the diagnosis of CA. The favorable efficacy of technetium (Tc)-99m labelled bone seeking tracers in single photon emission computed tomography (SPECT) (pyrophosphate (^{99m}Tc -PYP), 3, 3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc -DPD), and hydroxymethylene diphosphonate (^{99m}Tc -HMDP)) for diagnosing CA have been manifested in several studies [12–14]. Furthermore, positron emission tomography (PET) scans with tracers including ^{11}C -Pittsburgh compound B (PIB), ^{18}F -florbetapir, ^{18}F -florbetaben, ^{18}F -NaF, and ^{18}F -flutemetamol have been studied for cardiac amyloidosis [15–18]. Compared to SPECT, PET shows higher spatial resolution and may provide more accurate quantification of absolute tracer uptake [5, 14].

As far as we are concerned, accumulated studies and meta-analyses have evaluated diagnostic performance of non-invasive modalities for the confirmation of CA [12, 19–23]. Most of these meta-analyses are on single-modality basis. The aim of this study was to generate a more comprehensive comparison of CMR, SPECT, and PET in the identification of CA by pooling the data of available studies, and subsequently to provide updated evidence-based information and hints for not only scientific research but also for the implement and decision-making of clinical practitioners.

Methods

This meta-analysis was conducted strictly on the basis of the Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) [24]. Details on each procedure of the study were reported as follows.

Search strategy and study selection

The researchers did a comprehensive search of the electronic databases: PubMed, Embase, and Cochrane Library from January 1, 2011 to November 30, 2020, only articles in the English language was considered. The following key words or phrases were used for the database research: "cardiac magnetic resonance", "CMR", "single-photon emission computed tomography", "SPECT", "positron emission tomography", "PET", "Cardiac amyloidosis" and "CA". The references of these articles were also searched for potential eligible researches. The inclusion criteria of this meta-analysis were as follows: a) CMR, SPECT and/or PET were employed for the detection of CA in patients with suspected or diagnosed CA; b) specific gold standard reference was used to evaluate the diagnostic performance; c) absolute numbers of patients with true positive (TP), false positive (FP), true negative (TN) and false negative (FN) outcomes were depicted directly in the original article or the references or all these numbers could be calculated based on the articles. In case that the studies were carried out by the same research team, only those with the largest sample size or the most complete information were included. Studied without necessary parameters mentioned above, case reports, reviews, letters to the editorial, conference abstracts, and animal studies were not taken into account in the meta-analysis.

Two authors independently conducted the database search and study selection. Discrepancies were resolved by discussion until a final decision was reached.

Data extraction and quality assessments

Two reviewers independently performed the screening of types of articles, titles and abstracts according to the protocol of study selection, hereafter the full-text reading of the articles was conducted for the final inclusion. The following information was retrieved from each study included: name of first author, year of publication, number of patients analyzed, reference standard, type of detection modalities and type of radiopharmaceuticals used in the study, absolute number of participants with TP, TN, FP and FN results. Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) criteria was used to assess the quality of each included studies, this quality scale includes components in terms of participant selection, index test, reference standard, as well as flow and timing [25]. Any disagreements occurred in the process of data extraction and quality assessments were resolved by consensus.

Statistical analysis

Data were analyzed employing the Stata version 15.0 software and Review Manager version 5.3 software at the study level. A p value <0.05 was considered to be statistically significant. We calculated pooled sensitivity, specificity, positive and negative likelihood ratio (LR), diagnostic odds ratio (DOR), and their respective 95% confidence intervals (CIs) and the area under the summary receiver operating characteristic (SROC) curve (AUC). The Cochran Q and the I^2 statistics were introduced to assess the heterogeneity of studies included on qualitative and quantitative basis. I^2 values within 0-25%, 25-50%, 50-75%, and 75-100% manifested insignificant, low, moderate, and high heterogeneity, respectively [26]. Funnel plots were conducted to qualitatively assess potential bias of publication, A Deeks' method was used to statistically test the asymmetry of the funnel plots and detect publication bias. Moreover, we used sensitivity analysis to evaluate the impacts of each single study on the pooled outcomes.

Results

Study selection and characteristics

A total of 367 articles were identified from the databases searched. Among them, 51 duplicates were removed and 254 studies were excluded through an initial screening. After a full text assessment for eligibility of the remaining 62 articles, 31 articles with 37 studies, 2577 patients with confirmed or suspected CA were identified for inclusion in this meta-analysis. No additional studies were found through reference screening of the included papers. **Figure 1** shows the flow of the database search and literature selection process. The quality of the included studies was regarded as high according to the QUADAS-2 scale (**Figure 2**). **Table 1** details the characteristics of studies included.

