

Article

A Potential Approach to Bridge the Diagnostic Gap and Propose a Referral Pathway for Suspected ATTR-CA Based on Incidental Cardiac Uptake in ^{99m}Tc -MDP Bone Scans: A Pilot Descriptive Study

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Abstract

Background/Objectives: Early diagnosis of cardiac amyloidosis is crucial to improve patient outcomes. Although ^{99m}Tc -MDP is less sensitive than other bone-avid tracers for detecting ATTR-CA, it is widely used for routine bone imaging in this region. Incidental cardiac uptake on ^{99m}Tc -MDP bone scintigraphy may therefore offer a practical opportunity for identifying suspected ATTR-CA in resource-limited settings. To evaluate incidental cardiac uptake, warranting further evaluation for ATTR-CA on routine ^{99m}Tc -MDP bone scans as an incidental flag method for patients who require further evaluation and to propose a referral pathway in resource-limited settings. **Methods:** A retrospective review of 229 patients was performed. The assessment of myocardial uptake was performed using the Perugini visual score and H/CL ratio analysis. Patients' medical records were reviewed, and available cardiac imaging reports were evaluated for further assessment of cardiac involvement. **Results:** Nine patients demonstrated a Perugini score = 2; of these, five underwent echocardiography, demonstrating abnormalities that may indicate amyloid involvement. No patient had confirmatory ATTR-CA testing, AL-CA exclusion testing, (CMR), biopsy, or amyloid typing. In patients without prior cardiac disease, echocardiographic abnormalities may potentially represent subclinical disease, such as cardiac amyloidosis, though this requires further confirmation. In patients with HTN or diabetes, the echocardiographic changes may be attributed to the underlying conditions. Echocardiographic characteristics suggestive, but not specific, for cardiac amyloidosis were observed in patients selected based on positive ^{99m}Tc -MDP uptake. **Conclusions:** Incidental cardiac uptake with a Perugini score ≥ 2 can highlight patients for ATTR-CA investigation. These results provide preliminary evidence that incidental ^{99m}Tc -MDP cardiac uptake can flag patients who require further evaluation for ATTR-CA and support the implementation of a referral pathway from local evaluation to a specialized center.

Keywords: incidental cardiac uptake; ^{99m}Tc -MDP bone scintigraphy; ATTR-CA; bone-avid tracers; referral pathway; resource-limited settings



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1. Introduction

Cardiac amyloidosis (CA) is an infiltrative cardiac disease caused by the extracellular deposition of amyloid fibrils within the heart. It is primarily caused by two types of amyloid protein deposition: immunoglobulin light chains (AL-CA) and transthyretin (ATTR-CA). CA can lead to restrictive cardiomyopathy and a significant increase in morbidity and mortality rates, and while the progression of CA varies considerably, if left untreated, it typically leads to progressive heart failure and even death [1–3]. A previous report showed that the prevalence and incidence of the disease increased from 18 to 55.2 and from 8 to 16.6 per 100,000 person-years, respectively, between 2000 and 2012 [4,5]. The disease predominantly affects elderly men with certain clinical clues that should raise high suspicion, such as left ventricular wall thickening, diastolic dysfunction, heart failure with preserved ejection fraction (HFpEF), severe aortic stenosis, pericardial effusion, and reduced global longitudinal strain with apical sparing [1,4,5].

Timely detection of CA is crucial for effective disease management, making early diagnosis necessary. In the past, the diagnosis of CA relied primarily on invasive endomyocardial biopsy (EMB), which was often performed at later stages of the disease. This reliance was likely due to limited awareness of CA and the lack of alternative non-invasive diagnostic methods. This highlights the importance of non-invasive diagnostic tools in supporting early and accurate diagnosis of CA, ultimately improving patient outcomes [6–8].

Biomarkers play an important role in the early detection of cardiac involvement. N-terminal pro-Brain natriuretic peptide (NT-proBNP) and troponin are important markers of disease severity, with elevated levels indicating worse outcomes. Additionally, serum free light-chain assay and serum/urine immunofixation are essential biomarkers for detecting monoclonal proteins, which are required to distinguish AL-CA from ATTR-CA. Monoclonal protein testing is assessed early in the diagnostic algorithm, as differentiating between the two types is critical because diagnosis and management proceed differently [1,9].

Additionally, recent advancements in ATTR-CA therapies have demonstrated promising results, especially at early stages. For instance, tafamidis, a Food and Drug Administration (FDA)-approved drug for treatment of ATTR-CA, has shown reduced all-cause mortality and cardiac-related hospitalization compared to the placebo group. Since tafamidis appears to be more effective before the disease progresses to advanced stages, early diagnosis is essential to maximize treatment effectiveness. Recent advances also include transthyretin gene-silencing therapies such as patisiran and vutrisiran. The idea that early diagnosis of ATTR-CA can enhance treatment efficacy has prompted initiatives to raise awareness about a multidisciplinary diagnostic approach for patients with suspected ATTR-CA [10–13].

The diagnosis of ATTR-CA can be established through a multimodality imaging approach. Echocardiography is considered the first-line modality for patients with suspected ATTR-CA. It is widely accessible, portable, low cost, and quick to perform, making it an ideal initial imaging test. Cardiac magnetic resonance (CMR) is considered a complementary modality that supports echocardiographic findings. CMR offers high spatial resolution and tissue characterization. However, CMR is associated with higher cost and limited availability [14,15].

Recent advancements in cardiac scintigraphy with bone-avid tracers, along with increased awareness and improvement of different non-invasive diagnostic tools and therapies, have significantly enhanced the early diagnosis of ATTR-CA. These approaches are helping to shift the perception of this condition from a rare, often underdiagnosed disease to one that is more clinically recognized [2,16]. It has become evident that cardiac scintigraphy using bone tracers can non-invasively diagnose ATTR-CA and differentiate it from AL-CA with high sensitivity and specificity in certain clinical scenarios [2,6,17].

