Accuracy of 99mTc-Hydroxymethylene diphosphonate scintigraphy for diagnosis of transthyretin cardiac amyloidosis

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Background and Aim. **Either 99mTechnetium diphosphonate (Tc-DPD) or pyrophosphate (Tc-PYP) scintigraphy plays a relevant role in diagnosing transthyretin cardiac amyloidosis (CA), and labeled radiotracers have been extensively studied in diagnosing CA. Few studies have analyzed and validated 99mTc-Hydroxymethylene diphosphonate (Tc-HMDP). Our aim was to validate the diagnostic accuracy of Tc-HMDP total-body scintigraphy in a cohort of patients with biopsy-proven transthyretin CA.**

Methods and Results. **We retrospectively evaluated all patients undergoing 99mTc-HMDP total-body scintigraphy, in adjunct to a comprehensive diagnostic work-up for suspected CA. Sixty-five patients were finally diagnosed with CA, while it was excluded in 20 subjects with left ventricular hypertrophy of various etiologies. Twenty-six patients had AL-CA, 39 had TTR CA (16 TTRm, 23 TTRwt). At Tc-HMDP scintigraphy, 2 AL patients showed a Perugini score grade 1 heart uptake, while 24 showed no uptake. All TTR patients showed Tc-HMDP uptake, with three patients showing a Perugini score grade 1, 16 grade 2, and 20 grade 3, respectively. No uptake was observed in patients with left ventricular hypertrophy. A positive Tc-HMDP scintigraphy showed a 100% sensitivity and a 96% specificity for TTR CA identification.**

Conclusions. **Tc-HMDP scintigraphy is as accurate as Tc-DPD or Tc-PYP, and may therefore *de facto* be considered a valuable tool for the diagnosis of TTR CA. (J Nucl Cardiol 2019;26:497–504.)**

Key Words: Tc-HMDP • amyloidosis • scintigraphy

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Abbreviations

Tc-DPD	99mTc-3,3-diphosphono-1,2-propanodicarboxylic
Tc-PYP	99m-*Tc*-Pyrophosphate
Tc-HMDP	*99mTc*-Hydroxymethylene diphosphonate
NT-proBNP	N-terminal fragment of pro-brain natriuretic peptide
TTR CA	Transthyretin cardiac amyloidosis
AL CA	Light chain cardiac amyloidosis
LVH	Left ventricular hypertrophy

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INTRODUCTION

Systemic amyloidosis is associated with a variety of diseases characterized by extracellular deposition of protein-derived fibrils in different tissues and organs, including the heart.[1] Two types of amyloid commonly infiltrate the heart: immunoglobulin light-chain (AL) amyloid and transthyretin (TTR) amyloid. Transthyretin-related amyloidoses, in turn, encompass two forms of disease: familial disease arising from misfolding of a mutated or variant TTR, and a sporadic, non-genetic disease caused by misaggregation of wild-type transthyretin (senile systemic amyloidosis). Cardiac involvement is a progressive disorder finally resulting in early death due to congestive heart failure (HF) and arrhythmias. Echocardiography represents a cornerstone in diagnostic evaluation and prognostic stratification of cardiac amyloidosis (CA),[2-6] but its ability to correctly identify amyloid etiology is unsatisfactory.[7]

While the gold standard for definitive etiological diagnosis of CA is endomyocardial biopsy coupled with immunohistochemistry, immunogold electronic microscopy, or mass spectroscopy,[1] its use can raise ethical concerns especially in old patients, given the risk related to invasive procedures. Therefore, the value of an alternative accurate non-invasive and reproducible method to diagnose TTR CA is evident.

Since the seminal work of Perugini,[8] total-body scintigraphy with diphosphonates, either with 99mTc-3,3-diphosphono-1,2-propanodicarboxylic acid (Tc-DPD) or 99m-*Tc*-Pyrophosphate (Tc-PYP), has gained an important role in diagnosis of transthyretin CA.[8-18] More recently, Gillmore and co-authors[19] demonstrated that, in patients with HF, a grade 2 or 3 Perugini visual score at bone scintigraphy in the absence of a detectable monoclonal protein in plasma or urine, is sufficient element to reliably diagnose cardiac TTR amyloidosis, even in the absence of histological demonstration. In that research *99mTc*-Hydroxymethylene diphosphonate (Tc-HMDP) scintigraphy was performed in a little part of the studied population with majority of patient that underwent either a Tc-DPD or Tc-PYP scintigraphy.

