

My Approach to Imaging Cardiac Amyloidosis: Role of Bone-Seeking Tracers Scintigraphy

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Abstract

Amyloidosis is a systemic infiltrative disease characterized by the extracellular deposition of amyloid fibrils. Heart involvement is common and associated with a poor prognosis. The most predominant types of cardiac amyloidosis (CA) are amyloid immunoglobulin light chain (AL) and amyloid transthyretin (ATTR). Diagnosis of CA and differentiation between the types are important for prognosis, therapy, and genetic counseling. ATTR-CA is an under-diagnosed cause of heart failure. However, great accomplishments in non-invasive imaging methods, as well as the possibility of effective clinical treatment, have shifted ATTR-CA from a rare and untreatable disease to a condition that clinicians should consider on a daily basis. The advent of scintigraphy imaging with bone-seeking tracers has allowed the early diagnosis of ATTR-CA with high accuracy once monoclonal gammopathies have been excluded. Interpretation of cardiac scintigraphy with bone-seeking tracers requires expertise, and we propose a step-by-step guide to performing this exam in clinical practice according to the most recent guidelines. Moreover, we reviewed some crucial points that we believe are of paramount importance in clinical practice and patient outcomes.

Introduction

Amyloidosis is a systemic infiltrative disease characterized by the extracellular deposition of misfolded proteins which aggregate as amyloid fibrils. Heart involvement is common and, unfortunately, associated with a poor prognosis for those patients. The most predominant types of cardiac amyloidosis (CA) are amyloid immunoglobulin light chain (AL) and

amyloid transthyretin (ATTR). The latter is further subtyped into hereditary (ATTRv), which results from protein mutations, and wild type (ATTRw), formerly known as senile type, which is not associated with DNA mutations.¹

ATTR-CA has been considered a rare disease, but recent data have shown an exponential increase in incidence over the past 10 years, especially for ATTR-CA wild type.² Until very recently, only endomyocardial biopsy (EMB) could diagnose CA, and no specific treatment was available. Great accomplishments in non-invasive imaging methods, as well as the possibility of effective clinical treatment, have shifted ATTR-CA from a rare and untreatable disease to a condition that clinicians should consider on a daily basis.³ Bone-seeking tracers scintigraphy has assumed a central role in diagnosis since it is currently the only non-invasive imaging method capable of accurately diagnosing ATTR-CA.⁴

In order to guide good practice, consensus,^{5,6} practice points,⁷ and guidelines^{1,8} have been proposed by highly valued international societies. In this context, the authors decided to devise this guide based on their own experiences in the real world and call attention to some crucial points that we believe are of paramount importance in clinical practice and patient outcomes.

Bone-seeking tracers scintigraphy

Bone-seeking tracers

Amyloid deposits are the most direct targets to diagnose and type CA. They consist of insoluble β -pleated sheets of fibrils formed from misfolded precursor proteins, as well as non-fibrillar components of serum amyloid P (SAP), glycosaminoglycans, and calcium.⁹ Nuclear medicine methods act on a molecular level and can identify amyloid deposits even before structural and functional changes can be observed on echocardiography or cardiac magnetic resonance (CMR), leading to an early diagnosis that directly impacts prognosis.⁶

In the past, bone-seeking tracers were used to detect myocardial necrosis, and their potential use to diagnose CA has been recently described.¹⁰ The phosphate domains in those tracers are supposed to bind to calcium in transthyretin fibrils. Pepys et al.¹¹ suggest that the P-component could bind to amyloid fibrils via a calcium-mediated mechanism, and Stats et al.¹² showed microcalcifications in EMB samples. The

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precise molecular mechanism behind differential uptake in ATTR and AL-CA is not well known, but it has been postulated that it might be related to a higher calcium content, i.e., microcalcifications in TTR amyloid fibrils.¹⁰ Even so, in a few cases of AL-CA, the amount of microcalcifications is comparable to ATTR-CA, explaining why bone-seeking tracers are not specific for ATTR-CA.⁴

