

2021 Advocacy Statements for the Role of ^{99m}Tc -Pyrophosphate Scintigraphy in the Diagnosis of Transthyretin Cardiac Amyloidosis: A Report of the Taiwan Society of Cardiology and the Society of Nuclear Medicine of the Republic of China

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Transthyretin cardiac amyloidosis (ATTR-CM) is an increasingly recognized cause of heart failure with preserved ejection fraction. Favorable prognosis depends on early diagnosis and correct treatment strategy. Among patients for whom there is a high clinical suspicion of cardiac amyloidosis, ^{99m}Tc -labeled bone avid scintigraphy including ^{99m}Tc -pyrophosphate (PYP) scintigraphy may be of diagnostic and prognostic importance. Various international guidelines support the non-biopsy diagnosis of ATTR-CM using ^{99m}Tc -PYP scintigraphy, yet emphasize the gap in standardization of acquisition and imaging analysis protocols, as well as the appropriateness of its clinical use. Therefore, a joint expert consensus has been reached by the Taiwan Society of Cardiology and the Society of Nuclear Medicine of the Republic of China, to advocate for the application of ^{99m}Tc -PYP scintigraphy in the diagnosis of ATTR-CM. This article aims to highlight the recommendations on image acquisition, qualitative and quantitative assessments of cardiac ^{99m}Tc -PYP uptake, and diagnostic algorithms. We hope the implementation of these recommendations in Taiwan will facilitate the process and enhance the diagnostic rate of ATTR-CM.

Key Words: Cardiac amyloidosis • Cardiomyopathy • Heart failure • Scintigraphy • ^{99m}Tc -pyrophosphate (PYP) • Transthyretin

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INTRODUCTION

Heart failure (HF) is the leading cause of cumulative hospitalization days for cardiovascular disease in Taiwan, and rates of re-hospitalization and mortality are high.^{1,2} Due to different etiologies and disease severity, there is a large gap in treatment response and prognosis.³⁻⁵

The incidence and prevalence of HF with preserved ejection fraction (HFpEF) have increased in recent years.⁶ Among the different causes of HFpEF, cardiac amyloidosis (CA), where amyloid deposition occurs in the heart, still poses challenges to physicians in early diagnosis and treatment.^{7,8} The majority (> 95%) of patients with cardiac amyloidosis are affected either by a misfolded immunoglobulin light chain (AL), or by transthyretin (TTR) deposition in the heart.⁸ Cardiomyopathy is a clinical feature of transthyretin amyloidosis (ATTR), which is an under-recognized systemic disease whereby the transthyretin protein misfolds to form fibrils that deposit in various tissues and organs. Transthyretin cardiac amyloidosis (ATTR-CM) can be divided into two major forms — wild-type ATTR (ATTRwt) and ATTR from a genetic mutation (ATTRm).⁷

The primary manifestations of ATTRwt are cardiac amyloidosis and carpal tunnel syndrome. The prevalence of ATTRwt in HFpEF patients with left ventricular hypertrophy (LVH) (wall thickness > 12 mm) is about 13%, and the prevalence of ATTRwt in patients with aortic stenosis after aortic valve replacement is 6-16%.⁹⁻¹¹ The age of onset of ATTRm is variable, ranging from 30 to 80 years old. The symptoms of ATTRm correspond to different gene mutations. This hereditary form of ATTR manifests predominantly as polyneuropathy, cardiomyopathy, or mixed phenotype.¹² The Transthyretin Amyloidosis Outcomes Survey (THAOS) study found that among symptomatic patients with TTR mutations, approximately half have neurological manifestations as their primary symptom, followed by cardiac abnormalities and mixed phenotype, each constituting approximately a quarter, respectively.¹² ATTR genotypes and phenotypes are highly heterogeneous. Because there are no large-scale screening and registration studies, the actual prevalence of ATTR-CM in Taiwan remains unclear. The Ala97Ser mutation is the most common cause of ATTRm in Taiwan.^{13,14} It is considered both a form of cardiomyopathy and a polyneuropathic syndrome, and approxi-

mately 80% of them have LVH.¹⁴ Therefore, raising early awareness that ATTR-CM in Taiwan can manifest as a dominant cardiac phenotype mimicking hypertrophic cardiomyopathy (HCM) at presentation will facilitate the clinical recognition of this under-diagnosed disease.

ATTR is debilitating and associated with poor life expectancy, especially in those with cardiac dysfunction. Delayed or lack of treatment after diagnosis will result in poor prognosis, with a median survival period of only 2 to 3 years. Recently, a variety of new and promising treatment options have become available,⁷ including pharmacological therapy that slows or halts ATTR-CM progression and favorably affects clinical outcomes. Therefore, early recognition is essential to afford the best treatment efficacy.