While in the last 10 years, Tc-DPD[8-11] and Tc-PYP[12-14] labeled radiotracers have been extensively studied in diagnosing TTR CA, only few studies[15,16] and a case report[17] have proposed *99mTc*-Hydroxymethylene diphosphonate (Tc-HMDP) for the same purpose, with no comparison with AL amyloidosis,[15] or without validation against the gold standard of biopsy-proven diagnosis in all patients.[16] In Italy, both Tc-DPD and Tc-HMDP are authorized for clinical use presenting comparable costs and radiation dose profile. In our region due to regional health service buying policy, Tc-HMDP is the only available tracer.

Therefore, the aim of our study was to test the diagnostic accuracy of Tc-HMDP total-body scintigraphy in a cohort of patients with biopsy-proven cardiac TTR amyloidosis.

MATERIALS AND METHODS

The study was conducted in the two main amyloidosis referral center of Tuscany, Azienda Ospedaliero Universitaria Careggi, Florence, Italy, and Fondazione Gabriele Monasterio, Pisa, Italy, both providing a coordinated amyloidosis network involving neurology, cardiology, nuclear medicine, hematology, nephrology, and genetics services, during the years 2013-2016,

We retrospectively evaluated all patients undergoing Tc-HMDP total-body scintigraphy in adjunct to the usual diagnostic work-up to exclude or confirm a suspected CA. All patients underwent physical examination, ECG, transthoracic echocardiography and biochemistry evaluation, i.e., plasma assay of the N-terminal fragment of pro-brain natriuretic peptide (NT-proBNP), serum and urinary immunofixation and serum-free light chains, and serum creatinine. Cardiac magnetic resonance imaging (MRI) was performed in a minority of patients.

All patients gave written informed consent for their clinical records to be used for research purposes, in accordance with Institutional Review Board guidelines.

Diagnosis of Amyloidosis and Cardiac Involvement Definition

Diagnosis of light-chain (AL) amyloidosis was made by biopsy of abdominal fat pad or of an involved organ, which demonstrated the typical Congo Red birefringence when viewed under polarized light. All positive biopsies demonstrated typical Congo Red birefringence under polarized light and staining by anti-k or anti-λ light-chain antibodies, combined with elevated serum or urine levels of the corresponding monoclonal light chain.

Diagnosis of TTRm CA was based on tissue biopsy with anti-TTR antibody staining and presence of TTR mutation at

genotyping. Diagnosis of TTRwt amyloidosis was made by tissue biopsy with anti-TTR antibody staining and absence of mutation at genotyping.

Diagnosis of CA was made when a patient had histological confirmation of AL or TTR amyloid at endomyocardial biopsy, or at extracardiac biopsy together with an increased left ventricular wall thickness (>12 mm) at echocardiographic evaluation, without other evident causes of hypertrophy or a NT-proBNP level >332 ng/L.[20]

When patients had high suspicion of CA, due to multimodality evaluation (echocardiography, ECG and cardiac MRI) but showed repeatedly negative extracardiac biopsy, endomyocardial biopsy was suggested. When cardiac biopsy was not possible for patient refusal or severity of clinical status, the subject was withdrawn from the study.

Patients were considered to have left ventricular hypertrophy (LVH) not related to amyloidosis infiltration if they have a negative cardiac biopsy or at least two negative noncardiac biopsies with no suggestive signs of CA at noninvasive imaging evaluation (TTE and MRI). In those patients, further research to assess a cause of LVH was performed.