Perugini et al.¹³ first described that 3,3-diphosphono-1,2-propanodicarboxylic acid linked to technetium-99m (^{99m}Tc-DPD) scintigraphy is highly sensitive and specific in differentiating ATTR-CA from AL-CA in patients with documented CA. Subsequently, other authors have confirmed scintigraphy as an accurate diagnostic method, even when other types of bone-seeking tracers were used.¹⁴

Gillmore et al.⁴ have revolutionized clinical practice by proposing that ATTR-CA could be non-invasively diagnosed using bone scintigraphy. In a multicenter study involving 1217 patients with suspected CA, grades 2 or 3 of myocardial radiotracer uptake, in the absence of monoclonal gammopathies in serum or urine, had a specificity and positive predictive value of 100% to detect ATTR-CA. The results were similar among the most available bone-seeking tracers, as well as for patients with hereditary and wild-type ATTR-CA. Therefore, in this context, EMB is not needed, and specific treatment can be safely initiated.

As expected, after the publication of Gilmore et al.'s results,⁴ an increase in the number of patients referred to scintigraphy was observed. However, it is worth mentioning that the study had included patients with a high pretest probability of CA, i.e., symptoms of heart failure and echocardiogram or CMR consistent with CA, and the scans were carried out in reference centers following the best practices.

Nowadays, three types of ^{99m}Tc-labeled myocardial bone-avid radiotracer have been used for the diagnosis of ATTR-CA: ^{99m}Tc-pyrophosphate (^{99m}Tc-PYP), ^{99m}Tc-DPD, and ^{99m}Tc-hydroxymethylene diphosphonate (^{99m}Tc-HMPD), and all have shown high accuracy for imaging cardiac TTR amyloid.⁵

^{99m}Tc-PYP is the most used radiotracer in the United States and Brazil. ^{99m}Tc-DPD and ^{99m}Tc-HMPD are currently the most used in Europe and other countries. It is worth noting that, because of the ^{99m}Tc-PYP shortage, some centers in the United States have been using ^{99m}Tc-methylene diphosphonate (^{99m}Tc-MPD) as well. It is important to highlight that ^{99m}Tc-MDP is currently used for bone scintigraphy, but it is not recommended for ATTR-CA diagnosis because of its low sensitivity compared to the other bone-seeking tracers.¹³

Imaging protocols and interpretation

Since ^{99m}Tc-PYP is the only radiotracer used for ATTR-CA diagnosis in Brazil, it will be the focus of this document.

^{99m}Tc-PYP scintigraphy is a simple, inexpensive procedure available in major centers in Brazil. No absolute contraindications are described, and modern scans have allowed the use of lower doses of radiation. Furthermore, no preparation is required.^{5,15}

An activity dose of 10 to 20 mCi (370 to 740 MBq) of ^{99m}Tc-PYP is administered intravenously. Subsequently, 2 to 3 hours

after the injection, anterior and left lateral chest planar images are acquired, followed by a cardiac single photon emission computed tomography (SPECT) imaging. Whenever possible, a hybrid acquisition using SPECT associated to computed tomography (SPECT/CT) is advisable.^{5,15}

Former consensus⁵ and practice points¹⁵ recommended that planar and SPECT images should be obtained 1 hour after radiotracer injection. If a blood pool was present, a 3-hour image should be performed. Most recent data¹⁶ suggest that the 1-hour imaging is optional. Hutt et al.¹⁷ have demonstrated that myocardial and bone uptake over time is distinct. As the peak myocardial counts on planar images occur 1 hour after injection of ^{99m}Tc-DPD followed by a progressive decline over time, bone counts increase gradually and peak after 2 to 3 hours. Therefore, 1-hour imaging is more sensitive, and 3-hour imaging is more specific for ATTR-CA diagnosis. Similar kinetics is observed with the other radiotracers. It is important to emphasize that a 1-hour imaging protocol is equivalent to a 3-hour protocol since SPECT images are incorporated, which positively impacts patient comfort and laboratory output.¹⁸

