Diagn Interv Radiol 2021; 27:802–810

NUCLEAR MEDICINE AND MOLECULAR IMAGING

REVIEW

Performance of bone tracer for diagnosis and differentiation of transthyretin cardiac amyloidosis: a systematic review and meta-analysis

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PURPOSE
Bone tracers have been validated for many years in detecting transthyretin cardiac amyloidosis (TTR-CA). However, several new studies suggest conflicting results. Our study aimed to systematically evaluate the accuracy of bone radiotracers for diagnosis and differentiation of TTR-CA via a systematic review and meta-analysis.

METHODS
We retrieved articles assessing the performance of bone tracer in diagnosing and differentiating TTR-CA from PubMed, the Cochrane Library, ScienceDirect, and DOAJ databases, dating up to 10 July 2020. The meta-analysis was conducted through Stata 16 software, and the risk of bias for the included studies was assessed by the QUADAS-2 tool. Moreover, we made a comprehensive review.

RESULTS
Fourteen articles were included in the systematic review, and 9 in the meta-analysis. The pooled sensitivity was 0.97 (95% confidence interval [95% CI] 0.85–0.99) with heterogeneity (I^2=73.5, 95% CI 55.6–91.2), and the specificity was 0.92 (95% CI 0.82–0.96) with heterogeneity (I^2=42.0, 95% CI 0.0–86.9). The pooled positive and negative likelihood ratios were 11.49 (95% CI 5.07–26.0) and 0.03 (95% CI 0.01–0.18), respectively. The diagnostic odds ratio was 341 (95% CI 53–2194), and the area under the receiver operating characteristic curve was 0.96 (95% CI 0.94–0.97).

CONCLUSION
The findings evidence that the bone radiotracer is a valuable noninvasive approach that provides high accuracy for diagnosing TTR-CA and plays a modest role in differentiating TTR-CA from immunoglobulin amyloid light-chain cardiac amyloidosis. ^{99m}Tc-HMDP may be more accurate than ^{99m}Tc-PYP, ^{99m}Tc-DPD, and ^{18}F-NaF in the TTR-CA detecting process, and ^{18}F-NaF is a promising bone tracer to diagnose and differentiate TTR-CA.

Cardiac amyloidosis (CA) is a group of fatal diseases with poor prognosis (1, 2), which occurs when amyloid (misfolded protein fragments) are deposited in the myocardial extracellular matrix, small blood vessels, and the conduction system (1, 2). The two most frequent types of CA are transthyretin CA (TTR-CA) and immunoglobulin amyloid light-chain CA (AL-CA) (1–5). TTR-CA could be acquired from the aggregation of wildtype TTR (TTRwt), mutant TTR (TTRm), and other types of TTR (3–6). Without typical symptoms, TTR-CA is easily misdiagnosed and underdiagnosed (7, 8), especially in the early stage. From the clinical perspective, doctors often get frustrated in diagnosing TTR-CA and distinguishing TTR-CA from AL-CA, which would delay the optimal treatment and lead to poor prognosis (2).

The well-known gold standard for diagnosing TTR-CA depends on endomyocardial biopsy (EMB) (1, 7, 9). Other diagnostic criteria have also been considered (6, 10, 11), such as biopsies from involved organs combined with significant echocardiography findings. Early diagnosis and differentiation of TTR-CA are crucial for the treatment and prognosis (7, 11). Although biopsy combined with additional measures (genotyping or immunohistochemistry) can diagnose and differentiate TTR-CA, biopsy, especially the EMB, cannot be used as a routine procedure due to its possible invasive complications (1–5). Recently, plenty of studies on noninvasive examinations emerged, trying to discuss the early diagnosis of TTR-CA

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Received 19 August 2020; revision requested 17 September 2020; last revision received 1 December 2020; accepted 1 December 2020.

Published online 4 November 2021.

DOI 10.5152/dir.2021.20662

You may cite this article as: Zhao H, Hu H, Cui W. Performance of bone tracer for diagnosis and differentiation of transthyretin cardiac amyloidosis: a systematic review and meta-analysis. Diagn Interv Radiol 2021; 27:802–810.

and the differentiation between TTR-CA and AL-CA (10, 12–26). The most representative method is the application of gamma-emitting bone tracers, such as ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (^{99m}Tc-DPD), ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMDP) (12–24). Besides, the positron emission tomography (PET) bone tracer ^{18}F-sodium fluoride (^{18}F-NaF) has also been used to explore the diagnosis and differentiation of TTR-CA (25, 26).

Most studies suggest that bone tracers can diagnose and differentiate TTR-CA. A prior meta-analysis has partly reported the diagnostic accuracy of gamma-emitting bone tracers in TTR-CA (27). Nevertheless, the differentiation of TTR-CA from AL-CA was not fully elaborated, and it did not provide a systematic review and include the positron-emitting bone tracer ^{18}F-NaF. More importantly, several new studies have indicated that bone radiotracers present suboptimal sensitivity in detecting some TTR-CA (28, 29), which contradicts previous analyses. Therefore, we sought to provide further evidence on the role of bone tracers in TTR-CA diagnosis and CA subtype differentiation by performing a more comprehensive systematic review and a meta-analysis.

Main points

- Bone tracers provide high accuracy in diagnosing transthyretin cardiac amyloidosis (TTR-CA).
- Bone tracers present modest role for differentiating TTR-CA from immunoglobulin amyloid light-chain cardiac amyloidosis.
- Positron-emitting radiotracer ^{18}F-NaF is promising to diagnose and differentiate TTR-CA.
- Bone tracers could help guide clinical practice and even monitor response to therapy.
- Some new studies suggest that bone tracers present suboptimal sensitivity in detecting some TTR-CA, which is an issue that requires further investigations.

Methods

Study design

The current study was performed in accordance with the Preferred Reporting Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) 2015 (30) and the guideline of Systematic Review and Meta-analysis of Diagnostic Studies (31). Two independent authors participated in the whole process of literature searching and screening, data extraction, quality evaluation, and statistical analysis. Discrepancies were resolved by discussions with the corresponding author.

Data sources and retrieval strategy

We thoroughly examined PubMed and the Cochrane Library database for English-language literature from inception to 20 July 2020; ScienceDirect and DOAJ were used as supplementary databases. We also reviewed and searched the references of retrieved literature to ensure the complete inclusion of all relevant studies.

We used a combination of terms when searching PubMed and the Cochrane Library database: 1) "Amyloidosis" OR "Amyloid" AND 2) "Transthyretin" OR "TTR" OR "ATTR" AND 3) "Cardiac" OR "Myocardial" OR "Myocardium" OR "Cardiomyopathy" OR "Heart" AND 4) "Scintigraphy" OR "Scan" OR "Bone" OR "Skeleton" OR "Tracer" OR "Radiotracer". Keywords related to bone tracer for diagnosis of TTR-CA were also used in searching the ScienceDirect and DOAJ databases.