In cases of suspected ATTR-CA, myocardial uptake can be evaluated using qualitative and semi-quantitative methods. The qualitative assessment employs the Perugini visual score to grade myocardial uptake. A score of 0 indicates absence of cardiac uptake with normal bone (rib) uptake; a score of 1 reflects mild cardiac uptake, less than that of the bone (rib); a score of 2 represents moderate cardiac uptake, equivalent to bone (rib) uptake; and a score of 3 implies strong cardiac uptake that exceeds bone (rib) uptake. Additionally, semi-quantitative analysis is performed by calculating the heart-to-contralateral (H/CL) ratio. This ratio is determined by drawing a circular region of interest (ROI) over the heart and a corresponding ROI in the contralateral lung [7,8,18]. ATTR-CA can be diagnosed non-invasively if the visual score on cardiac scintigraphy using bone tracers is ≥ 2 , and AL-CA is ruled out by monoclonal protein tests, including negative serum free light chains and serum and urine immunofixation tests. Additionally, an H/CL ratio of ≥ 1.5 at 1 h or ≥ 1.3 at 3 h can further assist in the diagnosis of ATTR-CA under these conditions. Once ATTR-CA is confirmed, genetic testing can be performed to differentiate between hereditary and wild-type ATTR-CA [8,19,20]. It must be noted that although ATTR-CA can be diagnosed non-invasively in some scenarios, EMB remains the gold-standard diagnostic tool in other situations. EMB can be considered in cases with no cardiac uptake but a high suspicion of cardiac amyloidosis, as well as in cases with positive cardiac uptake and one or more positive tests for monoclonal proteins [14,19,20].

Pyrophosphate (^{99m}Tc -PYP), 3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), and hydroxymethylene diphosphonate (HMDP) are technetium-99m (^{99m}Tc)-labeled bone-avid radiopharmaceuticals that serve as promising non-invasive diagnostic tools in the evaluation of ATTR-CA [21]. Additionally, ^{99m}Tc methylene diphosphonate (MDP) is a widely available bone-seeking radiotracer that has exhibited accumulation in the cardiac regions of patients with confirmed or suspected ATTR-CA in individual case reports [6,22,23]; however, it is less sensitive compared to ^{99m}Tc -PYP, ^{99m}Tc -DPD, and ^{99m}Tc -HMDP [17,18,24]. Despite its lower sensitivity compared to other radiotracers, the widespread use of ^{99m}Tc -MDP in this region for routine bone imaging with various clinical indications might increase the likelihood of detecting incidental cardiac uptake and identifying potentially underdiagnosed populations.

Therefore, this study aims to retrospectively identify incidental cardiac uptake warranting further evaluation for ATTR-CA on routine ^{99m}Tc -MDP bone scans. We seek to demonstrate that such findings can serve as an opportunistic detection method to flag patients who may benefit from additional assessment, particularly in settings where access to laboratory tests or specific imaging such as ^{99m}Tc -PYP is limited. Recognizing these diagnostic challenges, the study also proposes a referral pathway to ensure timely and specialized patient management.

This opportunistic detection aligns with future directions to reduce diagnostic delays by leveraging existing imaging modalities for early detection in resource-limited settings. Ongoing research should prioritize developing more effective disease management strategies and integrating advanced imaging techniques that enhance sensitivity and specificity to differentiate ATTR-CA from AL-CA. The field emphasizes advancing non-invasive diagnostic tools, therapies, and patient management strategies that eliminate the need for invasive biopsy. While challenges persist across various aspects of the disease, both current and future investigations should address these issues while maintaining a focus on the safety, availability, and cost-effectiveness of the disease clinical approaches [25,26].

2. Materials and Methods

This study was approved by the Unit of Biomedical Ethics, Research Ethics Committee at the Faculty of Medicine at King Abdulaziz University, and King Abdulaziz University Hospital (Reference No. 396-24).

2.1. Study Design

A retrospective review of patients' records was done at King Abdulaziz University Hospital (KAUH) to identify incidental cardiac uptake, warranting further evaluation for ATTR-CA. All patients between December 2023 and May 2025 who had undergone ^{99m}Tc -MDP bone scans (MON.MDP KIT, Eczacıbaşı Monrol, Istanbul, Turkey, or MDP Tc-IK-10, Izotop, Institute of Isotopes Co., Ltd., Budapest, Hungary) were selected. In this study, all patients were scanned using the same imaging protocol. Patients were intravenously injected with 22–25 mCi of ^{99m}Tc -MDP. An anterior–posterior whole-body (WB) image was acquired 2–3 h post-injection to allow for optimal tracer biodistribution. In some cases, the WB image was followed by single-photon emission computed tomography/computed tomography (SPECT/CT) images. Image acquisition was performed using the Discovery 670 gamma camera (GE Healthcare, Milwaukee, WI, USA) and the SYMBIA T6 gamma camera (Siemens Healthcare GmbH, Erlangen, Germany).

To assess radiotracer pattern, qualitative assessment of myocardial uptake was performed using the Perugini visual score, and semi-quantitative analysis was performed to calculate the H/CL ratio for all scans. Perugini visual score for all cases was performed by a nuclear medicine consultant to ensure expert evaluation of the uptake in the myocardium and ribs. The Perugini visual assessment was conducted on anterior planar images, with a dedicated zoomed evaluation of the chest to assess myocardial tracer uptake in relation to the ribs. In line with expert consensus [27,28], SPECT images were additionally reviewed, when available, to visually confirm diffuse myocardial tracer uptake. H/CL measurement was obtained by placing two identical regions of interest (ROIs) in an anterior planar image at the level of the sternum on both sides of the chest (one over the heart and a corresponding ROI in the contralateral lung) (Figure 1). H/CL ratio was calculated as the ratio of the heart ROI mean counts to contralateral lung ROI mean counts. Both assessments were conducted independently and blinded to each other's results, ensuring unbiased measurements.



Figure 1. Semi-quantitative method for H/CL uptake measurement on planar imaging at 3 h post-tracer injection of ^{99m}Tc -MDP. Placement of ROI over the heart (A) and contralateral lung (B) is shown.