The first step in scan interpretation is to proceed to a visual or semi-quantitative analysis using planar imaging. Radiotracer uptake into the bones (ribs) is compared to heart uptake and rated as previously described by Perugini et al.:¹³ grade 0 (no heart uptake and normal rib uptake), grade 1 (heart uptake less than rib uptake), grade 2 (heart uptake equal to rib uptake) and grade 3 (greater than rib uptake with mild/absent rib uptake), as illustrated in Figure 1. Heart uptake must be confirmed in SPECT or SPECT/CT images. Scans showing visual scores greater than or equal to 2, i.e., 2 or 3 on planar and SPECT images, are classified as positive and suggestive of ATTR-CA (Figure 2). Analysis of planar images alone is no longer accepted, irrespective of the time between injection and scans, showing the importance of directly visualizing and confirming myocardial uptake. Then, we must always perform SPECT imaging.¹⁶

The second step is quantitative analysis. Bokhari et al.¹⁴ defined a simple technique based on drawing a circular region of interest (ROI) over the heart on the anterior chest planar imaging and mirroring this ROI over the contralateral chest to adjust for background and ribs. Heart-to-contralateral lung uptake ratio (H/CL) is calculated as a ratio of heart ROI mean counts to contralateral chest ROI mean counts. H/CL > 1.5 at 1 hour-imaging and H/CL > 1.3 at 3-hour imaging are highly accurate to diagnose ATTR-CA (Figure 3). Hence, some caution is required when drawing the ROI, for example, size adjustment to maximize coverage of the heart without including the adjacent lung and avoiding sternal, ribs, and right ventricle areas to obtain reliable ratios.

Planar imaging alone is limited in spatial resolution when compared to SPECT or SPECT/CT. Myocardial uptake cannot be differentiated from blood pool uptake; overlying rib uptake may add counts to the region of the heart, and attenuation correction is not feasible. SPECT overcomes these limitations and should always be performed.¹⁹ Indeed, Régis et al.²⁰ showed that visual analysis on SPECT imaging has led to fewer scans interpreted as equivocal when compared to quantitative analysis (H/CL ratio).