Diagnostic performance of noninvasive modalities

The numbers of studies included in the analysis of CMR, SPECT and PET were 8, 20 and 9, respectively. The pooled sensitivity of CMR, SPECT and PET were 0.84 [0.75, 0.90], 0.98 [0.94, 0.99] and 0.78 [0.54, 0.92], respectively. The overall specificities were 0.87 [0.77, 0.93], 0.92 [0.83, 0.97] and 0.83 [0.70, 0.91] for CMR, SPECT and PET, respectively. The AUC values of CMR, SPECT and PET were 0.92 [0.89, 0.94], 0.99 [0.98, 1.00] and 0.86 [0.82, 0.88] (**Figures 3-5**).

Diagnostic performance of prospective studies

With regard to prospective studies of these detection approaches, the respective overall sensitivities of CMR, SPECT and PET were 0.85 [0.76, 0.91], 0.98 [0.90, 0.99] and 0.85 [0.63, 0.95]. The pooled specificities were 0.89 [0.72, 0.96], 0.87 [0.73, 0.94] and 0.98 [0.68, 1.00] for CMR, SPECT and PET, respectively (**Supplementary Figures 1-3**). The AUC values of CMR, SPECT and PET were 0.92 [0.89, 0.94], 0.97 [0.96, 0.98] and 0.98 [0.97, 0.99].

Subgroup analysis of SPECT tracers

The numbers of studies using ^{99m}Tc -DPD, ^{99m}Tc -PYP, ^{99m}Tc -HMDP, and ^{99m}Tc -aprotinin for SPECT radiotracers were 5, 8, 5, and 2, respectively. Studies using ^{99m}Tc -aprotinin were not enrolled in pooled analysis for the inadequate number of studies. Overall results demonstrated that ^{99m}Tc -HMDP manifested the highest sensitivity (0.99 [0.83, 1.00]). ^{99m}Tc -PYP had the highest pooled specificity (0.95 [0.86, 0.99]). The pooled sensitivity of ^{99m}Tc -DPD and ^{99m}Tc -PYP reached 0.98 (**Supplementary Figures 4-6**). The AUC values of ^{99m}Tc -DPD, ^{99m}Tc -PYP, ^{99m}Tc -HMDP were 0.89 [0.86, 0.92], 0.99 [0.98, 1.00], and 0.99 [0.98, 1.00], respectively.

Subgroup analysis of PET tracers

The number of included studies using ^{11}C -PIB, ^{18}F -florbetaben, ^{18}F -flutemetamol, and ^{18}F -NaF for PET tracers were 4, 1, 1, and 3, respectively. Only PET studies utilizing ^{11}C -PIB was included in pooled analysis. It demonstrated a pooled sensitivity of 0.91 [0.81, 0.96], and its pooled specificity was 0.97 [0.81, 1.00] (**Supplementary Figures 7**). The AUC value of ^{11}C -PIB was 0.98 [0.97, 0.99]. Both the reported sensitivity and specificity of ^{18}F -florbetaben PET for the separation of patients with CA from patients without CA were 100%. The study of ^{18}F -flutemetamol showed a sensitivity of 0.17 with a high proportion of false-negative PET results.

Heterogeneity and publication bias

The I^2 values for meta-analysis of CMR were 64 (pooled sensitivity) and 61 (pooled specificity). The respective I^2 static for SPECT were 94 and 93. As for PET, the I^2 values for pooled analysis of sensitivity and pooled specificity were 84 and 0. Deek's funnel plot asymmetry tests for publication bias yielded p values of 0.89, 0.88, and 0.06 for CMR, SPECT and PET, which revealed that there may be no potential publication bias in the study.

Sensitivity Analysis

Sensitivity analysis was conducted to assess the potential influence of single study on the overall results. After omitting each study one by one, the pooled results of CMR, SPECT, PET and the corresponding subgroup analysis remained robust.

Discussion

Cardiac amyloidosis is part of systemic amyloidosis, it's characterized by the abnormal accumulation of amyloid fibrils within the extracellular of the myocardial tissue [27]. Accurate and timely confirmation of CA is of particular importance because cardiac involvement usually can be lethal [28]. Endomyocardial biopsy remains the gold standard for the detection and evaluation of prognosis of CA [29]. However, it's an invasive method and introduces potential damage to human body [30, 31]. Among those noninvasive modalities, cardiac ultrasound is widely used, but the diagnostic accuracy is relatively low [32]. It is reported that CMR manifested favorable sensitivity and specificity in the identification of CA regardless of its low cost-effectiveness [10, 33]. Furthermore, the administration of SPECT scans with ^{99m}Tc -DPD, ^{99m}Tc -PYP, ^{99m}Tc -HMDF revealed promising results [34–36]. Compared to SPECT, PET showed higher spatial resolution, it has been represented as a promising approach in the field of CA diagnosis [37–39].

