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Brief original article

Diagnosis of ATTR cardiac amyloidosis by ^{99m}Tc-PYP scintigraphy: case series

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ABSTRACT

Objectives. To describe the application of the noninvasive diagnostic algorithm for transthyretin cardiac amyloidosis (ATTR) using ^{99m}Tc-PYP scintigraphy in a Peruvian hospital. **Materials and Methods.** A descriptive case series was conducted between 2024 and 2025 at the Nuclear Medicine Department of Hospital Nacional Guillermo Almenara Irigoyen (Lima, Peru). Six patients with clinical suspicion of ATTR referred from Cardiology were included. A standardized protocol was applied, consisting of the administration of 20 mCi of ^{99m}Tc-PYP, planar imaging, and SPECT acquisition at 1 and 3 hours. Noninvasive diagnosis was established in the presence of visual myocardial uptake grade 2–3 (Perugini scale), confirmed by SPECT and after the exclusion of monoclonal plasma cell dyscrasia. The heart-to-contralateral lung (H/CL) ratio was used as a complementary quantitative parameter. **Results.** The average age was 69.7±10.3 years; 66.7% were male. All patients had left ventricular hypertrophy and 83.3% had heart failure. Three patients (50%) showed grade 2–3 uptake; among them, two (33.3%) met criteria for noninvasive ATTR diagnosis (grade 3, positive SPECT, and negative monoclonal screening), with H/CL values above diagnostic cutoffs. One grade 2 case had an IgG kappa monoclonal component and was classified as inconclusive. Three patients (50%) had grade 1 uptake, considered equivocal, with H/CL values below diagnostic thresholds. SPECT was essential to confirm true myocardial uptake and avoid overinterpretation in borderline cases. **Conclusions.** Structured application of the noninvasive diagnostic algorithm with ^{99m}Tc-PYP is feasible in our setting and allows for appropriate classification of patients with suspected ATTR.

Keywords: Amyloidosis; Radionuclide Imaging; Technetium Tc ^{99m} Pyrophosphate (Source: MeSH-NLM).

RESUMEN

Diagnóstico de amiloidosis cardíaca ATTR por gammagrafía con ^{99m}TC- PYP: serie de casos

Objetivos. Describir la aplicación del algoritmo diagnóstico no invasivo para amiloidosis cardíaca por transtiretina (ATTR) mediante gammagrafía con ^{99m}Tc-PYP en un hospital peruano. **Materiales y métodos.** Serie de casos descriptiva realizada entre 2024–2025 en el Servicio de Medicina Nuclear del Hospital Nacional Guillermo Almenara Irigoyen (Lima, Perú). Se incluyeron seis pacientes con sospecha clínica de ATTR derivados de Cardiología. Se aplicó el protocolo estandarizado con administración de 20 mCi de ^{99m}Tc-PYP, imágenes planares y SPECT a 1 y 3 horas. El diagnóstico no invasivo se estableció ante captación miocárdica visual grado 2–3 (escala de Perugini), confirmada por SPECT y con exclusión de discrasia monoclonal. La relación corazón/hemitórax contralateral (H/CL) se utilizó como parámetro cuantitativo complementario. **Resultados.** La edad media fue 69,7±10,3 años; 66,7% fueron varones. Todos presentaron hipertrofia ventricular izquierda y 83,3% insuficiencia cardíaca. Tres pacientes (50%) mostraron captación grado 2–3; de ellos, dos (33,3%) cumplieron criterios de ATTR no invasiva (grado 3, SPECT positivo y cribado negativo), con H/CL ≥ puntos de corte. Un caso grado 2 presentó componente monoclonal IgG kappa, clasificándose como no concluyente. Tres pacientes (50%) tuvieron captación grado 1, considerándose equívocos, con H/CL inferior a los umbrales diagnósticos. El SPECT permitió confirmar captación intramiocárdica y evitar sobreinterpretación en casos limítrofes. **Conclusiones.** La aplicación estructurada del algoritmo diagnóstico no invasivo con ^{99m}Tc-PYP es factible en nuestro medio y permite clasificar adecuadamente a pacientes con sospecha de ATTR.

