Annals of Nuclear Cardiology Vol. 11 No. 1 3–12

SPECIAL REVIEW ARTICLE: JSNC RECOMMENDATION

Nuclear Medicine Imaging for the Diagnosis of ATTR Cardiac Amyloidosis: Report of Japanese Society of Nuclear Cardiology Working Group

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Received: November 9, 2024 / J-STAGE advance published: July 18, 2025

This manuscript was previously published in Shinzo-Kaku-Igaku in Japanese [Kudo T, Kuji I, Nakajima K et al. 日本心臓核医学会ATTR心アミロイドーシス核医学画像診断ワーキンググループ報告. Shinzo-Kaku-Igaku 27: 10–23 https://doi.org/10.14951/jsnc.27-001].

1. Overview

Bone scintigraphy is widely recognized as a useful tool for diagnosing cardiac amyloidosis, particularly transthyretin-type (ATTR) cardiac amyloidosis. However, no consensus has been established regarding its optimal usage and evaluation methods. For instance, a combination of visual assessment using the Perugini Grade system and semi-quantitative evaluation of the heart-to-contralateral lung (H/CL) ratio using the Bokhari method is commonly employed. Imaging is performed either 1-hour or 3-hours post-administration, utilizing planar imaging, single photon emission computed tomography (SPECT) imaging, or SPECT/CT imaging. In Japan, two radiopharmaceuticals, ^{99m}Tc-PYP (pyrophosphate) and ^{99m}Tc-HMDP (hydroxymethylene diphosphonate), are used, yet a standardized approach remains lacking. Notably, given that probable diagnosis based on nuclear imaging has now been established as a diagnostic criterion for ATTR cardiac amyloidosis, a designated intractable disease, it is crucial to ensure accurate interpretation of imaging results. Misinterpretation may lead to clearly positive cases being overlooked or clearly negative cases being misdiagnosed as positive.

The objective of this Working Group (WG) report is to establish a standardized diagnostic framework for ATTR cardiac amyloidosis using bone scintigraphy in Japan and to provide guidelines aimed at minimizing misdiagnosis.

2. Background

2.1 Basics of cardiac amyloidosis

Various guidelines for cardiac amyloidosis have been published (1), providing detailed descriptions of the disease. Therefore, this section presents a brief overview.

Subtypes of cardiac amyloidosis relevant to cardiovascular care

Several subtypes of amyloidosis exist; however, the two most relevant to cardiovascular care are ATTR amyloidosis and light-chain (AL) amyloidosis.

ATTR amyloidosis

ATTR amyloidosis is further classified into wild-type (ATTRwt) and hereditary (ATTRv) forms.

These classifications influence the sensitivity and specificity of bone scintigraphy in diagnosing ATTR cardiac

DOI: 10.17996/anc.25-001

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amyloidosis, making it essential to understand their characteristics (2, 3).

ATTRwt

ATTRwt results from the deposition of wild-type transthyretin without genetic mutations, primarily affecting the heart and carpal tunnel. It is more prevalent in men. Although aging is believed to contribute to disease onset, the underlying mechanisms remain unclear.

ATTRv

In Japan, the Val30Met (p.Val50Met) mutation is the most common hereditary form. Some studies suggest that patients with the Val30Met mutation exhibit a slightly higher incidence of negative bone scintigraphy results (4–6).

AL amyloidosis

AL amyloidosis is characterized by amyloid deposition derived from immunoglobulin light chains and is classified into multiple myeloma-associated AL amyloidosis and primary AL amyloidosis unrelated to multiple myeloma.

2.2 Nuclear medicine diagnosis of cardiac amyloidosis

Bone scintigraphy radiopharmaceuticals

Globally, four radiopharmaceuticals are used for bone scintigraphy: ^{99m}Tc-PYP, ^{99m}Tc-HMDP, ^{99m}Tc-MDP (methylene diphosphonate), and ^{99m}Tc-DPD (3, 3-diphosphono-1, 2-propanodicarboxylic acid). However, ^{99m}Tc-DPD is not available in Japan. Although ^{99m}Tc-MDP is effective in diagnosing bone diseases, it has a very high false-negative rate for cardiac amyloidosis, rendering it unsuitable for this purpose.* Currently, ^{99m}Tc-PYP and ^{99m}Tc-HMDP are the only radiopharmaceuticals approved for diagnosing cardiac amyloidosis under Japan's health insurance system. Reported diagnostic performance for these agents in Japan shows a sensitivity of 70–100% and a specificity of 90–100% (7).