Eligibility criteria and study selection

The inclusion criteria were: 1) studies regarding bone tracer in diagnosing TTR-CA patients; 2) TTR-CA patients defined by biopsy and genotyping/immunohistochemistry; 3) subject groups including TTR-CA and AL-CA; 4) studies reporting more than 10 subjects; 5) the reported data could be derived to calculate sensitivity, specificity, and other extended indicators (such as positive and negative likelihood ratio). The exclusion criteria were: 1) duplicate literatures; 2) abstracts, book chapters, case reports, comments, conference articles, editorials or letters, review articles, and other unrelated articles; 3) articles irrelevant to the interest of this study; 4) language not in English. Articles were rejected if considered ineligible.

Data extraction and quality assessment

Variables were collected from included studies as follows: the first author, publication year, journal, population demographics (mean age, gender ratio, number of subjects enrolled and excluded), study characteristics (prospective or retrospective, blind or not, diagnostic criteria, types of CA), and image characteristics (bone tracer, time of image acquisition after injection, type of scintigraphic acquisition, image analysis). The number of true-positive, false-positive, false-negative, and true-negative scintigraphy results for diagnosing TTR-CA was extracted from each study. Studies with overlapping patient data, those with non-CA patients mixed in the subject groups, and those with unknown genotype in the groups were excluded from the meta-analysis. The methodological quality of available researches was evaluated by a checklist based on the Quality Assessment of Diagnostic Accuracy Studies-2 (QUADAS-2) (32).

Statistical analysis

Statistical analysis was performed using Stata (version 16.0; StataCorp LP). We calculated sensitivity, specificity, positive likelihood ratios (PLR), and negative likelihood ratios (NLR) (33) from the data extracted for TTR-CA diagnosed by bone tracers, with the corresponding 95% confidence interval (95% CI). The diagnostic odds ratio (DOR) (34) was obtained with 95% CI as well. As a measure of test performance, higher values of DOR indicate better discrimination. With the area under the curve (AUC) (35), we constructed the summary receiver operating characteristic curve (SROC) (36) to estimate the overall diagnostic efficacy. The SROC curve is a smooth curve based on data points of included studies, which reflects the pooled accuracy of the analysis. Furthermore, we computed the diagnostic accuracy of different bone tracers in TTR-CA by sub-analysis. Differential diagnostic value of TTR-CA from AL-CA was analyzed as well. Deeks' method was applied to examine the possible publication bias using the funnel plot (37). The heterogeneity of included studies was assessed in terms of Cochran's Q test and I^2 statistics (38). Specifically speaking, I^2 of 25%–50%, 50%–75%, and >75% represent a low, moderate, and high degree of heterogeneity, respectively (38, 39).

Results

After a systematic database search, we screened 599 potentially relevant articles and removed 141 duplicates first. Of the remaining 458 pieces, 212 records (30 abstracts, 56 case reports, 34 correspondences/letters, 24 editorials, 21 book chapters, and 47 discussions/other short articles) were ruled out through their titles and abstracts. Then we excluded 114 reviews and 92 irrelevant articles and eliminated 26 full-texts due to their insufficient data for our calculation. Finally, 14 articles (12–25) were included for the systematic review. Af-

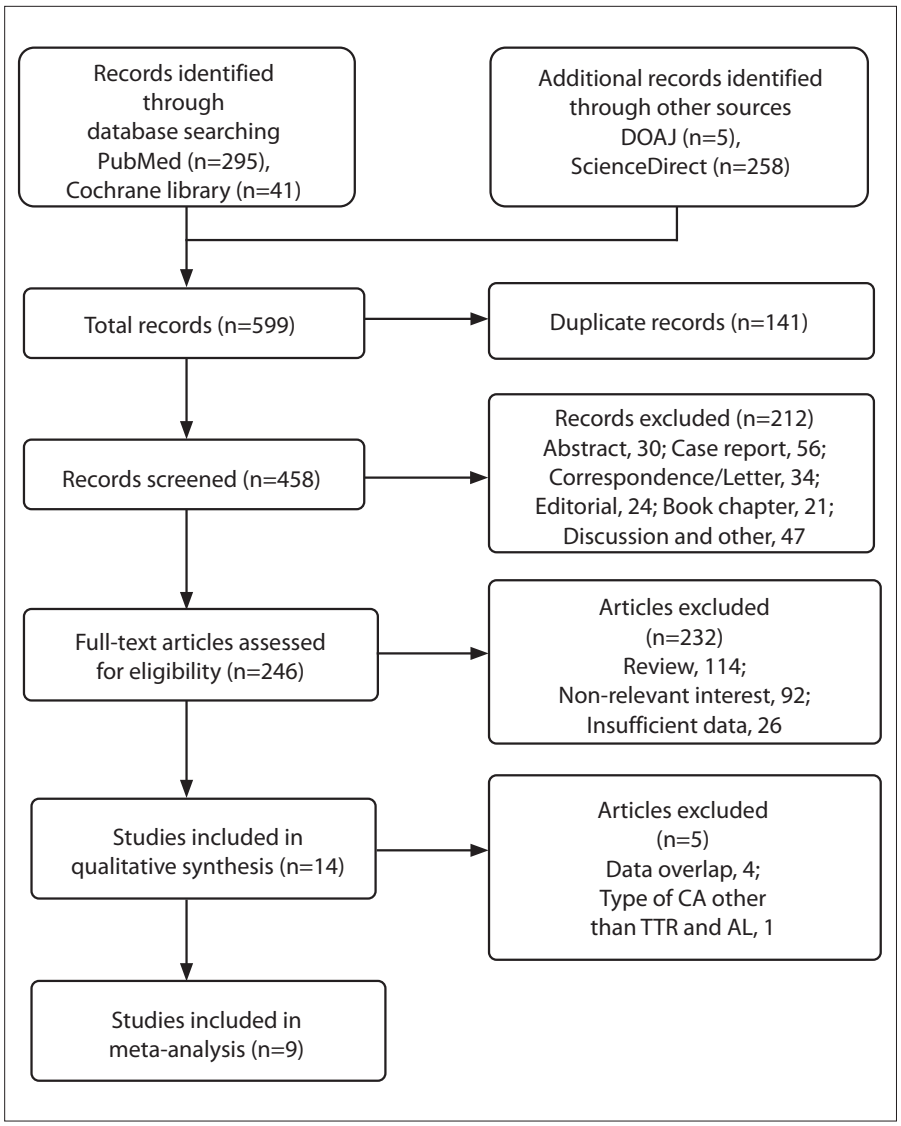

Figure 1. Flow chart describing the literature search and selection process.

ter rejecting 5 articles, four (14, 17, 18, 24) rejected for data overlap and one (20) for containing unknown type of CA different than TTR-CA with AL-CA, 9 articles (12, 13, 15, 16, 19, 21–23, 25) were eligible for the meta-analysis. No supplementary articles were found from the references of these studies. The detailed literature retrieval and screening process is shown in Fig. 1.