Several clinical signs can raise suspicion for CA. These red flags include abnormalities on electrocardiography (ECG), echocardiography, cardiac magnetic resonance imaging (CMR), or cardiac biomarkers.¹⁵⁻¹⁸ Noninvasive methods including ECG, echocardiography, CMR, and nuclear scintigraphy can assist in diagnosis.¹⁹ LVH is a common indicator used to detect CA. Red flags of CA on ECG include a low QRS voltage in combination with increased left ventricle thickness, a pseudo-infarction pattern, conduction abnormality, and arrhythmia.¹⁹⁻²¹ Red flags on echocardiography indicating CA include thickening of the atrioventricular valves and interatrial septum, a speckled and granular appearance of the myocardium, and a base-to-apex strain gradient with relative apical sparing of longitudinal strain (the so-called “cherry-on-top pattern”).^{19,22,23} CMR might show global diffuse myocardial late gadolinium enhancement in the subendocardial layers, elevated native T1 and extracellular volume fraction in T1 mapping.^{18,19,24} Endocardial biopsy is considered as the gold standard for the diagnosis of ATTR.¹⁹ Once CA is suspected, further confirmatory diagnosis could be reached through either non-invasive methods such as nuclear scintigraphy and the free light chain (FLC) test,²⁵⁻²⁷ or invasive methods such as biopsy and amyloid typing.

Bone-avid radiotracers including technetium-99m (^{99m}Tc)-pyrophosphate (PYP) have been reported to be useful in detecting CA.^{8,15-19,22-27} The exact mechanism is not fully understood. It may be related to amyloid microcalcification. Historically, ^{99m}Tc-PYP has been well-known for its role in diagnosing acute/recent myocardial infarc-

tion or rhabdomyolysis, thus also referred to as infarct or muscle scintigraphy. Semi-quantitative analyses based on the radiotracer uptake in the heart and surrounding ribs, expressed on a 0-3 point grading scale, help to distinguish different types of CA.²⁵⁻²⁷ Most patients with AL amyloidosis are of lower grades (grades 0-2), while patients with ATTR-CM are of higher grades (grades 2-3).²⁵⁻²⁷ In a study which enrolled 1,217 patients after excluding AL with suspected CA and using PYP scan grades 2-3 as criteria, the specificity and positive predictive values were both as high as 100%.²⁸ PYP scan has thus been considered a suitable alternative to EMB in some patients suspect of ATTR-CM.^{29,30} In contrast to echocardiography, EMB can truly demonstrate amyloid fibrils in clinically suspected patients mimicking hypertensive heart disease or HCM. It strengthens the importance of pathological confirmation of CA from other HCM, albeit diagnostic yield of extracardiac biopsies with the presence of amyloid protein in high-risk patients with conduction disturbances and advanced age could be relatively low. A feasible and less invasive tool such as PYP

scan will make diagnosis of ATTR-CM more applicable for both clinicians and patients.²⁷

Last but not least, with respect to promising therapeutic outcome from recent clinical trials, imaging techniques and reporting format standardization are of increasing importance. The Taiwan Society of Cardiology (TSOC) and the Society of Nuclear Medicine of the Republic of China (SNMROC) apprehend the acute necessity of establishing advocacy statements on when and how to use nuclear imaging procedures, adjust relevant acquisition parameters, standardize reporting format, and facilitate earlier therapeutic intervention and clinical research.

^{99m}Tc-PYROPHOSPHATE SCINTIGRAPHY

Image acquisition procedures

Recommendations for ^{99m}Tc-PYP scintigraphy acquisition parameters are listed in Table 1. Standard planar images for anterior, left anterior oblique and lateral

Table 1. Recommendations for ^{99m}Tc-pyrophosphate scintigraphy acquisition parameters

	Parameters
Imaging procedure	
Specific preparation	None; fasting is not required
Scan	Rest scan
Dose of ^{99m} Tc-PYP	<ul style="list-style-type: none"> • Recommended: 20 mCi for 3-hour acquisition • Adjust according to different models of instrument
Time interval between injection and acquisition	<ul style="list-style-type: none"> • Recommended: 3-hour planar and SPECT • Optional: 1-hour planar
Imaging parameters	
Field of view	Cardiac or chest
Image type	Cardiac or chest planar and SPECT (or SPECT/CT)
Position	Supine
Energy window	140 keV, 15-20%
Collimators	Low energy, high resolution
Matrix	128 × 128 recommended (64 × 64 minimum required) 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 left anterior oblique (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-gated imaging
Number of views/detectors	32-64
Time per stop	20 seconds

ECG, electrocardiography; keV, kilo-electronvolts; mCi, millicurie; PYP, pyrophosphate; SPECT, single-photon emission computed tomography; SPECT/CT, SPECT/computed tomography.

views are shown in Figure 1. Bilateral shoulders should be visible in the image to evaluate for musculoskeletal manifestations of amyloid deposition, such as the shoulder pad sign or joint swelling.³¹ Symmetric renal uptake should be minimized in planar images to avoid interference with the myocardial counts.

One-hour imaging results have higher detection sensitivity, while 3-hour imaging results offer higher detection specificity. This is because delayed clearance of blood pool activity after tracer injection is not uncommon in patients with poor renal function or low cardiac output. In our recommendation, 3-hour planar images are recommended for visual scoring and semi-quantitation and 1-hour images are optional. Single-photon emission computed tomography (SPECT) is necessary to distinguish blood pool activity from myocardial activity. In addition, SPECT/computed tomography

(SPECT/CT) is preferred for attenuation correction and anatomical localization. It accentuates differences in myocardial uptake patterns, allowing for more accurate classifications — absent, focal, diffuse, or focal on diffuse. Therefore, an injection dose of 20 millicurie (mCi) of ^{99m}Tc PYP is recommended for 3-hour planar and SPECT imaging. Although delayed-time-point imaging is expected to improve qualitative and semi-quantitative results, SPECT or SPECT/CT at 1 hour with low blood activity is also acceptable. If SPECT or SPECT/CT is performed, planar images of left anterior oblique and lateral views are optional to shorten the image acquisition time.