2.2. Study Population and Data Collection

A total of 248 ^{99m}Tc -MDP bone scans were initially included in the dataset. Most of these scans were performed for oncology purposes and cancer staging. To establish the suspected diagnosis of ATTR-CA based on positive cardiac uptake in ^{99m}Tc -MDP bone scans, a combination of a Perugini score of ≥ 2 and an H/CL ratio of ≥ 1.3 was initially required. However, a recent report on interpretation and reporting of cardiac scintigraphy with bone-avid tracers in suspected ATTR-CA [29] highlights the Perugini score as the primary indicator, while the H/CL ratio as an optional and supportive tool. Consequently, scans with a Perugini score of ≥ 2 and an H/CL ratio < 1.3 were also considered positive. Additionally, for all patients, medical records were reviewed to identify any cardiac imaging undertaken. For patients with available cardiac imaging, the corresponding reports were collected and evaluated to support further assessment of cardiac involvement. For positive patients according to the study criteria, nuclear medicine reports were reviewed to assess sternal and rib metastases that could confound cardiac uptake.

In cases where multiple scans were available for the same patient, only the initial scan was included for the analysis. This approach was adopted to prevent potential bias from counting multiple observations from the same patient and ensure that each patient contributes only to one data point to the study. We found no cases among patients with multiple scans in which the first scan did not meet the suspected ATTR-CA study criteria but a subsequent scan did. Following this, the final number of scans included in the study was 229 ^{99m}Tc -MDP bone scans, with a median patient age = 57 years (0.67–87) at the time of the scan; 69% ($n = 158$) were female.

Data were collected and analyzed using Microsoft Excel (Microsoft 365 Apps for Enterprise), version 2605 (Build 20026.20112). Descriptive statistics were used to summarize patients' characteristics and study outcomes. Patients' age was expressed as median with range, while categorical values (gender, Perugini score, and cancer type) were expressed as frequency and percentages. Missing data were reported as unavailable and were not imputed. Percentages were calculated using the available denominator. Repeated scans were excluded before applying the study positivity criteria. As this is a pilot descriptive study, no formal hypothesis testing or prespecified statistical plan was undertaken.

3. Results

Among the 229 ^{99m}Tc -MDP bone scans reviewed, nine scans (3.9%, 95% CI: 1.8–7.3%) met the study criteria and had a Perugini score of 2, while the remaining 220 scans had a Perugini score of 0 or 1, with no scans having a Perugini score of 3. This percentage represents only the frequency of scans meeting the predefined study criteria within this retrospective oncology-based cohort and should not be interpreted as the prevalence of ATTR-CA, diagnostic yield, or diagnostic accuracy of ^{99m}Tc -MDP. None of the nine patients has sternal or rib metastases that could confound cardiac uptake. Their records showed no cardiac-related imaging except for echocardiograms, which had been performed for five of the nine patients. Figure 2 represents the participants' flow diagram and illustrates the selection process from the initial assessment to the final number of scans that met the study criteria. Among patients who met the study criteria, the median age at the time of the scan was 68 years (44–79), with a predominance of females (66.7%). Seven of the nine positive patients were ≥ 65 years. Among all female patients undergoing ^{99m}Tc -MDP bone scans, 69.6% had breast cancer-related clinical indication (primary tumor evaluation or bone involvement), whereas among male patients, the majority had prostate cancer-related indications (33.8%), followed by bladder cancer (11.3%). Notably, all female patients who met the study criteria had breast cancer-related indications for the ^{99m}Tc -MDP bone scans, while all males presented with bladder cancer. Out of nine patients who underwent ^{99m}Tc -

MDP bone scans and showed cardiac uptake with a Perugini score of 2, five patients had H/CL ratios of ≥ 1.3 (1.64, 1.32, 1.36, 1.32, and 1.33), of which two patients (patient 1: 1.64 and patient 2: 1.32) had echocardiogram findings. The remaining four patients had H/CL ratios < 1.3 (1.01, 1.01, 0.98, 0.96), of which three patients (patient 3: 1.01, patient 4: 1.01, and patient 5: 0.98) had echocardiogram findings.