Fourteen studies (12–25), published from 2005 to 2020, were selected for the systematic review. The mean age of patients in the studies ranged from 58 to 76 years, with the exception of one study (17) that did not mention age; the percentage of males ranged from 58% to 90%, while two articles (17, 24) did not mention sex ratio. The majority of studies (71.4%) were retrospectively designed, with only 4 studies employing prospective design (12, 15, 18, 21); overall, 8 studies (57.1%) complied with the blind principle (12, 15, 18, 20, 21, 23–25). Five studies included patients with suspected CA (13, 14, 18, 17, 20), 2 studies evaluated patients undergoing the tracer scintigraphy to diagnose TTR-CA (16, 25), and 4 included AL-CA or TTR-CA patients for verifying the diagnostic accuracy of bone tracers (15, 21, 23, 24). Six studies explicitly used EMB as the diagnostic criteria for TTR-CA (12, 15, 16, 18, 21, 22), while 5 other studies claimed to have used biopsies but did not illustrate the involved tissue/organ (13, 14, 23–25). Most studies (92.9%) diagnosed TTRm or TTRwt CA based on genotyping/immunohistochemistry (12–18, 20–25).

The bone tracer ^{99m}Tc-DPD was used in 6 studies (15, 17, 20, 22–24), ^{99m}Tc-PYP in 5 studies (12, 16, 17, 19, 21), and ^{99m}Tc-HMDP in 4 studies (13, 14, 17, 18). One study (17) used all three above tracers at the same time, and one study (25) used ^{18}F-NaF. The planar scintigraphic acquisition was used in all studies and SPECT or SPECT/CT in 57.1% of studies (13, 15, 19–24). To analyze scintigraphic images, the qualitative way was adopted in all studies, the quantitative way in 14.3% of studies (12, 25), and the semi-quantitative way in 71.4% (13, 14–19, 21, 23, 24). The qualitative analysis was conducted using the Perugini visual score (24) (score 0, absent cardiac and normal bone uptake; score 1, mild cardiac uptake inferior to bone; score 2, moderate cardiac uptake equal to bone; score 3, strong heart uptake greater than bone) in all included studies. The quantitative and semi-quantitative analyses were performed through radiotracer retention ratio, such as heart/contralateral thorax uptake ratio (H/CL), heart/whole-body ratio (H/WB), heart/skull ratio (H/S), and heart/pelvis ratio (H/P) (12–24). Particularly, in one study (25) the quantitative analysis was carried out using an average target-to-background ratio (TBR_m) and standard uptake values (SUV_m) of ^{18}F-NaF over the left ventricle (LV). Table 1 presents the general characteristics of the studies included in the systematic review.

We applied the QUADAS-2 tool (32) to assess the overall quality of the included studies. Overall, the quality of the selected studies was deemed satisfactory. The outcome of the methodological quality is demonstrated in Table 2.

Ultimately, 9 studies (496 patients) (12, 13, 15, 16, 19, 21–23, 25), including TTR-CA and AL-CA groups, were eligible for the meta-analysis. To improve the accuracy (sensitivity and specificity) of bone tracer for TTR-CA, Perugini score ≥2 of any bone radiotracers (^{99m}Tc-DPD, ^{99m}Tc-PYP, ^{99m}Tc-HMDP, or ^{18}F-NaF) was defined to be capable of diagnosing TTR-CA and differentiating TTR-CA from AL-CA, which was consistent with the previous studies (12–18, 21, 22). Our pre-specified criteria for diagnosing TTR-CA were a sensitivity ≥0.95 and NLR ≤0.1 while criteria for differentiating TTR-CA from AL-CA were a specificity ≥0.95 and PLR ≥10. The summarized performance of bone tracers in diagnosing TTR-CA is listed in Table 3.

The overall sensitivity of the scintigraphy was 0.97 (95% CI 0.85–0.99), ranging from 0.57 to 1.00, with heterogeneity (I^2=73.5, 95% CI 55.6–91.2); the specificity was 0.92

Table 1. General characteristics of studies included for systematic review

Year, First author (Ref), Journal	Study design	Blinded evaluation	En/Ex (n)	MA (yrs)/ Male (%)	Ref standard	Radiotracer	Uptake time	Scintigraphic image	Image analysis	Type of CA(n)
2020, Flaherty (12), *Journal of Nuclear Cardiology*	Prospective	Yes	43/0	77/76.7	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-PYP	1 h	Planar (WB)	Qualitative and quantitative	3 AL, 1 TTRun, 3 TTRm, 20 TTRwt
2019, Martineau (25), *Journal of Nuclear Cardiology*	Retrospective	Yes	15/0	69/80	Biopsy and genotyping/ Immunohistochemistry	^{18}F-NaF	1 h	Planar (TH) and PET/CT (LV)	Qualitative and quantitative	4 AL, 7 TTR
2019, Gallini (13), *Journal of Nuclear Cardiology*	Retrospective	No	76/0	75/78	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-HMDP	2.5 h	Planar (WB) and SPECT	Qualitative and semi-quantitative	12 AL 16 TTRm, 37 TTRwt,
2019, Cappelli (14), *Journal of Nuclear Cardiology*	Retrospective	NR	131/46	76/78	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-HMDP	2.5 h	Planar (WB)	Qualitative and semi-quantitative	26 AL, 16 TTRm, 23 TTRwt
2017, Moore (15), *Heart, Lung and Circulation*	Prospective	Yes	21/0	64/90	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-DPD	3 h	Planar (WB) and SPECT/CT (TH)	Qualitative and semi-quantitative	8 AL, 3 TTRm, 8 TTRwt
2016, Castano (16), *JAMA Cardiology*	Retrospective	No	229/58	73/86	Biopsy and genotyping/ Immunohistochemistry	^{99m}TcPYP	1h or 3h	Planar (TH)	Qualitative and semi-quantitative	34 AL, 12 TTRun, 37 TTRm, 72 TTRwt
2016, Gillmore (17), *Circulation*	Retrospective	No	374/0	NR/NR	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-DPD, ^{99m}Tc-PYP, ^{99m}Tc-HMDP	1h or 3h	Planar (WB)	Qualitative and semi-quantitative	62 AL, 261 TTR, 4 Other
2015, Galat (18), *Amyloid*	Prospective	Yes	98/0	75/70	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-HMDP	10 min and 3h	Planar (WB)	Qualitative and semi-quantitative	14 AL, 26 TTRm, 21 TTRwt
2015, Papantoniou (19), *Hellenic Journal of Nuclear Medicine*	Retrospective	No	12/0	68/66.7	NR	^{99m}Tc-PYP	1, 2 and/ or 3h	Planar (WB) and SPECT (TH)	Qualitative and semi-quantitative	6 AL, 6 TTR
2014, Hutt (20), *European Heart Journal of Cardiovascular Imaging*	Retrospective	Yes	236/1	72/80	Biopsy and genotyping/ Immunohistochemistry combined with clinical and laboratory data	^{99m}Tc-DPD	3 h	Planar (WB) and SPECT/CT (TH)	Qualitative	44 AL, 46 TTRm, 132 TTRwt, 14 Other
2013, Bokhari (21), *Circulation: Cardiovascular Imaging*	Prospective	Yes	45/0	70/84	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-PYP	1 h over 8 min	Planar (WB) and SPECT (TH)	Qualitative and semi-quantitative	12 AL, 17 TTRm, 16 TTRwt
2012, de Haro-DelMoral (22), *Revista Española de Cardiología (English Edition)*	Retrospective	No	19/0	64.4/58	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-DPD	3 h	Planar (WB) and SPECT (TH)	Qualitative	11 AL, 3 TTRm, 5 TTRwt
2011, Rapezzi (23), *European Journal of Nuclear Medicine and Molecular Imaging*	Retrospective	Yes	94/15	62/80	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-DPD	5 min and 3 h	Planar (WB) and SPECT (TH)	Qualitative and semi-quantitative	34 AL, 28 TTRm, 17 TTRwt,
2005, Perugini (24), *Journal of the American College of Cardiology*	Retrospective	Yes	35/0	58/NR	Biopsy and genotyping/ Immunohistochemistry	^{99m}Tc-DPD	5 min and 3 h	Planar (WB) and SPECT (TH)	Qualitative and semi-quantitative	10 AL, 10 TTRm, 5 TTRwt