Standard and Tissue Doppler Imaging Echocardiography

Patients were referred to our laboratory for M-mode, two-dimensional, conventional, and tissue Doppler imaging echocardiographic study. Echocardiography was performed using a Vivid 9 System (Vingmed, General Electric, Horten, Norway) equipped with a 3S probe. According to the standards of the American Society of Echocardiography,[21] the following parameters were assessed: end-diastolic thickness of interventricular septum thickness (IVS) and LV posterior wall (PW), LV end-diastolic and end-systolic volumes (LVEDV and LVESV, respectively), ejection fraction (estimated with the biplane Simpson method), mitral peak flow velocity in early and late diastole (E and A, respectively), E-wave deceleration time, E/A ratio, and systolic displacement of the lateral portion of the tricuspid annular plane systolic excursion (TAPSE). We also evaluated pulsed tissue Doppler imaging-derived early diastolic peak velocity at mitral annulus (E'), and E/E' ratio as an index of LV filling pressure. Pulmonary artery systolic pressure (PASP) was approximated by adding to trans-tricuspid pressure gradient an estimate of right atrial pressure assessed by inferior vena cava dimension and respiratory variation.

Scintigraphy

All patients underwent Tc-HMDP whole-body scintigraphy (HMDP-TB). Tc-HMDP was prepared from commercial kit (OSTEOCIS®) following the prescriptions of the manufacturer. All the preparation were tested for total hydrolyzed and free 99mTc (<5%) and for radiochemical purity (>95%). Each patient received i.v. 700-740 MBq of Tc-HMDP, and a whole-body scan (anterior and posterior

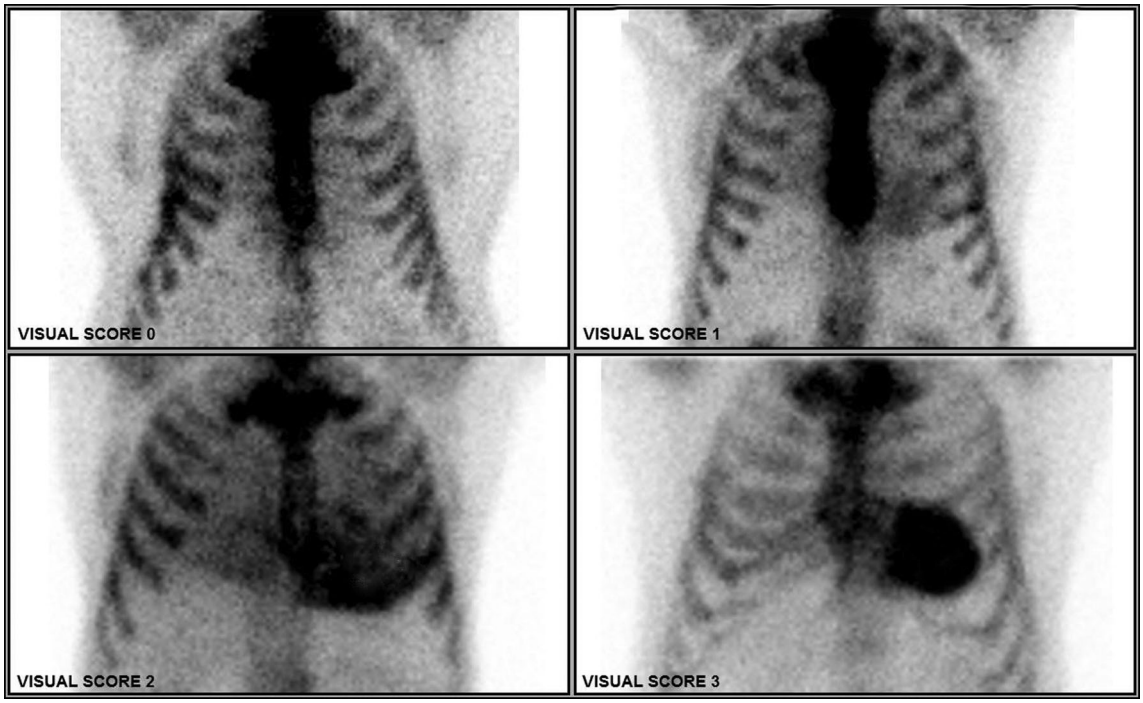

Figure 1. Examples illustrating the spectrum of 99mTc-HMDP uptake among patients using Perugini Visual Score. Perugini *0* absent cardiac uptake and normal bone uptake, Perugini *1* mild cardiac uptake, inferior to bone uptake, Perugini *2* moderate cardiac uptake associated with attenuated bone uptake, and Perugini *3* high cardiac uptake with decreased or absent bone uptake.