Palabras clave: Amiloidosis; Cintigrafía ;Tc ^{99m}-Pirofosfato (Fuente: DeCS-BIREME).

Introduction

Cardiac amyloidosis (CA) is an infiltrative disease characterized by extracellular deposition of amyloid. [1] Although several proteins are capable of infiltrating the myocardium, more than 98% of diagnosed cases result from fibrils composed of monoclonal immunoglobulin light chains (AL) and transthyretin-related amyloidosis (ATTR), either in its mutated form (ATTRv, formerly hereditary) or native/wild-type form (ATTRwt, formerly senile). [2] ATTR is emerging as an important and often underdiagnosed cause of heart failure and arrhythmias, especially in older adults, mainly due to increased recognition enabled by noninvasive techniques and population aging. [3,4]

ATTR should be suspected in individuals with heart failure and ventricular hypertrophy with grade 2 or greater diastolic dysfunction on echocardiography, or with typical findings on cardiac magnetic resonance (CMR) (subendocardial late gadolinium enhancement, elevated nativeT1 values, increased extracellular volume). [5,6] Until a decade ago, diagnosis required endomyocardial biopsy and immunohistochemical or proteomic typing, [7] which contributed to massive underdiagnosis. The development of disease-modifying therapies [8-11] has radically changed the landscape, making early and accurate diagnosis imperative.

In this context, cardiac scintigraphy with technetium-99m-labeled bone tracers, such as ^{99m}Tc-pyrophosphate (PYP), ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD), or ^{99m}Tc-hydroxymethylene diphosphonate (HMDP), has revolutionized the noninvasive diagnostic algorithm, and several studies have reported their high sensitivity and specificity for ATTR. [12,13] Recent studies highlight the value of DPD and/or PYP in differentiating ATTR from AL. [14] According to current diagnostic algorithms, a noninvasive diagnosis of ATTR can be established when there is intense visual myocardial uptake (grade 2–3 according to the Perugini scale), confirmed by SPECT to demonstrate true intramyocardial uptake, and after the prior exclusion of a monoclonal plasma cell dyscrasia. In this setting, the heart-to-contralateral hemithorax ratio (H/CL ≥1.5 at 1 hour or ≥1.3 at 3 hours) constitutes a complementary quantitative parameter that supports visual interpretation. Under these conditions, reported sensitivity and specificity approach 100% for ATTR, allowing diagnosis without the need for histological confirmation in most cases. [1,15,16]

In Peru, ATTR remains an underdiagnosed entity, partly due to the historically limited availability of these diagnostic tools in the public sector.[17] The Department of Nuclear Medicine of the Hospital Nacional Guillermo Almenara Irigoyen (HNGAI) has incorporated ^{99m}Tc-PYP scintigraphy into its portfolio of services, enabling the systematic evaluation of patients with clinical suspicion of ATTR. In this context, the present study aims to describe the implementation and application of the noninvasive diagnostic algorithm for transthyretin cardiac amyloidosis (ATTR) using ^{99m}Tc-PYP scintigraphy at our institution, integrating semiquantitative visual assessment, tomographic confirmation with SPECT, and complementary quantitative analysis in accordance with current international criteria.

Materials and methods

Study design

Descriptive case series study. The studies were performed at the Department of Nuclear Medicine Service of the Hospital Nacional Guillermo Almenara Irigoyen (HNGAI) in Lima, Peru, during the 2024–2025 period.

Scintigraphy findings were described in Peruvian patients of mestizo ethnicity with suspected transthyretin cardiac amyloidosis (ATTR), focusing the analysis exclusively on the noninvasive diagnosis using ^{99m}Tc-PYP, without evaluating clinical, therapeutic, or prognostic outcome variables.

