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Consensus
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2025 Update Consensus of ^{99m}Tc-Pyrophosphate Scintigraphy in the Transthyretin Cardiac Amyloidosis from the Taiwan Society of Cardiology and the Society of Nuclear Medicine of the Republic of China

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This 2025 updated consensus outlines the diagnostic strategy for transthyretin amyloid cardiomyopathy (ATTR-CM). Given that ATTR-CM is a significant contributor to heart failure, this article emphasizes the importance of making an early and precise diagnosis, particularly as new therapeutic options become available. Highlighting the critical importance of an early and accurate diagnosis, particularly in light of emerging therapeutic modalities, this consensus underscores the central role of ^{99m}Tc-pyrophosphate (PYP) scintigraphy as a non-invasive diagnostic tool. The consensus calls for the adoption of standardized imaging protocols and interpretation criteria to ensure consistency and reliability across diverse clinical settings. The integration of qualitative and quantitative imaging techniques within a structured diagnostic framework places particular focus on the use of single-photon emission computed tomography/computed tomography (SPECT/CT) imaging to enhance diagnostic precision by minimizing blood pool activity and eliminating overlapping interference. Three-hour imaging is considered to be critical for accurate evaluations and to reduce false-positive findings, and it is recommended for its superior diagnostic accuracy. Moreover, quantitative assessments are also considered to be essential for evaluating myocardial amyloid deposition. This updated consensus provides comprehensive guidelines for clinicians, with the aim of optimizing patient outcomes through precise diagnosis and effective management of ATTR-CM. The consensus concludes by advocating for continued research and refinement of imaging methodologies, particularly to enhance the clinical applicability of ^{99m}Tc-PYP scintigraphy and other future developments in nuclear molecular imaging.

Key Words: Cardiac amyloidosis • Heart failure • Standardized uptake value (SUV) quantification • Transthyretin amyloid cardiomyopathy (ATTR-CM) • ^{99m}Tc-pyrophosphate (PYP) scintigraphy

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Abbreviations

^{99m}Tc	^{99m}Technetium
A81V	p.Ala81Val
A97S	p.Ala117Ser
AL	Amyloid light chain
AL-CA	Amyloid light chain cardiac amyloidosis
ATTR	Transthyretin amyloid
ATTR-CM	Transthyretin amyloid cardiomyopathy
ATTRv	Variant transthyretin amyloidosis
ATTRwt	Wild-type transthyretin amyloidosis
CMR	Cardiac magnetic resonance
CPV	Cardiac pyrophosphate volume
DPD	3,3-diphosphono-1,2-propanodicarboxylic acid
ECV	Extracellular volume
EMB	Endomyocardial biopsy
FAPI	Fibroblast activation protein inhibitor
FDG	Fluorodeoxyglucose
H/CL	Heart-to-contralateral lung
H/M	Heart-to-mediastinum
H/WB Retention	Heart-to-whole body retention
HMDP	Hydroxy-methylene diphosphonate
HMR	Heart-to-mediastinum ratio
IQR	Interquartile range
MIBG	Metaiodobenzylguanidine
mRNA	Messenger RiboNucleic acid
NaF	Sodium fluoride
nSUVpeak	SUVpeak normalized to bone uptake
NT-proBNP	N-terminal pro B-type natriuretic peptide
PET	Positron emission tomography
PiB	Pittsburgh compound B
PYP	Pyrophosphate
ROI	Region of interest
SNMROC	Society of Nuclear Medicine of the Republic of China
SPECT/CT	Single-photon emission computed tomography/computed tomography
SUV	Standardized uptake value
SUVpeak	Peak standardized uptake value
TBR	Target-to-background ratio
TSOC	Taiwan Society of Cardiology
TTR	Transthyretin

INTRODUCTION

Heart failure is a critical condition that significantly impacts global health due to its high prevalence and severe outcomes. As a leading cause of hospitalization, particularly among older adults, heart failure imposes a substantial burden on healthcare systems.[1,2] In recent years, care for heart failure has seen notable improvements, including advances in differentiating disease subtypes and in both mechanical and pharmacological management.[3,4] Cardiac amyloidosis is a particularly important cause of heart failure that warrants increased public awareness.[5-7] The pathogenesis of cardiac amyloidosis involves the accumulation of misfolded proteins in the heart, leading to cardiac dysfunction.[8] Most cases of amyloidosis are caused by transthyretin amyloid (ATTR) and amyloid light chain (AL) cardiac amyloidosis.[5,8]

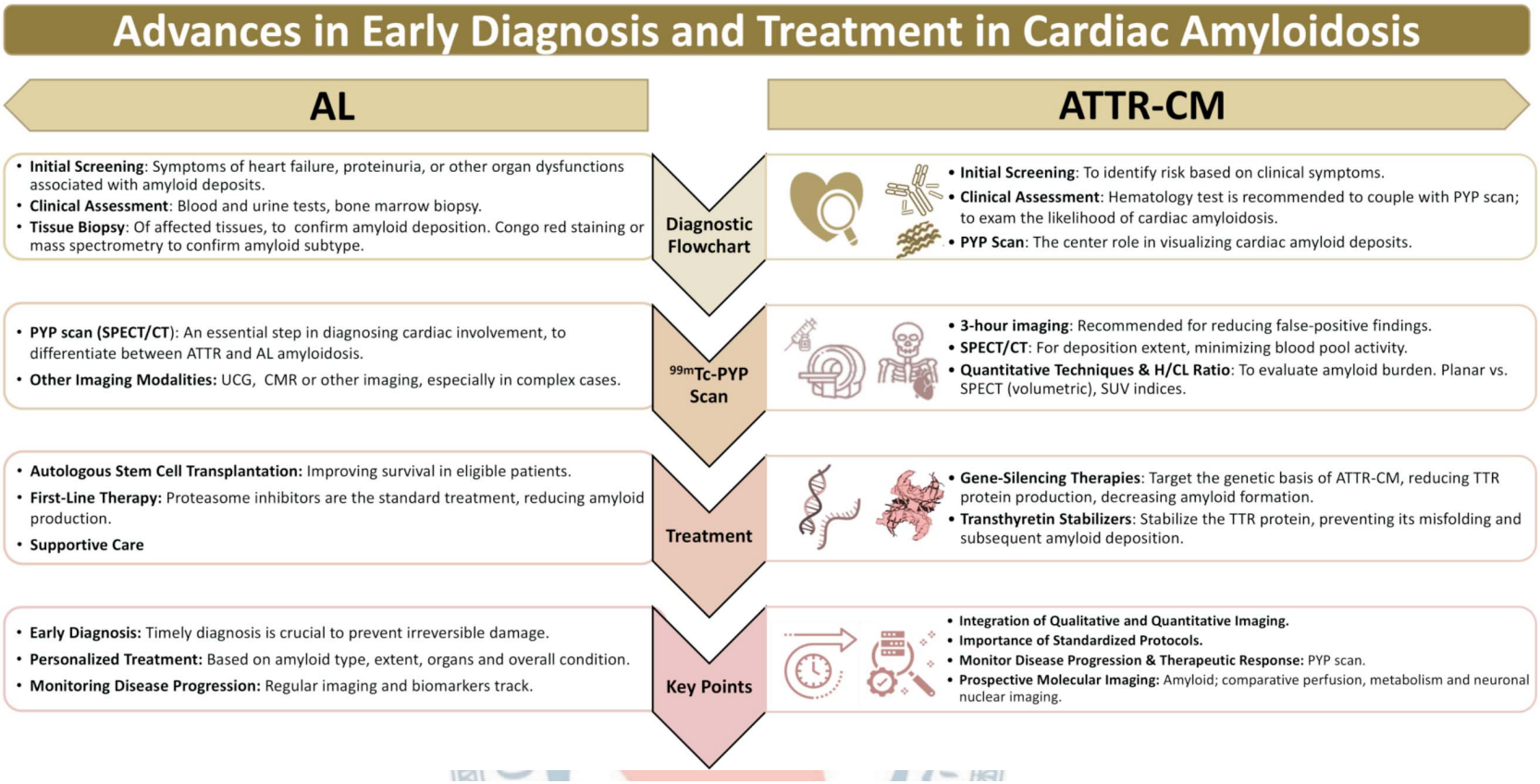
In recent years, several landmark randomized trials for the treatment of transthyretin amyloid cardiomyopathy (ATTR-CM) have been conducted, targeting various mechanisms such as transthyretin stabilization and mRNA silencing.[9-11] These advanced therapies for ATTR-CM have been shown to attenuate cardiac remodeling[12-15] and improve clinical outcomes.[9-11,16] While medications aimed at amyloid removal are still under investigation for both AL and ATTR cardiac amyloidosis,[17] the progress in treatment underscores the growing importance of making an early and accurate diagnosis and differentiating these diseases. As therapeutic options for ATTR-CM and AL cardiac amyloidosis continue to evolve, the need for a precise and timely diagnosis becomes increasingly critical to optimize patient outcomes.