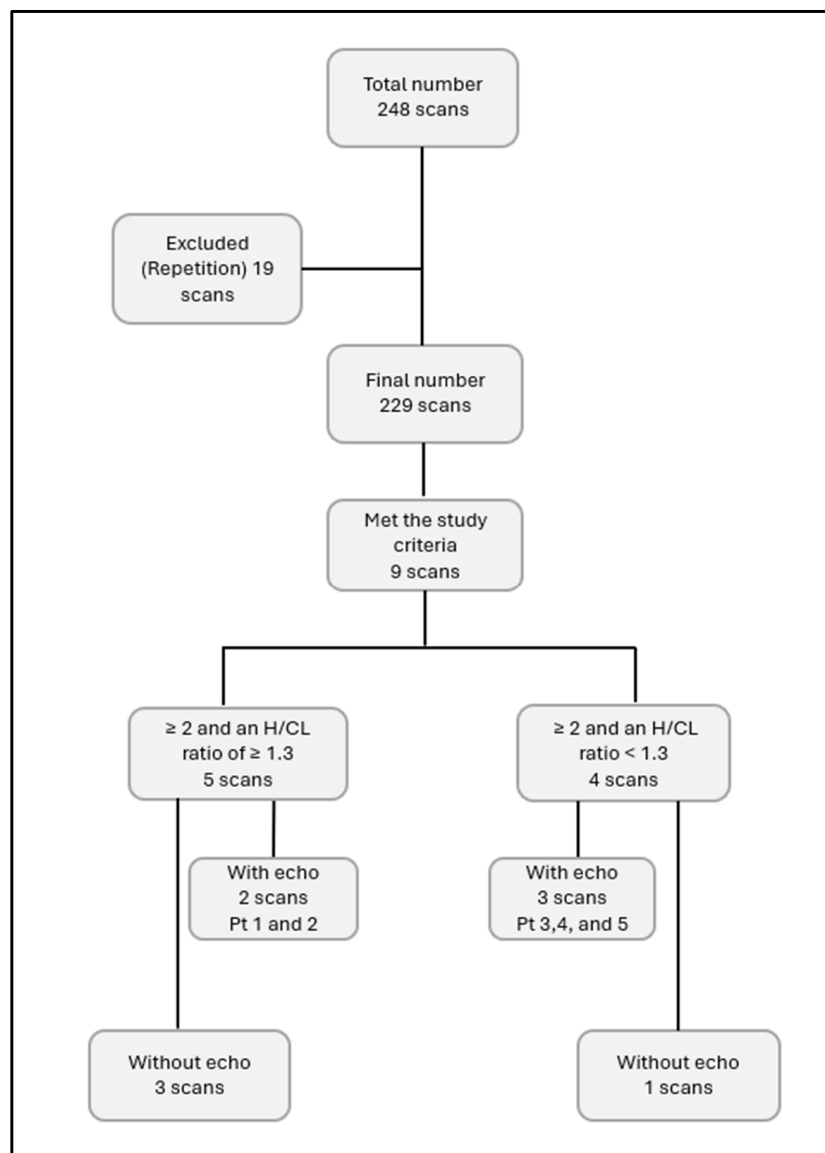


Figure 2. Flow diagram illustrating the selection process from the initial assessment to the final number of scans that met the study criteria. Pt: Patient.

Table 1 represents the clinical and echocardiogram characteristics of the five patients with echocardiogram findings. Except for one patient (patient five), all underwent echocardiograms for cancer-related indications, as part of pre-operative evaluation or chemotherapy assessments. Echocardiographic evaluation of patients one and two revealed normal interventricular septal (IVSd) and left ventricle posterior wall thickness (LVPWd). Patient one demonstrated normal systolic function with mildly reduced ejection fraction (EF) and elevated estimated pulmonary artery (PA) systolic pressure. Patient two showed grade 1 LV diastolic dysfunction (impaired relaxation), with normal left atrial filling pressure, a mildly dilated left atrium (LA), and preserved EF. Both patients exhibited thickening of mitral and aortic valves with mild aortic valve stenosis in patient two. Patient three, with a history of

hypertension (HTN) and diabetes mellitus, demonstrated mild concentric LV hypertrophy with moderately increased IVSd and LVPWd. Echocardiography revealed grade 1 LV diastolic dysfunction with preserved EF, elevated left atrial filling pressure, moderately dilated left atrium, and thickening of the mitral and aortic valves. Patient four, with a history of HTN, showed normal IVSd and LVPWd, with preserved EF and mildly increased LV size. Abnormal findings included grade 2 LV diastolic dysfunction (pseudonormal pattern) with elevated left atrial filling pressure, moderately dilated left atrium, elevated estimated PA systolic pressure, and thickening of the mitral and aortic valves. Finally, Patient five, with a history of heart failure with reduced ejection fraction (HFrEF), HTN, Ischemic heart disease (IHD), and diabetes mellitus, demonstrated normal IVSd and LVPWd. Echocardiography revealed grade 1 LV diastolic dysfunction and markedly decreased LV systolic function with severely reduced EF. Additional findings included small pericardial effusion and thickening of the mitral and aortic valves. Figures 3 and 4 show SPECT and CT images taken 3 h post- ^{99m}Tc -MDP injection, illustrating cardiac uptake with a Perugini score of 2 and either an H/CL ratio of ≥ 1.3 or < 1.3 for patients with a history of echocardiography, respectively. Similarly, Figures 5 and 6 display images representing the same patient groups without a history of echocardiography.

Table 1. Clinical and echocardiogram characteristics of the five patients with echocardiogram findings.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Gender	F	F	F	M	M
Age	68	44	76	79	75
^{99m}Tc -MDP scan indication	Breast Ca	Breast Ca	Breast Ca	Bladder Ca	Bladder Ca
Perugini score	2	2	2	2	2
H/CL	1.64	1.32	1.01	1.01	0.98
Echocardiogram indication	Pre-operative assessment	For chemo assessment	On-chemo assessment to R/O IE *	Pre-operative assessment	HFrEF, HTN, IHD, DM *
Time interval to ^{99m}Tc -MDP bone scans	17 days before	15 days after	110 days after	56 days before	18 days before
LV wall thickness					
IVSd * (mm)	10	8	13	10	10
LVPWd * (mm)	11	9	13	10	8
LV dimension					
LV size	Normal	Normal	Normal/ Mild concentric Hypertrophy	Increased	Normal
LV function					
EF * (%)	54	58	57	58	30
LV Diastology					
E Vmax * (m/s)	0.99	0.57	0.55	0.98	0.80
A Vmax (m/s)	0.95	0.83	1.24	0.91	1.22
E/A	1.05	0.68	0.45	1.08	0.65
e' medial (m/s)	-	0.07	0.03	0.06	-
E/e' medial	-	8.05	15.82	15.48	-
MV DecT * (ms)	222	173	-	263	171
Other					
Biatrrial size	Normal	LA * is mildly dilated	LA is moderately dilated	LA is moderately dilated	Normal
PA * pressure (mmHg)	43.9	21.5	16.3	57.3	26
MV thickening	Yes	Yes	Yes	Yes	Yes
Aortic valve thickening/stenosis	Yes/No	Yes/Yes	Yes/No	Yes/No	Yes/No
Pericardial effusion	Trivial	No	No	Trivial	Small

* R/O IE = Rule out Infective Endocarditis; HFrEF = Heart failure with reduced ejection fraction; HTN = Hypertension; IHD = Ischemic heart disease; DM = Diabetes mellitus; IVSd = Interventricular septal thickness during diastole; LVPWd = Left ventricular posterior wall thickness during diastole; EF = Ejection fraction; Vmax = Maximum velocity; MV DecT = Mitral valve deceleration time; LA = Left atrium; PA = Pulmonary artery.

