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REVIEW ARTICLE

Cardiac amyloidosis imaging

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ABSTRACT

Amyloidosis is a systemic disorder produced by the deposition of insoluble protein fibrils that fold and deposit in the myocardium. Patients with amyloidosis and cardiac involvement have higher mortality than patients without cardiac involvement. The two most prevalent forms of amyloidosis associated with cardiac involvement are AL amyloidosis, due to the deposition of immunoglobulin light chains, and ATTR amyloidosis, due to the deposition of the transthyretin (TTR) protein in mutated or senile form. This article aims to review the different cardiac imaging modalities (echocardiography, cardiac magnetic resonance imaging, nuclear medicine and tomography) that allow to determine the severity of cardiac involvement in patients with amyloidosis, the type of amyloidosis and its prognosis. Finally, we suggest a diagnostic algorithm to determine cardiac involvement in amyloidosis adapted to locally available diagnostic tools, with a practical and clinical approach.

Keywords: Amyloidosis/Diagnostic Imaging; Cardiomyopathies/Diagnostic Imaging; Echocardiography; Magnetic Resonance Imaging

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1. Introduction

Amyloidosis is a systemic disorder produced by the deposition of insoluble protein fibrils that fold and deposit in the myocardium[1,2]. Patients with amyloidosis and cardiac involvement have higher mortality than patients without such involvement[2,3]. There are more than 30 proteins that can produce amyloidosis; the two most prevalent forms of amyloidosis are AL amyloidosis, due to the deposition of immunoglobulin light chains, and ATTR amyloidosis, due to the deposition of the transthyretin (TTR) protein in mutated or senile form. This article aims to review the different cardiac imaging modalities (echocardiography, cardiac magnetic resonance imaging, nuclear medicine and tomography) that allow us to determine the severity of cardiac involvement in patients with amyloidosis, the type of amyloidosis and its prognosis.

2. Echocardiography

Echocardiography is usually the study of choice for an initial evaluation of cardiac involvement due to its wide availability, non-

invasive nature, optimal spatial and temporal resolution and low cost. Different signs lead us to think of cardiac amyloidosis (CA), which are neither confirmatory nor specific, especially in the initial stage of the disease[4-7]. A suggestive sign is the presence of thickening of the ventricular walls in the absence of valvular alteration or arterial hypertension, or whose magnitude is inappropriate with respect to ECG voltages[5]. In CA, a parietal thickening associated with low voltages is characteristic[8,9].

Phelan *et al.* compared echocardiographic parameters in ATTR and LA (*n*: 172). In the study, it was evident that patients with ATTR *wt* (wild type) had greater left ventricular wall thickness and similar systolic longitudinal strain compromise, but associated with lower morbidity than those with AL[10]. This suggests the presence of an additional mechanism to the amyloid infiltration that compromises the myocardium in AL, such as the direct toxicity of light chains.

Left ventricular hypertrophy (LVH) is typically concentric and symmetric, but up to 23% of patients have an asymmetric hypertrophy pattern on ATTR *wt*[11]. The presence of obstructive gradent is unusual and, in the Mayo Clinic experience, 0.9% of patients treated with myectomy had a diagnosis of amyloidosis[12].

Early cardiac involvement is associated with type I diastolic dysfunction that progresses to the restrictive pathophysiology typical in advanced disease[13]. Amyloidosis usually presents with preserved left ventricular ejection fraction (LVEF), but in advanced stages it can evolve with systolic dysfunction. Coronary involvement due to macrovascular or microcirculation disease can generate regional motility disorders[14]. Reduction of LVEF is more frequently observed in ATTR h (hereditary) with Val122Ile alteration compared to ATTR *wt*, which reflects a more advanced stage of the disease at the time of diagnosis and reduced survival[15].

Not only chamber function is affected, but also myocardial fiber function (**Figure 1**)[16-18].