Ref, reference; En/Ex, enrolled/excluded; MA, mean age; CA, cardiac amyloidosis; ^{99m}Tc-PYP, ^{99m}Tc-pyrophosphate; WB, whole body; AL, amyloid light-chain; TTR, transthyretin; TTRun, unknown genotype TTR; TTRm, mutant TTR; TTRwt, wildtype TTR; ^{18}F-NaF, ^{18}F-sodium fluoride; TH, thorax; LV, left ventricular; ^{99m}Tc-HMDP, ^{99m}Tc-hydroxymethylene diphosphonate; ^{99m}Tc-DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; NR, not reported; Other, other type of cardiac amyloidosis.

Table 2. Quality assessment of the included studies in the systematic review using the QUADAS-2 tool

	Risk of bias				Applicability concerns		
First author (Ref)	Patient selection	Index test	Reference standard	Flow and timing	Patient selection	Index test	Reference standard
Flaherty (12)	☺	☺	☺	☺	☺	☺	☺
Martineau (25)	?	☺	☺	☺	☹	☺	☺
Gallini (13)	☹	?	☺	☺	☹	☺	☺
Cappelli (14)	?	☺	☺	☺	☹	☺	☺
Moore (15)	☺	☺	☺	☺	☺	☺	☺
Castano (16)	?	☹	☺	☺	☹	☺	☺
Gillmore (17)	☹	?	☺	☺	☹	☺	☺
Galat (18)	☺	☺	☺	☺	☺	☺	☺
Papantoniou (19)	?	☺	?	☺	?	☺	?
Hutt (20)	?	☺	☺	☺	☹	☺	☺
Bokhari (21)	☹	☺	☺	☺	☺	☺	☺
de Haro-Del Moral (22)	?	☹	☺	☺	☺	☺	☺
Rapezzi (23)	☺	☺	☺	☺	☹	☺	☺
Perugini (24)	☹	☺	☺	☺	☺	☺	☺

Ref, reference; ☺, low risk; ☹, high risk; ?, unclear risk.

Table 3. Performance of bone tracer for the diagnosis of TTR-CA in the meta-analysis

	Pooled number of patients							
First author (Ref), radiotracer	TPV	FPV	FNV	TNV	SEN (%)	SPE (%)	PLR	NLR
Flaherty (12), ^{99m}Tc-PYP	24	0	0	19	100	100	39.20	0.04
Gallini (13), ^{99m}Tc-HMDP	48	0	5	23	91	100	43.11	0.10
Moore (15), ^{99m}Tc-DPD	13	1	0	7	100	87.5	5.79	0.04
Castano (16), ^{99m}TcPYP	106	6	15	44	88	88	7.30	0.14
Papantoniou (19), ^{99m}Tc-PYP	6	2	0	4	100	67	2.60	0.11
Bokhari (21), ^{99m}Tc-PYP	32	2	1	10	97	83	5.82	0.04
de Haro-Del Moral (22), ^{99m}Tc-DPD	8	0	0	11	100	100	22.67	0.06
Rapezzi (23), ^{99m}Tc-DPD	45	6	0	43	100	88	7.61	0.01
Martineau (25), ^{18}F-NaF	4	0	3	8	57	100	10.13	0.46
Pooled analysis	286	17	24	169	97 (95% CI 85–99)	92 (95% CI 82–96)	11.49 (95% CI 5.07–26.0)	0.03 (95% CI 0.01–0.18)

Ref, reference; TPV, true-positive; FPV, false-positive; FNV, false-negative; TNV, true-negative; SEN, sensitivity; SPE, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio; ^{99m}Tc-PYP, ^{99m}Tc-pyrophosphate; ^{99m}Tc-HMDP, ^{99m}Tc-hydroxymethylene diphosphonate; ^{99m}Tc-DPD, ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid; ^{18}F-NaF, ^{18}F-sodium fluoride. Five articles were excluded from the meta-analysis: four (14,17,18,24) for data overlap and one (20) for containing unknown type of CA different than TTR-CA with AL-CA.

(95% CI 0.82–0.96), ranging from 0.67 to 1.00, with heterogeneity (I^2=42.0, 95% CI 0.0–86.9) (Fig. 2). The pooled PLR and the NLR were 11.49 (95% CI 5.07–26.0) and 0.03 (95% CI 0.01–0.18), respectively (Table 3). Despite the mild-moderate heterogeneity, the results were acceptable. The DOR was 341 (95% CI 53–2194). Fig. 3 shows Fagan's nomogram for the scintigraphy, illustrating the relation between test probability and likelihood ratio. The SROC curve in Fig. 4 indicates the AUC as 0.96 (95% CI 0.94–0.97). The Deeks' funnel plot shows a *p* value of 0.957, i.e., there is no evidence on influencing publication (Fig. 5).