* A study by Perugini et al. found that all cases positive for ^{99m}Tc-DPD tested negative when re-evaluated with ^{99m}Tc-MDP, confirming its ineffectiveness for diagnosing cardiac amyloidosis (8).

Mechanism of radiotracer uptake

The exact mechanism by which bone scintigraphy radiopharmaceuticals accumulate in ATTR cardiac amyloidosis remains unclear.

One proposed theory suggests that high tissue calcium concentration and associated microcalcifications in ATTR cardiac amyloidosis contribute to selective radiotracer uptake (9). However, this hypothesis does not adequately explain the low sensitivity of ^{99m}Tc-MDP, and further validation is required.

3. Imaging (10–13)

3.1 Imaging protocol

Pretreatment

No special pretreatment is required before the examination.

Dosage

- ^{99m}Tc-PYP: 370–740 MBq
- ^{99m}Tc-HMDP: 370–740 MBq

Imaging timing

- 3-hours post-administration: This is the standard imaging time for ^{99m}Tc-PYP and ^{99m}Tc-HMDP. However, if imaging at 1-hour post-administration clearly shows myocardial uptake that is distinguishable from the blood pool, the 3-hour imaging may be omitted.
- 1-hour post-administration: For ^{99m}Tc-PYP, planar imaging is used to measure the heart to contralateral lung (H/CL) ratio. However, if myocardial uptake is not clearly visible on visual assessment, 3-hour imaging is required regardless of the H/CL value. ^{99m}Tc-HMDP can also be used to measure H/CL, but evidence regarding the appropriate threshold is insufficient.

3.2 Acquisition parameters (common to ^{99m}Tc-PYP and ^{99m}Tc-HMDP)

Energy window

- 140 keV, window width 15–20%

Collimator

- Low-energy, high-resolution collimator (recommended)

Matrix

- Planar imaging: 256 × 256
- SPECT imaging: 64 × 64 or 128 × 128

Pixel size

- 2.3–6.5 mm

Planar imaging

Imaging views

- Anterior (frontal) view: Required
- Lateral or left anterior oblique (LAO) view: Optional

Imaging count

- ≥750,000 counts

Magnification ratio

- Adjust to include the entire chest within the field of view

Notes

* When acquiring the anterior view, ensure that the sternum and vertebrae overlap to obtain an accurate frontal projection. This is crucial for correctly measuring the H/CL ratio. However, in elderly patients with severe kyphosis or scoliosis, achieving proper alignment may be difficult. In such cases, care should be taken to prevent vertebral overlap with the contralateral lung field, as it can interfere with accurate H/CL measurement.

* Lateral and oblique views are preferable because they enhance visualization of doughnut-shaped myocardial

uptake, making it easier to differentiate from blood pool activity. However, if imaging time is limited, SPECT imaging is preferred over lateral or oblique views.

SPECT imaging

- SPECT imaging is strongly recommended for facilities capable of performing it.

*According to the SCAN-MP study, even cases classified as Perugini Grade 2 on planar imaging were found to be false positives in 60% of cases. Therefore, SPECT imaging is strongly recommended not only for Grade 1 but also for Grade 2 findings on planar imaging (14).

Detector orientation

- 90° or 180°

Acquisition arc

- 180° or 360° (360° is preferable for CT fusion)

Electrocardiogram (ECG) gating

- Not required

Number of views per detector

- 40 views (180° acquisition)
- 32 views (360° acquisition)

Acquisition time per view

- 20 seconds (180° acquisition)
- 25 seconds (360° acquisition)

Magnification ratio

- 1.46 (180° acquisition)
- 1.00 (360° acquisition)

3.3 SPECT/CT

Recommendation level

- Highly recommended for facilities equipped with SPECT/CT.

Guidelines for SPECT/CT

- When performing SPECT/CT, generate fusion images and apply attenuation correction. Fusion images are useful for confirming that the radiotracer uptake is localized to the myocardium and for distinguishing myocardial uptake from ectopic or valvular calcifications. Attenuation correction enhances the accuracy of comparing rib and myocardial uptake.