Study population

Six patients evaluated at the Nuclear Medicine Service with suspected ATTR were included. All were referred from the Cardiology Service of the same hospital. All patients had previously undergone comprehensive clinical evaluation, including electrocardiograms, echocardiograms, and relevant laboratory studies, as part of the routine diagnostic workup.

Variables

The scintigraphy diagnosis of ATTR was measure based on current noninvasive diagnostic criteria [15,18]. Classification was established in three categories: compatible with ATTR (noninvasive diagnosis established), nondiagnostic/equivocal, and not compatible with ATTR. Findings were considered compatible with ATTR when visual myocardial uptake was graded 2 or 3 according to the Perugini scale, confirmed by SPECT to demonstrate true intramyocardial uptake, and after prior exclusion of a monoclonal plasma cell dyscrasia.

Cases with grade 1 uptake were classified as nondiagnostic or equivocal.

The heart-to-contralateral hemithorax ratio (H/CL), obtained from planar images and confirmed with SPECT at 1 and 3 hours using standardized regions of interest, was used as a complementary quantitative parameter to support visual interpretation and not as an independent diagnostic criterion.

Demographic characteristics (age and sex) and relevant cardiologic history were collected from medical records. No comparative analysis of clinical or therapeutic variables was performed, given the descriptive and diagnostic focus of the study.

Procedures

The standardized protocol of the American Society of Nuclear Cardiology (ASNC) [18] was used. A dose of 20 mCi of ^{99m}Tc-PYP was administered. Planar images were acquired in anterior, left anterior oblique, and lateral projections, along with non-gated SPECT studies over a 180° orbit using a step-and-shoot approach. Image acquisition was performed at 1 and 3 hours post-injection.

Analysis was performed through integrated interpretation of planar and SPECT images, following current noninvasive diagnostic criteria. [18] Primary evaluation was based on semiquantitative visual assessment of myocardial uptake using the Perugini scale, comparing cardiac uptake with rib uptake. Classification was as follows: grade 0 (no myocardial uptake), grade 1 (uptake less than rib uptake), grade 2 (uptake equal to rib uptake), and grade 3 (uptake greater than rib uptake).

The primary diagnostic criterion for ATTR was the presence of visual myocardial uptake grade 2 or 3, mandatorily confirmed by SPECT to demonstrate true intramyocardial uptake after prior exclusion of a monoclonal plasma cell dyscrasia. [18,19]

Cases with grade 1 uptake were considered nondiagnostic or equivocal and required clinical correlation and further evaluation.

Additionally, quantitative analysis was performed by measuring mean counts per pixel in regions of interest (ROI) of the heart (H) and contralateral lung (CL) to obtain the H/CL ratio.

H/CL cutoff values (≥1.5 at 1 hour and ≥1.3 at 3 hours) were interpreted only in the presence of myocardial uptake confirmed on SPECT and after exclusion of monoclonal gammopathy, in accordance with current diagnostic algorithms. The H/CL ratio was used as a complementary quantitative parameter to support visual interpretation and not as an independent diagnostic criterion.

Ethical considerations

This study corresponds to a retrospective case series based on the review of studies performed as part of routine diagnostic practice. No additional interventions or procedures beyond standard clinical care were conducted. Confidentiality was ensured through anonymization of data, without including information that could allow patient identification.

Data analysis

Data were analyzed using descriptive statistics. Continuous variables were summarized as mean ± standard deviation and range, while categorical variables were expressed as absolute frequencies and percentages. Given the descriptive nature of this case series and the small sample size, no inferential statistical tests were performed. Data analysis focused on the descriptive characterization of clinical variables and scintigraphy findings, including Perugini visual grading and heart-to-contralateral lung (H/CL) ratios.

Results

Six patients with suspected ATTR were included **(Table 1)**. The mean age was 69.7 ± 10.3 years (range: 58–87 years), and 66.7% were male. The most frequent comorbidities were heart failure (83.3%) and atrial fibrillation (66.7%). All patients showed echocardiographic signs suggestive of infiltrative disease, mainly left ventricular hypertrophy (100%) and moderate to severe diastolic dysfunction (83.3%). CMR, available in three cases, did not show characteristic signs of cardiac amyloidosis.

