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Diagnosis of cardiac amyloidosis: a systematic review on the role of imaging and biomarkers

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Abstract

Background: Cardiac Amyloidosis (CA) pertains to the cardiac involvement of a group of diseases, in which misfolded proteins deposit in tissues and cause progressive organ damage. The vast majority of CA cases are caused by light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR). The increased awareness of these diseases has led to an increment of newly diagnosed cases each year.

Methods: We performed multiple searches on MEDLINE, EMBASE and the Cochrane Database of Systematic Reviews. Several search terms were used, such as "cardiac amyloidosis", "diagnostic modalities cardiac amyloidosis" and "staging cardiac amyloidosis". Emphasis was given on original articles describing novel diagnostic and staging approaches to the disease.

Results: Imaging techniques are indispensable to diagnosing CA. Novel ultrasonographic techniques boast high sensitivity and specificity for the disease. Nuclear imaging has repeatedly proved its worth in the diagnostic procedure, with efforts now focusing on standardization and quantification of amyloid load. Because the latter would be invaluable for any staging system, those spearheading research in magnetic resonance imaging of the disease are also trying to come up with accurate tools to quantify amyloid burden. Staging tools are currently being developed and validated for ATTR CA, in the spirit of the acclaimed Mayo Staging System for AL.

Conclusion: Cardiac involvement confers significant morbidity and mortality in all types of amyloidosis. Great effort is made to reduce the time to diagnosis, as treatment in the initial stages of the disease is tied to better prognosis. The results of these efforts are highly sensitive and specific diagnostic modalities that are also reasonably cost effective.

Keywords: Amyloidosis, Cardiac amyloidosis, Heart failure, Echocardiography, Strain imaging, Biomarkers

Background

Amyloidosis refers to a group of diseases characterized by the deposition of amyloid fibrils in multiple tissues throughout the body, such as in the liver, kidney, eyes, heart and others. Amyloid fibrils result from the uncontrolled deposition of structurally abnormal proteins. Cardiac amyloidosis (CA) refers to the infiltration of the myocardium by amyloid fibrils, which cause cardiac dysfunction, eventually leading to heart failure [1]. The effect of amyloidosis on the quality of life and mortality rate of patients is substantial. A recent study enrolling patients with light chain amyloidosis (AL) found significant mental and physical impairment directly attributable to the disease [2].

Each disease that belongs to the umbrella term of amyloidosis is caused by copies of a specific protein that are folded in a fibrillogenic conformation. Not all types of amyloidosis affect the heart in the same frequency. Cardiac amyloidosis encountered in clinical practice is in the vast majority of cases caused by light chain (AL) or transthyretin amyloidosis (ATTR), with the latter consisting of two subtypes: Senile ATTR amyloidosis, which is caused by wild-type transthyretin deposition (ATTRwt), and familial ATTR amyloidosis, which is caused by mutant proteins that

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exhibit increased fibrillogenicity (ATTRm or ATTRv, where 'v' stems from 'variant') [1, 3, 4]. Secondary amyloidosis is the result of the overproduction of the acute-phase protein serum amyloid A (SAA) in chronic inflammatory conditions. SAA has been shown to deposit in cardiac tissue, but clinically significant cardiac involvement appears to be rare [5]. Isolated atrial amyloidosis (IAA) is a condition of great importance to the pathophysiology of arrhythmias that originate in the atria, such as atrial fibrillation [6]. IAA is caused by the deposition of Atrial Natriuretic Peptide (ANP) fibrils in the atria. It appears to be the most common type of amyloidosis to affect the heart, as more than 90% of people over 90 years old appear to have measurable ANP deposition in their hearts [7]. The disease's predilection for older women appears to stem from the fact that estradiol upregulates ANP expression in atrial cardiomyocytes [8].

Systemic amyloidosis is a quite rare disease, with its incidence in the English population in the year 2008 estimated to be at least 4/1.000.000, as extrapolated from epidemiological data. Most of the patients affected were aged between 60 and 79 years [9]. The minimum incidence of AL is similarly estimated at 3/1.000.000, and the prevalence of AL CA, i.e. the cardiac involvement in AL, is estimated at 8–12/1.000.000 [10]. AL CA affects patients aged between 55 and 60 years old, with men appearing to be slightly more vulnerable to the disease [11]. On the other hand, ATTRwt CA usually affects older patients, with the results of autopsies showing that 25% of people older than 80 years have their myocardium infiltrated by TTR amyloid depositions [10, 12]. Interestingly, ATTRwt CA has been proved via 99mTc-DPD scintigraphy to represent 13% of patients with Heart Failure with a Preserved Ejection Fraction (HFpEF), in a sample of 120 patients over 60 years old [13]. CA is the primary cause of restrictive cardiomyopathy (RCM) [14, 15]. In summary, cardiac amyloidosis' frequency among HF patients is increasingly being acknowledged by clinicians and researchers alike, as can be observed from its inclusion in the novel MOGES classification of cardiomyopathies [16].