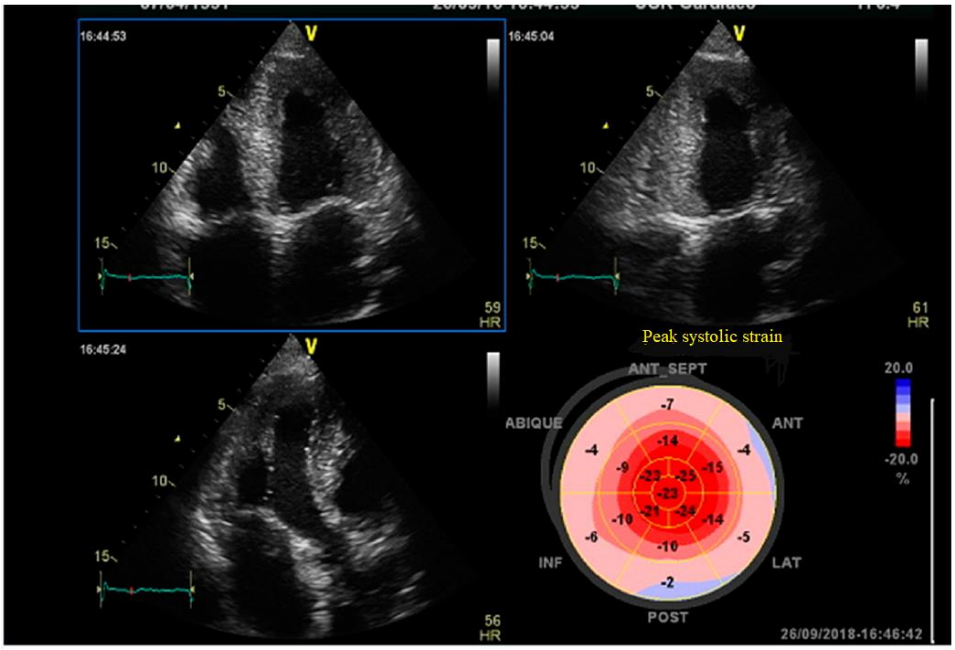

Figure 1. Echocardiogram with strain measurement. Note: Symmetric concentric hypertrophy of the left chambers, biauricular dilatation and the characteristic image of systolic longitudinal strain ("Japan flag") with reduced deformation of the basal and medial segments and maintenance of the apical component.

The prevalence of altered two-dimensional longitudinal strain in CA ranges from 93% to 100%, even with preserved systolic function[19]. In any form of CA, systolic deformation (by longitudinal *strain*) is preserved in the apical segments and significantly reduced in absolute values in the middle and basal segments. This pattern of apical preservation improves diagnostic specificity[10,20]. A ratio of apical strain/basal strain + medial strain >1 allowed differentiation from hypertrophic cardiomyopathy (sensitivity of 93%, specificity of 82% and area under the curve of 0.91) and aortic stenosis (sensi-

tivity of 93%, specificity of 82% and area under the curve of 0.97)[22]. This finding was also confirmed in Fabry disease and Friedrich's ataxia (**Figure 1**). In this sense, a cutoff point >4.1 in the relationship between LVEF and systolic longitudinal strain presented better performance in the differential diagnosis with other forms of hypertrophy (sensitivity 90%, specificity 92% and area under the curve of 0.9)[23]. Furthermore, in LA patients, the average longitudinal ventricular strain is a powerful predictor of clinical evolution, superior to the predictive elements of Doppler echocardiography[21].

Other echocardiographic signs associated with CA are right ventricular hypertrophy and dysfunction, tricuspid annular excursion <14 mm or reduced right ventricular basal segment deformation[24-27]. Mild pericardial effusion is present in 40%–60%[13,28]. In patients undergoing percutaneous valve implantation (TAVR) for aortic stenosis, the presence of an average tissue systolic velocity <6 cm/sec at the mitral annulus had a sensitivity of 100% for predicting a positive scan[29].

Up to 90% of patients with AL amyloidosis present cardiac involvement and, of these, approximately 50% present diastolic heart failure with clinical signs of right heart failure at the time of diagnosis[30]. The absence of a restrictive pattern does not rule out infiltrative involvement and not all restrictive patterns are secondary to CA[31-34]. Likewise, amyloid infiltration of the atrial wall is frequent with biauricular dilatation[35,36] and increased atrial septal thickness in 60% of cases[37], and the reduction of left atrial two-dimensional *strain* indicates advanced atrial compromise[38-41].