The differences in ^{99m}Tc-PYP scintigraphy imaging acquisition parameters between our recommendations and those of the 2019 American Society of Nuclear Cardiology (ASNC) practice points²⁶ are listed in Table 2.

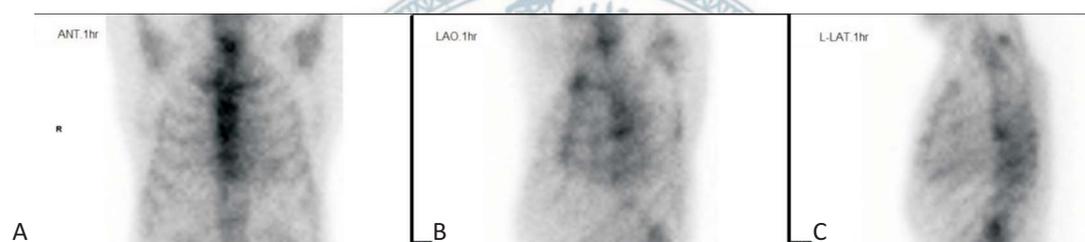


Figure 1. Standard planar images for (A) ANT (anterior), (B) LAO (left anterior oblique) and (C) LAT (lateral) views, acquired at 1 hour (hr) and/or 3 hrs, respectively. Optimal field of view (FOV) should cover the whole chest region, including bilateral shoulders while avoiding highly radioactive sites, such as injection sites or areas with marked renal activity.

Table 2. Differences in ^{99m}Tc-pyrophosphate scintigraphy acquisition parameters between ASNC* and TSOC/SNMROC consensus recommendations

	TSOC and SNMROC recommendations	2019 ASNC practice points recommendations*
Imaging procedure		
Dose of ^{99m} Tc-PYP	<ul style="list-style-type: none"> Recommended: 20 mCi for 3-hour acquisition Adjust according to different models of instrument 	<ul style="list-style-type: none"> 10-20 mCi
Time interval between injection and acquisition	<ul style="list-style-type: none"> Recommended: 3-hour planar and SPECT Optional: 1-hour planar 	<ul style="list-style-type: none"> Recommended: 1-hour planar and SPECT Optional: 3-hour SPECT or planar
Imaging parameters		
Matrix	<ul style="list-style-type: none"> Recommended: 128 × 128 for SPECT Required: 64 × 64 minimum for SPECT 256 × 256 for planar 	64 × 64 minimum
Planar imaging specific parameters		
Detector configuration	180 degrees	90 degrees
Magnification	1.45-1.5	1.46
SPECT imaging specific parameters		
Number of views/detector	32-64	40

ASNC, American Society of Nuclear Cardiology; ECG, electrocardiography; mCi, millicurie; PYP, pyrophosphate; SNMROC, Society of Nuclear Medicine of the Republic of China; SPECT, single-photon emission computed tomography; TSOC, Taiwan Society of Cardiology.

* Source: Dorbala S, et al. 2019 ASNC Practice Points.²⁶

SEMI-QUANTITATION

A visual grading scale is used to interpret the imaging results (Table 3). A visual grade of 0 is not suggestive of ATTR-CM. Grade 1 is equivocal. If clinically highly suspicious for CA, a specialist should perform further assessment. Grade 2 or 3 is diagnostic of ATTR-CM.

A heart to contralateral lung ratio (H/CL) on the planar anterior view is used for semi-quantitation as shown in Figure 2. A circular or elliptical region of interest (ROI) is drawn to include the left ventricle maximally while cautiously avoiding the sternal region and the adjacent lung. The ROI is mirrored to the contralateral chest, be-

ing careful to exclude any right heart or mediastinal activity and avoiding the subdiaphragmatic organs. Total and absolute mean counts are measured in each ROI. A H/CL ratio is calculated as the fraction of heart ROI mean counts to contralateral chest ROI mean counts. Alternatively, geometric means of the average counts of ROIs calculated from both anterior and posterior planar views can be used. Although different H/CL ratios and cut-off values for one hour or three hours have been reported,^{25-27,32} our consensus uphold the criteria of the 2019 ASNC recommendations^{25,26} and the 2020 JCS guideline.²⁷ For one-hour images, an H/CL ratio > 1.5 is used to identify ATTR-CM. For 3-hour images, an H/CL ratio ≥ 1.3 is

Table 3. Recommendations for standardized interpretation of ^{99m}Tc-pyrophosphate scintigraphy

Visual interpretation	
<ul style="list-style-type: none"> • Evaluate for cardiac radiotracer uptake on 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, a visual grade of 0 is given. 	
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
H/CL ratio interpretation	
If tracer uptake is not evident on SPECT images, obtaining 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

AL, immunoglobulin light chain amyloidosis; ATTR-CM, transthyretin cardiac amyloidosis; H/CL, heart to contralateral lung; SPECT, single-photon emission computed tomography; SPECT/CT, SPECT/computed tomography. Adapted and modified from references 25, 26.