4. Evaluation method

4.1 Basic principles

Approximately 20% of AL cardiac amyloidosis cases exhibit Grade 2 or higher radiotracer uptake (15). Therefore, before making a definitive diagnosis, it is essential to first rule out AL cardiac amyloidosis.

A positive finding is defined as significant radiotracer accumulation in the left ventricular myocardial wall.

To standardize and quantify this assessment, two methods are commonly used:

- Perugini Grade (qualitative evaluation)
- H/CL ratio (semi-quantitative evaluation)

Perugini Grade (Guideline for qualitative evaluation) (8, 13)

- Grade 0: No myocardial uptake
- Grade 1: Mild myocardial uptake, weaker than rib uptake
- Grade 2: Moderate myocardial uptake, equivalent to rib uptake
- Grade 3: Intense myocardial uptake, stronger than rib uptake

Important considerations

- ◦ Planar imaging limitations: The original Perugini grading system was developed for planar images. However, planar imaging alone makes it difficult to differentiate between myocardial uptake and blood pool activity.
- ◦ If myocardial uptake is not clearly distinguishable (e.g., it lacks a doughnut-shaped or U-shaped pattern consistent with myocardial anatomy), SPECT imaging should be performed to confirm myocardial involvement and avoid false positives.
- ◦ Grade 3: Many studies have reported no false positives at Grade 3. However, if there is any uncertainty about myocardial uptake, SPECT imaging is recommended.
- ◦ Grade 2: A high false-positive rate has been reported, primarily due to misinterpretation of blood pool activity as myocardial uptake. SPECT imaging is strongly recommended to improve diagnostic accuracy.
- ◦ Grade 1: Often classified as negative. However, if myocardial uptake is suspected, SPECT imaging should be used for further evaluation.

Indeterminate cases: If SPECT imaging still leaves room for uncertainty, the case may be classified as “pending judgment”. In such cases, biopsy or additional diagnostic methods may be required to confirm the diagnosis.

4.2 Decision tree

The decision tree for diagnosing ATTR cardiac amyloidosis is designed to categorize cases into positive, negative, or pending judgment based on the above criteria.

- Grade 0: Clearly negative—no further imaging required.
- Grade 3: Clearly positive—SPECT imaging is optional but can be used for confirmation in doubtful cases.
- Grades 1 and 2: Require SPECT imaging as the standard approach to differentiate myocardial uptake from blood pool activity.
- Whenever possible, fusion images with morphological imaging (e.g., CT) should be used to enhance diagnostic accuracy.

Pending judgment

A “pending judgment” classification does not indicate a negative result; rather, it signifies that the imaging findings are inconclusive regarding myocardial radiotracer uptake.

Cases classified as pending judgment include:

- Situations where planar imaging is inconclusive for myocardial uptake but SPECT imaging is unavailable.
- Cases where SPECT/CT suggests myocardial uptake, but the findings are not definitive.

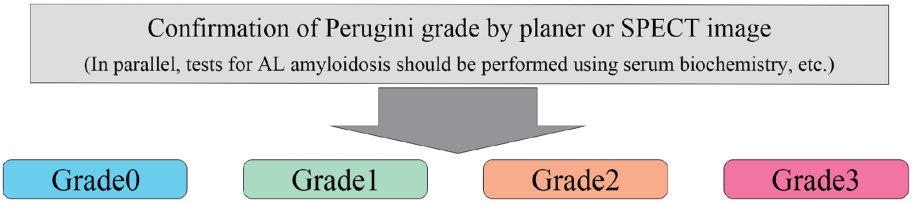
Some pending judgment cases can be confirmed through biopsy or other diagnostic methods. Additionally, since early-stage cardiac amyloidosis may not exhibit significant radiotracer uptake (16), some cases may later progress to a positive diagnosis during follow-up.