2.1 Echocardiography recommendations

- Doppler echocardiogram with evaluation of longitudinal strain in all patients with suspected CA.
- The different echocardiographic parameters suggesting the presence of CA are not confirmatory of the disease or amyloid subtypes.
- In the presence of systemic amyloidosis diagnosed by biopsy of non-cardiac tissue, characteristic echocardiographic or cardiac MRI findings combined with clinical parameters and serum biomarkers may be sufficient to define cardiovascular involvement.
- Longitudinal strain analysis is useful in the follow-up of patients with CA. It is suggested to repeat it at an interval of no less than 6 months or in the presence of clinical worsening.

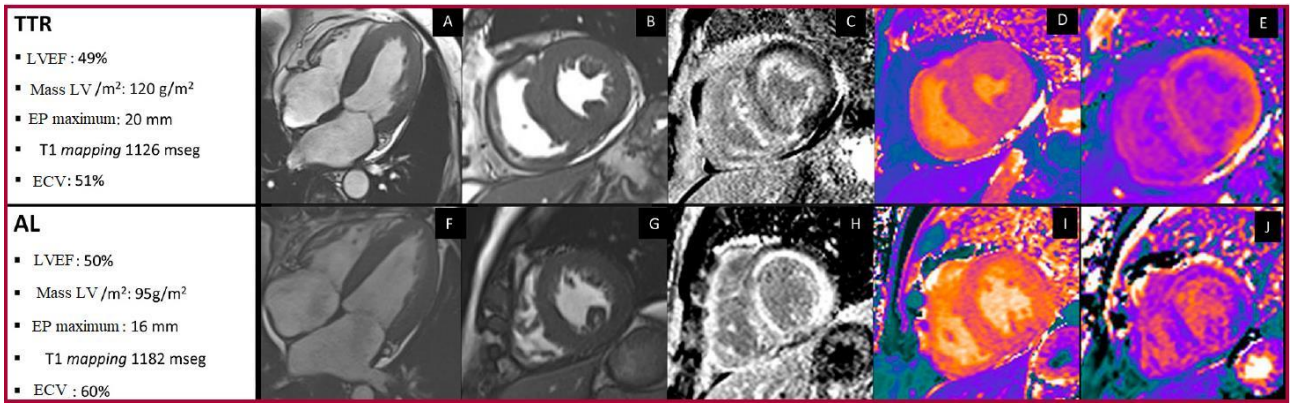

Figure 2. Cardiac magnetic resonance in patients with TTR and AL amyloidosis. *Top row*: Patient with TTR amyloidosis. *Bottom row*: patient with AL amyloidosis. The two men have similar ventricular systolic function compromise. TTR amyloidosis has more increased ventricular mass and thickness than AL amyloidosis, AL amyloidosis has somewhat higher ECV. T1 *mapping* was similar in the two patients. In the *top row*, **A)** and **B)** cinerresonance images in four-chamber and medial short-axis views; **C)** late gadolinium enhancement image with subendocardial enhancement; **D)** native T1 *mapping* image; **E)** post-gadolinium T1 *mapping* image. In the bottom row, **F)** and **G)** cinerresonance images in four-chamber and medial short-axis views; **H)** late gadolinium enhancement image with subendocardial enhancement; **I)** native T1 *mapping* image; **J)** post-gadolinium T1 *mapping* image. Note: ES: wall thickness; LVEF: left ventricular ejection fraction; ECV: extracellular volume; LV: left ventricular.

3. Cardiac magnetic resonance imaging

Cardiac magnetic resonance (CMR) provides a high-definition image for structural evaluation, with high resolution and reproducibility, and, additionally, can perform tissue characterization (**Figure 2**)

3.1 Cinerresonance imaging

In patients with a poor ultrasound window, CMR is an alternative for the evaluation of amyloidosis, as it can assess end-diastolic and end-systolic volumes, systolic volume, wall thicknesses and LVEF, and is therefore the standard technique for determining these parameters[42]. CMR is frequently used in AL amyloidosis when there are doubts about LVEF, which is an important prognostic parameter.