There are two types of ATTR-CM: variant (ATTRv) and wild-type (ATTRwt), each with distinct clinical presentations.[5] ATTRv cardiac amyloidosis is an autosomal dominant disease that typically manifests before the age of 65 and includes neurological symptoms.[5,8] In Taiwan, the most common genetic variant is A97S (p.Ala117Ser), with other variants including A81V (p.Ala81Val),[18-20] V122I (p.Val142Ile) also being reported. ATTRwt cardiac amyloidosis generally presents later in life, typically after the age of 75, with fewer neurological symptoms and primarily manifesting as heart failure.[5,8] The diagnosis of ATTR-CM requires clinician awareness. Patients with heart failure and preserved ejection fraction, aortic stenosis, or a hypertrophic cardiomyopathy phenotype are all at risk of ATTR-CM.[21-23] Serum N-terminal pro B-type natriuretic peptide (NT-proBNP) and troponin can serve as both diagnostic and prognostic markers.[24] In diagnosing ATTR-CM, bone-avid radiotracers such as ^{99m}technetium pyrophosphate (^{99m}Tc-PYP) are essential for confirmation.[5,25] In the study by Gillmore JD et al., 1217 patients were

enrolled, showing that Tc-labeled bone scintigraphy with grades 2-3 has a sensitivity of > 99% and a specificity of 86% for ATTR-CM. When combining the absence of a monoclonal protein in serum or urine with visual grades 2-3, the specificity and positive predictive value reach 100%.[26] Consequently, ^{99m}Tc-PYP imaging is considered to be a suitable alternative to endomyocardial biopsy (EMB) for some patients suspected of having ATTR-CM.[5,8] However, standardized protocols and experienced interpretation are required to maximize the diagnostic accuracy. Earlier studies suggested that ATTR-CM may present more transmural patterns of late gadolinium enhancement compared to AL, recent meta-analyses have shown that cardiac magnetic resonance (CMR) does not reliably differentiate these subtypes, with sensitivity ranging from 28.1% to 99.0% and specificity from 11.0% to 60.0%.[27] While CMR with standardized T1 and extracellular volume fraction (ECV) analyses may aid in differentiation of the etiology of left ventricular hypertrophy, and both native T1 mapping and ECV are used as non-invasive markers to assess myocardial involvement in amyloidosis, its ability to distinguish between amyloid subtypes, particularly AL and ATTR cardiac amyloidosis, is limited, because both cardiac amyloidosis presents with high native T1 and ECV values.[28] Additional diagnostic tests, such as tissue biopsy and bone scintigraphy, are recommended for accurate differentiation.[27,29,30] The Taiwan Society of Cardiology (TSOC) recently presented a consensus on the diagnosis and treatment of cardiac amyloidosis.[5] According to this consensus, ^{99m}Tc-PYP and free light chain assessments are critical steps in the diagnostic process. The diagnosis of ATTR-CM can be made with a typical ^{99m}Tc-PYP scan result and the exclusion of light chain disease. In cases with suspected light chain disease, tissue proof via biopsy is often required. Although the diagnostic process is now relatively standardized globally, there are still numerous techniques for performing and interpreting ^{99m}Tc-PYP imaging, which is the most important step in diagnosing the disease.[5-7,31] In addition, recent studies suggest that ^{99m}Tc-PYP imaging may also serve as a tool to monitor disease-modifying treatments of ATTR-CM. ^{99m}Tc-PYP scan signal intensities have been shown to decrease following ATTR-CM treatments including stabilizers, mRNA silencers, and amyloid removal agents.[32-35] Given the rapid increase in the number of studies and the critical need to standardize the ^{99m}Tc-PYP scan protocol, reporting format, and prevent misinterpretation of results, the Society of Nuclear Medicine of the Republic of China (SNMROC) and TSOC have jointly updated this statement. Healthcare professionals should consider this Joint Consensus as a significant reference in their clinical practice, as well as in developing and implementing preventive, diagnostic, and therapeutic strategies, as summarized in the Central Illustration. PYP scan is primarily used to differentiate between ATTR and AL cardiac amyloidosis. If the PYP yields positive results, it is still essential to conduct hematological tests to rule out AL, as some patients may have both conditions. Though simultaneous testing allows for a more efficient diagnostic process, hematological tests could be conducted earlier at some situations, considering radiation safety and the availability of nuclear scans.