Previous meta-analysis commonly focused on single detection tool of CA [19, 21–23]. We conducted a meta-analysis to directly compare the performance of CMR, SPECT and PET for the diagnosis of CA. The analysis was on the updated articles with respect to study design, type of radiotracers in SPECT and PET scans. This is one of the strengths of this study. It is worth noting 20 of the total 31 articles included in this meta-analysis were published in the years of 2019 and 2020, which indicated that noninvasive diagnostic modalities especially SPECT and PET scans have been extensively investigated. In general, results of this meta-analysis revealed that CMR, SPECT, and PET presented high sensitivity and specificity for the diagnosis of CA. The pooled sensitivity (0.92 [0.94, 0.99]) and specificity (0.92 [0.83, 0.97]) of SPECT scans were the highest. The AUC values of CMR, SPECT and PET were 0.92 [0.89, 0.94], 0.99 [0.98, 1.00] and 0.86 [0.82, 0.88], respectively. When prospective studies were considered, overall sensitivity of SPECT was still the highest (0.98 [0.90, 0.99]). Interestingly, PET scans showed the highest specificity (0.98 [0.68, 1.00]). On the basis of this difference in results, we can make a preliminary conclusion that the study design could be the source of heterogeneity of enrolled studies. Besides, results manifested ^{99m}Tc -HMDF had the highest sensitivity (0.99 [0.83, 1.00]), ^{99m}Tc -PYP had the highest pooled specificity (0.95 [0.86, 0.99]). ^{99m}Tc -PYP and ^{99m}Tc -HMDF revealed good diagnostic performance with AUC values of 0.99 [0.98, 1.00] and 0.99 [0.98, 1.00], respectively. As for PET scans, PET studies using ^{11}C -PIB was included in pooled analysis, both the pooled sensitivity and specificity reached more than 0.90, the AUC value of was surprisingly 0.98. One study reported that the sensitivity and specificity of ^{18}F -florbetaben PET for the detection of CA were 100%, the level of evidence in this study was relatively lower than a meta-analysis, and therefore a possibly pooled analysis of PET scans using ^{18}F -florbetaben is recommended in the future.

In this meta-analysis, we comprehensively searched the online database to enhance the possibility of retrieving as more eligible studies as we could. Two researchers independently performed the whole process of information extraction under the guidance of the study protocol. Moreover, the heterogeneity between the studies included were assessed using statistical methods. In general, there existed significant heterogeneities among studies. The sources of heterogeneity may be attributed to difference in the year of publication, study design (as mentioned above), and patient characteristics. We indented to conduct meta-regression to explore the possible origins of heterogeneity, unfortunately, the numbers of PET and CMR studies was insufficient to complete meta-regression. The underlying sources of heterogeneity would be investigated in further studies. Moreover, results of sensitivity analysis claimed that after omitting individual study one after another, the pooled indicators were robust in this study. The Deek's funnel plot asymmetry tests for publication bias revealed that there may not be publication bias in the meta-analysis. Despite the existence of heterogeneity, we may conclude based on the pooled results that this analysis could provide evidence-based information for scientific research and practical applications in the process of CA diagnosis. As far as scientific research is concerned, prospective studies and PET radiotracers with higher spatial resolution need to be further investigated on the basis of results of this meta-analysis. Meta-analysis with larger sample-sized and amount of studies are recommended. With regard to applications in clinical settings, decision-making of practitioners in the diagnosis of CA should be made according to technical merit, consideration of cost-effectiveness, and the availability of specific modalities. In order to enhance diagnostic accuracy of CA, if possible, the combination of different diagnostic tools is recommended.

Abbreviations

CA, Cardiac amyloidosis

AL, systemic light chain amyloidosis

ATTR, transthyretin amyloidosis

CMR, cardiac magnetic resonance

SPECT, single photon emission computed tomography

PET, positron emission tomography

CT, computerized tomography

PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-analysis

TP, true positive

FP, false positive

TN, true negative

FN, false negative

PPV, positive predictive value

NPV, negative predictive value

DOR, diagnostic odds ratio

CI, confidence interval

SROC, summary receiver operating characteristic

AUC, area under the SROC curve

QUADAS-2, Quality Assessment of Diagnostic Accuracy Studies-2

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and/or analysed during the current study available from the corresponding author on reasonable request.