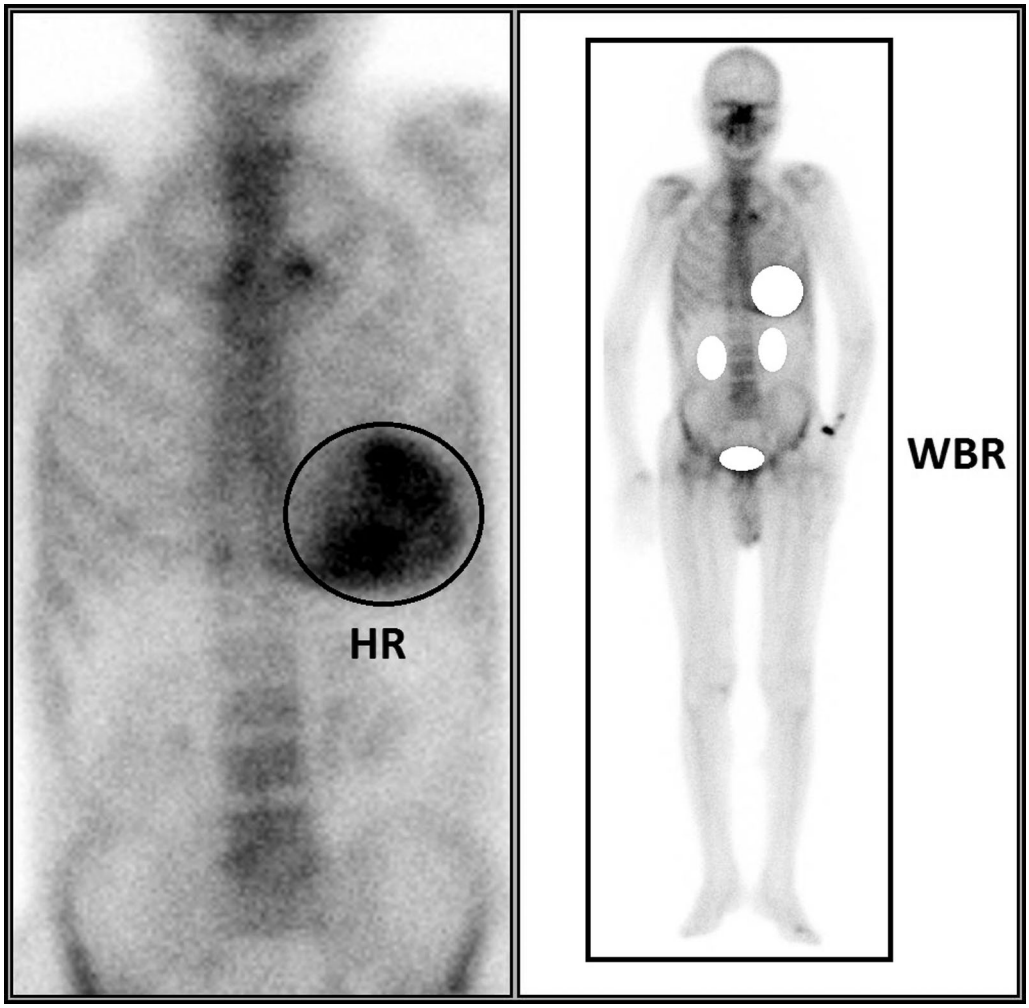

Figure 2. HR and WBR measurement on total-body scan: ROI over heart's shape for HR (*left*) and ROI around total-body's shape after subtraction of heart, kidneys, and bladder activity (*right*).

projections) was performed 150 min later, in a 256*1024 matrix. All acquisitions were planar, and no myocardial single-photon emission computed tomography (SPECT) study was performed. Images were acquired by different gamma cameras using low-energy, high-resolution collimators and an appropriate scan speed to reach over 2.000.000 counts. Each scintigraphy was evaluated, using the Perugini visual score[8] (Fig. 1) and with a semiquantitative score based on the ratio of Heart Retention (HR) on Whole-Body Region of interest (HR/WBR), without counts in hearth, kidneys, and bladder (Fig. 2).

