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 amyloidosis (CA). The purpose of this study is to directly compare CMR, SPECT, and PET 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-HMPDP 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-HMPDP 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 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 nosetologies, 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-HMPDP)) 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.

Data 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.

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-HMDP 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 (0.98 [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-HMDP 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-HMDP 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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References

1. Merlini G, Bellotti V: Molecular mechanisms of amyloidosis. The New England journal of medicine 2003, 349(6):583-596.
2. Martinez-Naharro A, Hawkins PN, Fontana M: Cardiac amyloidosis. Clinical medicine (London, England) 2018, 18(Suppl 2):s30-s35.
3. Fontana M, Banypersad SM, Treibel TA, Abdel-Gadir A, Maestrini V, Lane T, Gilbertson JA, Hutt DF, Lachmann HJ, Whelan CJ et al: Differential Myocyte Responses in Patients with Cardiac Transthyretin Amyloidosis and Light-Chain Amyloidosis: A Cardiac MR Imaging Study. Radiology 2015, 277(2):388-397.
4. Zhang KW, Stockerl-Goldstein KE, Lenihan DJ: Emerging Therapeutics for the Treatment of Light Chain and Transthyretin Amyloidosis. JACC Basic to translational science 2019, 4(3):438-448.
5. Bhogal S, Ladia V, Sitwala P, Cook E, Bajaj K, Ramu V, Lavie CJ, Paul TK: Cardiac Amyloidosis: An Updated Review With Emphasis on Diagnosis and Future Directions. Current problems in cardiology 2018, 43(1):10-34.
6. Singh V, Falk R, Di Carli MF, Kijewski M, Rapezzi C, Dorbala S: State-of-the-art radionuclide imaging in cardiac transthyretin amyloidosis. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology 2019, 26(1):158-173.
7. Bokhari S, Shahzad R, Castaño A, Maurer MS: Nuclear imaging modalities for cardiac amyloidosis. Journal of nuclear cardiology: official publication of the American Society of Nuclear Cardiology 2014, 21(1):175-184.
8. Yang M, Arsanjani R, Roarke MC: Advanced Nuclear Medicine and Molecular Imaging in the Diagnosis of Cardiomyopathy. AJR American journal of roentgenology 2020, 215(5):1208-1217.

9. Austin BA, Tang WH, Rodriguez ER, Tan C, Flamm SD, Taylor DO, Starling RC, Desai MY: Delayed hyper-enhancement magnetic resonance imaging provides incremental diagnostic and prognostic utility in suspected cardiac amyloidosis. JACC Cardiovascular imaging 2009, 2(12):1369-1377.

10. Maceira AM, Joshi J, Prasad SK, Moon JC, Perugini E, Harding I, Sheppard MN, Poole-Wilson PA, Hawkins PN, Pennell DJ: Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation 2005, 111(2):186-193.

11. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, Kotecha T, Francis R, Hutt DF, Rezk T et al: Magnetic Resonance in Transthyretin Cardiac Amyloidosis. Journal of the American College of Cardiology 2017, 70(4):466-477.

12. Treglia G, Glaudemans A, Bertagna F, Hazenberg BPC, Erba PA, Giubbini R, Ceriani L, Prior JO, Giovanella L, Slart R: Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. European journal of nuclear medicine and molecular imaging 2018, 45(11):1945-1955.

13. Ramsay SC, Cuscaden C: The current status of quantitative SPECT/CT in the assessment of transthyretin cardiac amyloidosis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020, 27(5):1464-1468.

14. Masri A, Bukhari S, Eisele YS, Soman P: Molecular Imaging of Cardiac Amyloidosis. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2020, 61(7):965-970.

15. Dorbala S, Vangala D, Semer J, Strader C, Bruyere JR, Jr., Di Carl MF, Moore SC, Falk RH: Imaging cardiac amyloidosis: a pilot study using ⁹⁹mTc-aptospentin SPECT/CT: a pilot study. Mayo Clinic proceedings 2019, 94(4):915-922.

16. Minamimoto R, Awaya T, Iwama K, Hotta M, Nakajima K, Hirai R, Okazaki O, Hiroi Y: Significance of (11)C-PiB PET/CT in cardiac amyloidosis compared with (99mTc)-aptomatrin scintigraphy: A pilot study. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020, 27(1):202-209.