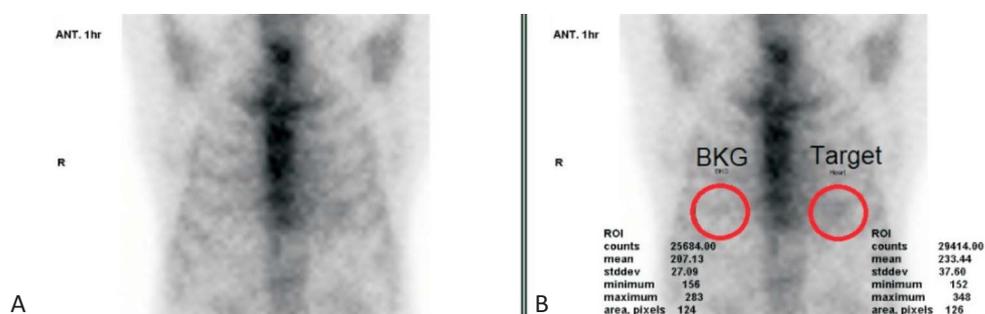


Figure 2. Quantitation of cardiac ^{99m}Tc-PYP uptake using the H/CL ratio. (A) Planar anterior view, (B) Region of interest (ROI) demonstration. Circular target ROI (red circles), which includes the heart, is drawn over the planar anterior image, and is mirrored over the contralateral lung. Total and mean counts are calculated, and the H/CL ratio is derived from mean counts of ROIs. BKG, background; H/CL, heart to contralateral lung; PYP, pyrophosphate; stddev, standard deviation.

used to identify ATTR-CM.

^{99m}Tc -PYP quantitative SPECT is a feasible and objective tool for assessing the burden of CA in the diagnosis of ATTR-CM.^{33,34} Dual-isotope SPECT using ^{99m}Tc -PYP/ ^{201}Tl might augment visual differentiation compared to single-isotope SPECT.³⁵ However, the methodology is not standardized. As such, further investigation is warranted.

The recently introduced cadmium zinc telluride SPECT cameras have the potential to reduce radiation exposure to patients and shorten imaging time. The value of ^{99m}Tc PYP imaging utilizing the newer “cardiac only” SPECT cameras also needs further validation.³⁶⁻⁴⁰

INTERPRETATION AND REPORTING

Recommendations for image interpretation and reporting of ^{99m}Tc -PYP scintigraphy are listed in Tables 3 and 4.

Interpretation of ^{99m}Tc -PYP scintigraphy should include a visual evaluation of planar and SPECT images for any radiotracer uptake, visual grading, and the semi-quantitative H/CL ratio. In the absence of any tracer uptake in the myocardium on SPECT imaging, a visual grade of 0 is given. Visual scores ≥ 2 on planar imaging are regarded as ATTR-positive. An H/CL ratio > 1.5 on one-hour imaging or ≥ 1.3 on three-hour imaging is indicative of ATTR-CM if plasma cell dyscrasia has been excluded. If myocardial uptake patterns on SPECT are focal or focal on diffuse, use the maximal uptake for visual grading is recommended.

After excluding AL, ^{99m}Tc -labeled bone tracer scintigraphy is used to diagnose ATTR-CM with high sensitivity and specificity.³⁷ False positives on ^{99m}Tc -PYP scans may arise from AL, blood pool uptake, rib fractures, myocardial infarction, quinine drug toxicity, or other rare forms of CA. False negatives may be due to minimal myocardial infiltration (early-stage disease) or scar tis-

Table 4. Recommendations for standardized reporting of ^{99m}Tc -pyrophosphate scintigraphy

Parameters	Components																
Demographics	Patient name, age, sex, study date and reason, previous imaging procedures, and results of biopsy if available. Heart failure severity (NYHA classification, LVEF %), recent myocardial infarction history (within 3 months), and renal function (eGFR or cCr within 3-6 months, or presence of ESRD) should be provided as supportive information (recommended)																
Methods	Image acquisition parameters and technique, dose and mode of radiotracer administration, time interval between injection and scan, and scan (planar and SPECT) performed (required)																
Findings	Quality of the image Visual grading interpretation in relation to rib uptake (required) Semi-quantitative H/CL ratio (required)																
Ancillary findings	Consider attenuation correction in CT interpretation if SPECT/CT scanners are used (recommended)																
Conclusions	1. Findings can be interpreted and categorized as follows: <table border="1" data-bbox="352 1469 1445 1621"> <thead> <tr> <th></th> <th>Visual Score</th> <th>H/CL ratio at 1-hour</th> <th>H/CL ratio at 3-hour</th> </tr> </thead> <tbody> <tr> <td>Not suggestive</td> <td>0</td> <td>< 1</td> <td>< 1.3 (negative)</td> </tr> <tr> <td>Strongly suggestive</td> <td>2 or 3</td> <td>> 1.5</td> <td>≥ 1.3 (positive)</td> </tr> <tr> <td>Equivocal</td> <td>1</td> <td>1-1.5</td> <td></td> </tr> </tbody> </table>		Visual Score	H/CL ratio at 1-hour	H/CL ratio at 3-hour	Not suggestive	0	< 1	< 1.3 (negative)	Strongly suggestive	2 or 3	> 1.5	≥ 1.3 (positive)	Equivocal	1	1-1.5	
	Visual Score	H/CL ratio at 1-hour	H/CL ratio at 3-hour														
Not suggestive	0	< 1	< 1.3 (negative)														
Strongly suggestive	2 or 3	> 1.5	≥ 1.3 (positive)														
Equivocal	1	1-1.5															
Notes	2. Interpret the results in the context of prior cardiac evaluation, assessment for systemic AL amyloidosis using serum and urine immunofixation, and serum free light chain assay. 3. If echo/CMR are strongly positive and ^{99m}Tc -PYP scan is negative, consider further evaluation including endomyocardial biopsy. A negative or mildly positive ^{99m}Tc -PYP does NOT exclude AL Equivocal results could represent either AL or early ATTR																