Competing interests

The authors declare that they have no competing interests.

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There is no fund support for this study.

Authors' Contributions

ZW conceived and designed this study. ZW and CY were responsible for the collection, extraction, and analysis of the data. ZW was responsible for data analysis and writing the paper. CY performed the quality evaluation of the writing and polished the English language. All authors reviewed the paper and reached an agreement to approve the final manuscript.

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Not applicable.

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Tables

Table 1. Study characteristics

Name of the first author	Year of publication	No. of participants	Men (%)	Age (SD or IQR)	Population	Study design	Reference test	Modalities	Image analysis	Trials
Abulizi	2019	27	70	70 (12)	Known or suspected CA	Prospective	Myocardial histology	PET	Semiquantitative	18
Aquaro	2014	79	61	69 (10)	Known CA	Prospective	Myocardial histology electrocardiographic criteria	CMR	Qualitative	N/A
Asif	2020	133	53	76 (12)	Suspected CA	Retrospective	Myocardial histology	SPECT	Semiquantitative	99
Awaya	2020	10	70	61 (12)	Suspected CA	Prospective	Myocardial histology	SPECT	Qualitative	99 articles
Baggiano	2020	436	66	67 (13)	Suspected CA	Prospective	Myocardial histology	CMR	Qualitative	N/A
Baroni	2018	21	74	58 (12)	Suspected CA	Prospective	Myocardial histology	CMR	Qualitative	N/A
Bellevre	2020	30	53	84 (7)	Suspected CA	Retrospective	Myocardial histology	SPECT	Semiquantitative	99
Bhatti	2016	126	64	63 (10)	Suspected CA	Retrospective	Myocardial histology	CMR	Qualitative	N/A
Cappelli	2019	85	79	77 (9)	Suspected CA	Retrospective	Myocardial histology	SPECT	Semiquantitative	99
Ezawa	2018	18	61	51 (15)	Known or suspected CA	Prospective	Myocardial histology	PET	Qualitative	11
Flaherty	2020	43	7	77 (9)	Suspected CA	Prospective	Myocardial histology	SPECT	Quantitative	99
Gallini	2019	76	80	77 (8)	Known or suspected CA	Retrospective	Myocardial histology	SPECT	Semiquantitative	99
Gillmore	2016	374	NR	NR	Known or suspected CA	Prospective	Myocardial histology and genetic findings	SPECT	Qualitative	99
Karamitsos	2013	53	66	62 (11)	Known or suspected CA	Prospective	Myocardial histology	CMR	Qualitative	N/A
Kircher	2019	21	64	65 (14)	Suspected CA	Prospective	Myocardial histology	CMR	Qualitative	N/A
Lee	2015	19	46	65 (10)	Suspected CA	Prospective	Myocardial histology	CMR	Qualitative	N/A
Malka	2020	308	75	73 (8)	Known CA and controls	Retrospective	Myocardial histology	SPECT	Semiquantitative	99
Martineau	2019	7	100	76 (7)	CA	Retrospective	Myocardial histology	PET	Qualitative	18
Masri	2020	233	69	77 (14)	Suspected CA	Prospective	Diffuse myocardial uptake	SPECT	Semiquantitative	99
Minamimoto	2020	9	67	64 (14)	Suspected CA	Prospective	Myocardial histology	SPECT	Qualitative	99 articles
Moore	2017	21	91	NR	Suspected CA	Prospective	Myocardial histology	SPECT	Semiquantitative	99
Papantoniou	2015	12	67	69 (12)	Suspected CA	Prospective	Myocardial histology	SPECT	Semiquantitative	99
Papathanasiou	2020	17	88	71 (9)	Known CA and controls	Retrospective	Myocardial histology	PET	Qualitative	18 full-text
Poterucha	2020	91	84	72 (9)	Suspected CA	Retrospective	Myocardial histology	SPECT	Qualitative	99
Rapezzi	2011	63	62	53 (41-	Known or suspected	Prospective	Myocardial histology	SPECT	Qualitative	99

				66)	CA					
Régis	2020	40	73	75 (10)	Suspected CA	Retrospective	H/CL ratio	SPECT	Qualitative	99
Rosengren	2020	51	73	69 (13)	Known and suspected CA	Prospective	Myocardial histology	PET	Qualitative	11
Sperry	2020	100	75	77 (72- 82)	Suspected CA	Retrospective	Semiquantitative grade and H/CL ratio	SPECT	Semiquantitative	99
White	2014	25	58	62 (13)	Suspected CA	Prospective	Myocardial histology	CMR	Semiquantitative	N.
Wollenweber	2020	32	722	73 (11)	Suspected CA	Prospective	Myocardial histology	SPECT	Qualitative	99
Zhang	2020	17	94	77 (8)	Known and suspected CA	Prospective	Myocardial histology	PET	Qualitative	18

CA, Cardiac amyloid. SD, standard deviation. IQR, interquartile range. CMR, cardiac magnetic resonance. SPECT, single photon emission computed tomography. PET, positron emission tomography. NR, not reported. NA, not applicable.