In the latter stages, CA, as a typical example of restrictive cardiomyopathy, manifests with the classical triad of congestive HF symptoms, i.e. shortness of breath, fatigue and edema [1]. Cardiac pump dysfunction progressively emerges as amyloid aggregates in the heart tissue [17]. ECGs of patients already diagnosed with the disease are seldom normal, the most frequent abnormalities for both AL and ATTRwt CA being low voltage QRS and a pseudoinfarction pattern. Conduction disorders and arrhythmias are also common, especially atrial fibrillation and atrioventricular disorders [18, 19]. Nonetheless, amyloidosis is probably still under-diagnosed, especially in subsets of the population like elderly patients with HF [20]. Endomyocardial biopsy remains the gold standard of CA amyloidosis' diagnosis [21]. Regarding AL, fat pad biopsy has been proven to have great sensitivity to confirm the diagnosis [22]. A quick and efficient diagnostic approach in CA is of great significance given the accelerated deterioration observed in advanced stages of the disease. It is known that the onset of a restrictive pathophysiology is independently linked to a significantly poor prognosis in CA [23]. Additionally, early diagnosis offers more therapeutic options, as advanced cardiac failure is a contraindication for other therapies such as orthotopic liver transplantation [24]. The diagnostic modalities that will be discussed below represent efforts to offer the clinicians with tools in order to minimize lost cases, significantly reduce the time needed for making the diagnosis, whilst simultaneously maintaining reasonable cost-effectiveness.

Methods

Adhering to PRISMA guidelines and aiming to procure the latest literature on the subject of the methods used to diagnose cardiac amyloidosis, all studies would be evaluated for eligibility based on the following criteria: Only (1) original studies (2) published in peer-reviewed journals (3) within the past 5 years were considered eligible for inclusion in this systematic review. (4) Only studies written in English were evaluated for inclusion.

Studies were looked up on MEDLINE, EMBASE, PMC and the Cochrane Database of Systemic Reviews through PubMed and Google Scholar. Several search terms were used, such as "cardiac amyloidosis diagnosis", "staging cardiac amyloidosis", "TTR amyloidosis imaging" and "cardiac amyloidosis ultrasound", "cardiac amyloidosis GLS", "cardiac amyloidosis EFSR", "cardiac amyloidosis MRI", "cardiac amyloidosis LGE", "cardiac amyloidosis CMR", "cardiac amyloidosis nuclear imaging", "cardiac amyloidosis FDG-PET", "cardiac amyloidosis PET". All studies in the first three pages of results for each search query were evaluated for inclusion in this systematic review based on the aforementioned eligibility criteria. The search results that appeared eligible on the basis of their title, publication date and abstract were given full consideration and were included in the systematic review, provided a comprehensive examination of their full text confirmed their eligibility (Fig. 1).

Results

The search that was conducted yielded 674 results, of which 60 were confirmed to be duplicates. Seven studies included were recommended by experts on the field. 621 records were screened on the basis of title and abstract, of which 602 were excluded from the review. Of the remaining 19 studies, 2 were not suitable for our review. The remaining 17 articles were finally included in the systematic review.