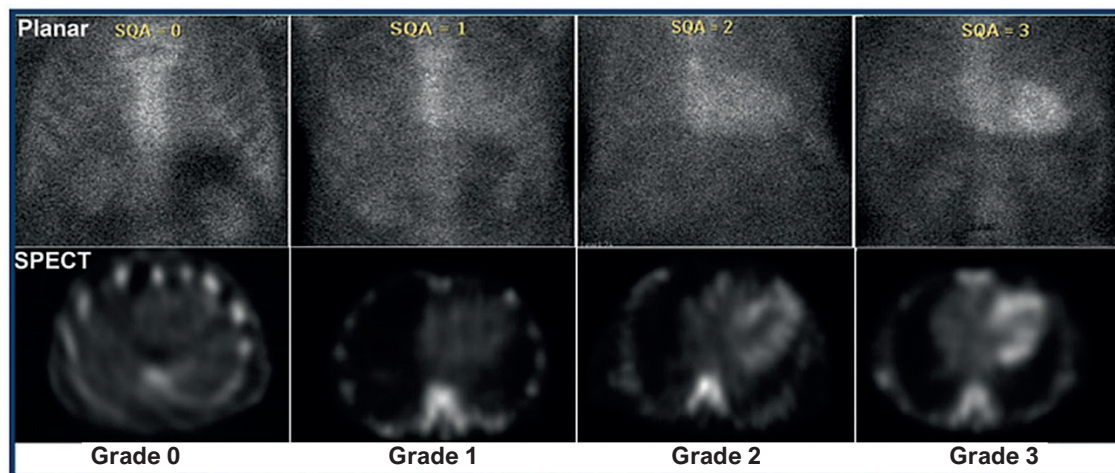


Figure 1 – Grading ^{99m}Tc -PYP uptake on planar and SPECT images. This figure illustrates visual semi-quantitative analysis of cardiac ^{99m}Tc -PYP uptake using planar (upper) and SPECT (lower) imaging. Radiotracer uptake into the rib is compared to heart uptake and rated: grade 0 (no heart uptake and normal rib uptake), grade 1 (heart uptake less than rib uptake), grade 2 (heart uptake equal to rib uptake) and grade 3 (greater than rib uptake with mild/absent rib uptake). From “ ^{99m}Tc -pyrophosphate Imaging for Transthyretin Cardiac Amyloidosis” by Dorbala et al., 2019, ASNC Cardiac Amyloidosis Practice Points. Copyright 2019 by American Society of Nuclear Cardiology. Reprinted with permission.¹⁵ ^{99m}Tc -PYP: ^{99m}Tc -pyrophosphate; SPECT: single photon emission computed tomography; SQA: semiquantitative score.

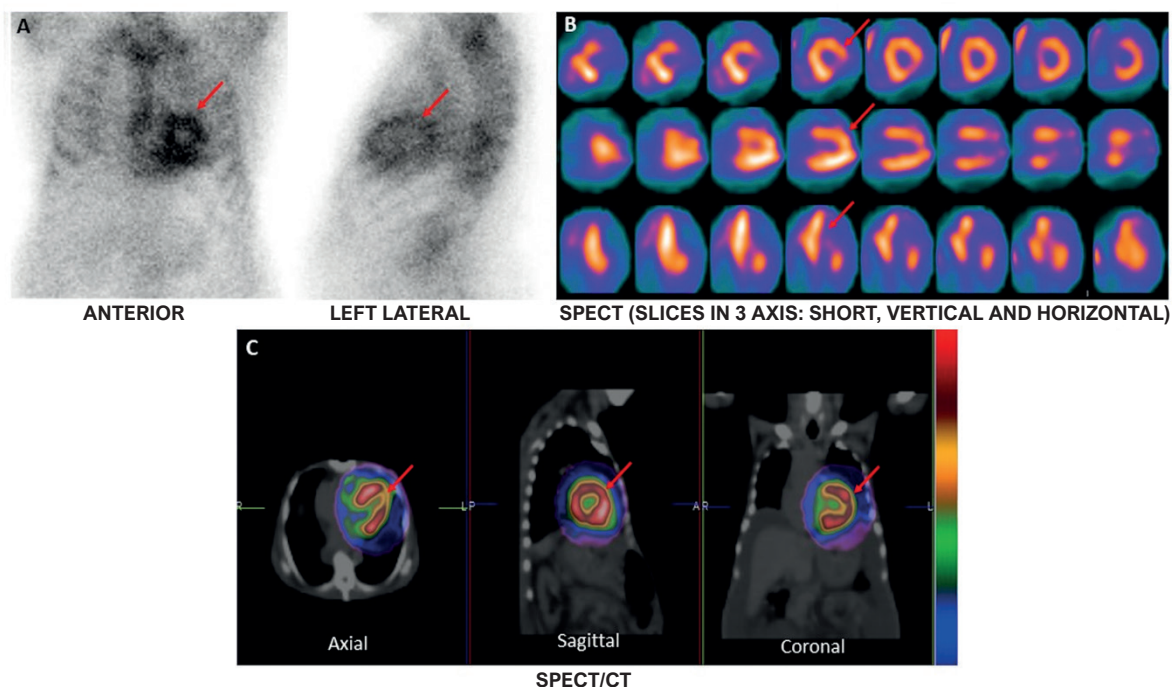


Figure 2 – Positive cardiac ^{99m}Tc -PYP scintigraphy. Planar images (A) demonstrate abnormally increased radiotracer activity in the heart (arrows) and greater than the ribs (Perugini grade 3), and SPECT (B) and SPECT/CT (C) images confirm radiotracer uptake throughout the left ventricle (arrows). Those findings are highly suggestive of ATTR-CA. The advantage of SPECT/CT imaging is to better identify myocardial ^{99m}Tc -PYP uptake. Source: the authors. ATTR-CA: amyloid transthyretin cardiac amyloidosis; ^{99m}Tc -PYP: ^{99m}Tc -pyrophosphate; SPECT: single photon emission computed tomography; SPECT/CT: single photon emission computed tomography associated to computed tomography.