General principles for image interpretation

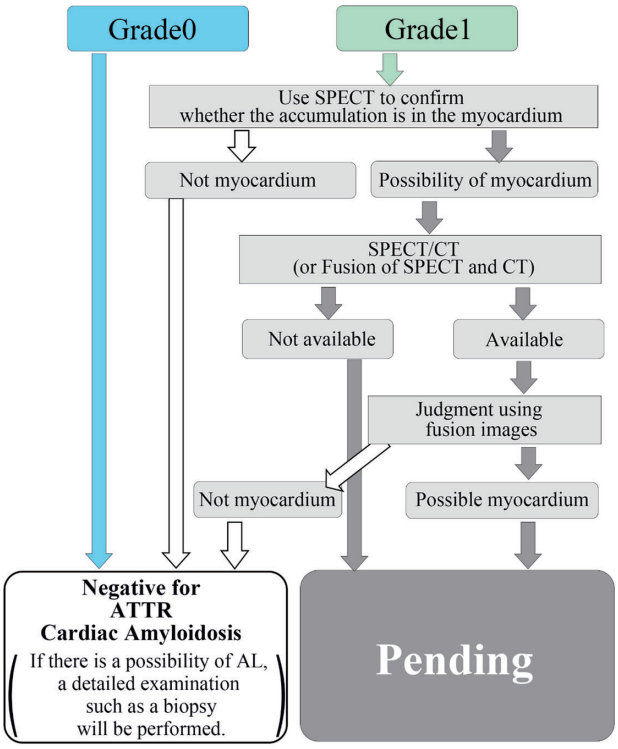
- Negative: Myocardial uptake is not visually observed.
- Positive: Myocardial uptake is clearly visible.
- Pending judgment: Myocardial uptake is visually inconclusive.

As a general rule, if myocardial uptake cannot be visually identified, the case should be classified as negative.

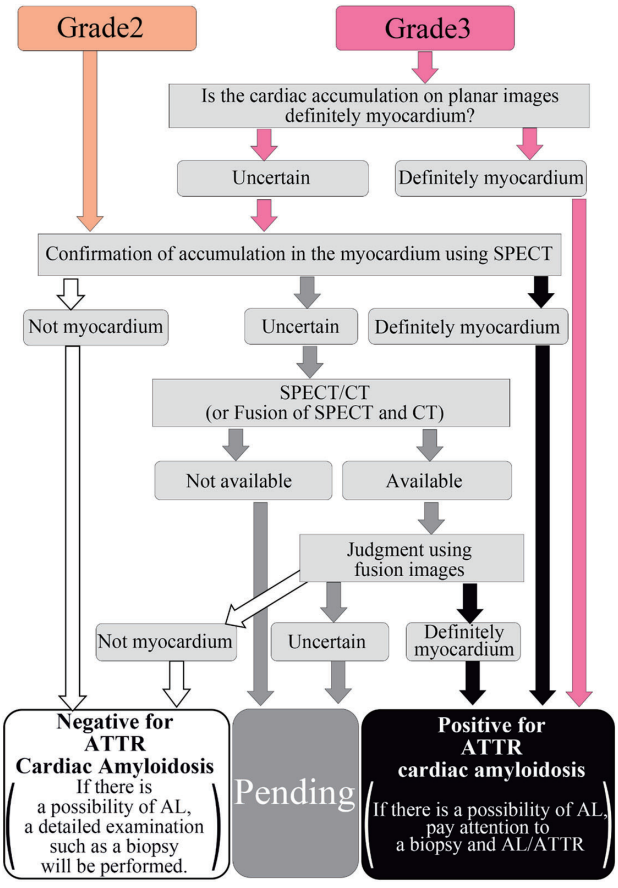
Judgment trees



Grade0－1 trees

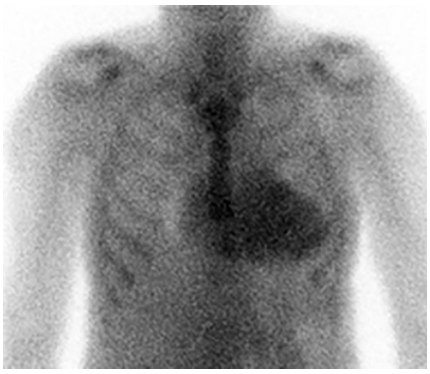
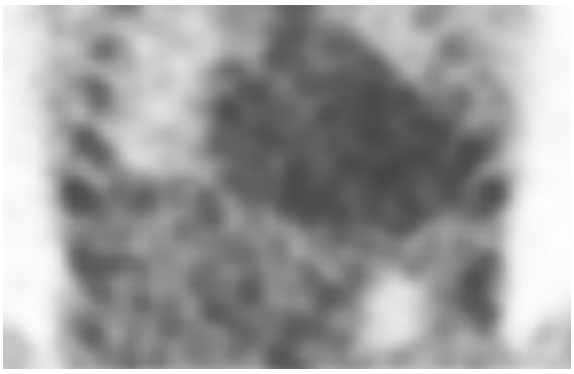