Statistical Analysis

Continuous variables are expressed as median values and standard deviation, and categorical variables as frequencies and percentages. Multiple comparisons for continuous variables were performed with ANOVA followed by Scheffè test for post hoc analyses. Area under the receiver operating characteristics curve (ROC) analysis was performed to determine the best HR/WBR cut-off value to correctly identify TTR CA amyloidosis patients.

All statistical analyses and comparisons were performed with SPSS 20 Version IBM Package and we considered statistical significance a P value < 0.05.

RESULTS

Study Population

Our study population consisted in 131 patients with suspected CA. According to the above-mentioned criteria, 65 patients were finally diagnosed with CA, while after thorough diagnostic work-up 20 subjects showed LVH not caused by amyloid infiltration. In this subgroup, 16 patients showed hypertensive cardiomyopathy, while in four patients a genetically confirmed diagnosis of hypertrophic cardiomyopathy (HCM) was performed.

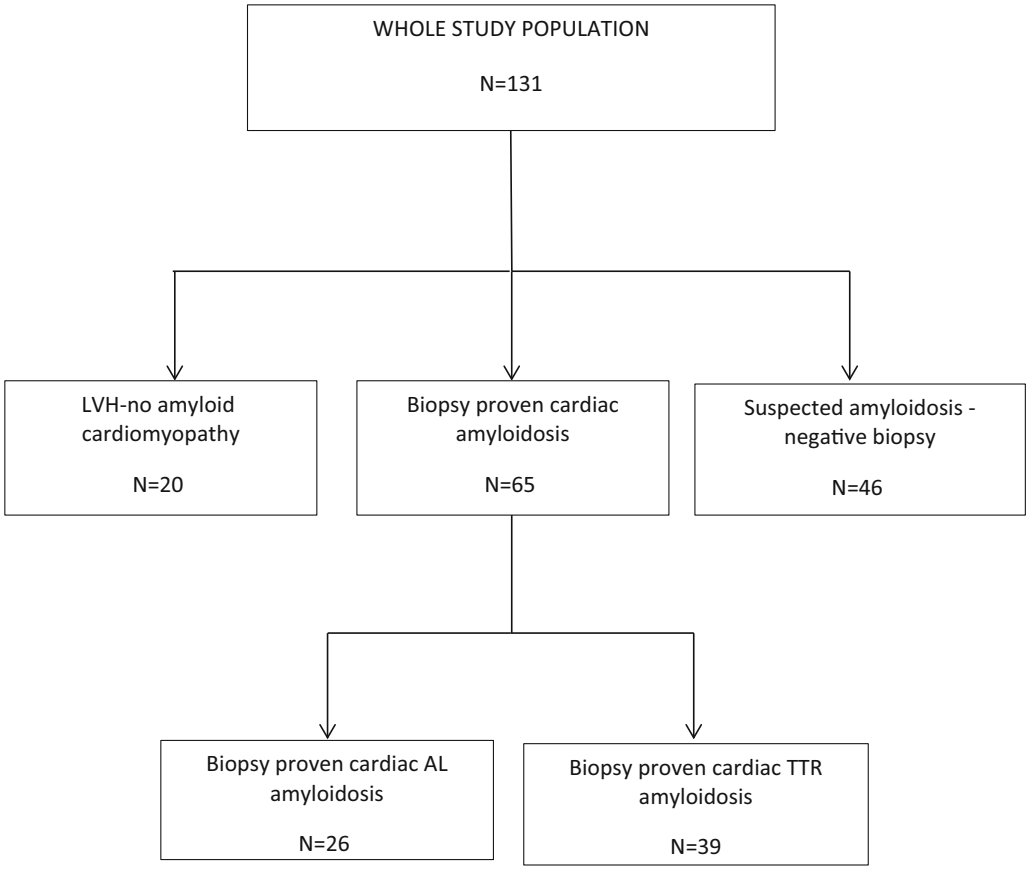

Figure 3. Study population flow chart.

After initial diagnostic procedures, 46 patients showed highly suggestive non-invasive imaging test for CA with repeated negative fat pad or salivary gland biopsies. Those patients refused cardiac biopsy or such an invasive procedure was considered unethical due to patient status/age; therefore, this group of patients was excluded (Fig. 3).