DIAGNOSTIC ALGORITHM

Figure 1 shows the proposed diagnostic algorithm for patients suspected of having ATTR-CM. Although the World Heart Federation Consensus[36] and the 2023 American College of Cardiology Expert Consensus[37] suggest that initial hematology tests may be arranged due to the approximately 10% likelihood of identifying AL cases, the TSOC Expert Consensus recommends[5] arranging a ^{99m}Tc-PYP scan in conjunction with hematology tests, considering both the availability of hematology resources and the rapidly progressive nature of the disease. This approach is consistent with the practices outlined in the ESC working group statement[7] and the Japan Circulation Society 2020 Guidelines.[38] Based on the 2021 advocacy statements from the TSOC and SNMROC[31] and the 2023 expert consensus of the TSOC,[5] we established a structured diagnostic framework for assessing patients suspected of having ATTR-CM. This framework emphasizes the significance of imaging techniques, particularly ^{99m}Tc-PYP scintigraphy, in the diagnostic process. The 2021 advocacy statements present a straightforward algorithm focusing on initial imaging and clinical assessment;[31] however, the latest 2025 expert consensus incorporates quantitative imaging techniques and multimodal approaches, providing a more comprehensive framework for the diagnosis and therapy monitoring. The integration of quantitative imaging techniques allows for the



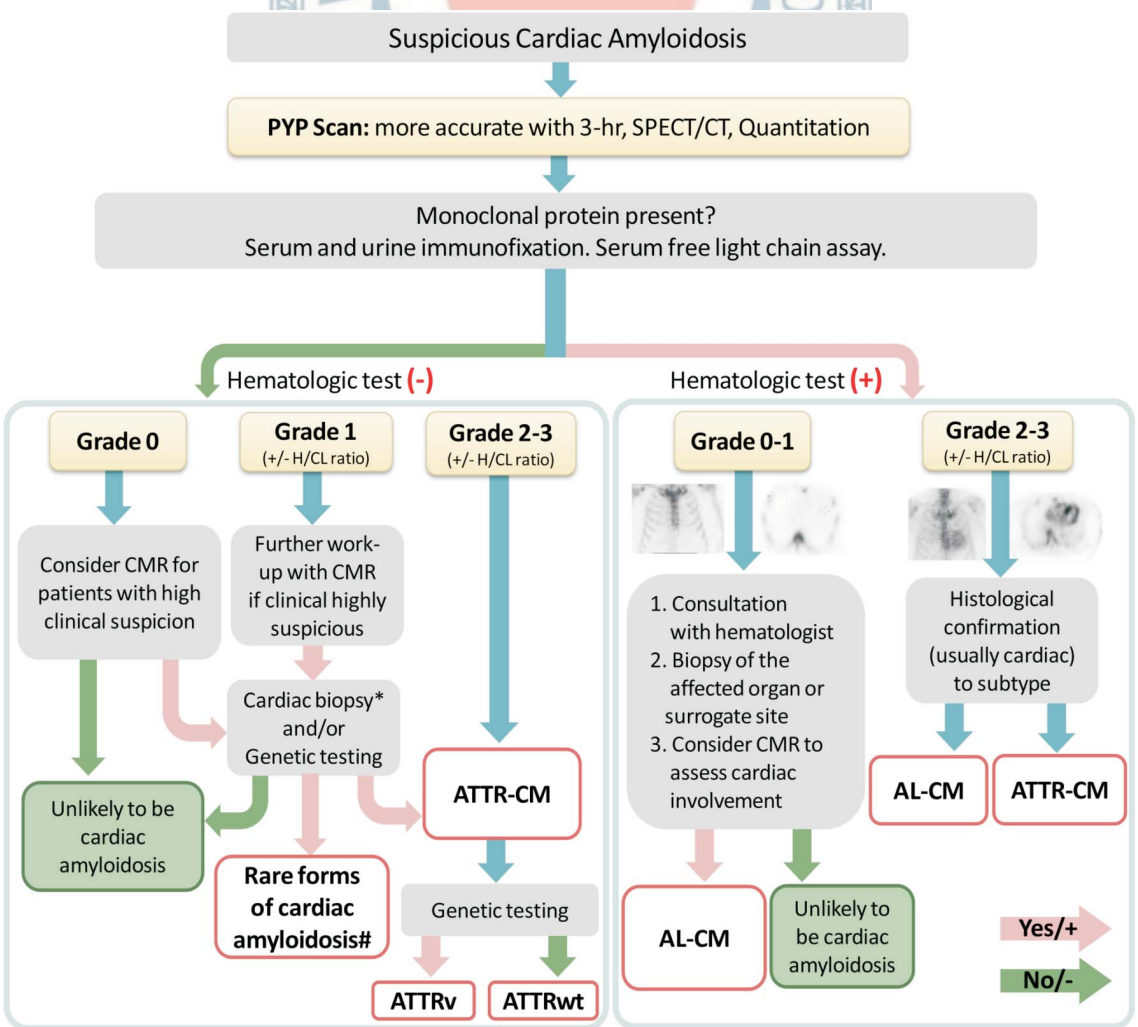
Central Illustration. *Key advances in the early diagnosis and treatment of cardiac amyloidosis, highlighting the role of ^{99m}Tc-PYP scan in diagnostic accuracy and treatment monitoring. AL, amyloid light chain; ATTR-CM, transthyretin cardiac amyloidosis; CMR, cardiac magnetic resonance; H/CL, heart-to-contralateral lung ratio; PYP, pyrophosphate; SPECT/CT, single-photon emission computed tomography/computed tomography; SUV, standardized uptake value; TTR, transthyretin. UCG, echocardiogram.*

precise evaluation of myocardial amyloid deposits, which is essential for an accurate diagnosis and effective treatment planning. The transition from the 2021 advocacy statements[31] to the 2025 expert consensus reflects the significant advances in the understanding, diagnosis, and management of ATTR-CM. The interpretation of the comprehensive PYP study must be done after excluding AL amyloidosis, and when it cannot be distinguished by a survey of M-protein in urine/serum, an endomyocardial biopsy is still recommended.[39]

^{99m}Tc-PYROPHOSPHATE SCINTIGRAPHY

Image acquisition procedures

Planar imaging and single-photon emission computed tomography/computed tomography (SPECT/CT) are essential for the diagnosis of ATTR-CM. An anterior planar view is crucial for visual grading and semi-quantitation. Optional left anterior oblique and left lateral views can also assist in visual grading. SPECT/CT with attenuation correction and image fusion can help exclude



* Cardiac biopsy in patients with Grade I and negative hematology tests should only be performed after a thorough risk-benefit assessment and detailed discussion with the patient.
# Rare forms of cardiac amyloidosis, such as Apo AI, AIV amyloidosis or Phe64Leu ATTRv, frequently present with Grade 0 or 1 on PYP scan.