17. Law WP, Wang WY, Moore PT, Mollee PN, Ng AC: Cardiac Amyloid Imaging with 18F-Florbetaben PET: A Pilot Study. Journal of nuclear medicine : official publication, Society of Nuclear Medicine 2016, 57(11):1733-1739.

18. Kircher M, Ihne S, Brumberg J, Morbach C, Knop S, Bucman K, Reiter T, Bauer WR et al: Detection of cardiac amyloidosis with 18F-Florbetaben-PET/CT in comparison to echocardiography, cardiac MRI and DPD-scintigraphy. European journal of nuclear medicine and molecular imaging 2019, 46(7):1407-1416.

19. Zhao L, Tian Z, Fang Q: Diagnostic accuracy of cardiovascular magnetic resonance for patients with suspected cardiac amyloidosis: a systematic review and meta-analysis. BMC cardiovascular disorders 2016, 16:129.

20. Wang TKM, Brizneda MW, Kwon DH, Popovic ZB, Flamm SD, Hanna M, Griffin BP, Xu B: Reference Ranges, Diagnostic and Prognostic Utility of Native T1 Mapping and Extracellular Volume for Cardiac Amyloidosis: A Meta-Analysis. Journal of magnetic resonance imaging : JMRI 2020.

21. Pan JA, Kerwin MJ, Salerno M: Native T1 Mapping, Extracellular Volume Mapping, and Late Gadolinium Enhancement in Cardiac Amyloidosis: A Meta-Analysis. JACC Cardiovascular imaging 2020, 13(6):1299-1310.

22. Kim YJ, Ha S, Kim YI: Cardiac amyloidosis imaging with amyloid positron emission tomography: A systematic review and meta-analysis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020, 27(1):123-132.

23. Kim SH, Kim YS, Kim SJ: Diagnostic performance of PET for detection of cardiac amyloidosis: A systematic review and meta-analysis. Journal of cardiology 2020, 76(6):618-625.

24. Moher D, Liberati A, Tetzlaff J, Altman DG: Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. International journal of surgery (London, England) 2010, 8(5):336-341.

25. Reitsma JB, Moons KG, Bossuyt PM, Linnet K: Systematic reviews of studies quantifying the accuracy of diagnostic tests and markers. Clinical chemistry 2012, 58(11):1534-1545.

26. Cumpston M, Li T, Page MJ, Chandler J, Welch VA, Higgins JP, Thomas J: Updated guidance for trusted systematic reviews: a new edition of the Cochrane Handbook for Systematic Reviews of Interventions. The Cochrane database of systematic reviews 2019, 10 Ed000142.

27. Cuddy S, Dorbala S, Di Carli MF: Imaging of cardiac amyloidosis: Will this become a unique application for dual-isotope imaging? Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020, 27(1):38-40.

28. Hotta M, Minamimoto R, Awaya T, Hiroe M, Okazaki O, Hiroi Y: Radionuclide Imaging of Cardiac Amyloidosis and Sarcoidosis: Roles and Characteristics of Various Tracers. Radiographics : a review publication of the Radiological Society of North America, Inc 2020, 40(7):2029-2041.

29. From AM, Małeżewski JJ, Rihal CS: Current status of endomyocardial biopsy. Mayo Clinic proceedings 2011, 86(11):1095-1102.

30. Donnelly JP, Hanna M: Cardiac amyloidosis: An update on diagnosis and treatment. Cleveland Clinic journal of medicine 2017, 84(12 Suppl 3):12-26.

31. Siddiqi OK, Ruberg FL: Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. Trends in cardiovascular medicine 2018, 28(1):10-21.

32. Barbero U, Desteфанис P, Pozzi P, Longo F, Piga A: Exercise Stress Echocardiography with Tissue Doppler Imaging (TDI) Detects Early Systolic Dysfunction in Beta-Thalassemia Major Patients without Cardiac Iron Overload. Mediterranean journal of hematology and infectious diseases 2012, 4(1):e2012037.

33. Maurer MS, Ruberg FL, Weinsaft JW: More Than Meets the Eye: Time for a New Imaging Paradigm to Test for Cardiac Amyloidosis. J Card Fail 2018, 24(2):87-89.