Another important change in diagnostic criteria is the role of the H/CL ratio. In a former consensus,⁶ H/CL ratio > 1.5 was considered as strongly suggestive of ATTR-CA. Currently, a scan is strongly suggestive of ATTR-CA if diffuse myocardial uptake grade 2 or 3 is observed in SPECT imaging, even if the H/CL ratio is < 1.5. Nevertheless, the H/CL ratio can still be useful to reclassify equivocal exams as positive or negative.¹⁶

False-positive and false-negative results

As previously stated, scintigraphy with bone-seeking tracers is a highly accurate method to diagnose ATTR-CA. However, some peculiar scenarios should always be considered, given that false-positive and false-negative results may occur, as described in Table 1.^{6,8,21}

Regarding possible false negatives of scintigraphy for detecting ATTR-CA, the most common causes are an early-stage disease where myocardial infiltration can be minimal or mild and not yet detectable, as well as some pathogenic TTR mutations such as Phe64Leu, Val30Met, Thr59Lys, Se77Tyr, and Glu61Ala;²² Val122Ile has more recently been described in some subjects as well.²³ It is well known that the sensitivity of bone avid tracer scintigraphy in hereditary ATTR-CA might be lower in some cases.^{5,21}

Scintigraphy with bone-seeking tracers has led to fewer cases where EMB is required, but EMB is still considered the gold standard for the diagnosis of CA. EMB should always be considered in the following cases: 1) ^{99m}Tc-PYP scan is negative or equivocal, but clinical suspicion is high, i.e., echocardiogram or CMR show typical findings in patients with suggestive symptoms; 2) ^{99m}Tc-PYP scan is positive, but free light chains are elevated, or monoclonal gammopathy is present. It has been described in the literature that, in elderly patients, AL-CA and ATTR-CA might coexist; 3) Bone-seeking tracer scintigraphy is unavailable.²¹

It is worth mentioning that fat-pad biopsy is not highly sensitive to exclude ATTR amyloidosis and should not be routinely ordered.²¹

How to properly exclude gammopathies

Clinicians must not rely solely on imaging to confirm or exclude ATTR-CA. Gilmore et al.⁴ have shown that any grade of radiotracer uptake was associated with 99% sensitivity and 68% specificity to diagnose ATTR-CA. The poorer specificity was due to false positives related to AL-CA. Indeed, 40% of patients with AL-CA might show any grade of radiotracer uptake on scintigraphy. Therefore, only uptake grade 2 or 3 after the exclusion of AL-CA was associated with 100% specificity and positive predictive value for the non-invasive diagnosis of ATTR-CA.

Serum-free light chain concentration and serum and urine immunofixation electrophoresis is > 99% sensitive to detect AL amyloidosis. However, serum plasma and urine plasma electrophoresis are much less sensitive and should be avoided.⁸ It is important to point out that up to 40% of patients with ATTR-CA may have a condition called monoclonal gammopathy of unknown significance (MGUS), and EMB is necessary to confirm ATTR-CA. Also, in some cases, MGUS may progress to AL amyloidosis or multiple myeloma, and those patients must be closely followed by a hematologist.²⁴

Algorithms to diagnose CA

The Brazilian Society of Cardiology has proposed a very practical algorithm to guide CA diagnosis based on two main routes: Hematological and Cardiological (Figure 4).²⁵

Perspectives for the near future

Studies have demonstrated that cardiac absolute quantification of ^{99m}Tc-PYP uptake is feasible with cadmium-zinc-telluride gamma cameras (SPECT/CT), and that different quantification parameters correlated strongly with extracellular volume obtained by CMR. Larger studies are necessary to definitively establish the value of quantification in ATTR-CA and move to the next frontier in the non-invasive diagnostic evaluation of CA.²⁶