Figure 1. *The current proposed diagnostic algorithm of suspected cardiac amyloidosis in Taiwan. AL-CM, amyloid light-chain cardiac amyloidosis (AL-CA); ATTR-CM, transthyretin amyloid cardiomyopathy; ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type transthyretin amyloidosis; CMR, cardiac magnetic resonance; EMB, endomyocardial biopsy; H/CL ratio, heart-to-contralateral lung ratio; PYP, pyrophosphate; SPECT/CT, single-photon emission computed tomography/computed tomography.*

blood pool activity and highlight differences in myocardial uptake patterns, such as absent, focal, diffuse, or focal-on-diffuse uptake. Performing imaging 3 hours after ^{99m}Tc-PYP injection is strongly recommended to minimize the influence of blood pool retention. Planar imaging and SPECT/CT obtained at 1 hour with low blood pool activity are acceptable alternatives. Including both bilateral shoulders is necessary to evaluate the musculoskeletal manifestations of amyloid deposition, such as the shoulder pad sign or joint swelling.[40] Efforts should be made to minimize symmetric renal counts in planar images to enhance myocardial signal detection. The recommended parameters for the imaging techniques are detailed in Table 1. A recent study comparing 1- and 3-hour ^{99m}Tc-PYP scintigraphy in patients with suspected ATTR-CM revealed that 1-hour planar imaging often results in equivocal findings, 61% of cases downgrade in 3-hour imaging. SPECT/CT results were more stable, with only 14% of cases downgraded over time. Therefore, 3-hour imaging, especially SPECT/CT, enhances the diagnostic accuracy of ^{99m}Tc-PYP scintigraphy.[41] The other study also confirmed that 3-hour imaging provides the most balanced diagnostic performance in terms of sensitivity and specificity, making it more reliable for ruling in or out ATTR-CM compared to the 1-hour scan, which is more sensitive but less specific.[43]

Visual grading scale and semi-quantitation

Image interpretation is primarily conducted through visual grading. The relative uptake of tracer in the myocardium compared to the ribs, as visualized on planar and SPECT imaging, is categorized using a four-point scale. Grade 0 is characterized by no myocardial uptake with normal bone uptake present. Grade 1 is defined by myocardial uptake that is less than rib uptake. Grade 2 occurs when myocardial uptake is equal to rib uptake. Grade 3, the most severe, is identified when myocardial uptake exceeds that of the ribs, accompanied by mild or absent rib uptake.[5] A visual grade of 0 indicates a negative ^{99m}Tc-PYP scan result, while a grade of 1 requires further assessment if there is strong clinical suspicion of ATTR-CM. Grades 2 and 3 are considered positive ^{99m}Tc-PYP scan results. Visual grading is performed using both planar and SPECT/CT images. If no myocardial uptake is observed on SPECT/CT images, the visual grade should be 0.

The heart-to-contralateral lung (H/CL) ratio on anterior planar images is used for semi-quantitation, as illustrated in Figure 2.[31] The region of interest (ROI) of heart generally involves selecting a circular or elliptical region that encompasses the heart's uptake area while avoiding surrounding structures such as the sternum and subdiaphragmatic organs. The ROI of heart should cover the myocardium, and this ROI is then mirrored onto the contralateral lung region, ensuring that the right heart and subdiaphragmatic organs are excluded. Also, a similar size of ROI for contralateral lung is suggested. The H/CL ratio is calculated by dividing the mean counts of the heart ROI by the mean counts of the contralateral lung ROI. Although different threshold values for the H/CL ratio have been reported for 1-hour and 3-hour images, our consensus are otherwise in line with the criteria of the American Society of Nuclear Cardiology recommendations[42] and the Japan Circulation Society guidelines.[38] Although an H/CL ratio greater than 1.5 for 1-hour images and an H/CL ratio of 1.3 or higher for 3-hour images may suggest a positive ^{99m}Tc-PYP scan, the interpretation of a positive ^{99m}Tc-PYP scan should not rely solely on the H/ CL ratio. The visual score and standardized interpretation criteria are outlined in Table 2, which remain unchanged from the 2021 version.[31] As comparing the diagnostic values of visual score and quantitative ratio, H/CL ratios alone do not provide enough sensitivity, but combining them with visual scores improves specificity, particularly at the 3-hour image.[43]

The diagnosis of ATTR-CM using ^{99m}Tc-PYP scans is currently primarily based on visual grading from three views of planar and SPECT images, and the H/CL ratios from anterior planar images. To accurately monitor therapeutic effects, a more precise quantification of myocardial amyloid burden is desirable. A practical suggestion for utilizing SPECT in ATTR-CM diagnosis and monitoring would be to implement a standardized imaging and quantification protocols based on current best practices and validated parameters. The example protocol for clinical practice of utilizing imaging protocol and analyses is listed in Table 1. Figure 2 calculates the H/CL ratio using anterior planar images, while Figure 3 performs SPECT/CT analysis and derive standardized uptake values (SUV) for quantification of myocardial amyloid burden. When feasible, use the volumetric H/L from SPECT/CT images, which provides a more accurate measure of amyloid deposition (Figure 3D).

Table 1. The protocol of utilizing ^{99m}Tc-PYP scan and SPECT/CT for ATTR-CM with acquisition parameters

Patient selection	Indications: • Patients with symptoms of heart failure, particularly those with preserved ejection fraction (HFpEF). • Patients with unexplained left ventricular hypertrophy or suspicion of amyloid cardiomyopathy. • Consider in patients with ATTRv or ATTRwt in older adults.
Image procedure	Parameters
Specific preparation	• Fasting is not required
Scan	• Rest scan
Dose of ^{99m}Tc-PYP	• Recommended: 20 mCi for 3-hour and SPECT acquisition • Adjust according to different models of instrument
Time interval between injection and acquisition	• Recommended: 3-hour planar and SPECT or SPECT/CT • Optional: 1-hour planar and SPECT
General imaging parameters	
Field of view	• Cardiac or chest
CT attenuation correction	• Recommended
Position of planar and SPECT	• Cardiac or chest
Position	• Supine
Energy window	• 140 keV, 15-20%
Collimators	• Low energy, high resolution
Matrix	• Recommended: 128 × 128 for SPECT • Minimum required: 64 × 64 for SPECT, 256 × 256 for planar
Pixel size	• 2.3-6.5 mm (may change with different matrix)
Planar imaging specific parameters	
Number of views	• Anterior, lateral, and LAO
Detector configuration	• 180 degrees
Image duration	• 750,000 counts
Magnification	• 1.45-1.5
SPECT imaging specific parameters	
Angular range	• 360 degrees
Detector configuration	• 180 degrees
ECG gating	• Off; non-gating imaging
Number of views/detectors	• 32-64
Time per stop	• 20 seconds
Quantitative and semi-quantitative analysis	
H/CL ratio	• On the anterior planar image, define a ROI over the heart and contralateral lung. • May consider ATTR-CM if H/CL ratio ≥ 1.5 on a 1-hour image or ≥ 1.3 on the 3-hour image. This semi-quantitative measure should support the visual diagnosis.
SUVpeak or volumetric H/L ratio	• Using quantitative measures of myocardial amyloid burden. These provide a more detailed and objective assessment, particularly useful in follow-up evaluations.
Diagnosis and interpretation	
Positive for ATTR-CM if	• Visual Grade is 2 or 3 • H/CL ratio meets the positive threshold. • Quantitative parameters (e.g., SUVpeak) support a high amyloid burden.
Equivocal or negative results	• If results are equivocal or inconsistent (e.g., low-grade visual score but high H/CL ratio), consider additional modalities like CMR or repeating the scan for further clarification.
Reporting and documentation	• Provide a comprehensive interpretation in the report, correlating the imaging findings with clinical symptoms and other diagnostic markers.
Follow-up and monitoring	• If the patient is undergoing therapy, may follow-up SPECT/CT scans. • A reduction in SUV or H/CL ratio suggests a decrease in amyloid burden, while stable or increased values may indicate disease progression or suboptimal therapeutic response.