Figures

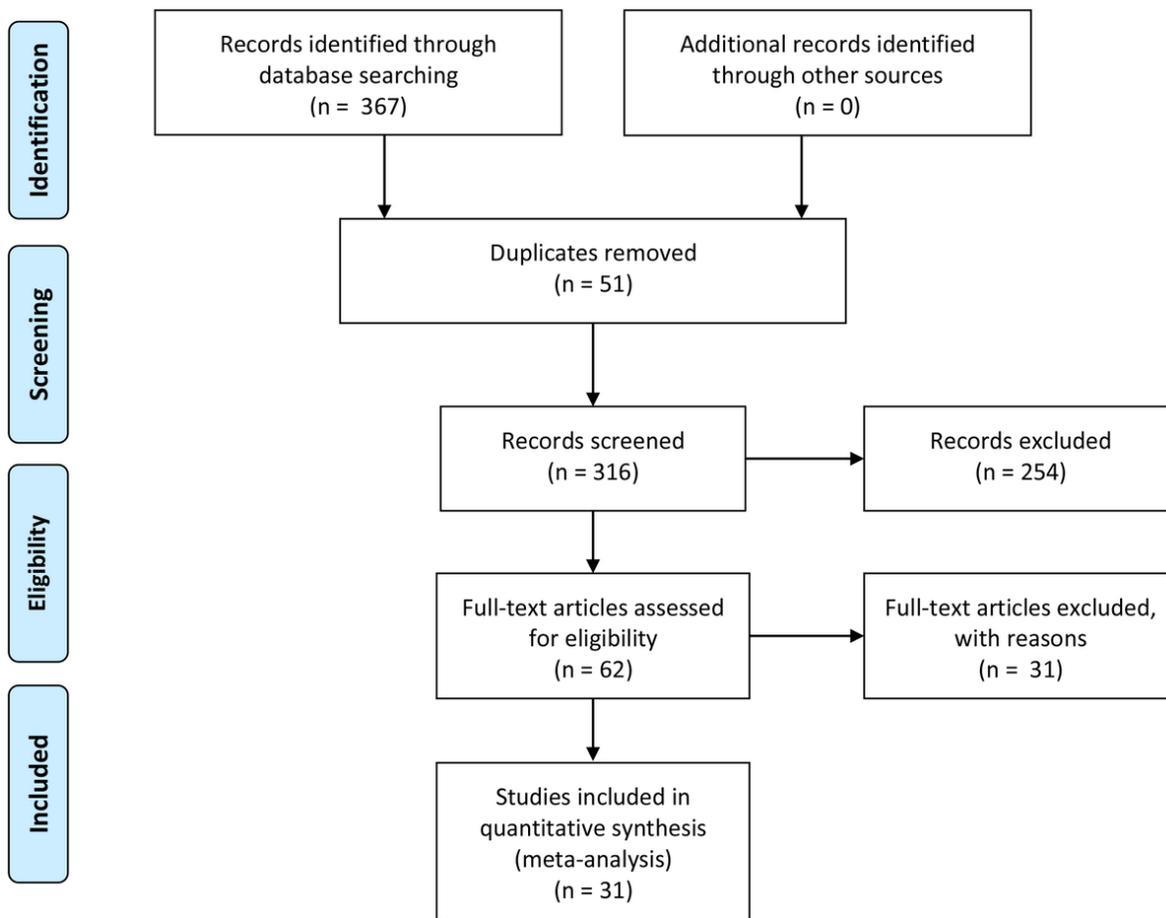


Figure 1

Search results and flow chart of the meta-analysis.