3.2 Late gadolinium enhancement images

Late gadolinium enhancement (LGE) is the most relevant image for the diagnosis of CA. The characteristic pattern is diffuse subendocardial or transmural enhancement involving the left ventricle associated with blood pool inflation. This enhancement pattern is very accurate for the diagnosis of amyloidosis (sensitivity 86% and specificity 92%)[43]. There are atypical forms of presentation with focal intramyocardial enhancement that may indicate incipient forms[44]. Very extensive myocardial involvement with transmural LGE and greatly increased spectrums may suggest TTR amyloidosis[45]. However, the distinction of ATTR and AL is not precise. The correct timing for LGE imaging is earlier, 4 to 5 min after gadolinium injection; and simultaneous or early nulling of the myocardium from the blood pool indicates marked retention of gadolinium in the myocardium[46]. Phase-sensitive LGE imaging (PSIR) allows access to adequate nulling images automatically[47,48].

RTG quantification is not standardized[48], and in patients with renal involvement, gadolinium administration may be contraindicated. These two limitations can be addressed with T1 mapping images.

3.3 T1 mapping images and extracellular space volume

T1 *mapping* techniques evaluate the relaxation time, pixel by pixel, to characterize the myocardium without contrast[49]. The native signal (without contrast) is prolonged in the myocardium with deposition of amyloid material and is specific for the diagnosis of CA[48]. T1 *mapping* values in 1.5 tesla equipment (>1,060 msec) allowed the identification of patients with CA[47-53]. However, diagnostic T1 *mapping* values or cut-off points in 1.5 or 3.0 tesla equipment and different brands of resonators require greater standardization.

By measuring T1 relaxation before and after gadolinium, the myocardial extracellular space volume (ECV) can be estimated. Under normal conditions, ECV is less than 25% of myocardial mass[48]. ECV is a standardized measure independent of the power of the equipment (e.g. 1.5 or 3.0 tesla), its brand and dose of gadolinium administered. Increased ECV is associated with worse prognosis in patients with CA and would be a better predictor of events than native T1 *mapping*[49-51]. Finally, determination of ECV, by accurately quantifying the degree of amyloid infiltration, may be useful in assessing response to treatment[50].

3.4 RMC recommendations

- Alternative in patients with poor ultrasound window and suspected amyloidosis.
- Confirm CA in patients with parietal thickening, subendocardial enhancement and blood pool reversal.
- CMR findings do not differentiate the type of amyloidosis, AL or ATTR.
- The ECV assessed by CMR could be useful to evaluate response to treatment.

4. Cardiac scintigraphy with phosphonates

Several studies have shown that scintigraphy with ^{99m}Tc-labeled phosphonates has a high sensitivity and specificity for the diagnosis of ATTR[54,55]. Differentiating the subtype of amyloidosis is crucial to guide diagnosis, prognosis and treatment[56]. Phosphonate scintigraphy allows accurate diagnosis of TTR cardiomyopathy in patients without a monoclonal process, which in most cases avoids endomyocardial biopsy (sensitivity 92.2% and specificity 95.4%)[57,58].

The phosphonates labeled with ^{99m}Tc recommended by international guidelines are pyrophosphate (^{99m}Tc-PYP), hydroxymethylene diphosphonate (^{99m}Tc-HMDP) and 3,3-diphosphono-1,2-propanedicarboxylic acid (^{99m}Tc-DPD); the first two

are the ones used in our setting[59-61]. The ^{99m}Tc-methylenediphosphonate (^{99m}Tc-MDP) is not recommended due to its lower diagnostic sensitivity[54,55]. Endocardial myocardial biopsies of patients with ATTR showed higher density of microcalcifications than those of patients with AL forms, which would support the hypothesis of a calcium-mediated binding mechanism of these tracers in ATTR[62,63].