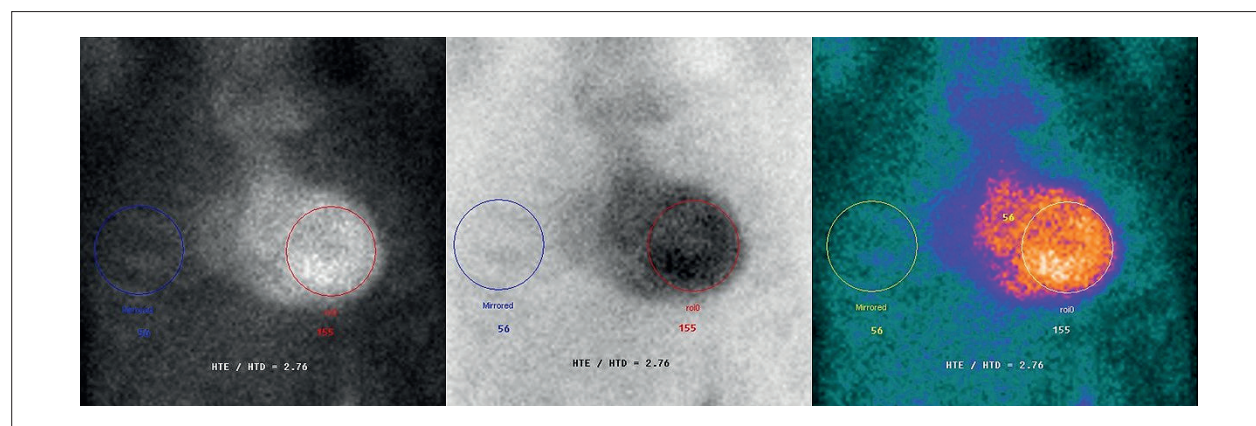


Figure 3 – Quantitation of cardiac ^{99m}Tc-PYP using heart-to-contralateral (H/CL) lung uptake ratio over the heart on the anterior chest planar imaging. This image (shown in 3 different colors) was acquired 3 hours after the radiotracer injection. The H/CL was 1.76, which is highly accurate to diagnose ATTR-CA. Source: the authors. ATTR-CA: amyloid transthyretin cardiac amyloidosis; ^{99m}Tc-PYP: ^{99m}Tc-pyrophosphate

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Table 1 – Possible causes of false-positive scans for detecting transthyretin CA.

AL-CA: AL-CA is the most common and important cause of misdiagnosis. Most clinicians are not familiar with the fact that nearly 20% of scans can be positive in patients with AL-CA; therefore, **always properly rule out AL-CA**.

Blood pool uptake in planar images: Although they are not recommended, some labs still use solely planar images to diagnose CA, and a blood pool can be interpreted as a positive scan. Cardiac uptake must always be confirmed in SPECT images. **Always perform SPECT**.

Rib fractures, valvular and annular calcifications, and breast implants: These structures may overlay the heart, thereby affecting H/CL results. Currently, H/CL alone is not recommended to diagnose CA. **Always perform SPECT**.

Acute or subacute myocardial infarction (< 4 months): Focal uptake may be present, and scintigraphy should not be used to diagnose CA in this early phase.

Hydroxychloroquine cardiotoxicity (histological confirmation).

Rare forms of CA for example, apolipoprotein A1).

AL-CA: amyloid immunoglobulin light chain cardiac amyloidosis; CA: cardiac amyloidosis; H/CL: heart-to-contralateral lung uptake ratio; SPECT: single photon emission computed tomography.