Furthermore, we analyzed the performance of different bone radiotracers in diagnosing TTR-CA. Four studies (12, 16, 19, 21) used ^{99m}Tc-PYP as the radiopharmaceutical and 3 studies (15, 22, 23) used ^{99m}Tc-DPD. The remaining 2 studies used ^{99m}Tc-HMDP (13) and ^{18}F-NaF (25), respectively. Consistent with the foregoing, all diagnoses and differentiation of TTR-CA were performed using the Perugini score. The quantitative or semi-quantitative methodology may assist in the diagnosis and differentiation of TTR-CA. In studies that used ^{99m}Tc-PYP, a cutoff value of H/CL ratios 1.5 or 1.6, was achieved for TTR-CA identification (13, 16, 19, 21). When using ^{99m}Tc-HMDP (13), the author considered H/WB ratios to be the most accurate (100%) in diagnosing

Table 4. Performance of different bone tracer for the diagnosis of TTR-CA in the meta-analysis

Radiotracer (Ref)	Cases (n)	Pooled number of patients				SEN (%)	SPE (%)	PLR	NLR
		TPV	FPV	FNV	TNV				
^{99m}Tc-DPD (15, 22, 23)	134	66	7	0	61	100	90	9.13	0.01
^{99m}Tc-PYP (12, 16, 19, 21)	271	168	10	16	77	91	89	7.94	0.10
^{99m}Tc-HMDP (13)	76	48	0	5	23	91	100	43.11	0.10
^{18}F-NaF, (25)	15	4	0	3	8	57	100	10.13	0.46
Pooled analysis	496	286	17	24	169	97 (95% CI 87–100)	90 (95% CI 85–94)	11.49 (95% CI 5.07–26.0)	0.03 (95% CI 0.01–0.18)

Ref, reference; TPV, true-positive; FPV, false-positive; FNV, false-negative; TNV, true-negative; SEN, sensitivity; SPE, specificity; PLR, positive likelihood ratio; NLR, negative likelihood ratio.

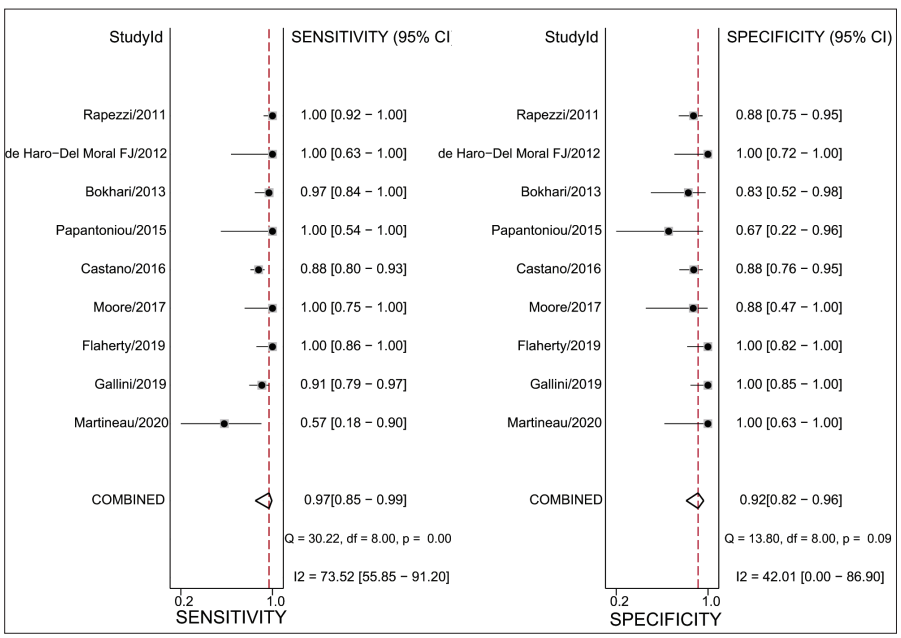

Figure 2. Forest plot of pooled sensitivity and specificity of bone tracer for diagnosing TTR-CA.

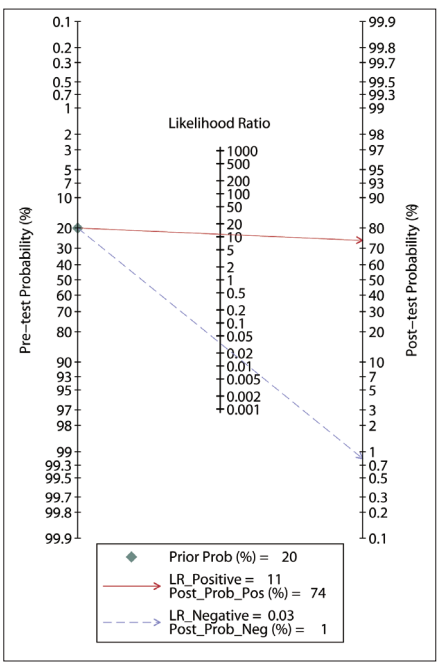

Figure 3. Fagan's nomogram for bone tracer accounting for post-test probability with a fixed pre-test probability 20% for TTR-CA. When PLR and NLR are as data above, at fixed pre-test probability of 20%, the post-test probability of positive is 74% and the post-test probability of negative is 1% for TTR-CA.

TTR-CA, with the H/WB profile of 3.28 and H/WB rectangular ROI ratio of 3.26. In the study employing ^{18}F-NaF, the TBRm cutoff value of 0.89 resulted in a sensitivity/specificity of 75%/100% for the diagnosis of TTR-CA. Nevertheless, various evaluation criteria (e.g., H/CL, H/P, H/S, H/WB) were used without a unified standard. The pooled analysis is presented in Table 4.

Discussion

In the current meta-analysis, we systematically analyzed the performance of gamma-emitting and positron-emitting bone tracers on diagnosis and differentiation of TTR-CA. Our meta-analysis suggested that TTR-CA patients could be diagnosed by the bone tracers (Perugini score of ≥2) with high sensitivity, high AUC, and low NLR. Furthermore, the results showed that bone tracers could differentiate TTR-CA from AL-CA (Table 3) with high PLR, but the specificity (0.92) did not fully meet our expectation (≥0.95). We suggest that earlier use of this scintigraphy in patients with suspected CA may improve the diagnostic rate, advance professional and optimal treatment, and produce a prognostic efficacy in TTR-CA.