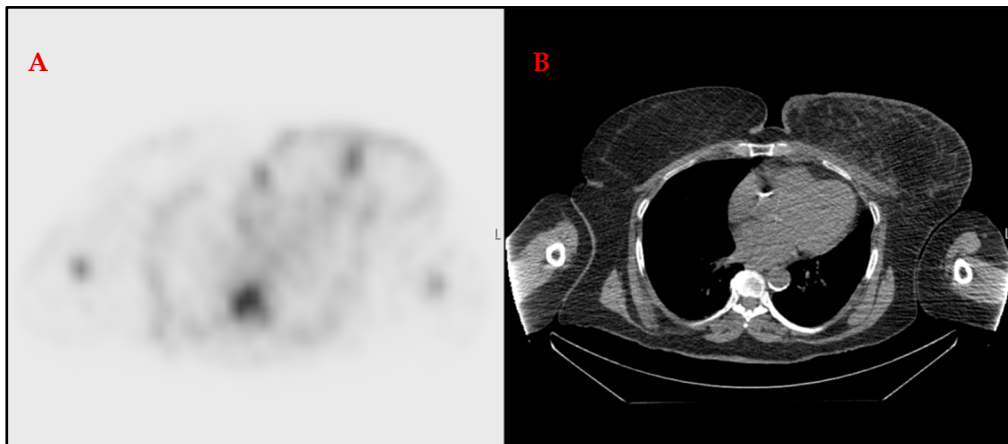


Figure 3. (A) SPECT and (B) CT images obtained 3 h post-injection of a 68-year-old female patient (Pt 1) who underwent a ^{99m}Tc -MDP scan demonstrating cardiac uptake with a Perugini score of 2 and $\text{H/CL} \geq 1.3$.

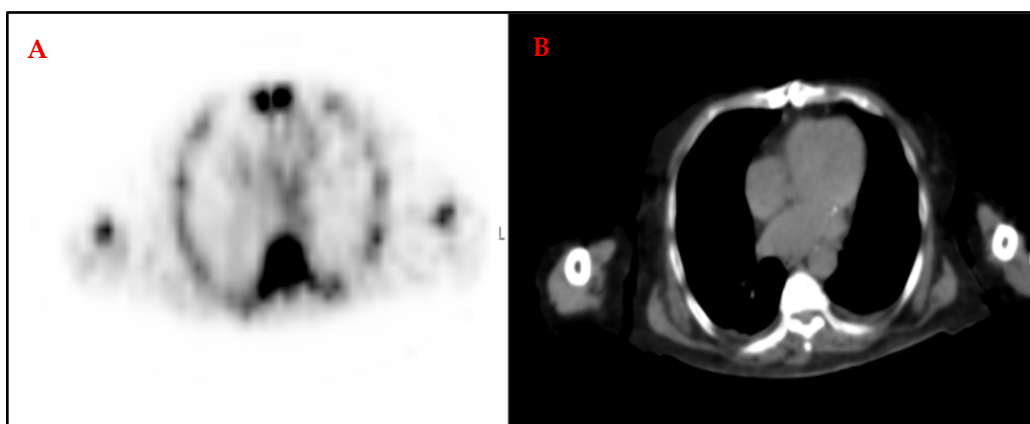


Figure 4. (A) SPECT and (B) CT images obtained 3 h post-injection of a 75-year-old male patient (Pt 5) who underwent a ^{99m}Tc -MDP scan demonstrating cardiac uptake with a Perugini score of 2 and $\text{H/CL} < 1.3$.

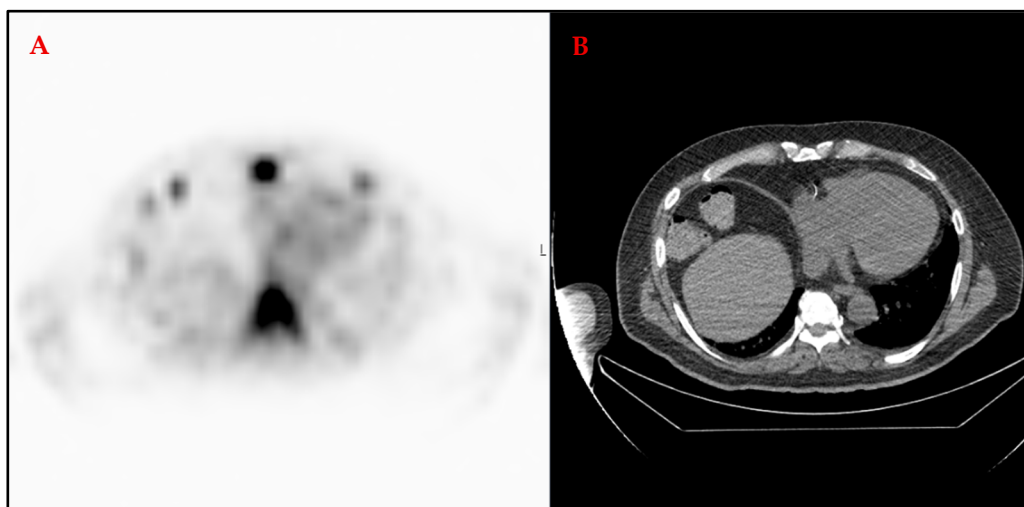


Figure 5. (A) SPECT and (B) CT images obtained 3 h post-injection of a 69-year-old male patient who underwent a ^{99m}Tc -MDP scan demonstrating cardiac uptake with a Perugini score of 2 and $\text{H/CL} \geq 1.3$.