AL, immunoglobulin light chain amyloidosis; ATTR, transthyretin amyloidosis; cCr, creatinine clearance; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; ESRD, end stage renal disease; H/CL ratio, heart to contralateral lung ratio; LVEF, left ventricular ejection fraction; NYHA, New York Heart Association; PYP, pyrophosphate; SPECT, single-photon emission computed tomography; SPECT/CT, SPECT/computed tomography. Adapted and modified from reference 25, 26.

sue formation after myocardial infarction. Therefore, the severity of heart failure [i.e., New York Heart Association (NYHA) functional classification or left ventricular ejection fraction (LVEF) percentage], a recent history of myocardial infarction (within 3 months), and current renal function [estimated glomerular filtration rate (eGFR) or creatinine clearance (cCr) within 3-6 months, or presence of end-stage renal disease] are recommended supportive information to consider to avoid false positives. Visual grading and semi-quantitative H/CL ratios are required. SPECT/CT with attenuation correction is also recommended to distinguish blood pool or rib activity. If background or blood pool activity is still high, further delayed imaging may be considered. An overall interpretation of the findings separates patients into three categories — not suggestive, strongly suggestive, or equivocal — for ATTR-CM. Examples of ^{99m}Tc -PYP scintigraphy are shown in Figures 3 to 7.

There is an increasing trend towards the use of non-invasive testing with ^{99m}Tc -PYP for the evaluation of ATTR-CM. In addition, monoclonal protein testing and SPECT imaging are critical components for ruling out AL and distinguishing myocardial retention from blood pooling.^{36,41} The diagnostic combination of the FLC test

and ^{99m}Tc -PYP scintigraphy can reveal four possible outcomes. Firstly, if both tests are negative, it is unlikely to be AL or ATTR-CM. Secondly, if the FLC test is negative and ^{99m}Tc -PYP scintigraphy is positive with grade 2-3 radiotracer uptake, ATTR-CM is implicated. Thirdly, if the FLC test is positive and ^{99m}Tc -PYP scintigraphy is negative, it points to AL, and histological confirmation is required. Lastly, if FLC test is positive and ^{99m}Tc -PYP scintigraphy shows visual grade of 1 to 3, further histological confirmation is necessary to differentiate between AL and ATTR-CM. To diagnosis ATTR-CM noninvasively (i.e. not requiring EMB), the patient should demonstrate both a positive ^{99m}Tc -PYP scan (visual grade 2 or greater) and a negative FLC test. Otherwise, a single negative or mildly positive ^{99m}Tc -PYP scan does not exclude AL. Equivocal results (visual grade 1) on ^{99m}Tc -PYP scintigraphy only could represent either AL or early ATTR-CM. The clinical information should be clearly reviewed and an EMB may be needed in the case of equivocal imaging findings or discordant data. Herein, we proposed a simplified clinical diagnostic algorithm of CA where the presence of monoclonal proteins in serum and urine should be analyzed before performing the ^{99m}Tc -PYP scintigraphy (Figure 8).

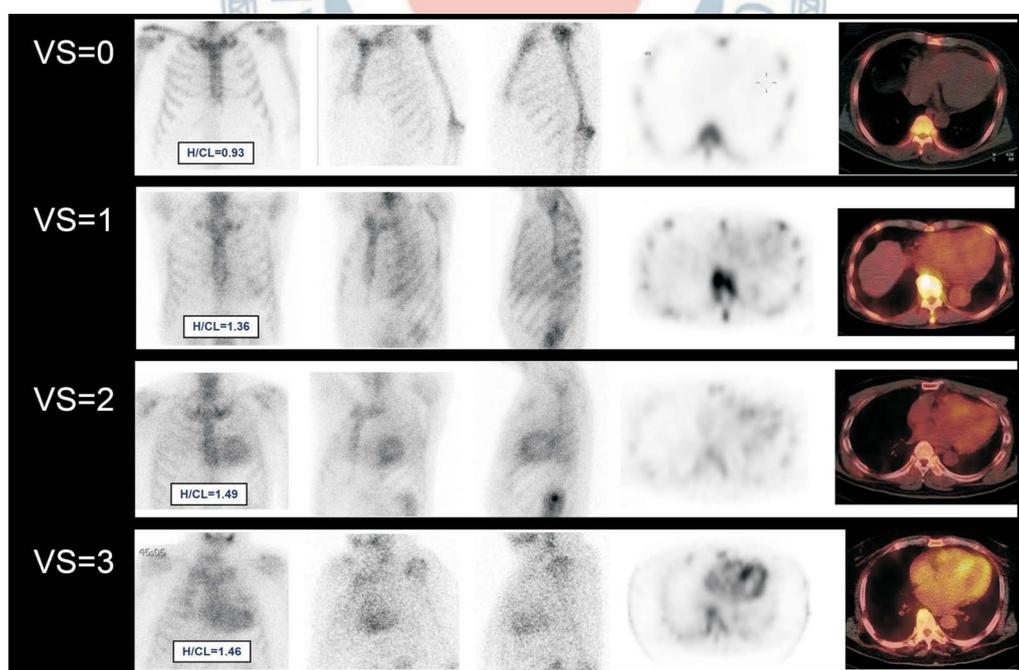


Figure 3. Visual scores. Examples of visual scores from 0 to 3 based on ^{99m}Tc -PYP planar (anterior, left anterior oblique, and lateral views), axial SPECT, and axial fused SPECT/CT images at 3 hours post-injection of radiotracer. H/CL ratio, heart to contralateral lung ratio; PYP, pyrophosphate; SPECT/CT, single-photon emission computed tomography/computed tomography.