Grade2－3 trees



Inconclusive case

The following is an example of a case where both planar imaging and SPECT imaging at 1-hour post-administration resulted in a pending judgment diagnosis. In the planar image, radiotracer uptake in the heart is clearly higher than in the ribs, which would typically correspond to Perugini Grade 3. However, the uptake does not exhibit a ring-shaped pattern, making it uncertain whether the accumulation is truly myocardial. Similarly, the SPECT image does not clearly differentiate myocardial uptake from blood pool activity. As a result, the final diagnosis was classified as pending judgment. This case was later confirmed to be AL cardiac amyloidosis.

Note:

Should Perugini Grade be evaluated using planar imaging or SPECT?

The original Perugini method defines Perugini Grade based on planar imaging, and most published studies determine Perugini Grade using planar images. However, many studies have demonstrated that a significant proportion of Grade 2 cases on planar imaging are false positives. Therefore, Perugini Grade 2 should not be automatically considered positive. In many cases, SPECT imaging is required for confirmation.

The American Society of Nuclear Cardiology guidelines present both planar and SPECT images for comparison, and this WG also recommends incorporating SPECT imaging into the determination of Perugini Grade.

If the Perugini scores differ between the 1-hour and 3-hour imaging time points, which grade should be used—the higher or the lower?

Use a higher grade.

Relationship between quantitative (H/CL ratio) and visual assessments

Relying solely on H/CL ratio as a diagnostic criterion can lead to many false positives and false negatives. Additionally, the H/CL ratio is only validated for ^{99m}Tc-PYP, and there is insufficient evidence for ^{99m}Tc-HMDP and ^{99m}Tc-DPD. Therefore, H/CL should be considered only as a supplemental diagnostic tool rather than a primary criterion. (See Section 6: Tips for further details.)

Possibility of AL / ATTR combination of cardiac amyloidosis

In clinical practice, serum biochemical tests are performed to diagnose AL cardiac amyloidosis, while bone scintigraphy is used to diagnose ATTR cardiac amyloidosis. These diagnostic processes are often conducted in parallel. If a patient exhibits significant radiotracer uptake on ^{99m}Tc-PYP or ^{99m}Tc-HMDP imaging but is subsequently diagnosed with AL cardiac amyloidosis, the case should be retrospectively excluded from the ATTR diagnostic pathway.

However, AL and ATTR cardiac amyloidosis can coexist, as reported in a small number of published cases (17–19). If coexisting AL/ATTR cardiac amyloidosis is suspected, a biopsy evaluation is required for definitive diagnosis.

5. Differential diagnosis

Ectopic calcification (metastatic calcification) (20–23)

Biochemical evaluation

- Assess for hyperphosphatemia and hypercalcemia.
- Evaluate renal and parathyroid function, and determine whether the patient is undergoing dialysis.

Imaging findings

- Plain CT: Presence of calcification and calcium deposition in the myocardium and other organs.
- SPECT/CT: If performed, CT images should be carefully examined to confirm calcifications.

Valve calcification

- Severe mitral valve calcification has been reported to show radiotracer accumulation on bone scintigraphy (23).
- Accumulations on calcifications that are clearly visible on CT are not due to amyloid deposits, but rather radiotracer accumulation in calcified tissue.

Cardiac sarcoidosis (24–27)

- ^{99m}Tc-PYP uptake in cardiac sarcoidosis was first described in the 1992 diagnostic guidelines for cardiac sarcoidosis (28), with several subsequent reports.
- When differentiation from cardiac sarcoidosis is necessary, diagnosis with ^{18}F-FDG PET is recommended.