The high accuracy of biopsy is well known, but the procedure itself is invasive and risky (1–5). Over the past decades, research on noninvasive diagnostic measures for TTR-CA has been developing rapidly (40, 41). Historically, several myocardial imaging radiotracers including Ga-67 citrate were used to identify infiltrative myocardial pathologies of the heart; Thallium-201 chloride was used to diagnose myocardial inflammation, such as sarcoidosis and infiltrative-malignant processes such as lymphoma (42, 43). The use of bone radiotracer (^{99m}Tc-DPD) for diagnosing TTR-CA began with a study in 2002 (44). The mechanism of bone tracers in diagnosing amyloidosis is not entirely clear, while some studies suggest that it is related to the calcium deposit levels in amyloidosis (45, 46). Many following studies (12–26, 47) indicated different diagnostic and differential values of bone traces on TTR-CA.

Perugini et al. (24) first used ^{99m}Tc-DPD scintigraphy as a noninvasive tool to study the diagnosis of TTR-CA with a sensitivity and specificity of 100%. However, the sample size was very small (25 patients) and

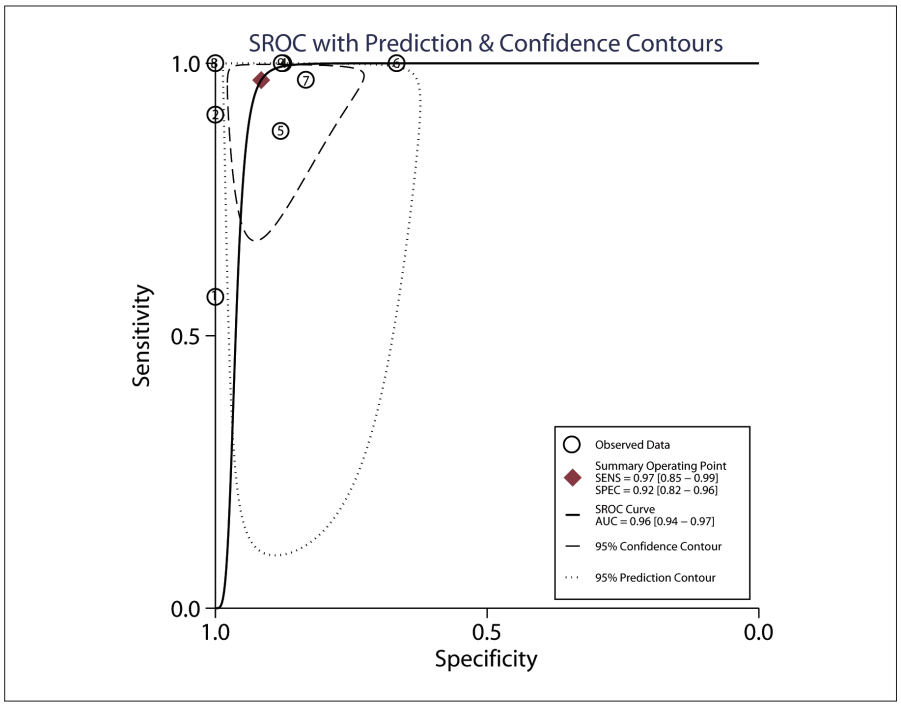

Figure 4. The summary receiver operating characteristic (SROC) of bone tracer for diagnosing TTR-CA.

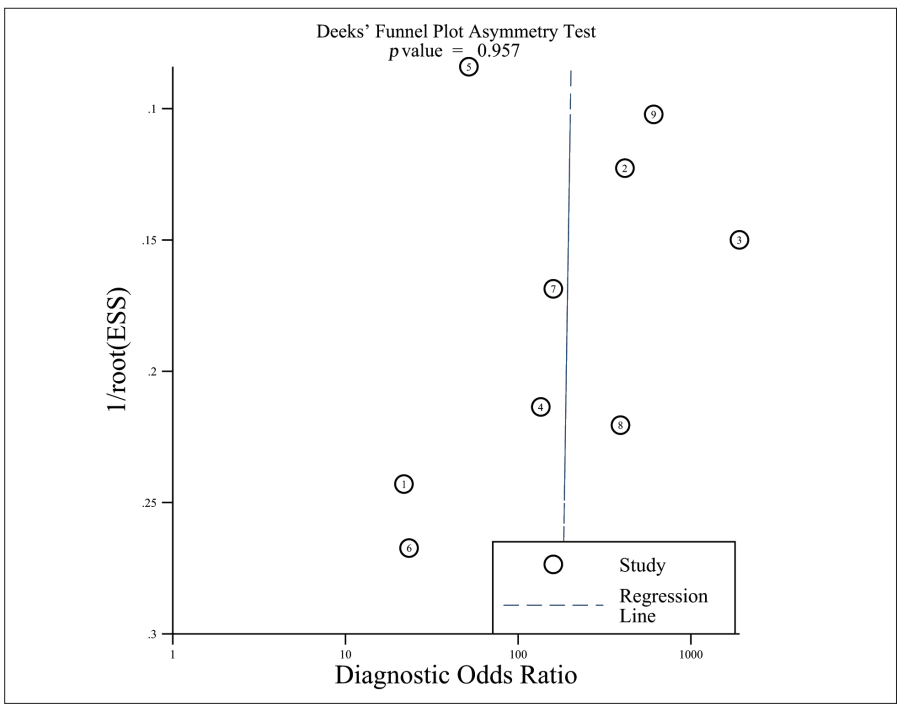

Figure 5. Deeks' funnel plot asymmetry test for publication bias.

amyloidotic polyneuropathy was included in the study. In the subsequent research (23), they confirmed the value for differentiating TTR-CA from AL-CA, but found a mild degree of tracer uptake in some AL-CA patients (Perugini score=1). This could explain why most of the following studies (12–18, 21, 22) defined a Perugini score ≥2 as the positive diagnosis of TTR-CA. Then, Hutt et al. (20) observed the uptake of ^{99m}Tc-DPD in different genotypes of TTR-CA. Other studies (13, 18) considered ^{99m}Tc-HMDP could aid in differentiating TTR-CA from AL-CA, but the results were not systematically validated by EMB. In an extensive survey of 374 patients, Gillmore et al. (17) reported that TTR-CA could be diagnosed without immunohistochemistry, given a Perugini score ≥2, using ^{99m}Tc-PYP, ^{99m}Tc-DPD, or ^{99m}Tc-HMDP. However, all patients in their study were suspected of CA, which would lead to selection bias. Moreover, the findings did not deny the importance of histological demonstration and typing of CA. One study applied a ^{99m}Tc-HMDP semi-quantitative method to analyze multiple body parts (13), while Flaherty et al. (12) developed and validated a new way of imaging ^{99m}Tc-PYP cardiac scintigraphy, using cadmium zinc telluride (CZT) crystal gamma camera to diagnose TTR-CA with high sensitivity. Moreover, recent studies employed positron-emitting bone radiotracer ^{18}F-NaF to diagnose TTR-CA (25, 26, 48, 49). Compared with gamma-emitting radiotracers, PET imaging devices are different in hardware and physical characteristics, and the quantitative analysis of ^{18}F-NaF was more accurate than qualitative analysis for diagnosing TTR-CA (25). So far, however, no single study has reported using bone tracer alone to diagnose and differentiate TTR-CA.