Five patients (83.3%) had no monoclonal component on hematologic screening. One patient (16.7%) showed an IgG kappa component, which modified the diagnostic interpretation according to the international algorithm.

Scintigraphy interpretation combined semiquantitative Perugini assessment and H/CL quantification at 1 and 3 hours.

Semiquantitative Classification (Perugini Scale)

Two patients (33.3%) showed myocardial uptake significantly greater than bone uptake (Perugini 3), one patient (16.7%) showed myocardial uptake similar to or equal to bone uptake (Perugini 2), and three patients (50%) showed myocardial uptake lower than bone uptake (Perugini 1). Overall, 50% of patients demonstrated positive uptake of grade 2 or 3.

In cases with borderline uptake (grade 1), the inclusion of SPECT was crucial to confirm that the uptake, although weak, did not correspond to residual blood pool activity but rather to myocardial tissue, thereby reinforcing diagnostic accuracy.

Quantitative Assessment (H/CL Ratio)

The H/CL ratio was calculated from planar images. The diagnosis of ATTR was considered positive if H/CL ≥ 1.5 at 1 hour or ≥ 1.3 at 3 hours, provided AL was excluded **(Table 1)**.

Final diagnostic classification according to the algorithm

The final diagnostic classification of patients was determined by combining the findings from monoclonality screening, scintigraphy, and SPECT.

- **Definitive Noninvasive ATTR Diagnosis:** Two patients (Cases 1 **(Figures 1 and 2)** and Case 2) showed grade 3 myocardial uptake according to the Perugini scale, confirmed by SPECT, and had negative monoclonal protein testing, fulfilling criteria for a noninvasive diagnosis consistent with ATTR. In both cases, the H/CL ratio was concordantly elevated at both 1 hour (≥ 1.5) and 3 hours (≥ 1.3), providing

Table 1. Clinical characteristics, cardiac imaging findings, monoclonal protein screening results, and ^{99m}Tc-PYP scintigraphy findings in the six evaluated patients.

			CARDIAC IMAGING ECC Y/O CMR			SCINTIGRAPHY FINDINGS WITH ^{99m}Tc-PYP			
Case	**Age/ Sex**	**Clinical history**	**LVE (%)**	**Findings**	**MPSC**	**Perugini (*)**	**H/CL (1 h)**	**H/CL (3 h)**	**Interpretation**
1	87/F	ICC, AF	25	Echo: LVHc, granular sparkling pattern	(-)	3	3.6	2.2	Definite ATTR
2	58/M	CHF	29	Echo: LVHe	(-)	3	2.5	1.7	Definite ATTR
3	73/F	CHF, AF, HTN	35	Echo: LVHe, diastolic dysfunction grade III, dilated LV, severe biatrial dilation CMR: no signs of CA	monoclonal component in IgG with KAPPA light chains	2	1.6	1.5	Non-conclusive – rule out AL
4	75/M	CHF, AF. HTN	37	Echo: LVHe CMR: no signs of CA	(-)	1	1.4	1,2	Unlikely / Equivocal ATTR
5	60/M	CHF	23	Echo: Dilated LV, LVHe	(-)	1	1.4	1.2	Unlikely / Equivocal ATTR
6	65/M	Hypertrophic cardiomyopathy, atrial flutter	52	Echo: Severe LVHc CMR: no signs of CA	(-)	1	1.3	1.1	Unlikely / Equivocal ATTR