Among patients with biopsy-proven CA, 26 patients had AL, 16 had TTRm (five patient with Val 122Ile and 11 with Ile68Leu mutation), and 23 patients suffered of TTRwt. In AL patients, biopsy site was abdominal fat in ten patients (38%), bone marrow in 7 (27%), myocardium in 5 (19%), both fat pad and bone marrow in 4 (16%). In TTR patients, biopsy site was abdominal fat in 23 patients (59%), myocardium in 15 (39%), and minor salivary gland in 1 (2%).

Demographic and clinical characteristics of three groups are reassumed in Table 1.

A significant difference in NT-proBNP level was present between groups with lower values in TTR patients and higher values in AL amyloidosis patients. AL patients showed also the highest proportion of subjects with overt symptoms of heart failure (NYHA class III-IV). No significant differences were observed in echocardiographic variables between groups, except for a significant increase in left ventricular posterior wall thickness in TTR CA patients.

99mTc-HMDP Total-Body Scintigraphy

As shown in Table 2, only two patients with AL CA demonstrated a mild heart uptake at Tc-HMDP scintigraphy, grade 1 according to Perugini score, while 24 showed no bone tracer cardiac uptake. Conversely, all patients diagnosed with TTR CA showed Tc-HMDP heart uptake with 3 subjects showing grade 1 Perugini visual score, 16 grade 2, and 20 grade 3 score.

These results indicate that a positive Tc-HMDP-TB scintigraphy (grade 1-3, cardiac uptake) showed a 100% sensitivity for TTR CA identification and a 96% specificity (negative scan in 44 of 46 patients without TTR CA). Furthermore, considering three patients with grade 1 scan in TTR group, a Perugini grade 2-3 cardiac uptake on a HMDP scintigraphy showed a 93% sensitivity and a 100% specificity.

Analyzing cardiac Tc-HMDP uptake, using a semi-quantitative method (HR/WBR), TTR patient showed significantly higher values compared to other groups

Table 1. Demographic and clinical characteristics

	AL (N = 26)	TTR (N = 39)	LVH (N = 20)	*P*
Age, years	73.1 ± 11	78.7 ± 8.1	78.7 ± 8.3	0.044
Gender, M/F	18 (69%)/8	33 (85%)/6	16 (80%)/4	0.373
NYHA class, III-IV	19/26 (73%)	14/39 (36%)	9/20 (45%)	0.022
Creatinine, mg/dL	1.1 ± 0.3	1.14 ± 0.47	0.79 ± 0.60	0.788
NT-proBNP, ng/ml	11914 ± 14176	4145 ± 2690	8545 ± 10734	0.008
IVS, mm	16.1 ± 1.7	17.9 ± 4	17.1 ± 3.3	0.103
PW, mm	14.1 ± 2.4	16.3 ± 3.1[a]	15.1 ± 3	0.001
LVEDV, ml	85.1 ± 30.3	91.7 ± 22.8	89.2 ± 35.8	0.666
LVESV, ml	42.7 ± 19.5	46.7 ± 20.1	47.1 ± 26.7	0.743
EF, %	52 ± 11	48.2 ± 1.4	56.1 ± 10.7	0.143
E, cm/s	81.8 ± 24.5	87.6 ± 17.7	80.8 ± 26.5	0.502
A, cm/s	51.6 ± 24.6	52.4 ± 22.4	62.2 ± 27.3	0.546
E/A	1.9 ± 1.1	2.1 ± 0.9	1.2 ± 0.8	0.149
DT, ms	190 ± 70	173 ± 54	213 ± 71	0.189
E/E'	16.8 ± 6.8	17.8 ± 4.2	17.5 ± 6.4	0.821
PASP, mmHg	40.1 ± 9.9	37.4 ± 9.5	36.8 ± 14.7	0.526
TAPSE mm	16.1 ± 3.6	17.1 ± 4.6	19.4 ± 3.6	0.089

AL, Light-chain amyloidosis; *TTR*, transthyretin amyloidosis; *LVH*, left ventricular hypertrophy; *NYHA*, New York Heart Association; *IVS*, interventricular septum; *PW*, posterior wall; *LVEDV*, left ventricular end-diastolic volume; *LVESV*, left ventricular end-systolic volume; *EF*, ejection fraction; *DT*, deceleration time; *PASP*, Pulmonary artery systolic pressure; *TAPSE*, Tricuspid Annular Systolic Excursion
[a] post hoc analysis $P < 0.05$ TTR vs other groups