ATTRv, variant transthyretin amyloidosis; ATTRwt, wild-type ATTR; CMR, cardiac magnetic resonance; CT, computed tomography; ECG, electrocardiography; H/CL, heart-to-contralateral lung; keV, kilo electron volts; LAO, left anterior oblique; mCi, millicurie; PYP, pyrophosphate; ROI, region of interest; SPECT, single-photon emission computed tomography; SUV, standardized uptake value. The table was adapted and modified from 2021 Advocacy statements.[28]

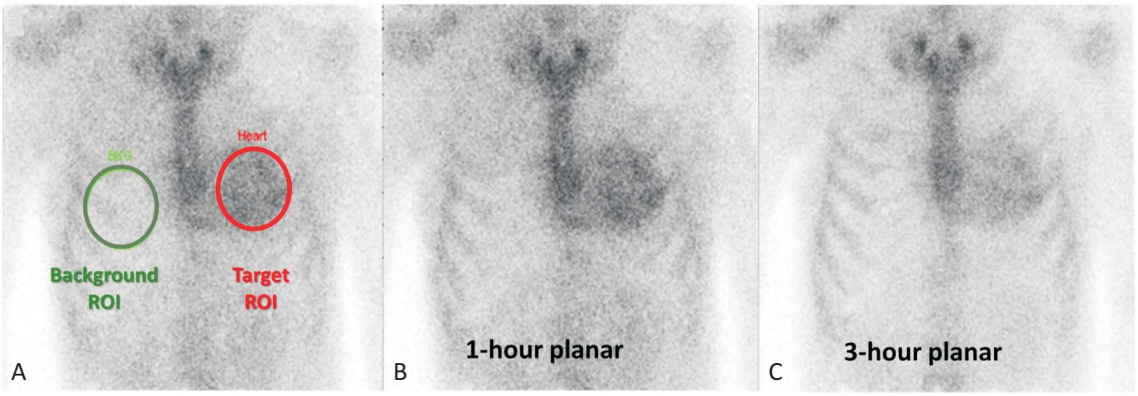


Figure 2. *Determining the region of interest (ROI) for the quantitation of cardiac ^{99m}Tc-Pyrophosphate (PYP) uptake. (A) The H/CL ratio involves carefully selecting the area of the heart on the planar image. (B) The 1-hour planar image with an H/CL ratio of 1.99 and (C) the 3-hour image with an H/CL ratio of 1.92 show mild washout at a late time point, both in visualization and quantitation. The images courtesy of the Department of Nuclear Medicine, Far Eastern Memorial Hospital. H/CL, heart-to-contralateral lung.*

Table 2. Recommendations for standardized interpretation of ^{99m}Tc-PYP scintigraphy

Visual interpretation
• Evaluate for cardiac radiotracer uptake on both planar and myocardial uptake on SPECT or SPECT/CT images.
• If SPECT images show radiotracer uptake in the myocardium, proceed with visual grading.
• In the absence of any myocardial tracer uptake on SPECT, assign a visual grade of 0.
Visual grading
The relative tracer uptake in the myocardium to ribs seen on planar and SPECT images is graded on the following scale:
• Grade 0: No myocardial uptake and normal bone uptake
• Grade 1: Myocardial uptake less than rib uptake
• Grade 2: Myocardial uptake equal to rib uptake
• Grade 3: Myocardial uptake greater than rib uptake with mild/absent rib uptake
If the visual grading of planar and SPECT images is inconsistent, it is recommended to rely on the visual score obtained from the *SPECT* images.
H/CL ratio interpretation
If significant blood pool activity is observed on SPECT images, calculating the H/CL ratio is *not* recommended.
H/CL ratios can help identify ATTR-CM if systemic AL amyloidosis is excluded by the following values:
• 1-hour images: H/CL ratio > 1.5
• 3-hour images: H/CL ratio ≥ 1.3
Diagnostic value of visual scores (Saitou T, et al.)[43]
• Overall PYP scan performance for ATTR-CM: Sensitivity: 80.5%. Specificity: 86.8%. PPV: 78.6%. NPV: 88.1%.
• 1-hour imaging performance: Sensitivity: 97.6%. Specificity: 55.9%. PPV: 57.1%. NPV: 97.4%.
• 3-hour imaging performance: Sensitivity: 80.5%. Specificity: 86.8%. PPV: 78.6%. NPV: 88.1%.
• SPECT imaging performance: Sensitivity: 68.3%. Specificity: 67.6%. PPV: 56.0%.
Diagnostic value of 1-h and 3-h H/CL ratios[43]
• 1-hour with an H/CL ratio of > 1.5: Sensitivity: 51.2%. Specificity: 85.3%. PPV: 67.7%. NPV: 74.4%.
• 1-hour combination of an H/CL ratio of > 1.5 and a VS of ≥ 2: Sensitivity: 51.2%. Specificity: 88.2%. PPV: 72.4%. NPV: 75.0%.
• 3-hour with an H/CL ratio of > 1.3: Sensitivity: 68.3%. Specificity: 67.6%. PPV: 56.0%. NPV: 78.0%.
• 3-hour combination of an H/CL ratio of > 1.5 and a VS of ≥ 2: Sensitivity: 61.0%. Specificity: 88.2%. PPV: 75.8%. NPV: 78.9%.

AL, immunoglobulin light chain amyloidosis; ATTR-CM, transthyretin cardiac amyloidosis; H/CL, heart to contralateral lung; NPV, negative predictive value; PPV, positive predictive value; SPECT, single-photon emission computed tomography; SPECT/CT, SPECT/computed tomography. The table was adapted and modified from the 2021 Advocacy statements.[28]

Several semiquantitative and quantitative parameters derived from SPECT images have been proposed, including myocardial peak standardized uptake value (SUVpeak),[44,45] SUVpeak normalized to bone uptake (nSUVpeak),[44] SUV