34. Sperry BW, Burgett E, Bybee KA, McGhie AI, O’Keefe JH, Saeed IM, Thompson RC, Bateman TM: Technetium pyrophosphate nuclear scintigraphy for cardiac amyloidosis: Imaging at 1 vs 3 hours and planar vs SPECT/CT. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020, 27(5):1802-1807.
35. Malka N, Abulizi M, Kharoubi M, Oghina S, Galat A, Le Bras F, Moktefi A, Guendouz S, Molinier-Frenkel V, Fanen P et al. Extracardiac soft tissue uptake, evidenced on early (99m)Tc-HMDP SPECT/CT, helps typing cardiac amyloidosis and demonstrates high prognostic value. European journal of nuclear medicine and molecular imaging 2020, 47(10):2396-2406.

36. Wollenweber T, Rettl R, Kretschmer-Chott E, Rasul S, Kulterer O, Rainer E, Raidl M, Schaffarich MP, Matschitsch S, Stadler M et al. In Vivo Quantification of Myocardial Amyloid Deposits in Patients with Suspected Transthyretin-Related Amyloidosis (ATTR). Journal of clinical medicine 2020, 9(11).

37. Zhang LX, Martineau P, Finnerty V, Giraldeau G, Parent MC, Harel F, Pelletier-Galameau M: Comparison of 18F-sodium fluoride positron emission tomography imaging and 99mTc-pyrophosphate in cardiac amyloidosis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020.

38. Rosengren S, Skibsted Clemmensen T, Tolbod L, Granstam SO, Eiskjaer H, Wikstrom G, Vedin O, Kero T, Lubberink M, Harms HJ et al. Diagnostic Accuracy of [(11)C]PIB Positron Emission Tomography for Detection of Cardiac Amyloidosis. JACC Cardiovascular imaging 2020, 13(6):1337-1347.

39. Papathanasiou M, Kessler L, Carpinteiro A, Hagenacker T, Nensa F, Umutlu L, Forsting M, Brainman A, Kleinschnitz C, Antoch G et al. (18)F-flutemetamol positron emission tomography in cardiac amyloidosis. Journal of nuclear cardiology : official publication of the American Society of Nuclear Cardiology 2020.

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 | Ti |
|-------------------------|---------------------|---------------------|---------|----------------|------------|-------------|----------------|------------|---------------|----|
| 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 | Ns |
| 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 |
| Baggiano                | 2020                | 436                 | 66      | 67 (13)        | Suspected CA | Prospective  | Myocardial histology | CMR  | Qualitative | Ns |
| Baroni                  | 2018                | 21                  | 74      | 58 (12)        | Suspected CA | Prospective  | Myocardial histology | CMR  | Qualitative | Ns |
| 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 | Ns |
| 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 | Ns |
| Kircher                 | 2019                | 21                  | 64      | 65 (14)        | Suspected CA | Prospective  | Myocardial histology | CMR  | Qualitative | Ns |
| Lee                     | 2015                | 19                  | 46      | 65 (10)        | Suspected CA | Prospective  | Myocardial histology | CMR  | Qualitative | Ns |
| 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 |
| Moore                   | 2017                | 21                  | 91      | NR             | Suspected CA | Prospective  | Myocardial histology | SPECT | Semiquantitative | 99 |
| Papantonioiu            | 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 |
| Poterucha               | 2020                | 91                  | 84      | 72 (9)         | Suspected CA | Retrospective | Myocardial histology | SPECT | Qualitative | 99 |
| Rapezzi                 | 2011                | 63                  | 62      | 53 (41-99)     | Known or suspected CA | Prospective  | Myocardial histology | SPECT | Qualitative | 99 |
| Last name | Year | N   | Age | Diagnosis | Time | Methodology | CA category | Test | Quantitative | 99 |
|-----------|------|-----|-----|-----------|------|-------------|-------------|------|--------------|----|
| 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**

![Flowchart Image]

**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

This is a list of supplementary files associated with this preprint. Click to download.

- SupplementaryFigure1.tif
- SupplementaryFigure2.tif
- SupplementaryFigure3.tif
- SupplementaryFigure4.tif
- SupplementaryFigure5.tif
- SupplementaryFigure6.tif
- SupplementaryFigure7.tif