Table 2. Scintigraphic characteristics

	AL (N = 26)	TTR (N = 39)	LVH (N = 20)	*P*
Perugini score				
Score 0	24 (92%)	0	20 (100%)	0.0001
Score 1	2 (8%)	3 (7%)	0	
Score 2	0	16 (41%)	0	
Score 3	0	20(52%)	0	
HR/WBR	2.2 ± 0.4	6.2 ± 1.4[a]	1.6 ± 0.7	0.0001

HR, Heart retention; *WBR*, whole-body retention; *AL*, light-chain amyloidosis; *TTR*, transthyretin amyloidosis; *LVH*, left ventricular hypertrophy
[a] post hoc analysis $P < 0.05$ TTR vs other groups

(Table 2). Moreover, HR/WBR was similar between AL amyloidosis patients and subjects with LVH, with no overlapping with TTR group. Accordingly to ROC curve analysis, using a 3.3 HR/WBR cut-off value an accuracy of 100% was achieved for TTR CA identification (Fig. 4).

DISCUSSION

Our study confirms that 99mTc-HMDP scintigraphy is a useful tool for differentiating AL and TTR CA.

Diagnosis of CA is often challenging, especially in elderly patients, in the presence of dual pathologies, acting as confounding factors, such as history of arterial hypertension or evidence of significant aortic stenosis. Moreover, in patients with TTRwt, sensitivity of extracardiac biopsy is often low, and endomiocardial biopsy (EMB) may be unethical or refused by patient due to periprocedural risk. Recently, Gillmore et al.[19] have demonstrated that bone scintigraphy enables diagnosis of cardiac TTR amyloidosis, without the need of histological confirmation in patients without