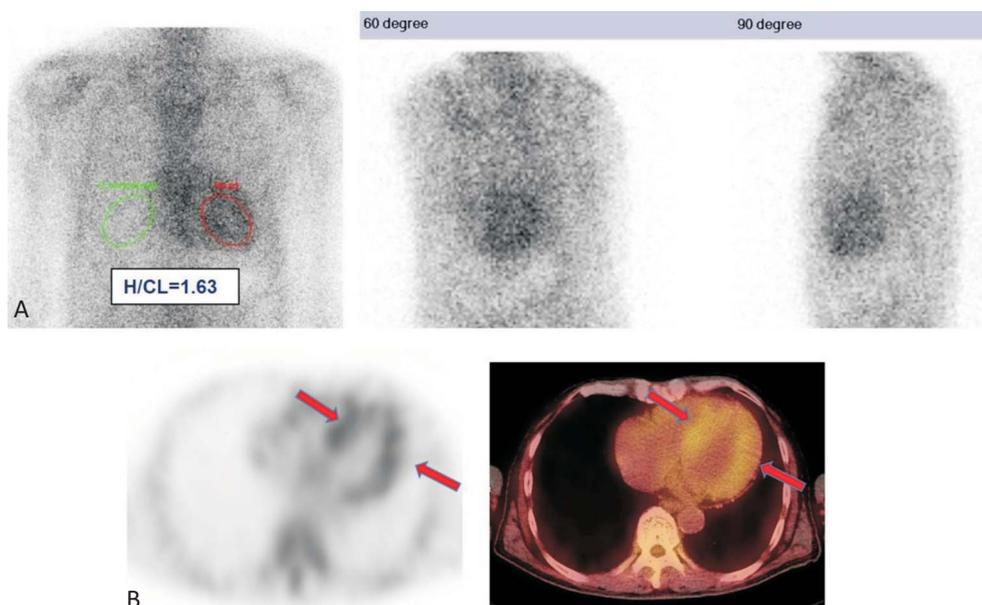


Figure 4. ATTR amyloidosis, hereditary subtype. A 62-year-old man presented with a two-year history of progressive numbness and tingling in all four limbs. In the last six months, he developed exertional dyspnea. Coronary catheterization revealed patent coronary arteries and endomyocardial biopsy showed amyloidosis cardiomyopathy. ^{99m}Tc -PYP planar (A) and SPECT/CT (B) imaging demonstrated diffuse intense uptake in the LV myocardium at 3 hours post-injection, significantly greater than rib activity with mildly decreased rib uptake (red arrows, visual score of 3). The H/CL ratio at 3 hours post-injection was 1.63. Nerve conduction velocity exam revealed sensorimotor polyneuropathy with axonal degeneration, manifesting as bilateral median entrapment neuropathy. Urine, blood, and cerebral spinal fluid immunofixation electrophoresis showed no evidence of monoclonal gammopathy. Sural nerve biopsy also revealed amyloid neuropathy. Familial amyloid polyneuropathy stemming from a transthyretin (TTR) Ala97Ser mutation was further confirmed. ATTR, transthyretin amyloidosis; H/CL, heart to contralateral lung; LV, left ventricular; PYP, pyrophosphate; SPECT/CT, single-photon emission computed tomography/computed tomography.