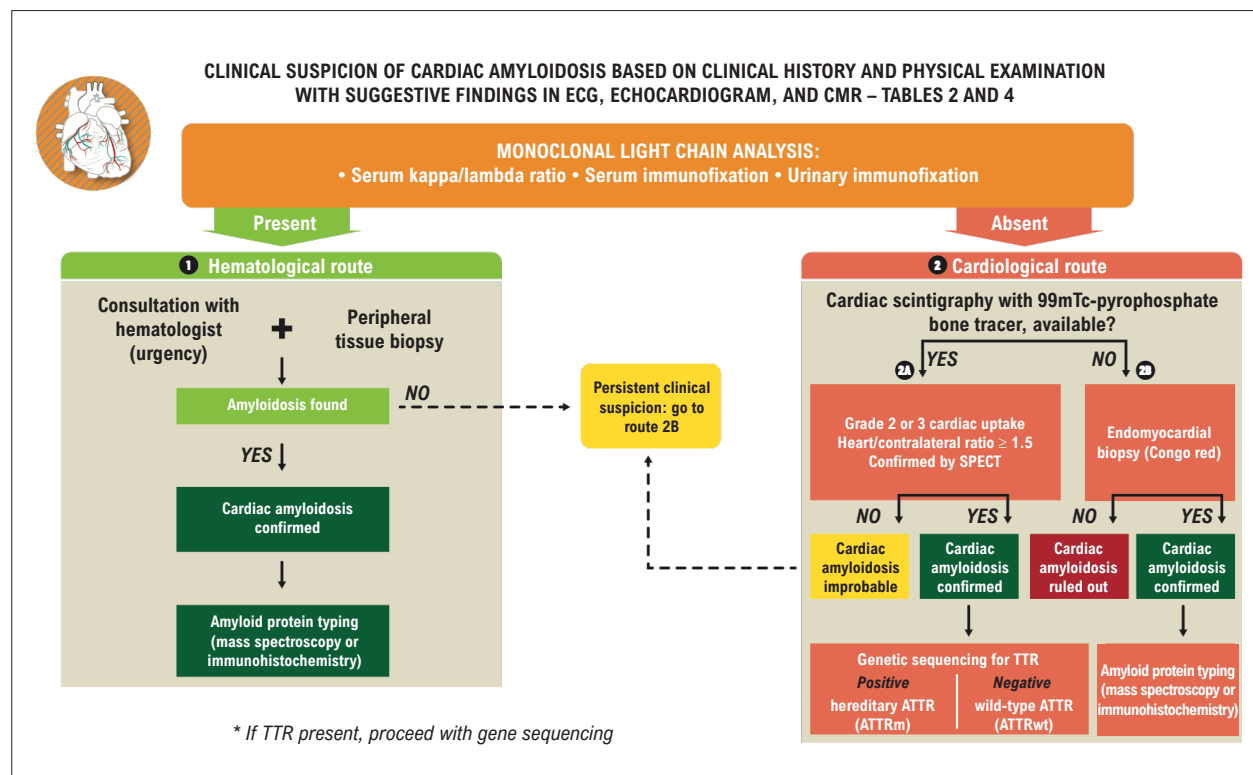


Figure 4 – Flowchart for diagnosing cardiac amyloidosis. Brazilian Society of Cardiology practical algorithm to diagnose CA based on two main routes: Hematological and Cardiological. Adapted from Position Statement on Diagnosis and Treatment of CA – 2021.²⁵ CMR: cardiac magnetic resonance; ECG: eletrocardiogram; ATTR: amyloid transthyretin; TTR: transthyretin; SPECT: single photon emission computed tomography

The advent of specific positron emission tomography (PET) amyloid-binding radiotracers has the potential to change currently employed diagnostic algorithms for imaging CA. These PET tracers have promising potential for the early detection of a particular type of CA, pursuing relevant medical intervention, assessing amyloid burden, monitoring treatment response, and determining overall prognosis.²⁷

Final considerations

The advent of scintigraphy imaging with bone-seeking tracers has allowed the diagnosis of ATTR-CA with high accuracy once monoclonal gammopathies have been excluded. Interpretation of cardiac ^{99m}Tc-PYP images requires expertise, and we have proposed a step-by-step guide to performing this exam in clinical practice according to the most recent guidelines. We would like to highlight the importance of always performing SPECT imaging to truly ensure a positive test result and emphasize that false negatives can also occur, mostly in some inherited forms of ATTR-CA; in this scenario, an EMB might be necessary.

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Author Contributions

Conception and design of the research, acquisition of data, analysis and interpretation of the data, writing of the manuscript and critical revision of the manuscript for intellectual content: Glavam AP, Lopes RW, Brandão SCS.

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This article does not contain any studies with human participants or animals performed by any of the authors.

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