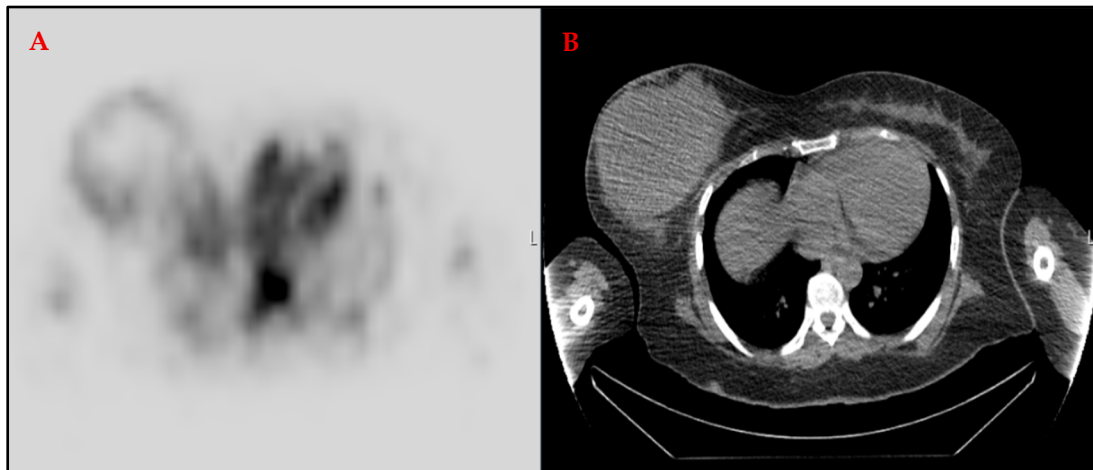


Figure 6. (A) SPECT and (B) CT images obtained 3 h post-injection of a 44-year-old female patient who underwent a ^{99m}Tc -MDP scan demonstrating cardiac uptake with a Perugini score of 2 and $\text{H/CL} < 1.3$.

The available echocardiograms were performed as part of routine oncologic care, including pre-operative and chemotherapy assessments, rather than as part of an amyloidosis-specific evaluation.

4. Discussion

In this retrospective study, incidental cardiac uptake, warranting further evaluation for ATTR-CA, was identified on ^{99m}Tc -MDP bone scans as a potential indicator for patients who need further evaluation in resource-limited settings. Myocardial uptake was evaluated using both Perugini and H/CL ratio assessment methods, and available cardiac imaging reports were reviewed to further assess cardiac involvement.

Among the original cohort, nine patients with cardiac uptake and a Perugini score of 2 were identified, representing 3.9% of the dataset. This finding should be interpreted in light of the known lower sensitivity of ^{99m}Tc -MDP for detecting cardiac amyloid uptake compared with tracers such as ^{99m}Tc -DPD or PYP [17,18,20]. Importantly, this study was designed to evaluate whether incidental ^{99m}Tc -MDP cardiac uptake can help flag patients with suspected ATTR-CA. This approach may help overcome diagnostic barriers in settings where AL-CA exclusion tests or specialized imaging, such as ^{99m}Tc -PYP, are not readily available and may facilitate timely patient referral to specialized centers for further assessment and management.

In this study, the Perugini score was used as the primary indicator for positive scans, as mentioned in the methods section. The H/CL thresholds currently used in clinical practice have been primarily derived from ^{99m}Tc -PYP protocols and have not been fully validated for routine ^{99m}Tc -MDP bone scintigraphy. Therefore, the H/CL values reported in this study should be interpreted descriptively rather than diagnostically. The apparent discrepancy between the Perugini score and the H/CL ratio observed in several patients likely reflects methodological differences between qualitative and semi-quantitative assessment, together with the limited validation of H/CL thresholds for ^{99m}Tc -MDP imaging. Although the H/CL ratio may provide supportive information, its interpretation is limited to positive cases where scans have a Perugini score ≥ 2 . In this study, only nine patients had a Perugini score of 2, with five patients having $\text{H/CL} \geq 1.3$ and four patients having $\text{H/CL} < 1.3$. Therefore, comparative analysis between the two groups could not be carried out.

Characterization of the positive cohort reveals important patterns relevant to implementation of the proposed referral pathway. Nine patients fulfilled the study criteria by

having a Perugini score of 2. Although the main sample included patients with a wide age range due to the study design, all nine patients were adults, with a median age of 68 years, which is consistent with ATTR-CA being predominantly a disease affecting older adults [5]. Six of the nine positive patients (66.7%) were female, which aligns with the original dataset that showed that most patients (69%) were females. All female patients who met the study criteria underwent ^{99m}Tc -MDP bone scans due to breast cancer-related indications. This finding is consistent with the reference population, where 69.6% of female patients had breast cancer-related indications for ^{99m}Tc -MDP bone scans. This is not surprising, as breast cancer is a significant global health burden and the leading cancer diagnosis in women [30,31]. On the other hand, all male patients (three patients) who met the study criteria underwent ^{99m}Tc -MDP bone scans for bladder cancer-related indications. This differs from the overall study population, in which most male patients had prostate cancer-related indications (33.8%) and only 11.3% presented with bladder cancer.

Previous case reports in elderly men have described incidental cardiac uptake suggestive of or consistent with ATTR-CA on ^{99m}Tc -MDP bone scans performed for prostate cancer or thyroid carcinoma [6,22,23]. However, to the best of our knowledge, incidental cardiac uptake in a ^{99m}Tc -MDP bone scan for bladder cancer had not been documented in the literature. Bone scans are routinely used for staging prostate cancer, which is one of the most frequently diagnosed malignancies in men [31], and since incidental cardiac uptake is more predominant in elderly patients [32], coexistence of the two conditions is plausible. In this study, although only three male patients met the study criteria, limiting the generalizability of the observation. This observation is presented descriptively only, and no association between bladder cancer and incidental cardiac ^{99m}Tc -MDP uptake can be inferred from the present study. Future studies with larger male cohorts are needed to determine whether there is an association between positive cardiac uptake on ^{99m}Tc -MDP bone scans and a history of bladder cancer that represents a true underlying relationship or simply reflects random variation due to small sample size.

In addition, the echocardiographic assessment of patients with a Perugini score of 2 on ^{99m}Tc -MDP bone scans in this study revealed a variable degree of cardiac involvement. Among the five patients with available echocardiographic data, four (patients two, three, four, and five) demonstrated diastolic dysfunctions, ranging from grade 1 (impaired relaxation) to grade 2 (pseudonormal pattern). Current literature indicates that although grade 1 diastolic dysfunction may be present in the early stages of the disease, most patients have grade 2 or more advanced dysfunction at the time of diagnosis [28,33].

In two patients (patients three and four), elevated filling pressure was also observed, in accordance with the amyloid infiltration pattern [28,34]. Additionally, LV hypertrophy with IVSd and LVPWd thickness exceeding 12 mm was observed in one patient (patient three), while all five patients exhibited thickening of the mitral and aortic valves, with aortic valve stenosis in one patient. These findings are consistent with cardiac amyloidosis manifestations [14,28,34,35]. However, it should be acknowledged that these echocardiographic findings are non-specific and that they may also be explained by other conditions.