Acute myocardial infarction

- Differentiation should be based on the clinical course, including: symptoms, ECG abnormalities, serum biomarkers (e.g., Troponin T, CK/CK-MB), cardiac ultrasound findings, coronary angiography. Particular caution is required when ^{99m}Tc-PYP or ^{99m}Tc-HMDP uptake is localized. If both acute myocardial infarction and cardiac amyloidosis are suspected, re-evaluation after the acute phase is recommended.

Acute myocardial injury (including myocarditis) (29–36)

- ^{99m}Tc-PYP uptake has been reported in cases of acute myocardial injury, including myocarditis, where myocardial necrosis occurs in the early pathological phase (29–34).

- Additional reports include:
  - Radiotracer accumulation at the electrode pad site after DC shock (35).
  - Circumferential endocardial uptake following severe aortic valve stenosis attacks (36). Differentiation based on clinical findings, including symptoms, ECG abnormalities, and serum biomarkers (e. g., Troponin T) are recommended.

Myocardial damage due to chloroquine (37)

Review the patient's chloroquine treatment history. Chloroquine has been widely used for COVID-19 treatment internationally, and cases of chloroquine-induced myocardial damage have been reported.

Other causes of false positives

A false-positive case of ^{99m}Tc-HMDP uptake has been reported in an elderly patient with hypertrophic cardiomyopathy (38). This case showed Perugini Grade 3 uptake, but SPECT imaging was not performed. MRI and histopathology suggested that local necrosis occurred in the hypertrophied septum, with radiotracer accumulation via a mechanism similar to acute myocardial infarction. This is an extremely rare case, made more complex by the patient's concurrent carpal tunnel syndrome, making differentiation particularly challenging.

6. Tips

SPECT display method

We strongly recommend using a three-section display: axial, coronal, and sagittal views.

In cases of weak accumulation, the right and left ventricular blood pools may appear to merge with the septum and lateral wall in axial images. In such situations, the left ventricular wall typically presents as a transverse U-shape in coronal images and a ring-like shape in sagittal images, which can aid in distinguishing the blood pool.

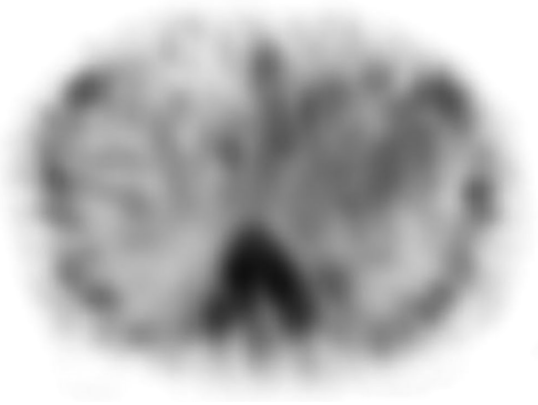
Triaxial images, similar to those used in myocardial perfusion scintigraphy, may be used when feasible. However, when accumulation is unclear, generating triaxial images can be challenging. Therefore, axial, coronal, and sagittal views are preferred to ensure display consistency.

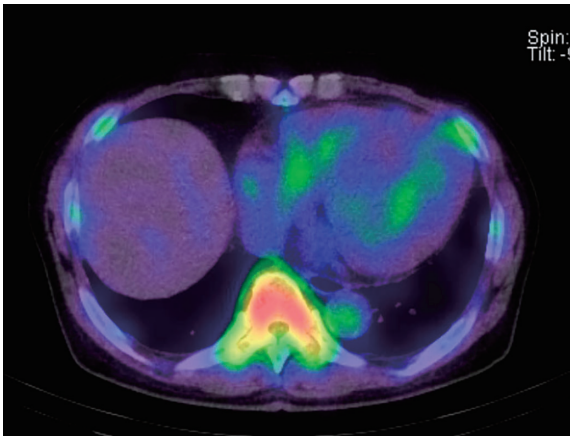
Additionally, when displaying SPECT images, using a color scheme—such as a rainbow color display—rather than black and white makes it easier to compare accumulation levels with the ribs.