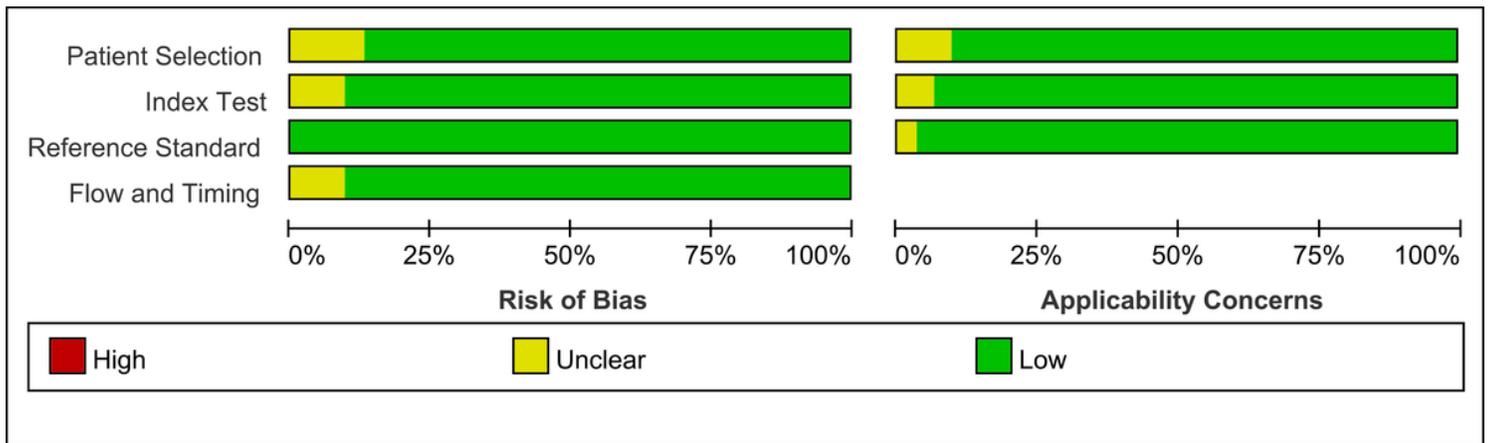


Figure 2

Risks of bias and applicability concerns on the QUADAS-2 tool of the enrolled studies.