For patients one and two, who had no known cardiac disease and were referred for echocardiography for non-cardiac indications, the echocardiographic abnormalities might reflect subclinical disease, such as early cardiac amyloidosis, particularly in the context of positive bone scintigraphy, though this requires further confirmation. In these patients, the cardiac uptake on ^{99m}Tc -MDP bone scans is more likely to represent an incidental but clinically relevant finding rather than being driven by known heart disease. However, for patients three and four, the echocardiographic changes could partly or predominantly result from their histories of HTN (and diabetes mellitus, for patient three), which are known to cause cardiac alterations that can mimic the effects of amyloid infiltration [28,34,36].

In such cases, the observed cardiac uptake in ^{99m}Tc -MDP may be influenced by these pre-existing conditions rather than indicating isolated ATTR-CA. Notably, all four patients demonstrated preserved EF, which is consistent with the typical presentation of many cardiac amyloidosis cases [14,28].

Patient five differed from the preceding cases by having HF rEF , HTN, IHD, and diabetes mellitus, which, unlike in the other patients, were the primary clinical indication for performing echocardiography. The patient exhibited grade 1 diastolic dysfunction and reduced LV systolic function, with markedly decreased EF. Although preserved EF is typical in many cases of cardiac amyloidosis, reduced EF may occur in more advanced stages of the disease [22,28]. In patient five, the pre-existing cardiac conditions and reduced EF, together with the targeted cardiac referral, are therefore more likely to have influenced, or even primarily caused, the observed cardiac changes and the positive ^{99m}Tc -MDP uptake.

Overall, the findings of this study indicate that positive ^{99m}Tc -MDP cardiac uptake (Perugini score of 2), along with echocardiography, can identify patients with cardiac abnormalities that may indicate ATTR-CA involvement, though these findings do not establish a definitive diagnosis. Echocardiographic characteristics suggestive of, but not specific for, cardiac amyloidosis were observed in patients selected based on positive ^{99m}Tc -MDP uptake. This supports the use of this imaging combination as a feasible initial approach that warrants further evaluation, particularly in resource-limited settings where more specific tracers or comprehensive laboratory testing are not readily available. Echocardiography has been used as an imaging modality in the evaluation of suspected cardiac amyloidosis, according to current reviews and experts' opinion [37–39]. However, coexisting cardiac conditions, especially when echocardiography follows targeted cardiac referral (such as in patient 5), may contribute substantially to the observed cardiac changes, making attribution to ATTR-CA alone challenging without additional testing.

Our data therefore suggest that all nine patients with positive ^{99m}Tc -MDP cardiac uptake should be considered for further evaluation: five with echocardiographic abnormalities suggestive of, but not specific for, cardiac amyloidosis (patients one through five), supported by imaging; and four without echocardiographic data due to the incidental scintigraphy finding alone. It should be noted that the absence of echocardiographic information in these patients does not imply negative results; rather, it reflects a lack of data in their records. Further work-up should include laboratory testing to exclude AL-CA, and scintigraphy with a more specific tracer for ATTR-CA [19,20]. The present results therefore provide preliminary evidence that incidental ^{99m}Tc -MDP cardiac uptake can serve as an opportunistic initial detection point for patients who require further evaluation for ATTR-CA. The results emphasize the need for standardized referral pathways for additional cardiology and amyloidosis evaluation. This approach would translate the preliminary observations into a practical pathway, minimizing diagnosis uncertainty and delay, particularly in resource-limited settings.

This study has several limitations that should be acknowledged. Due to the retrospective single-center design of the study, several limitations are introduced. Patient follow-up was hindered, making confirmation of additional imaging or diagnosis and follow-up on patients' records at other hospitals not feasible. Among these, some clinical data were missing from patients' medical records, which prevented collection of detailed clinical features for all patients, including ECG findings. Because the data were collected from a non-amyloidosis-specialized center and the echocardiograms were performed for non-amyloidosis indications, several key echocardiographic parameters and laboratory work were not available. These included global longitudinal strain, apical sparing, LV mass index, left atrial volume index, RV involvement, ECG voltage-to-mass discordance, NT-proBNP, and troponin. Fused SPECT/CT images could not be retrospectively retrieved from the

archived examinations. Future prospective studies should include fused SPECT/CT images to further improve anatomical localization of myocardial tracer uptake. Additionally, only a few patients were missing SPECT/CT images, and for these patients the Perugini score may be less accurate for visually confirming diffuse myocardial tracer uptake. Detailed patient-level documentation of SPECT/CT availability and fused myocardial localization was not consistently available in this retrospective study and should be systematically collected in future prospective studies. Further follow-up, including confirmation of ATTR-CA diagnosis, cannot be done; therefore, this study does not provide a definitive ATTR-CA diagnosis. No patient had confirmatory ATTR-CA testing, AL-CA exclusion testing, (CMR), biopsy, or amyloid typing. The positive sample size of the study is limited to nine patients in a single center, which limits the generalizability of the findings. The small number of positive cases has also restricted in-depth interpretation of the H/CL ratio within the positive sample. Larger multicenter studies are needed to validate the results and allow more robust analysis.

Proposed Referral Pathway in Resource-Limited Settings

Based on this study's findings and existing diagnostic workflow for ATTR-CA [14,19], a referral pathway can be proposed as an expert-informed suggestion, particularly for older adults with incidental ^{99m}Tc -MDP cardiac uptake in resource-limited settings (Figure 7). The pathway begins with incidental cardiac uptake on a ^{99m}Tc -MDP bone scan showing a Perugini score of ≥ 2 . All patients with a Perugini score of ≥ 2 warrant consideration for further evaluation. In such cases, the nuclear medicine report should describe the degree and pattern of cardiac uptake and recommend further cardiac evaluation to determine the underlying cause. The proposed referral pathway was not prospectively evaluated in this study and should be regarded as an expert-informed clinical framework requiring future validation.