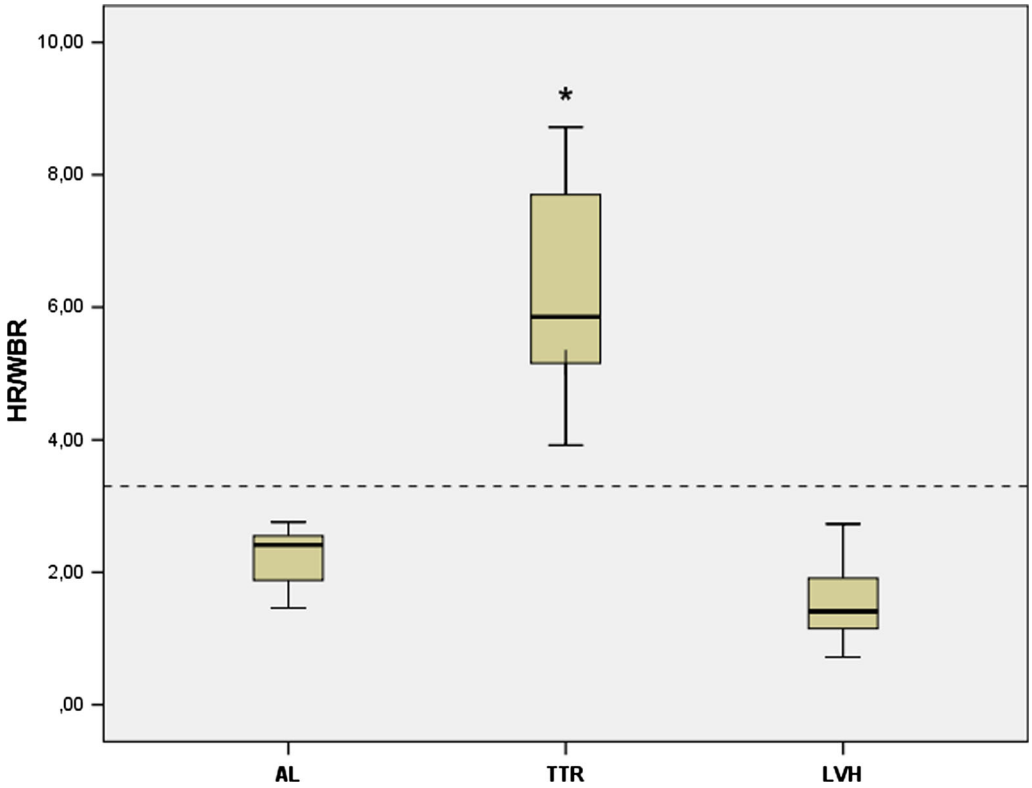

Figure 4. Comparison of 99mTc-Hydroxymethylene diphosphonate (Tc-HMDP) heart uptake in patients with TTR cardiac amyloidosis (TTR), AL cardiac amyloidosis (AL), and patients with left ventricular hypertrophy (LVH). The *dotted line* identifies a 3.3 cut-off value that is able to separate TTR cardiac amyloidosis patients from other two groups. *HR/WBR*, Heart retention/whole-body retention at Tc-HMDP scintigraphy. $*P < 0.05$ TTR cardiac amyloidosis vs other two groups.

monoclonal gammopathy. In his large multicenter study, the majority of patient underwent either a Tc-DPD or Tc-PYP scintigraphy, with Tc-HMDP scintigraphy performed in less than 10% of EMB population. Authors stated that Tc-HMDP has same clinical results of Tc-DPD and Tc-PYP, but admitted that, due to the small sample size, further studies were needed to test this hypothesis.

Our study minded this gap, demonstrating and confirming that Tc-HMDP is able to accurately identify patients with biopsy-proven TTR cardiomyopathy, with a very high sensitivity and specificity. In fact, all patients with TTR CA demonstrated a visually evident Tc-HMDP heart uptake (sensitivity 100%; specificity 96%). Furthermore, all patients with a visual score ≥ 2 were diagnosed with TTR CA (100% specificity; 93% sensitivity).

Moreover, our data demonstrated that with the use of an easy semiquantitative method such as HR/WBR, it is possible to correctly separate TTR CA patients from AL CA or other reason of LVH. This semiquantitative marker could be used, along with Perugini visual score, to help clinicians to correctly identify patients with TTR cardiomyopathy.

Two small single-center comparative studies suggested that Tc-DPD and Tc-PYP could be superior to TC-MDP in TTR amyloidosis identification.[22,23] Nevertheless, to the best of our knowledge, no comparative study has already been published between Tc-HMDP and other bone tracer in amyloidosis management. Therefore, our study, as already suggested by research by Glaudemans[15] et al and Galat et al[16] confirm that Tc-HMDP could be a valuable and effective alternative to Tc-DPD or Tc-PYP reaching comparable results in TTR amyloidosis identification. Therefore, in our opinion, Tc-HMDP is a valuable tracer to be used in TTR amyloidosis diagnostic route.

A limitation of our study is the small sample size mainly due to the fact that amyloidosis is a rare disease. Moreover, in our population, several patients refused cardiac biopsy or it has been considered unethical in elderly patients, reducing the group of subjects with certain CA. Further comparative studies among bone tracers are needed to confirm and extend these results.

CONCLUSIONS

Present findings demonstrated that Tc-HMDP is able to accurately identify patients with biopsy-proven TTR cardiomyopathy, with a very high sensitivity and specificity, maybe as accurate as Tc-DPD or Tc-PYP, and may therefore *de facto* be considered a valuable tool for the diagnosis of TTR CA. Moreover, all patients with a Perugini visual score ≥ 2 were diagnosed with TTR CA. Furthermore, our data demonstrated that using an easy semiquantitative method such as HR/WBR, it is possible to correctly distinguish TTR CA from AL CA, or LVH of various etiologies. Therefore, 99mTc-HMDP could be de facto considered as an additional valuable radiotracer for the diagnosis of TTR amyloidosis.

NEW KNOWLEDGE GAINED

Tc-HMDP scintigraphy is as accurate as Tc-DPD or Tc-PYP in TTR CA identification, and may therefore *de facto* be considered a valuable tool for the diagnosis of TTR CA. Moreover using an easy semiquantitative method such as HR/WBR it is possible to correctly distinguish TTR CA from AL CA, or LVH of various etiology.

Disclosure

The authors declare that they have no conflict of interest.

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