Scintigraphy protocols involve acquisition of planar cardiac images followed by single photon emission tomography (SPECT) imaging to target myocardial uptake[54,59,60]. The recommended time between radiopharmaceutical injection and cardiac image acquisition is 1 h or 3 h[64,65]. Phosphonate scintigraphy is a relatively simple study, and can be used in patients with atrial fibrillation, implantable devices, renal insufficiency and contrast allergy[55].

4.1 Interpretation of images

Quantification of myocardial uptake of the radiotracer[66-68].

1. Semi-quantitative analysis: Visual comparison with bone uptake (ribs) at 3 h as described by Perugini *et al.*[66] (**Figure 3** and **Table 1**).
   A visual method score ≥2 on planar or SPECT images is considered positive for ATTR and <2 as negative.

2. Quantitative analysis: Contralateral heart-to-lung ratio (H/CL).
   a. 1 h: Postinjection of ^{99m}Tc-PYP described by Bokhari *et al.*[67]: H/CL ratio ≥1.5 at 1 h is classified as positive for ATTR; when <1.5, as negative.

   b. 3 h: The validated cutoff value is ≥1.3 (**Figure 4**).

Myocardial uptake of phosphonates is not always due to ATTR: LA, myocardial infarction (acute/subacute), hydroxychloroquine toxicity and rare forms of amyloidosis can cause false positives. In equivocal studies due to blood pool uptake, rib fractures or osteodegenerative pathologies, low-dose computed tomography fused with SPECT imaging can identify these factors. The interpretation of the scintigraphy should be performed in the context of a global evaluation of the patient[64,65].

Table 1. Semiquantitative analysis

Grade	Myocardial uptake of the radiotracer
Grade 0	No uptake in myocardium and normal uptake in ribs
Grade 1	Uptake lower than rib uptake
Grade 2	Capture equal to that of the ribs
Grade 3	Superior to costal uptake (with mild or absent rib uptake)

Note: Visual grading of myocardial uptake of ^{99m}Tc (-PYP, -DPD, -HMDP) by comparison with bone uptake.

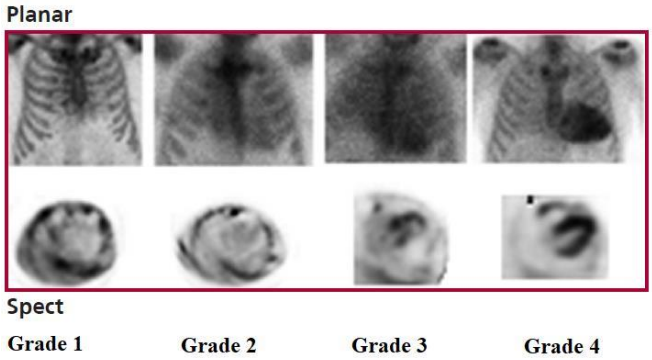

Figure 3. Semiquantitative analysis of the uptake of ^{99m}Tc-HMDP: Planar and SPECT images.

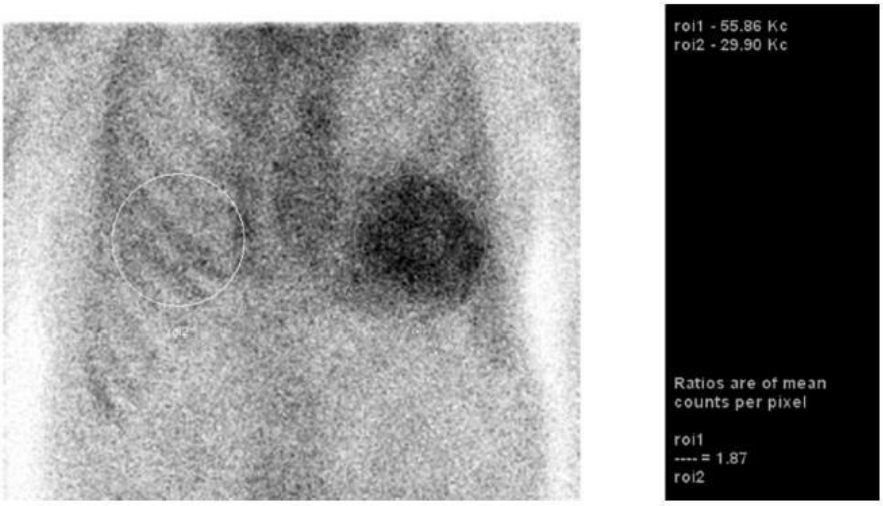

Figure 4. Quantitative analysis: Example of quantification of cardiac uptake of ^{99m}Tc- PYP by means of the ratio of counts between the heart and the contralateral lung (H/CL).