We pooled both gamma-emitting and positron-emitting bone tracers to make a meta-analysis of their accuracy in the diagnosis of TTR-CA. Compared with a prior study (27), the current meta-analysis indicated a better accuracy for use of bone tracers in the diagnosis of TTR-CA, but a bit modest specificity. That means bone tracers display high performance in diagnosing TTR-CA. But to differentiate TTR-CA from AL-CA more accurately in a noninvasive way, other workups such as genotyping, serum and urine immunofixation, serum-free light-chains may still be needed. In subanalysis (Table 4), we assessed the diagnostic manifestations of TTR-CA with tracers separately. Overall, the performance of diagnosing TTR-CA and differentiating TTR-CA from AL-CA was different for gamma-emitting and positron-emitting bone tracers. In our meta-analysis, <14% of AL-CA patients appeared to have the bone tracer uptake and the number of false-positive patients was less than 3.5%; more than 90% of TTR-CA patients showed uptake of bone radiotracers, the overwhelming majority of whom with a high-grade score. Moreover, one study (13) used ^{99m}Tc-HMDP to diagnose CA. It demonstrated a better performance in distinguishing TTR-CA from AL-CA, whose specificity and PLR were superior to other bone tracers (^{18}F-NaF, ^{99m}Tc-PYP and ^{99m}Tc-DPD). In the meantime, compared

with ^{99m}Tc-PYP and ^{99m}Tc-DPD, ^{18}F-NaF exhibited stronger performance in differentiating TTR-CA from AL-CA. Nonetheless, it was not to say other bone tracers did not work well. Many studies have demonstrated the outstanding diagnostic efficacy of other bone tracers (15, 19, 21–23, 25).

Our study has several limitations. First, a mild-moderate heterogeneity existed in the summarized results. It might result from study design, demographic baselines, or the methodological diversity of included studies, especially when including both gamma-emitting and positron-emitting bone tracers at the same time. Second, only one study with ^{18}F-NaF was included in our meta-analysis, which cannot be fully compared with gamma-emitting bone tracers. More research inspecting the performance of ^{18}F-NaF in TTR-CA patients is needed in the future. Third, due to insufficient data, we did not conduct further analysis of the subtypes of TTR-CA. Thus, we particularly expect more focus on studies of using bone tracer to differentiate AL from TTRwt and TTRm groups. Fourth, without a unified standard, we failed to analyze using a quantitative or semi-quantitative methodology, and future research is needed for some insight into this area.

In conclusion, this meta-analysis demonstrates that the bone tracer provides high accuracy in diagnosing TTR-CA. Bone tracer also presents a certain value in differentiating TTR-CA from AL-CA, especially gamma-emitting bone tracer ^{99m}Tc-HMDP, although it still needs confirmation from other auxiliary methods (genotyping, immunofixation, and serum-free light-chains). Positron-emitting bone tracer ^{18}F-NaF is also a promising candidate to diagnose and differentiate TTR-CA. Bone tracers could guide clinical practice in the diagnostic and differentiation workup of TTR-CA patients, and even monitor response to therapy. In the future, more studies with higher quality are required to further support our results.

Conflict of interest disclosure

The authors declared no conflicts of interest.