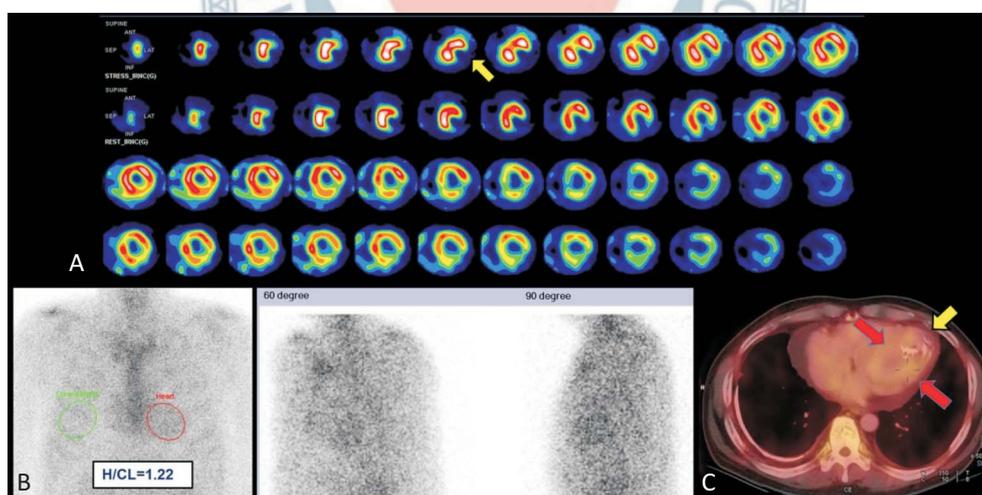


Figure 5. AL amyloidosis. A 60-year-old man who presented with paroxysmal nocturnal dyspnea and orthopnea was diagnosed with heart failure with preserved ejection fraction of 58.2% (NYHA Functional Classification II). Standardized dipyridamole stress myocardial perfusion imaging showed scarring at the apical inferolateral wall (A, yellow arrow), but cardiac angiography revealed patent coronary arteries (figure not shown). Further ^{99m}Tc -PYP planar and SPECT/CT images demonstrated diffuse, mildly elevated tracer activity in the LV myocardium at 3 hours post-injection (B, red circle; and C, red arrows), equal to rib activity (visual score of 2). The H/CL ratio at 3 hours post-injection was 1.22. SPECT/CT images revealed the increased tracer uptake unseen at the LV apex, corresponding to an area of scarred myocardium (C, calcification seen at yellow arrow). Endomyocardial biopsy confirmed the patient has AL amyloidosis. Interstitial plasmacytosis (10-20%) was seen in the bone marrow biopsy, and a diagnosis of plasma cell myeloma was given. AL, immunoglobulin light chain amyloidosis; H/CL, heart to contralateral lung; LV, left ventricular; NYHA, New York Heart Association; PYP, pyrophosphate; SPECT/CT, single-photon emission computed tomography/computed tomography.

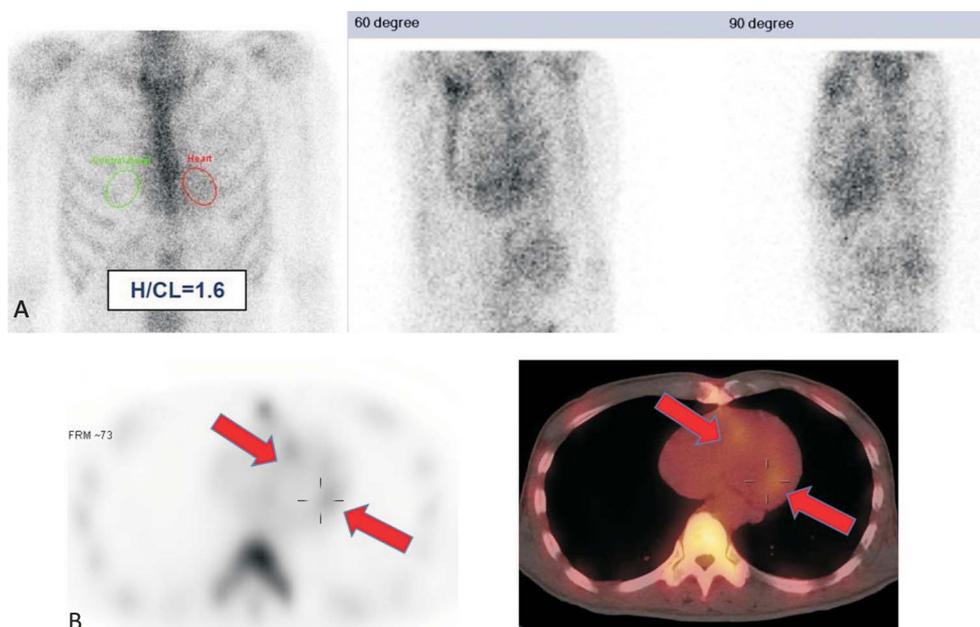


Figure 6. ATTR amyloidosis, hereditary subtype. A 59-year-old man presented with a one-year history of progressive bilateral ascending numbness, as well as orthostatic hypotension, frequent diarrhea, and frequent episodes of palpitation. Many of his family members were diagnosed with familial amyloidotic polyneuropathy. A transthyretin gene study was performed with positive confirmation of the Ala97Ser mutation. ^{99m}Tc-PYP planar (A) and SPECT/CT (B) images demonstrated a visual score of 2, with radiotracer uptake localized to the LV myocardium (red arrows). The H/CL ratio at 3 hours post-injection was 1.6. ATTR, transthyretin amyloidosis; H/CL, heart to contralateral lung; LV, left ventricular; PYP, pyrophosphate; SPECT/CT, single-photon emission computed tomography/computed tomography.

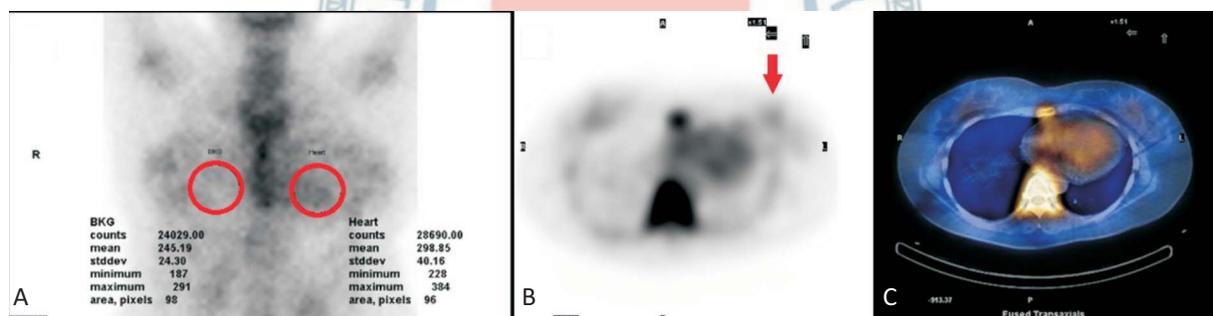


Figure 7. Breast uptake overlapping the heart in planar and SPECT images. (A) Although the ROI (red circles) was well-delineated in planar view, marked breast physiological uptake was also noted. (B) An axial SPECT slice reveals marked breast uptake (red arrow) and blood pool activity. (C) SPECT/CT fusion images reveal potential causes for false positives of cardiac ^{99m}Tc-PYP uptake including blood pool activity, soft tissue uptake such as in the breast, osseous uptake, lung parenchymal lesions, overlying devices, or myocardial infarction. SPECT or SPECT/CT clearly demonstrates uptake in the myocardium or other areas. BKG, background; PYP, pyrophosphate; ROI, region of interest; SPECT/CT, single-photon emission computed tomography/computed tomography; stddev, standard deviation.