The next step consists of a local cardiac assessment by the treating physician, including a review of the patient's clinical records and any available electrocardiography (ECG), echocardiography, or other cardiac imaging. Referral to a cardiologist may be warranted when findings suggest the need for specialist assessment, and if suspicion persists, referral to a specialized center for further amyloid evaluation is recommended. Among patients with a Perugini score of ≥ 2 , those with cardiac imaging abnormalities compatible with amyloid involvement on other imaging modalities should be prioritized over those without such abnormalities.

At specialized referral centers, recommended investigations include exclusion of AL-CA through serum and urine immunofixation plus serum free light-chain analysis. If AL-CA is excluded and suspicion for ATTR-CA persists, scintigraphy with a more specific ATTR-CA tracer (such as ^{99m}Tc -PYP) should be performed to confirm ATTR-CA non-invasively.

This pathway leverages routine ^{99m}Tc -MDP imaging as an accessible point of detection within the validated diagnostic workflow, facilitating earlier recognition of ATTR-CA in resource-limited settings while remaining aligned with current standards.

This proposed referral pathway is both cost-effective and feasible, particularly in resource-limited settings. ^{99m}Tc -MDP bone scintigraphy is widely available in this region and routinely available in most nuclear medicine departments. Importantly, ^{99m}Tc -MDP bone scintigraphy is already being performed for oncology purposes in this study population, making the detection of incidental cardiac uptake a cost-effective opportunistic method without additional cost. However, the final diagnosis cannot be confirmed without further testing.

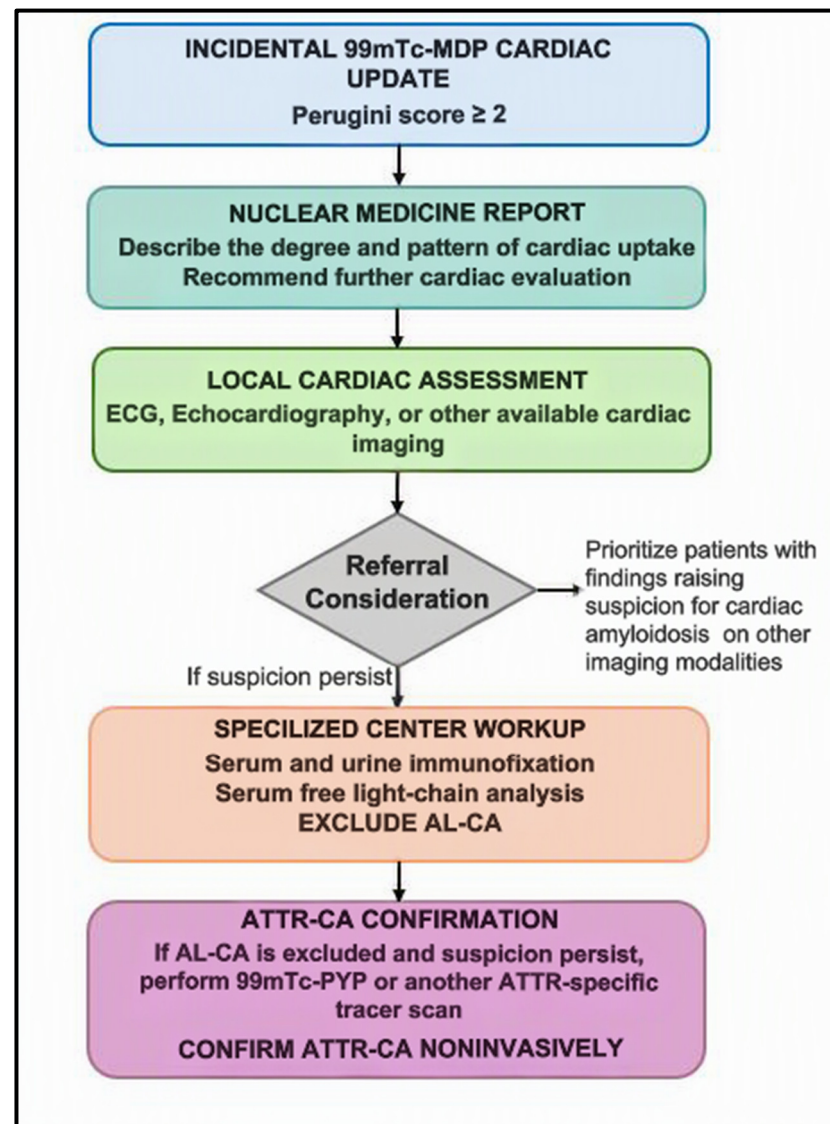


Figure 7. Proposed referral pathway for patients with incidental ^{99m}Tc -MDP cardiac uptake, utilizing routine imaging to facilitate earlier recognition of ATTR-CA in resource-limited settings, remaining aligned with current standards. Incidental cardiac uptake represents a trigger for further evaluation and not confirmation of ATTR-CA.

5. Conclusions

Cardiac amyloidosis is a progressive disease that can lead to substantial morbidity and mortality if not recognized early. Because early diagnosis is essential for appropriate management and improved outcomes, approaches that facilitate timely detection remain clinically important. This study retrospectively assessed incidental cardiac uptake on routine ^{99m}Tc -MDP bone scans as an opportunistic detection method for identifying possible ATTR-CA and proposing a referral pathway in resource-limited settings. The findings suggest that incidental cardiac uptake with a Perugini score ≥ 2 , particularly when accompanied by echocardiographic findings suggestive of, but not specific for, cardiac amyloidosis, may identify clinically relevant patients who warrant further evaluation. These findings occurred even when the bone scan and echocardiogram were obtained for non-cardiac indications.

Based on the findings of this study, a referral pathway can be proposed in which incidental ^{99m}Tc -MDP cardiac uptake with a Perugini score ≥ 2 is first reported in a nuclear

medicine report. Followed by local review of available cardiac imaging and a cardiologist review. Patients with persistent suspicion should then be referred to specialized centers for non-invasive confirmation of ATTR-CA.

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Data Availability Statement: The raw data supporting the conclusions of this article will be made available by the authors on request.

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