SPECT/CT fusion imaging

We strongly recommend using SPECT/CT fusion imaging when possible, as it is highly effective in differentiating blood pool from myocardial accumulation. Even when using a standalone SPECT system, reliable myocardial accumulation assessment can be achieved by fusing the images with a separate CT scan. Therefore, we recommend this approach in cases where SPECT alone does not provide a definitive determination.

(The image below serves as a negative example. While SPECT/CT clearly visualizes the cardiac blood pool, SPECT alone may lead to misinterpretation, as the right ventricular blood pool and left ventricular blood pool can be mistaken for septal and lateral wall accumulations, respectively.)





^{201}Tl/^{99m}Tc simultaneous acquisition

Detecting blood flow defects can help identify myocardial infarction.

Additionally, this method is useful for locating the myocardium when it is not clearly visualized using ^{99m}Tc-PYP or ^{99m}Tc-HMDP.

Quantitative analysis:

H/CL Ratio (39)

To calculate the H/CL ratio, the myocardium and the contralateral lung field must be accurately defined as regions of interest (ROIs).

A circular ROI should be placed over the heart in the planar image, with a corresponding ROI positioned symmetrically in the contralateral chest while considering background activity and rib structures.

Ideally, the ROI should tightly enclose the heart. However, in cases of unclear accumulation, the ROI size can be adjusted based on clinical judgment and experience.

The H/CL ratio is determined by dividing the average count (counts/pixel) within the myocardial ROI by the value obtained for the contralateral lung field ROI.

If the ROIs for the heart and contralateral lung field are of equal size, the ratio can alternatively be calculated using total counts instead of average counts, yielding nearly identical results.

If it is not possible to place a perfectly symmetrical ROI on the contralateral lung due to anatomical factors, adjustments may be made. In cases where high rib accumulation is observed (e.g., due to rib fractures), asymmetrical ROIs may be used, provided this is explicitly noted in the findings. If pathological accumulation in the ribs is unavoidable, the H/CL ratio should be interpreted as a reference value, as pathological bone accumulation may interfere with accurate quantification.

Imaging time for H/CL measurement

For ^{99m}Tc-PYP, the standard measurement time is 1-hour post-administration. If necessary, an additional measurement can be performed 3-hours post-administration.

H/CL threshold values at 1-hour and 3-hours

- 1-hour post-administration threshold: 1.5
  - This value is widely adopted in the literature, following Bokhari's key study.
- 3-hour post-administration threshold: 1.3
  - This value is supported by SCAN-MP study evidence (14).
  - However, false positives tend to occur more frequently at 3-hours than at 1-hour.

Regarding quantitative values (H/CL)

The H/CL ratio serves as a supplementary tool for visual assessment. Studies have reported that incorporating the H/CL ratio does not enhance diagnostic accuracy when SPECT-CT fusion imaging is used for visual evaluation (40). Therefore, we recommend prioritizing visual assessment based on the chart shown above. In particular, for cases classified as indeterminate according to the chart, it is not advisable to determine positivity or negativity solely based on the H/CL criteria. While some studies indicate that the 3-hour H/CL value has a significantly larger AUC and is more accurate than the 1-hour value, others have reported that using a 1. 3 threshold for the 3-hour value increases the incidence of false positives (14, 41). Additionally, ^{99m}Tc-HMDP has been reported to cause high lung accumulation, which may affect H/CL values (42). In any case, it is important to recognize that H/CL is only an auxiliary tool for clinical judgment.

Other quantitative indices

- Bone SUV (43, 44)
- Heart-to-body ratio (45, 46)
- Heart-to-mediastinum ratio by SPECT (47)
- Heart-to-lung ratio by SPECT (48)
- Heart-to-mediastinum ratio by planar imaging (49, 50)

However, we do not recommend using these indices. The values of quantitative measurements can vary significantly depending on the device, analysis method, and whether attenuation correction is applied.

Handling of incidental myocardial accumulation in bone scintigraphy

When myocardial ectopic accumulation is detected incidentally on bone scintigraphy, it is highly suggestive of ATTR cardiac amyloidosis, particularly in elderly patients, except in cases using ^{99m}Tc-MDP. Therefore, in such cases, a cardiology consultation should be considered in parallel with the above assessments.