The table includes age, sex, cardiovascular history, left ventricular ejection fraction, echocardiographic and cardiac magnetic resonance patterns, presence of a monoclonal protein disorder, Perugini visual grade, and heart-to-contralateral lung ratio (H/CL) at 1 and 3 hours. The final column shows the diagnostic interpretation (definite ATTR, unlikely/equivocal, or non-conclusive evaluation).
F: female. M: male. CHF: chronic heart failure. AF: atrial fibrillation. HTN: hypertension. LVEF: left ventricular ejection fraction. LVHc: concentric left ventricular hypertrophy. LVHe: eccentric left ventricular hypertrophy. LV: left ventricle. CMR: cardiac magnetic resonance. Echo: echocardiogram. H/CL: heart-to-contralateral lung ratio. CA: cardiac amyloidosis. MPCS: monoclonal protein screening. ATTR: transthyretin cardiac amyloidosis. (*): confirmed by SPECT.

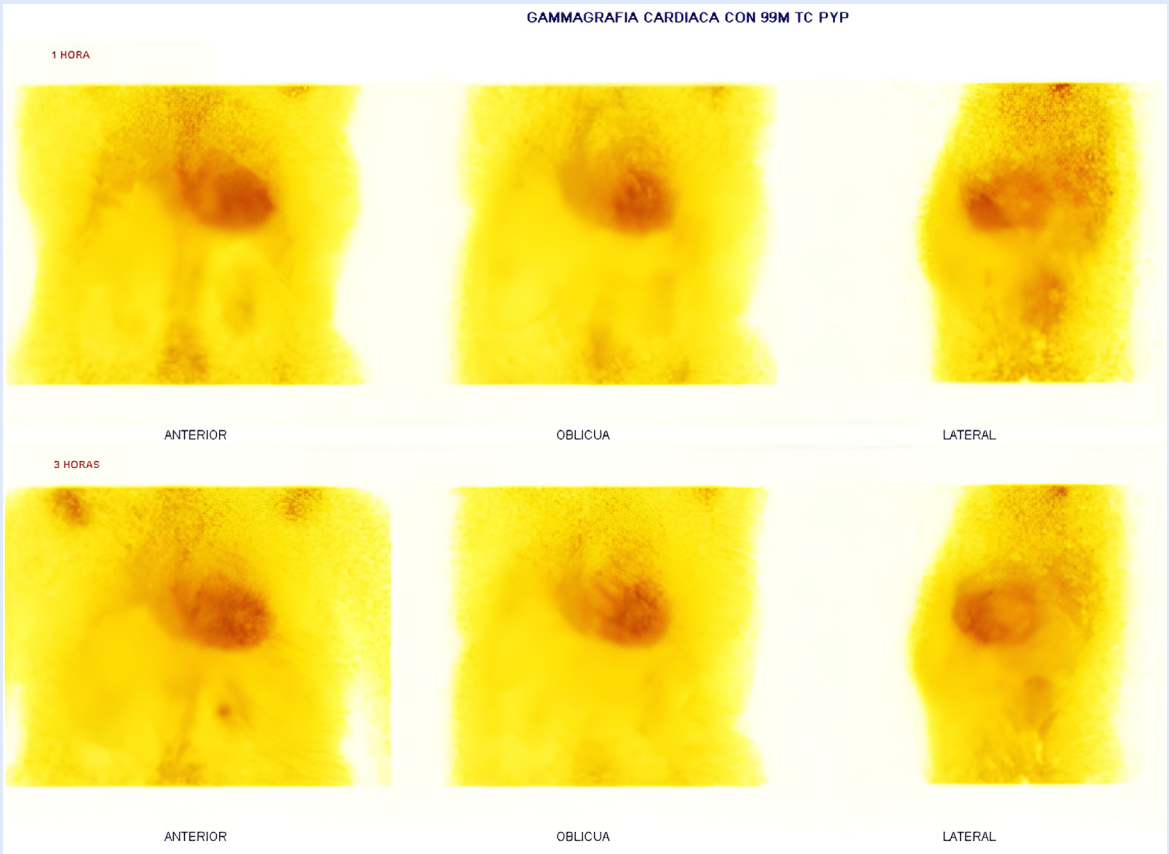

Figure 1. ^{99m}Tc-PYP cardiac scintigraphy of Case 1. Planar images in anterior, oblique, and lateral projections obtained at 1 hour (upper) and 3 hours (lower) post-injection show marked myocardial uptake with intensity greater than the adjacent bone activity, consistent with Perugini grade 3. These findings support the diagnosis of transthyretin cardiac amyloidosis (ATTR) in this patient.