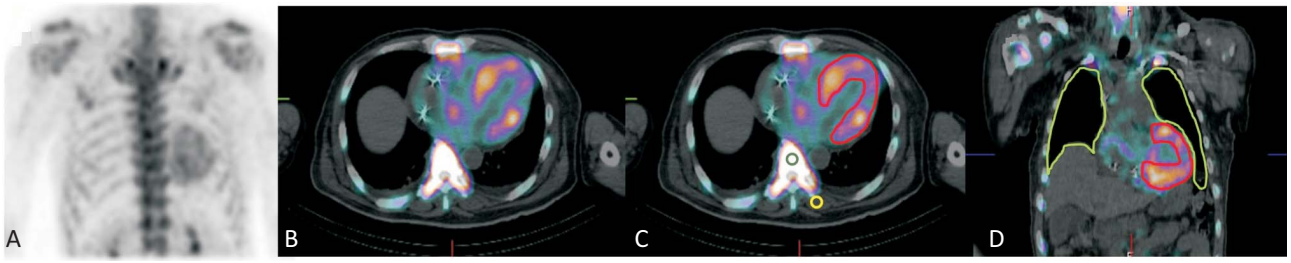


Figure 3. *Single-photon emission computed tomography/computed tomography (SPECT/CT) and further quantitative analysis add sensitivity and accuracy. (A) The planar image shows overlapping activity in the myocardium and blood pool, whereas (B) SPECT/CT shows a clearer view. (C) SPECT/CT with the volume of interest (VOI) for the myocardium (red line) and reference areas (dark green line: vertebra, yellow line: para-spinal muscle) provides standard uptake value quantitation indices. (D) Volumetric heart-to-lung ratio with segmentation contouring of the bilateral lungs (light green line) and myocardium (red line).*

retention index,[45] cardiac amyloid activity,[46] percentage injected dose,[46] and cardiac pyrophosphate volume (CPV 1.2 and CPV1.4).[47] Semi-automated tools help to contour based on the intensity of myocardial tracer uptake, and also CT density information. These tools can help delineate the myocardial boundary by focusing on the regions with the highest signal intensities, avoiding areas with lower counts (such as the blood pool). The software delineates the myocardial boundary by focusing on regions with the highest signal intensities, using a preset threshold of 20%, 40%, or 60% of SUVmax, for example. This approach avoids organs or areas with lower counts, such as the lung or blood pool. When it comes to lung contouring, it is important to use CT to determine the boundary. Due to the significant density difference between the lungs and adjacent organs, non-contrast CT is sufficient for this purpose. Hence, in combination with CT, the myocardium, lung or skeleton can be delineated properly.[48]

However, these methods are not standardized, and no direct comparison studies or validation by pathology or prognosis have been conducted. Bone scintigraphy imaging is frequently used to investigate patients with suspected ATTR-CM. However, the reported accuracy for interpretation approaches has changed over time. A meta-analysis showed that bone scintigraphy imaging is highly accurate for identifying patients with ATTR-CM, with between study heterogeneity in part explained by differences in disease prevalence. Quantitative analysis of SPECT imaging had the highest specificity (97%) followed by planar visual grade (96%) and H/CL ratio (93%).[49]

Recently, advanced AI algorithms have been developed to improve the objective interpretation of PYP scans, offering greater accuracy and consistency in diagnosing cardiac amyloidosis. Further validation through large-scale clinical trials and standardized evidence are still required to establish their reliability and integration into routine clinical practice.[50]

DISEASE PROGRESSION AND THERAPEUTIC RESPONSE MONITORING

Recent therapeutic developments, including transthyretin (TTR) stabilizers, silencers and antibodies, have been demonstrated improved clinical outcomes for patients with ATTR-CM.[51] Reliable and validated parameters for accurately monitoring the therapeutic effects on the hearts of these patients are increasingly important.

Numerous bone-avid radiotracers, including ^{99m}Tc-PYP, have shown potential in monitoring treatment responses in patients with ATTR-CM (Table 3). Although a lower visual grade following therapy has been reported in these patients,[32] visual grading is considered to be suboptimal because it is subjective rather than quantitative, and less sensitive in detecting minor changes in cardiac uptake. Other semiquantitative parameters derived from planar images, such as heart-to-mediastinum, heart-to-thigh, and heart-to-whole body retention ratios, have been used to quantify changes in cardiac uptake following treatment with a TTR stabilizer (tafamidis) or antibody (NI006).[34,52-54] Herein, we recommend using the planar H/CL ratio to assess treatment response, based on the consistency of the image acquisition procedure and standardized interpretation previously established. A reduction in planar H/CL ratio has been reported after

Table 3. Published researches of bone scintigraphy in monitoring disease progression and therapeutic response in ATTR-CM patients

Authors	No. of treated/ non-treated patients	Monitoring parameters	Visual score (VS)finding	Planar ratios finding	SPECT/CT parameters finding	[^{99m}Tc]-labeled tracers	Treatment with
Yu AL, et al.[32]	21/6	(1) VS (2) Planar H/CL (3) Volumetric H/L	Treated: reduction in 10 of 21, stabilization in 11 of 21.	Treated: 1.63 (baseline) vs. 1.43 (20 mo), p < 0.001; Non-treated: 1.68 (baseline) vs. 1.63 (17.8 mo), NS	Treated: 3.80 (baseline) vs. 2.975 (20 mo), p < 0.001; Non-treated: 4.141 (baseline) vs. 3.952 (17.8 mo), NS	PYP	Tafamidis
Doumas A, et al.[52]	5/0	(1) Planar HtT		Reduction in 4 of 5.		DPD/HMDP	Tafamidis
Garcia-Pavia P, et al.[53]	40/0	(1) Planar H/WB retention		5.7% (baseline, n = 12) vs. 3.8% (4 mo, n = 11) vs. 2.5% (12 mo, n = 6).		DPD/HMDP	Antibody NI006
Odouard S, et al.[34]	52/8	(1) Planar H/M % change		Treated:-11% decreased Non-treated: +3 % increased, p < 0.001		HMDP	Tafamidis
Tingen HAS, et al.[54]	32/0	(1) VS (2) Planar H/WB retention	1. Reduction in 5 of 20 after Patisiran 2. Increase in 1 of 12 after Tafamidis/Diflunisal	1. Patisiran: 4.84 (baseline) vs. 4.49 (12 mo) vs. 4.16 (30 mo), p < 0.001 2. Tafamidis/Diflunisal: 4.46 (baseline) vs. 4.96 (24 mo), p = 0.01		HDP	Patisiran/ Tafamidis/ Diflunisal
Lee TH, et al.[55]	3/2	(1) Planar H/CL		Treated: 1.92 (baseline) vs. 1.67 (34.8 mo), p = 0.02 Non-treated:1.62 (baseline) vs. 1.63 (15.4 mo), NS		PYP	Tafamidis
Papathanasiou M, et al.[35]	14/0	(1) Planar H/CL (2) SUVmax	Reduction in 5 of 14, stabilization in 9 of 14.	Reduction in 12 of 14. 2.2 (baseline) vs. 1.8 (44 mo), p = 0.009	Reduction in 10 of 13. 11.9 (baseline) vs. 7.5 (44 mo), p = 0.005	DPD	Tafamidis
Castano A, et al.[56]	0/20	(1) VS (2) Planar H/CL	3 (baseline) vs. 3 (follow up), NS	1.79 (baseline) vs. 1.76 (follow-up), NS		PYP	None
Ross JC, et al.[59]	0/62	(1) Planar H/CL (2) % of administered activity		Overall: no significant differences between baseline and any other year.	Overall: significant differences between years (p = 0.049), with year-on-year progression.	DPD	None
Rettl R, et al.[57]	9/0	(1) VS (2) SUV retention index	Reduction in 1 of 9.		Reduction in 7 of 9. 5.09 g/mL (baseline) vs. 3.19 g/mL (12 mo), p = 0.028	DPD	Patisiran/ Inoterson
Rettl R, et al.[58]	40/0	(1) VS (2) SUV retention index	Reduction in 3 of 40.		4.96 g/mL (baseline) vs. 3.27 g/mL (9 mo), p < 0.001	DPD	Tafamidis
Fontana M, et al.[60]	16/16	(1) % of administered activity			Treated: reduction in 15 of 16, stabilization in 1 of 16. 19.6 % of administered activity reduction.	DPD	Patisiran
Yu AL, et al.[33]	6/7	(1) VS (2) Planar H/CL (3) Volumetric H/L	Treated: reduction in 2 of 6, stabilization in 4 of 6. Non-treated: stabilization in 5 of 7, increased in 2 of 7.	Treated: 1.561 (baseline) vs. 1.473 (20.2 mo), NS Non-treated: 1.701 (baseline) vs. 1.657 (16.3 mo), NS	Treated 3.774 (baseline) vs. 2.979 (20.2 mo) p = 0.028; Non-treated: 4.079 (baseline) vs. 3.915 (16.3 mo), NS	PYP	Eplonterson