References

1. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: an update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med 2018; 28:10–21. [Crossref]
2. Zhao L, Fang Q. Recent advances in the noninvasive strategies of cardiac amyloidosis. Heart Fail Rev 2016; 21:703–721. [Crossref]
3. Maleszewski JJ. Cardiac amyloidosis: pathology, nomenclature, and typing. Cardiovasc Patho 2015; 24:343–350. [Crossref]
4. Bhogal S, Ladia V, Sitwala P, et al. Cardiac amyloidosis: an updated review with emphasis on diagnosis and future directions. Curr Probl Cardiol 2018; 43:10–34. [Crossref]
5. Chacko L, Martone R, Cappelli F, Fontana M. Cardiac amyloidosis: updates in imaging. Curr Cardiol Rep 2019; 21:108. [Crossref]
6. Garcia Y, Collins AB, Stone JR. Abdominal fat pad excisional biopsy for the diagnosis and typing of systemic amyloidosis. Hum Pathol 2018; 72:71–79. [Crossref]
7. Shah KB, Mankad AK, Castano A, et al. Transthyretin cardiac amyloidosis in black Americans. Circ Heart Fai 2016; l 9:e002558. [Crossref]
8. Griffin JM, Maurer MS. Cardiac amyloidosis a rare disease in older adults hospitalized for heart failure? Circ Heart Fail 2019; 12:e006169. [Crossref]
9. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2019; 73: 2872–2891. [Crossref]
10. Fine NM, Arruda-Olson AM, Dispenzieri A, et al. Yield of noncardiac biopsy for the diagnosis of transthyretin cardiac amyloidosis. Am J Cardiol 2014; 113:1723–1727. [Crossref]
11. Maurer MS, Bokhari S, Damy T, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. Circ Heart Fail 2019; 12:e006075. [Crossref]
12. Flaherty KR, Morgenstern R, Pozniakoff T, et al. 99mTechnetium pyrophosphate scintigraphy with cadmium zinc telluride cameras is a highly sensitive and specific imaging modality to diagnose transthyretin cardiac amyloidosis. J Nucl Cardiol 2020; 27:371–380. [Crossref]
13. Gallini C, Tutino F, Martone R, et al. Semi-quantitative indices of cardiac uptake in patients with suspected cardiac amyloidosis undergoing 99mTc-HMDP scintigraphy. J Nucl Cardiol 2021; 28:90–99. [Crossref]
14. Cappelli F, Gallini C, Di Mario C, et al. Accuracy of 99mTc-hydroxymethylene diphosphonate scintigraphy for diagnosis of transthyretin cardiac amyloidosis. J Nucl Cardiol 2019; 26:497–504. [Crossref]
15. Moore PT, Burrage MK, Mackenzie E, Law WP, Korczyk D, Mollee P. The utility of 99mTc-DPD scintigraphy in the diagnosis of cardiac amyloidosis: an Australian experience. Heart Lung Circ 2017; 26:1183–1190. [Crossref]
16. Castano A, Haq M, Narotsky DL, et al. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol 2016; 1:880–889. [Crossref]
17. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. Circulation 2016; 133:2404–2012. [Crossref]
18. Galat A, Rosso J, Guellich A, et al. Usefulness of 99mTc-HMDP scintigraphy for the etiologic diagnosis and prognosis of cardiac amyloidosis. Amyloid 2015; 22:210–220. [Crossref]
19. Papantoniou V, Valsamaki P, Kastritis S, et al. Imaging of cardiac amyloidosis by 99mTc-PYP scintigraphy. Hell J Nucl Med 2015; 18(Suppl 1):42–50.
20. Hutt DF, Quigley AM, Page J, et al. Utility and limitations of 3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in systemic amyloidosis. Eur Heart J Cardiovasc Imaging 2014; 15:1289–1298. [Crossref]
21. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. 99mTc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013; 6:195–201. [Crossref]
22. de Haro-del Moral FJ, Sánchez-Lajusticia A, Gómez-Bueno M, García-Pavía P, Salas-Antón C, Segovia-Cubero J. Role of cardiac scintigraphy with 99mTc-DPD in the differentiation of cardiac amyloidosis subtype. Rev Esp Cardiol (Engl Ed) 2012; 65:440–446. [Crossref]
23. Rapezzi C, Quarta CC, Guidalotti PL, et al. Usefulness and limitations of 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy in the aetiological diagnosis of amyloidotic cardiomyopathy. Eur J Nucl Med Mol Imaging 2011; 38:470–478. [Crossref]
24. Perugini E, Guidalotti PL, Salvi F, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy. J Am Coll Cardiol 2005; 46:1076–1084. [Crossref]
25. Martineau P, Finnerty V, Giraldeau G, Authier S, Harel F, Pelletier-Galarneau M. Examining the sensitivity of 18F-NaF PET for the imaging of cardiac amyloidosis. J Nucl Cardiol 2021; 28:209–218. [Crossref]
26. Morgenstern R, Yeh R, Castano A, Maurer MS, Bokhari S. 18Fluorine sodium fluoride positron emission tomography, a potential biomarker of transthyretin cardiac amyloidosis. J Nucl Cardiol 2018; 25:1559–1567. [Crossref]
27. Treglia G, Glaudemans AWJM, Bertagna F, et al. Diagnostic accuracy of bone scintigraphy in the assessment of cardiac transthyretin-related amyloidosis: a bivariate meta-analysis. Eur J Nucl Med Mol Imaging 2018; 45:1945–1955. [Crossref]
28. Musumeci MB, Cappelli F, Russo D, et al. Low sensitivity of bone scintigraphy in detecting Phe64Leu mutation-related transthyretin cardiac amyloidosis. JACC Cardiovasc Imaging 2020; 13:1314–1321. [Crossref]
29. Möckelind S, Axelsson J, Pilebro B, Lindqvist P, Suhr OB, Sundström T. Quantification of cardiac amyloid with ((18)F)Flutemetamol in patients with V30M hereditary transthyretin amyloidosis. Amyloid 2020; 27:191–199. [Crossref]
30. Shamseer L, Moher D, Clarke M, et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 350:g7647. [Crossref]
31. Sadeghi R, Treglia G. Systematic reviews and meta-analyses of diagnosticstudies: a practical guideline. Clin Transl Imaging 2017; 5:83–87. [Crossref]
32. Whiting PF, Rutjes AWS, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med 2011; 155:529–536. [Crossref]
33. Grimes DA, Schulz KF. Refining clinical diagnosis with likelihood ratios. Lancet 2005; 365: 1500–1505. [Crossref]
34. Glas AS, Lijmer JG, Prins MH, Bonsel GJ, Bossuyt PM. The diagnostic odds ratio: a single indicator of test performance. J Clin Epidemiol 2003; 56:1129–1135. [Crossref]
35. Walter SD. The partial area under the summary ROC curve. Stat Med 2005; 24: 2025–2040. [Crossref]

36. Jones CM, Athanasiou T. Summary receiver operating characteristic curve analysis techniques in the evaluation of diagnostic tests. Ann Thorac Surg 2005; 79:16–20. [Crossref]
37. Deeks JJ, Macaskill P, Irwig L. The performance of tests of publication bias and other sample size effects in systematic reviews of diagnostic test accuracy was assessed. J Clin Epidemiol 2005; 58:882–893. [Crossref]
38. Melsen WG, Bootsma MC, Rovers MM, Bonten MJ. The effects of clinical and statistical heterogeneity on the predictive values of results from meta-analyses. Clin Microbiol Infect 2014; 20:123–129. [Crossref]
39. Higgins JPT, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. BMJ 2003; 327: 557–560. [Crossref]
40. Quintana-Quezada RA, Yusuf SW, Banchs J. Use of Noninvasive imaging in cardiac amyloidosis. Curr Treat Options Cardiovasc Med 2016; 18:46. [Crossref]
41. Qin J, Zhan C, Li H, et al. Noninvasive diagnosis of hereditary transthyretin-related cardiac amyloidosis: A case report. Medicine (Baltimore) 2019; 98:e16566. [Crossref]
42. Chin BB, Civelek AC, Mudun A. Resting Tl-201 scintigraphy in the evaluation of myocardial sarcoidosis. Clin Nucl Med 1997; 22:475–478. [Crossref]
43. Civelek AC, Brinker JA, Camargo EE, Links JM, Wagner HN. Rest thallium-201 myocardial perfusion imaging in a patient with leukaemic infiltration of the heart. Eur J Nucl Med 1992; 19:306–308. [Crossref]
44. Puille M, Altland K, Linke RP, et al. 99mTc-DPD scintigraphy in transthyretin-related familial amyloidotic polyneuropathy. Eur J Nucl Med Mol Imaging 2002; 29:376–379. [Crossref]
45. Janssen S, Piers DA, van Rijswijk MH, Meijer S, Mandema E. Soft-tissue uptake of 99mTc-diphosphonate and 99mTc-pyrophosphate in amyloidosis. Eur J Nucl Med 1990; 16:663–670. [Crossref]
46. Worsley DF, Lentle BC. Uptake of technetium-99m MDP in primary amyloidosis with a review of the mechanisms of soft tissue localization of bone seeking radiopharmaceuticals. J Nucl Med 1993; 34:1612–1615.
47. Stats MA, Stone JR. Varying levels of small microcalcifications and macrophages in ATTR and AL cardiac amyloidosis: implications for utilizing nuclear medicine studies to subtype amyloidosis. Cardiovasc Pathol 2016; 25:413–417. [Crossref]
48. Gagliardi C, Tabacchi E, Bonfiglioli R, et al. Does the etiology of cardiac amyloidosis determine the myocardial uptake of (18F)-NaF PET/CT? J Nucl Cardiol 2017; 24:746–749. [Crossref]
49. Ng QKT, Sethi P, Saunders TA, Pampaloni MH, Flavell RR. Discordant findings on 18F-NaF and 99m Tc-HDP bone scans in a patient with ATTR cardiac amyloidosis (Letters). Clin Nucl Med 2018; 43:89–92. [Crossref]