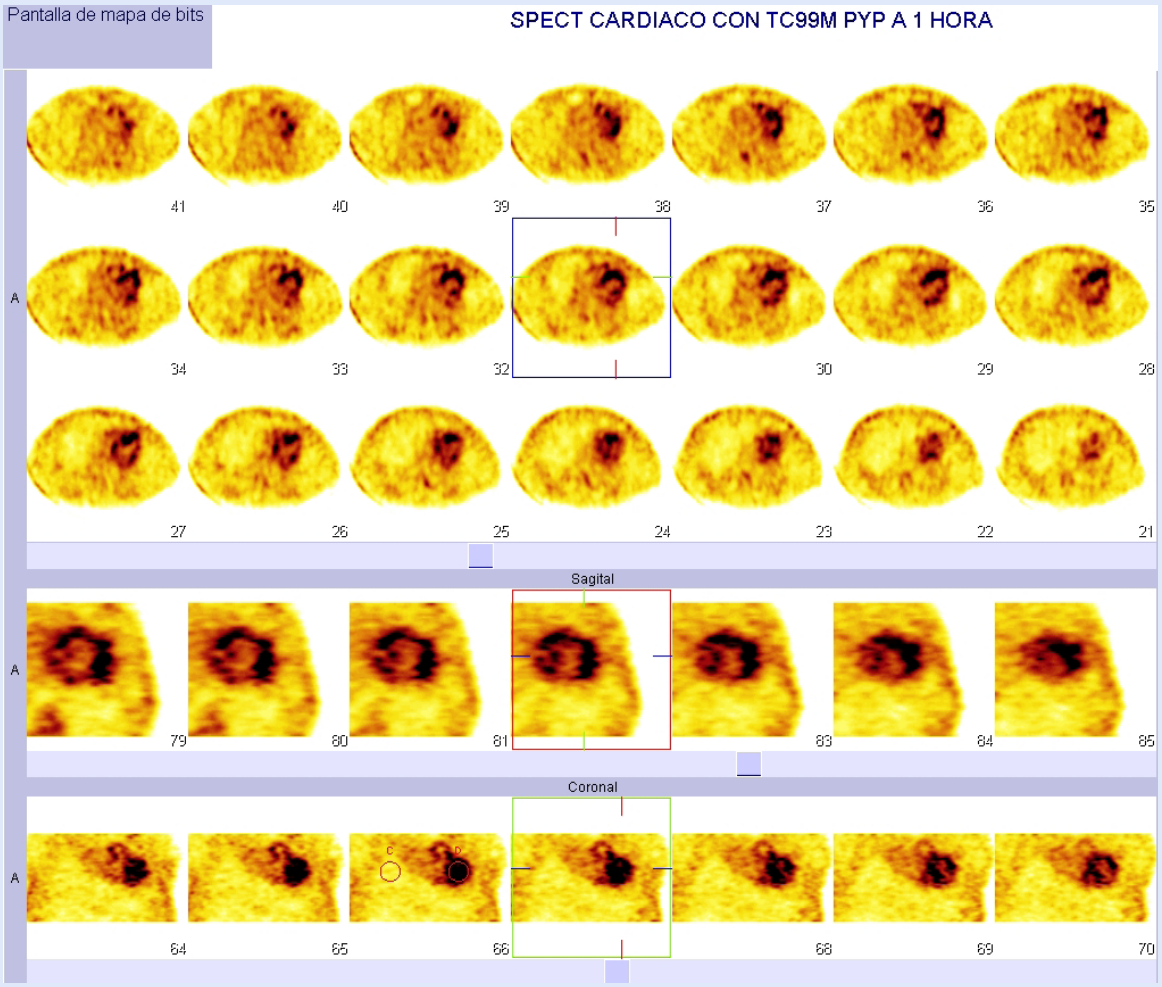

Figure 2. Case 1. Cardiac SPECT was acquired one hour after the injection of 20 mCi of ^99mTc-PYP. Axial, sagittal, and coronal tomographic images demonstrate diffuse radiotracer uptake throughout the myocardium, confirming that the activity is not due to residual blood-pool signal.

complementary quantitative support to the visual interpretation.