DPD, 3,3-diphosphono-1,2-propanodicarboxylic; HDP, hydroxydiphosphonate; HMDP, hydroxymethylene; H/WB retention, heart-to-whole body retention; NS, not significant; Planar H/CL, planar heart-to-contralateral ratio; Planar H/M, planar heart-to mediastinum ratio; Planar HtT, planar heart-to-thigh ratio; PYP, pyrophosphate; mo, months; SPECT/CT, single-photon emission computed tomography/computed tomography; SUV, standardized uptake value; Volumetric H/L, volumetric heart-to-lung ratio; [^{99m}Tc], ^{99m}-Technetium.

TTR stabilizer (tafamidis) therapy in patients with ATTR-CM,[32,35,55] while no statistically significant differences in planar H/CL ratios from serial ^{99m}Tc-PYP[56] and ^{99m}Tc-3,3-diphosphono-1,2-propanodicarboxylic acid (DPD)[57] scans have been noted in untreated patients.

As there is increasing focus on quantitative SPECT/CT methods for detecting ATTR-CM, further research into their application for monitoring disease progression and therapy response is essential. SPECT/CT, with its ability to avoid overlapping interference from planar images (Figure 3A, 3B), has emerged as a more suitable tool. The availability and validation of SUV quantitation have enabled more precise and consistent measurements across different studies and clinical settings. When SUV quantitation is feasible, SUV_{max} or SUV retention index (defined as [SUV_{peak} cardiac/SUV_{peak} vertebral] × SUV_{peak} paraspinal muscle) can be used (Figure 3C),[58] along with measurements of pre- and post-injection activities. In cases where SUV information is unavailable due to the lack of absolute quantification software, alternative measures such as the percentage of administered activity or volumetric heart-to-lung ratio can be used (Figure 3D).[32,33,57,59,60] In addition, research has shown that SPECT/CT-derived parameters are more sensitive than the planar H/CL ratio in monitoring therapy responses,[33,59] and they have been shown to correlate well with changes in speckle tracking echocardiography-derived global longitudinal strain and the cardiac biomarker NT-proBNP.[57,59] The importance of SPECT/CT quantitative imaging in evaluating treatment response is expected to grow, however further research is needed to fully establish the clinical utility of bone scintigraphy in monitoring ATTR-CM.

While bone scintigraphy using ^{99m}Tc-labeled tracers such as PYP, DPD, hydroxy-methylene diphosphonate (HMDP), and hydroxydiphosphonate is highly sensitive for detecting ATTR-CM, it is not designed to differentiate between ATTRwt and ATTRv. The clinical management and prognosis for ATTRwt and ATTRv may vary significantly; however, the primary utility of bone scintigraphy is to confirm the presence of cardiac amyloidosis rather than to specify its subtype. Genetic testing or tissue biopsy remains necessary for distinguishing between these forms. Therefore, the inability of bone scintigraphy to differentiate between ATTRwt and ATTRv should not be considered a limitation of its diagnostic capacity for ATTR-CM.[26] Without genetic testing or tissue biopsy, the inability of bone tracers to distinguish between these two forms can complicate accurate diagnosis and treatment planning for TTR cardiac amyloidosis.[24] Secondly, Musumeci et al.[61] reported that bone tracer (DPD or HMDP) had low sensitivity (10.5%) for detecting cardiac involvement in patients with the Phe64Leu ATTRv. Despite clear clinical, electrocardiographic, and CMR findings suggestive of cardiac amyloidosis, bone scintigraphy frequently showed low or absent myocardial uptake in this mutation cohort, although it is not common in Taiwan. It highlighted the need for a multimodal diagnostic approaches, including CMR, other molecular imaging, and possibly biopsy, to avoid misdiagnosis in this subset of TTR mutations where bone scintigraphy might be insufficient.

Although the binding mechanisms of bone tracers and their correlations with amyloid load remain unclear, bone scintigraphy shows greater promise in detecting the early impact of treatment compared to conventional follow-up parameters. This observation supports the hypothesis that molecular changes precede alterations in myocardial contraction.[62] The lack of sufficient long-term data on treated ATTR-CM patients contributes to the uncertainty in monitoring disease progression and response to therapy. There are currently no reliable specific parameters for monitoring the therapeutic response.[17] Therefore, further research and clinical evidence are needed to validate the use of bone scintigraphy in the therapeutic monitoring of ATTR-CM.

OTHER PROSPECTIVE NUCLEAR IMAGING MODALITIES

The diagnosis and management of cardiac amyloidosis is challenging due to its complex biochemical nature.[63,64] Advances in nuclear imaging have expanded the diagnostic capabilities beyond the commonly used ^{99m}Tc bone agents. Table 4 summarizes other potential SPECT and positron emission tomography (PET) radiotracers. In general, bone tracers are particularly sensitive for the detection of the ATTR type of amyloidosis,[65,66] whereas amyloid agents show a higher affinity for the AL type.