4.2 Recommendations and most frequent indications for phosphonate scintigraphy for cardiac amyloidosis

- Heart failure of unexplained cause and increased left ventricular wall thickness (>12 mm).
- Heart failure of unknown cause in >60 years with preserved left ventricular systolic function.
- Patients (especially older men) with neuropathy, bilateral carpal tunnel syndrome, low-flow, low-gradient aortic stenosis or atrial arrhythmias of unexplained cause with signs/symptoms of heart failure.
- Diagnosis of ATTR in individuals with CMR or echocardiogram compatible with CA.
- Cardiac evaluation in patients with known hereditary amyloidosis.
- Scintigraphy is not indicated in post-treatment follow-up of cardiac ATTR.

5. Multidetector cardiac tomography

Multidetector cardiac tomography (MDCT) allows assessment of volumes, systolic function, thickness and ventricular mass with high accuracy. In elderly patients evaluated for TAVR, there is a high prevalence of ATTR*wt* (14% to 16%) and disproportionate ventricular mass increase may be suspected on MDCT images[69-74]. There are new developments in MDCT that take advantage of iodinated contrast kinetics similar to those observed in CMR with gadolinium kinetics and can be used to measure ECV volume[75-78]. The normal value of ECV by CT is 27%. A value higher than 31% has shown a sensitivity of 94% and specificity of 48% for diagnosing CA[75-79].

6. Image integration and conclusions

In this article, we have reviewed the different cardiac imaging modalities to determine the degree of cardiac involvement in patients with amyloidosis. The challenge for the physician who suspects or evaluates a patient with amyloidosis is to rationally integrate the different images to determine cardiac involvement and its etiology. A tentative diagnostic algorithm is proposed, highlighting the primordial role of the echocardiogram in the suspicion and initial evaluation of patients with amyloidosis (**Figure 5**). The presence of the following findings on echocardiography suggests amyloidosis:

- Increased ventricular wall thickness without clear cause with reduction of systolic longitudinal strain (apical preservation).
- Discordance between ventricular wall thickness and ECG voltage.
- Heart failure with preserved LVEF with signs of right congestion and restrictive phenotype.
- Increased biventricular parietal thickness.
- Low flow/low gradient aortic stenosis.

In either clinical setting, the presence of natriuretic peptide levels disproportionately elevated to clinical findings, the presence of persistent positive troponin in the absence of acute coronary syndrome, a history of carpal tunnel syndrome, narrow lumbar canal or spontaneous biceps tendon rupture, a diagnosis of myeloma or monoclonal gammopathy, and a family history of cardiomyopathy are informative[42].

In many cases, the diagnosis of amyloidosis is suspected from a CMR requested in the initial characterization of cardiomyopathies. LGE with diffuse subendocardial pattern and diffusely increased thickness strongly suggest amyloidosis. The scintigram is central in determining whether it is an AL or ATTR amyloidosis. The diagnosis of familial forms of ATTR requires genetic analysis. If echocardiography or CMR is highly suggestive of amyloidosis and the scintigraphy is negative or equivocal, further evaluation, such as endomyocardial biopsy, should be considered. The diagnostic criteria for the combination of imaging in different clinical scenarios are summarized in **Figure 5**.

Clinical suspicion, evaluation and rational integration of other parameters such as biomarkers, free light chains, electrophoretic proteinogram and imaging are the keys to diagnosis and to defining the extent of cardiac involvement and the type of amyloidosis. Once the disease has been characterized, the prognosis and the different therapeutic modalities can be established.