- **Inconclusive Diagnosis:** One patient (Case 3) showed grade 2 uptake, a finding suggestive of amyloidosis. However, this patient presented an IgG kappa monoclonal component. According to the diagnostic algorithm, this scenario invalidates a noninvasive diagnosis and requires histologic evaluation with amyloid typing to rule out AL amyloidosis, ATTR with concomitant monoclonal gammopathy of undetermined significance (MGUS), or coexistence of both. The H/CL ratio in this case was 1.6, confirming significant uptake.
- **Equivocal Cardiac ATTR:** Three patients (Cases 4, 5, and 6) showed grade 1 uptake. All three cases had negative monoclonal protein screening results, and the H/CL ratio at 1 hour (1.4, 1.4, and 1.3) was below the diagnostic threshold of H/CL ≥ 1.5, as was the H/CL ratio at 3 hours (1.2, 1.2, and 1.1), values below the diagnostic threshold of H/CL ≥ 1.3.

Discussion

The recognition of ATTR as an underdiagnosed cause of heart failure has been revolutionized by the availability of ^{99m}Tc-PYP scintigraphy. Our study demonstrates the application of the standardized noninvasive diagnostic protocol endorsed by societies such as the ASNC and the European Society of Cardiology (ESC) in a local cohort of patients with high clinical suspicion.

^{99m}Tc-PYP scintigraphy, combined with SPECT imaging and systematic exclusion of monoclonality, allows for appropriate stratification of the noninvasive diagnosis of ATTR. The proportion of significant uptake (Perugini 2–3) was

50% of patients, consistent with clinical cohorts in which the prevalence of ATTR among patients with longstanding heart failure and unexplained hypertrophy approaches similar figures. [3,6] The sex distribution and mean age (70 years) also align with the typical phenotype described for ATTRwt, predominantly affecting older men. [3,4]

Our findings reaffirm the value of the noninvasive diagnostic algorithm initially validated by Gillmore *et al.*, [7] in which the combination of grade 2 or 3 bone tracer uptake and absence of a monoclonal component allows for a definitive diagnosis without the need for biopsy. In our study, two patients (cases 1 and 2) clearly met these criteria. However, one patient showed grade 2 uptake with an IgG kappa component, which, according to ESC guidelines, [1] the American College of Cardiology (ACC), [6] and the consensus of the World Heart Federation on transthyretin amyloid cardiomyopathy, [5] invalidates a noninvasive diagnosis of ATTR and mandates further evaluation to exclude AL amyloidosis or ATTR with concomitant monoclonal gammopathy of undetermined significance (MGUS). This is a critical point, as AL amyloidosis carries a very short median survival (6 months if heart failure is present at diagnosis and untreated), and prognosis improves with early initiation of targeted chemotherapy.

Fifty percent of our patients (cases 4, 5, and 6) were classified as unlikely/equivocal ATTR due to grade 1 Perugini uptake. Grade 1 is considered borderline and lacks the diagnostic specificity required for ATTR. [18,20] Regarding quantification, although the international protocol defines quantitative positivity as a planar H/CL ≥1.5 at 1 hour, the planar H/CL values in these three cases were below this threshold.

ASNC states that definitive classification relies primarily on visual assessment (grade 2 or 3). Although the H/CL ratio may be helpful in resolving uncertainty in grade 1 cases, the predominance of visual grade 1 classification combined with planar H/CL values below the diagnostic cutoff reinforces the need to classify these cases as equivocal or inconclusive, requiring investigation of alternative diagnoses, follow-up, or histological confirmation if clinical suspicion persists.