CONCLUSIONS

Transthyretin cardiac amyloidosis is an increasingly recognized cause of HFpEF. Favorable prognosis depends on early diagnosis and correct treatment strategy. This article highlights the recommendations of ^{99m}Tc-PYP imaging among patients with clinical suspicion of cardiac amyloidosis. The diagnostic accuracy of ATTR-CM can be fur-

ther improved and therapies applied earlier through the implementation of these recommendations in Taiwan.

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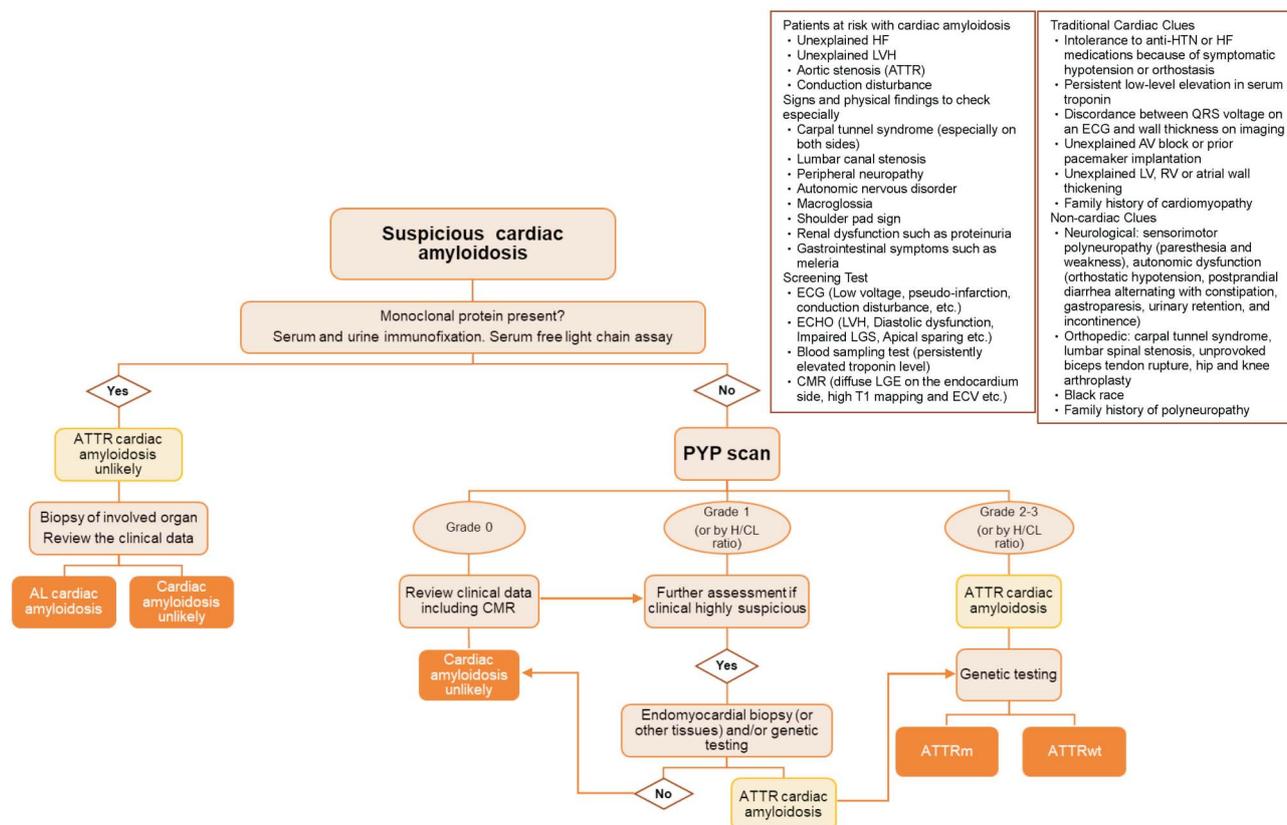


Figure 8. The proposed diagnostic algorithm of suspected cardiac amyloidosis in Taiwan. AL, immunoglobulin light chain amyloidosis; ATTR, transthyretin amyloidosis; AV, atrioventricular; CMR, cardiac magnetic resonance; ECG, electrocardiography; ECV, extracellular volume fraction; Gr., grade; H/CL ratio, heart to contralateral lung ratio; HF, heart failure; HTN, hypertension; LGE, late gadolinium enhancement; LGS, longitudinal global strain; LV, left ventricle; LVH, left ventricular hypertrophy; PYP, pyrophosphate; RV, right ventricle. (Adapted and modified from references 25, 41).

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CONFLICT OF INTEREST

All the authors declare no conflict of interest.

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