^{99m}Tc-aprotinin, a serine protease inhibitor, has the benefit of detecting amyloid deposits mainly in the heart, and it has been used to diagnose AL.[67,68] However, due

Table 4. Other potential SPECT and PET radiotracers in cardiac amyloidosis

	Mechanisms	Key study	Population	Key findings
SPECT				
^{99m}Tc-aprotinin	As a serine protease inhibitor, to detect amyloid deposits by binding to proteases located within.	Awaya T, et al.[67]	AL	By visual interpretation of planar and SPECT/CT images. Positive findings in 4 out of 5 patients with amyloid deposits on endomyocardial biopsy and all 5 patients showing positive results on SPECT/CT.
^{123}I-metaiodobenzylguanidine (MIBG)	Uptake by myocardial sympathetic nerves, reflecting integrity and function of adrenergic nerves.	Delahaye N, et al.[85]	ATTRv	Mean late HMR in patients 1.36 ± 0.26 vs. in healthy controls 1.98 ± 0.35 ($p < 0.001$), no difference in washout.
PET				
^{11}C-Pittsburgh Compound B (PiB)	Derivative of thioflavin-T which had been thoroughly used to bind β amyloid.	Rosengren S, et al.[87]	ATTR, AL	Using visual inspection and semiquantitative methods. ^{11}C-PiB uptake was significantly higher in AL-CA than in ATTR-CM patients ($p < 0.001$) and discriminated AL-CA from controls with 100% (95% CI: 88% to 100%) accuracy for both the semi-quantitative measures.
^{18}F-Florbetapir (Amyvid®)	As a fluorescent dye that binds to amyloid plaques.	Singh V, et al.[88]	ATTR, AL	Significant myocardial uptake of Florbetapir in patients with both AL and ATTR-CM. Higher trend of AL uptake, but significant overlap in values making a distinction of AL from ATTR.
^{18}F-Flutemetamol (Vizamyl®)	Similar to ^{11}C-PiB, but to overcome the short half-life limitations of ^{11}C.	Dietemann S, et al.[89]	ATTR, AL	The TBR was significantly higher in CA patients: 1.46, IQR 1.32-2.06 versus 1.06, IQR 0.72-1.1 ($p = 0.033$).
^{18}F-Florbetaben (Neuraceq®)	Binding to amyloid plaques.	Law WP, et al.[90]	ATTR, AL	A correlation between myocardial retention and severity of myocardial dysfunction in cardiac amyloidosis patients.
^{18}F-NaF	Bone tracer.	Martineau P, et al.[91]	ATTR	Unique apical sparing pattern in ATTR.

AL-CA, amyloid light chain cardiac amyloidosis; ATTR-CM, transthyretin cardiac amyloidosis; ATTRv, variant transthyretin amyloidosis; CI, confidence interval; HMR, heart-to-mediastinum ratio; IQR, interquartile range; MIBG, metaiodobenzylguanidine; NaF, sodium fluoride; PiB, Pittsburgh compound B; SPECT/CT, single-photon emission computed tomography/computed tomography; TBR, target-to-background ratio.

to its physiological uptake, its potential is limited regarding the detection of amyloid deposits in the liver, kidneys, and spleen. Other ^{99m}Tc-labelled amyloid SPECT tracers such as peptide p5+14 remain in the preclinical stage.[69,70]

PET tracers have shown promise in the ability to bind selectively, providing high-resolution images and more reliable semiquantitative measures. The ability to non-invasively and quantitatively detect amyloid throughout the body, even in at-risk populations, before clinical manifestation would be invaluable. Cardiac PET/ CT and PET/ magnetic resonance imaging permit combined assessments of metabolic/functional/structural analyses of various cardiac diseases, and offer the potential to detect amyloid deposits in multiple organs.[71] High ^{18}F-fluorodeoxyglucose (FDG) uptake may be present in patients with AL amyloidosis. A major limitation of ^{18}F-FDG is physiologic uptake in the myocardium, even after prolonged fasting.[72] Recently, amyloid-targeting PET used for Alzheimer dementia has been investigated as an imaging method for cardiac amyloidosis. The earliest reports on human cardiac amyloidosis used ^{11}C-Pittsburgh Compound B (PiB), subsequently followed by ^{18}F-florbetapir, ^{18}F-florbetaben[73,74] and ^{124}I-evuzamitide in PET studies,[75-78] which have differing affinities for ATTR and AL. New developments in technology have further allowed for disease burden quantification.[79] These advantages enable a more targeted approach to treatment, thereby influencing therapeutic decisions. Although further studies are still required, amyloid-targeting shows potential as an imaging method for cardiac amyloidosis, particularly in AL.

The role of non-invasive functional molecular imaging is expected to expand beyond conventional diagnosis alone to prognostic prediction and monitoring the therapeutic effect. For example, low myocardial external efficiency derived from ^{11}C-acetate PET in cardiac amyloidosis patients has been associated with shorter survival.[80]

Gallium-68-labeled fibroblast activation protein inhibitor 04 (^{68}Ga-FAPI-04) has recently been introduced for imaging fibroblast activation in cardiac diseases, and it has been shown to be able to detect myocardial fibroblast activation in patients with AL cardiac amyloidosis in correlation with myocardial remodeling.[81] Of particular note, ^{123}I-metaiodobenzylguanidine (MIBG) has been shown to play an important role in evaluating the severity and extent of sympathetic nerve dysfunction in cardiac amyloidosis. A lower heart-to-mediastinum ratio (HMR) reflects cardiac sympathetic denervation, and has been associated with a poor prognosis in various cardiac conditions, including amyloidosis and heart failure.[82] The potential of exploring mismatched pathophysiological changes in the myocardium using integrated fusion techniques is increasingly being recognized. ^{123}I-MIBG is mainly useful in patients with variant and wild-type ATTR cardiac amyloidosis, but not in AA (secondary) amyloidosis or AL amyloidosis. Patients with reduced HMR may be at a higher risk of arrhythmias and adverse cardiac events, even after liver transplantation.[83-85] In addition, ^{123}I-MIBG scintigraphy can detect cardiac denervation in ATTR patients before signs of amyloidosis are evident on echocardiography.[84-86] The potential role of PET to evaluate cardiac sympathetic innervation in amyloidosis has not yet been identified.

CONCLUSIONS

The current 2025 updated consensus on the role of ^{99m}Tc-PYP scintigraphy in ATTR-CM highlights significant advances in the understanding and management of the disease. The integration of qualitative and quantitative imaging techniques into a structured diagnostic framework underscores the critical importance of an early and accurate diagnosis. As therapeutic options for ATTR-CM continue to evolve, the role of imaging, particularly ^{99m}Tc-PYP scintigraphy, is becoming increasingly important for monitoring disease progression and evaluating the therapeutic response. The implementation of standardized imaging protocols and interpretation criteria is crucial for ensuring consistent and reliable outcomes across diverse clinical settings. This consensus serves as a comprehensive guide for clinicians, facilitating enhanced patient outcomes through accurate diagnosis and effective management of ATTR-CM. Ongoing research and further refinement of imaging techniques are imperative to advance the clinical utility of ^{99m}Tc-PYP scintigraphy and other nuclear imaging modalities in the future.

DECLARATION OF CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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