The prevalence of incidental findings varies based on the population studied and evaluation criteria, making it difficult to provide a precise estimate (51, 52). However, a meta-analysis estimated the incidence to be approximately 1% (53), indicating that such findings are not rare.

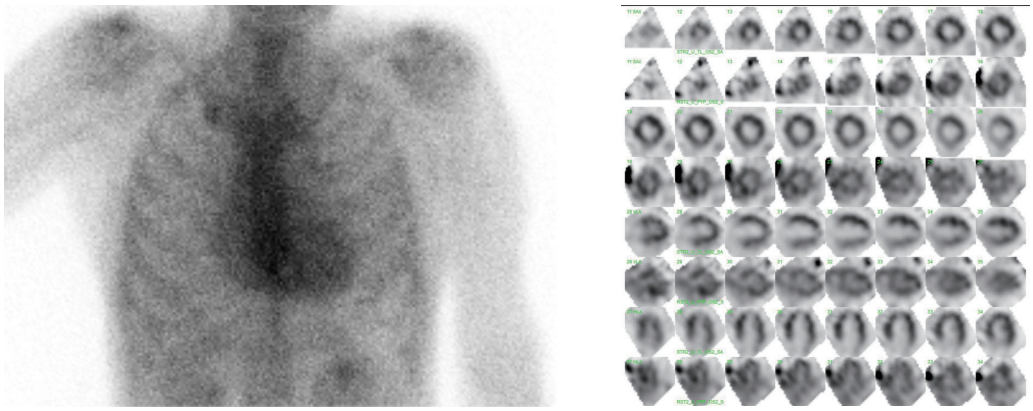
Recording H/CL ratios: 1-hour vs. 3-hour

If both 1-hour and 3-hour imaging are available, it is preferable to record both values. However, if only one value is available, we recommend recording the 1-hour H/CL ratio.

Imaging with dedicated cardiac scanner

In dedicated cardiac imaging systems, such as D-SPECT and Discovery NM530C, planar images are generated as virtual planar images. Further validation is needed to confirm whether quantitative indices derived from planar imaging, such as the H/CL ratio, can be reliably measured using these virtual images. However, this WG report recommends prioritizing visual evaluation and classifying cases as negative, positive, or indeterminate. This approach can also be applied directly to evaluations using dedicated cardiac imaging systems.

Cases of dedicated cardiac scanner



The images above provide examples of planar scans obtained using a semiconductor cardiac SPECT system alongside dual SPECT images of ^{201}Tl/^{99m}Tc-PYP (first row: ^{201}Tl, second row: ^{99m}Tc-PYP). Although this case is classified as Perugini Grade 2 or 3 based on planar imaging, the ring-shaped accumulation pattern is not definitively observed. Consequently, if this case had been imaged using an Anger camera, it would have fallen into the category requiring SPECT imaging according to the flowchart.

False positives and false negatives

Even in AL cardiac amyloidosis, approximately 20% of cases show positive scintigraphy findings (3). Sympathetic nerve dysfunction has been reported to precede ^{99m}Tc-DPD myocardial accumulation (16). Therefore, in very mild or early-stage cases, false negatives may occur.

Prevalence of coexisting AL and ATTR cardiac amyloidosis

A study reported that 39% of biopsy-confirmed ATTR cardiac amyloidosis cases were associated with monoclonal gammopathy of undetermined significance (54). If blood tests are used to exclude suspected AL cardiac amyloidosis before diagnosing ATTR cardiac amyloidosis via scintigraphy, a significant number of ATTR cases may be inadvertently excluded from the diagnostic process. When serum biochemistry tests suggest the presence of either AL or ATTR cardiac amyloidosis, a comprehensive evaluation -including biopsy and additional diagnostic modalities- is necessary to determine the predominant cause.

Acknowledgments

None.

Sources of funding

None.

Conflicts of interest

Kenichi Nakajima; PDR farma (joint research, endowed course), Nihon-Medi physics (endowed course), Siemens Healthcare (endowed course)
Kenji Fukushima; Nihon-Medi physics, PDR farma (lecture fee)
Nobuo Iguchi; Pfizer (lecture fee)
Toru Kubo; Pfizer (lecture fee)
Seiji Takashio; Pfizer (lecture fee)
Yasuhiro Izumiya; Pfizer (lecture fee)

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