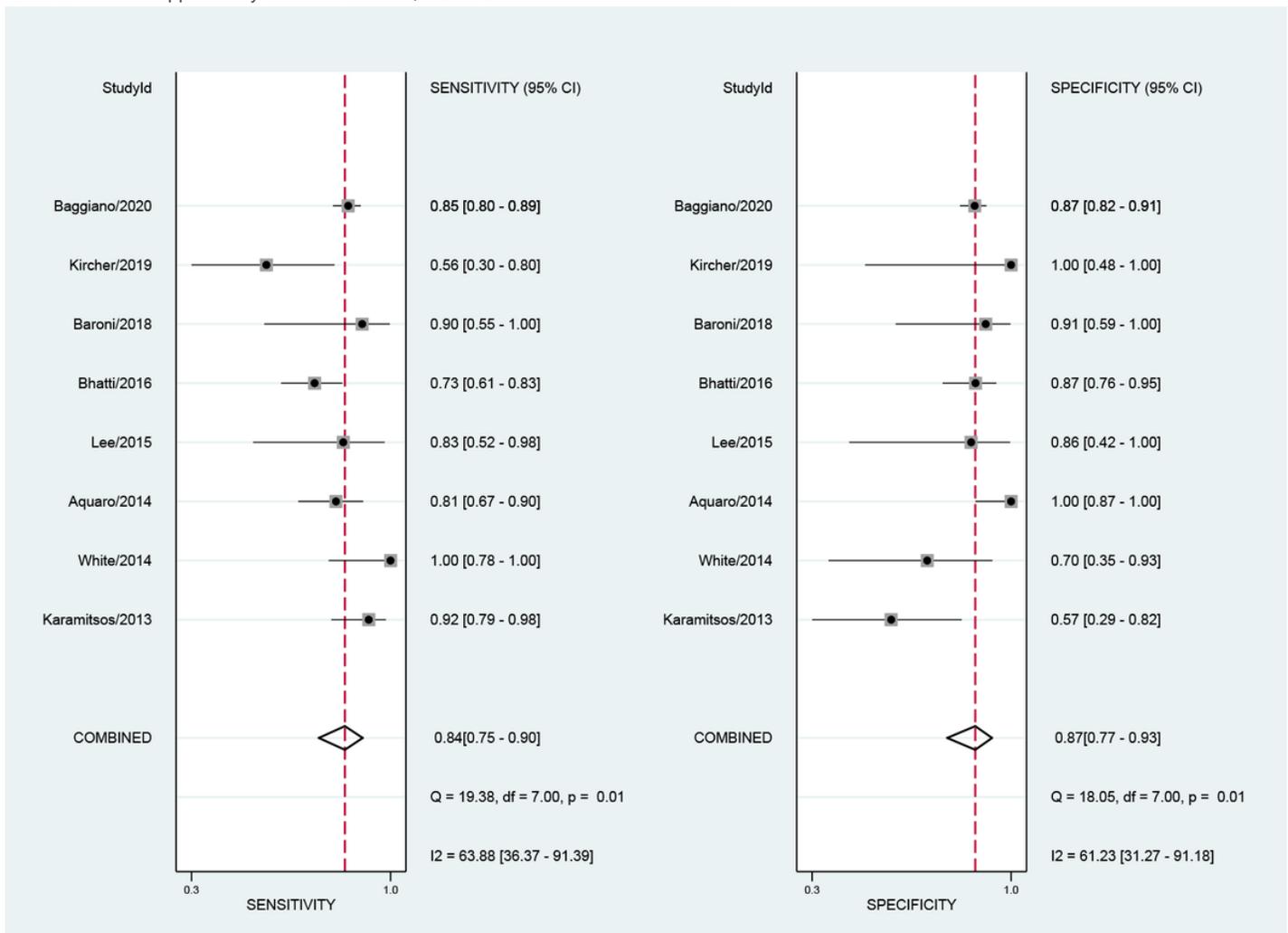


Figure 3

Forest plot for diagnostic performance of CMR

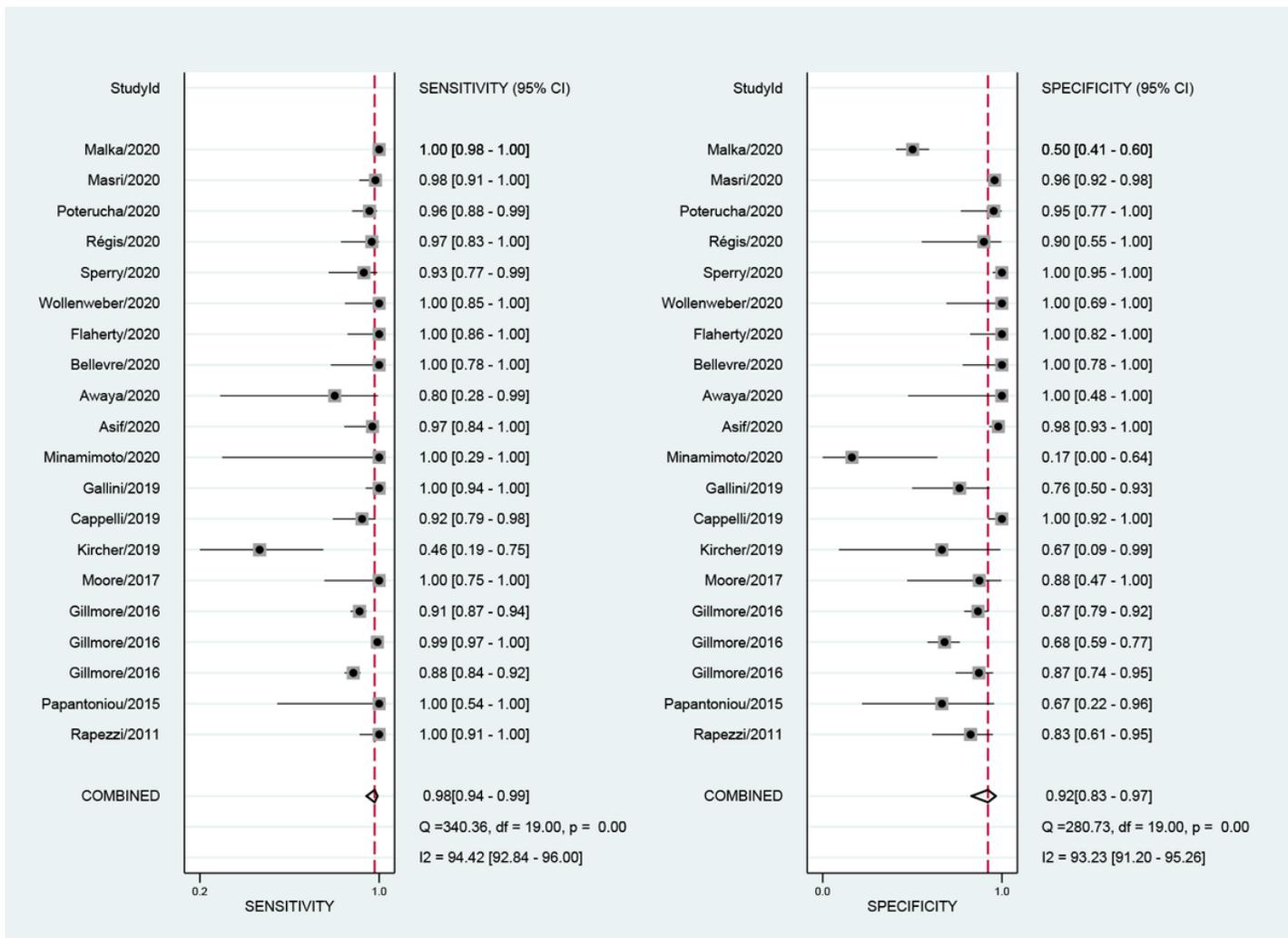


Figure 4

Forest plot for diagnostic performance of SPECT