SPECT proved crucial in ruling out false-positive infiltration, reinforcing the importance of the multimodal approach proposed by ESC, ACC, and ASNC. [1,6,19] Its inclusion was fundamental in grade 1 cases, as it confirmed that the observed uptake, although weak, localized to the myocardium rather than representing residual blood pool activity or bone overlap. The requirement for SPECT in the protocol is an explicit recommendation, including in the 2025 update of the Taiwanese PYP consensus, [15] to reduce interpretation errors.

From an epidemiological perspective, our series aligns with the global trend of increasing ATTR diagnoses due to the wider availability of bone tracer scintigraphy and recognition of the broader clinical spectrum of the disease. [4]

Regarding therapeutic management, although our series focused on diagnosis, accurate identification of ATTR is clinically relevant given the impact of specific therapies. Drugs such as tafamidis have demonstrated reductions in mortality and hospitalizations, [9] while gene-silencing therapies targeting TTR, patisiran and inotersen, have shown significant improvements in neurological function and cardiac parameters. [10,11] Proper application of the algorithm enables rapid identification of candidates for these therapies, whereas equivocal or inconclusive cases require multidisciplinary collaboration with hematology for further evaluation. Recently, studies exploring imaging biomarkers for therapeutic monitoring, such as response to eplontersen using quantitative SPECT-CT, [21] suggest that functional imaging will play an increasingly important role in longitudinal follow-up.

Overall, this series demonstrates that structured interpretation, appropriate use of SPECT, and systematic exclusion of monoclonality allow rigorous application of the current algorithm and help avoid diagnostic errors, particularly in borderline uptake cases. [1,5,6,15,18,20]

Our study is a descriptive case series with a small number of patients (n=6), which represents the main limitation and precludes advanced statistical analysis or definitive conclusions regarding prevalence. However, this limitation does not invalidate the findings within the context of our population. The objective was to describe the utility and implementation of the diagnostic protocol in a local setting with high clinical suspicion, confirming that the diagnostic algorithm is applicable in our practice.

Additionally, patients were referred with high clinical suspicion (presenting "red flags" such as unexplained left ventricular hypertrophy or atrial fibrillation), introducing referral bias. This bias is common in rare disease studies but does not diminish the value of the findings, as we demonstrate the utility of scintigraphy in the clinical scenario where its diagnostic yield is highest.

In conclusion, the noninvasive diagnostic algorithm for transthyretin cardiac amyloidosis (ATTR) using ^{99m}Tc-PYP scintigraphy was successfully implemented in our institution. Grade 2–3 visual myocardial uptake confirmed by SPECT and after exclusion of monoclonal proteins served as the primary diagnostic criterion, with the H/CL ratio providing complementary support. Cases with grade 1 uptake were considered non-diagnostic or equivocal, highlighting the importance of SPECT in accurately interpreting borderline findings. Continued use of the standardized protocol-including planar imaging, SPECT, and H/CL quantification-is recommended to minimize interpretation errors. Systematic exclusion of monoclonal plasma cell dyscrasia remains mandatory, and patients with equivocal uptake or abnormal monoclonal protein results should be referred to a multidisciplinary team for further evaluation. Awareness

of clinical "red flags," such as unexplained left ventricular hypertrophy, atrial fibrillation, or bilateral carpal tunnel syndrome, is essential to ensure timely referral and early diagnosis. This approach allows appropriate classification of patients with suspected ATTR and facilitates the prompt identification of candidates for disease-modifying therapies.

Author contributions

DSO: Conceptualization, Methodology, Research, Data Curation, Formal Analysis, Visualization, Supervision, Project Management, Writing, Original Draft. **RMS:** Conceptualization, Methodology, Research, Data Curation, Visualization, Writing, Review, and Editing.

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