Clinical suspicion

- Heart failure with preserved ventricular function.
- Low-gradient aortic stenosis.
- History of carpal tunnel or narrow medullary canal.
- Intolerance to beta-blockers or antihypertensive drugs.
- Normalization of blood pressure in hypertensive patients.
- Renal insufficiency/nephrotic syndrome.
- Micro-voltage in ECG or pathological Q-waves.
- Macroglossia/periorbital purpura.
- Fine fiber neuropathy.
- Orthostatic hypotension.
- Left ventricular hypertrophy/RV or valvular thickening.
- Diagnosis of hypertrophic cardiomyopathy in older patients.
- Family history of TTR amyloidosis.
- Elevation of Pro BNP and troponin marker.

Diagnostic criteria for amyloidosis

- Diagnosis of ATTR: at least positive scintigraphy and a compatible echocardiogram or CMR. Biopsy is generally not necessary for diagnosis.
- ATTRm requires confirmation by genetic testing for known mutation or compatible family history.
- The diagnosis of LA requires biopsy of an organ (e.g., abdominal fat, gums, extracardiac organ), monoclonal light chains, and typical involvement with at least two imaging techniques.
- Amyloidosis involvement requires that at least two images (echocardiogram, CMR or scintigraphy) show a characteristic alteration of amyloidosis.
- AA amyloidosis requires histologic confirmation with techniques.
- Grade 0 scintigraphy indicates very low probability of TTR amyloid dose.

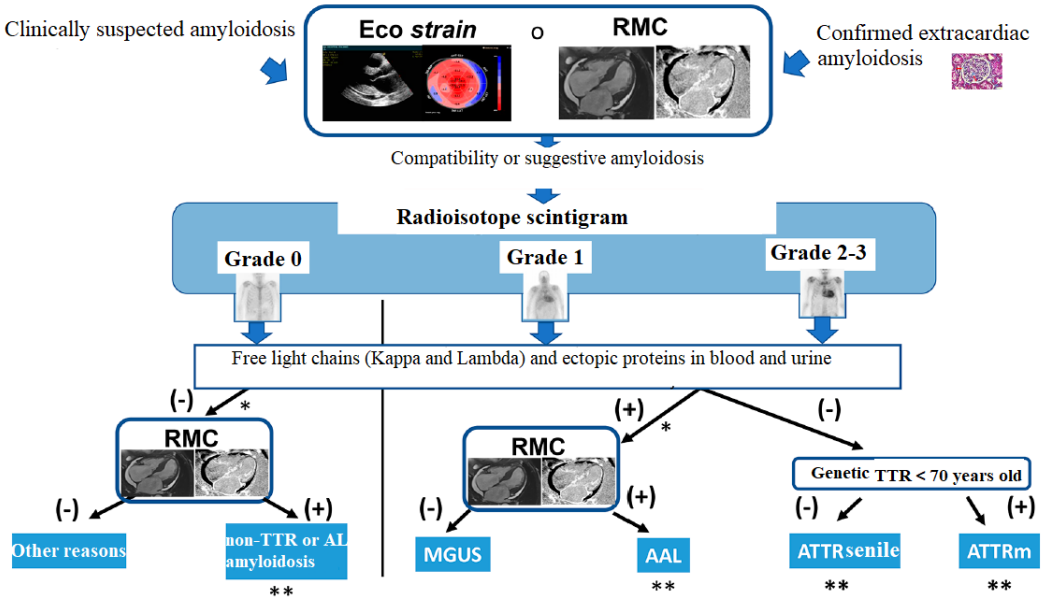

Figure 5. Diagnostic imaging algorithm in amyloidosis. AL: light chain amyloidosis; Echo strain: echocardiogram with strain; MGUS: monoclonal gammopathy of uncertain significance; CMR: cardiac magnetic resonance imaging, wall thickness; TTR: transthyretin; ATTR: transthyretin amyloidosis; ATTRm: mutated transthyretin amyloidosis. *Review or request CMR with gadolinium and mapping techniques. **CMR with extracellular volume estimation mapping can quantify the degree of myocardial infiltration involvement during follow-up.

Conflict of interest

The authors declare that they have no conflict of interest.

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