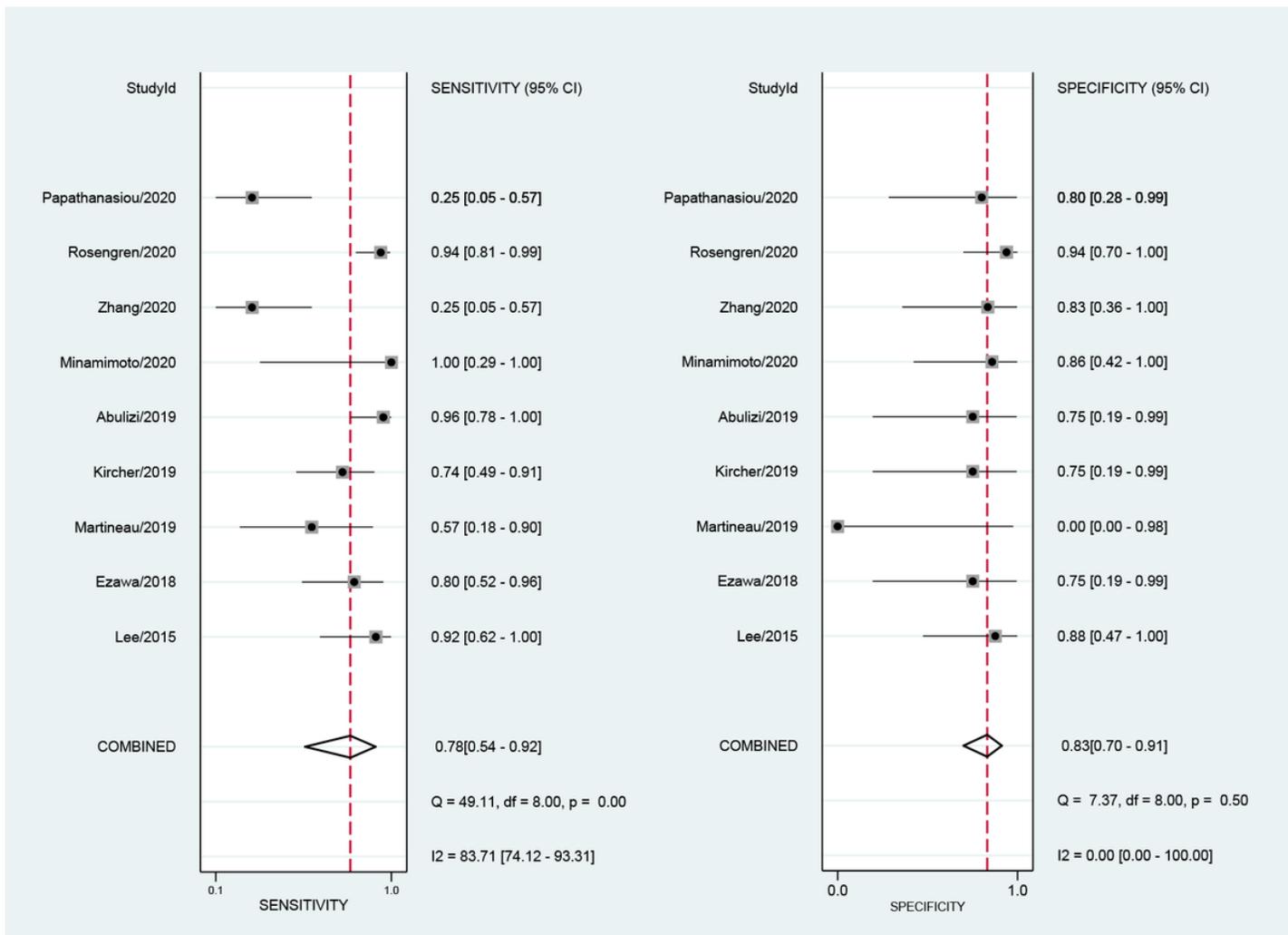


Figure 5

Forest plot for diagnostic performance of PET

Supplementary Files

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