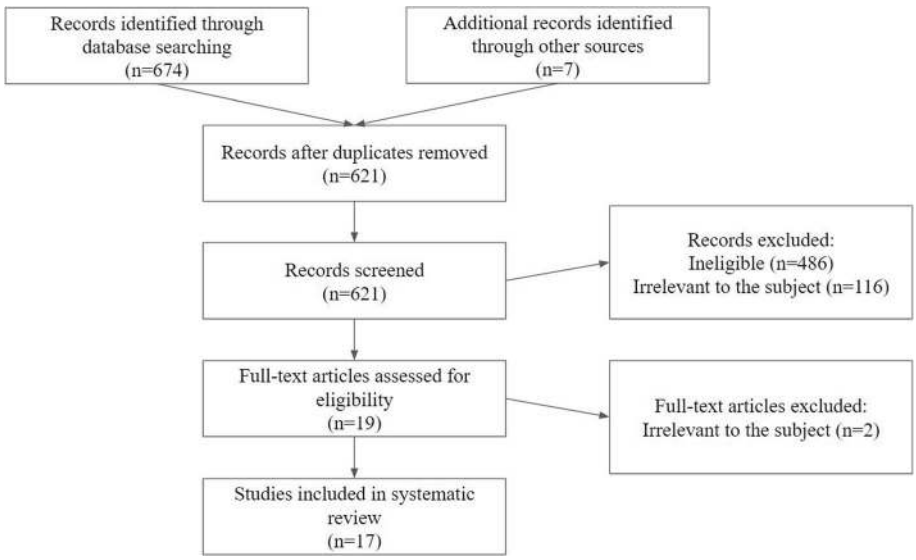

Fig. 1 Flowchart of literature review process

Imaging methods

Cardiac ultrasound

Cardiac ultrasound is a widely available, easy to use, radiation-free and relatively inexpensive bedside tool. Cardiac ultrasound has been established as the first step in the amyloidosis diagnostic workup, as a tool of "ruling in" the diagnosis, identifying patients likely to have the disease and prompting further workup. Nowadays, advanced ultrasonographic protocols, utilizing state of the art ultrasound technology are hugely improving the method's sensitivity and specificity.

The most common two-dimensional (2D) echocardiographic findings observed in CA are biatrial dilatation and increased left and right ventricular wall thickening [25, 26]. It should be noted that there is a mismatch between ECG and echocardiographic findings, as low QRS voltage is not consistent with ventricular hypertrophy. Granular sparkling appearance of myocardium is a common echocardiographic finding in CA, which is attributed to the increased echogenicity of the amyloid protein [25, 26]. Furthermore, valvular thickening could be also found in specific types of CA, such as TTR amyloidosis. However, it should be noted that the frequency of these findings increases at the later stages of the disease. Clinical data demonstrated the importance of a more multiparametric approach, including the evaluation of more advanced techniques such as Tissue Doppler Imaging (TDI) and 2D strain imaging. Findings of RCM are typical in CA. The severity of diastolic function is related to the degree of amyloid infiltration, while high filling pressures and restrictive mitral inflow pattern are also observed. At the initial stages, an abnormal relaxation pattern is observed. However, the increase of wall thickness with the progression of the disease leads to shortened deceleration time, high early velocity (E-wave) and low atrial velocity (A-wave) leading to E/A ratio > 2 and deceleration time < 150 ms, compared to E/A ratio < 1 at the early stages [23, 27, 28]. Peak early diastolic velocity (E') assessed by TDI is decreased in the earliest stages of the disease, and further decreases with the disease progression, a fact that also helps in the differential diagnosis with other diseases, such as constrictive pericarditis or hypertrophic cardiomyopathy (HCM), in which E' is normal or mildly reduced [29]. Furthermore, numerous studies confirmed that impaired longitudinal function assessed by TDI plays key role in the early diagnosis of CA. It has been demonstrated that basal and mid LV longitudinal myocardial deformation were significantly decreased in asymptomatic CA patients [27]. This abnormal finding was observed before wall thickening. Interestingly, it was shown that impaired longitudinal function assessed by TDI could discriminate between patients with CA and patients with amyloidosis without cardiac involvement [27, 28]. However, it should be noted that the TDI technique has significant limitations related to the Doppler effect as well the influence of noise and angle dependence on measurements. Beyond TDI, myocardial performance index (MPI also called Tei index), calculated by combining systolic and diastolic time intervals, could provide significant information on myocardial function of CA patients, while it could also serve as an outcome indicator [30, 31].

Speckle tracking technique for the evaluation of myocardial deformation helped us to overcome these limitations. Based on the interaction between ultrasounds and tissues and the use of specific software, two-dimensional speckle tracking (2DST) is able to evaluate longitudinal, radial and circumferential deformations. From the very first studies, it has been

demonstrated that global longitudinal strain (GLS), circumferential and radial deformations were significantly decreased in CA patients, compared to patients with hypertrophic cardiomyopathy or hypertensive heart disease [32]. Notably, it has been reported that patients with AL and TTR cardiac amyloidosis and preserved ejection fraction (EF) had impaired basal and mid LV longitudinal strain (LS), also visible via TDI, while apical LS was preserved [33]. Further, Phelan et al. compared the global and regional strain parameters of 55 patients diagnosed with AL CA to that of 30 patients with HCM of different etiology. They used the parameter of relative apical longitudinal strain (RALS), average apical LS/(average basal LS + average mid-LS). An abnormally high RALS displayed a sensitivity of 93% and a specificity of 82% at detecting CA. Relative apical sparing is characteristic of both AL and TTR CA [34]. Pagourelias et al. used the ratio of GLS to the EF, which is characteristically disrupted by amyloid deposits. They introduced the ejection fraction strain ratio (EFSR) as a reliable tool to diagnose CA [35] and confirmed that it is currently the most specific (91.7%) and sensitive (89.7%) echocardiographic parameter in diagnosing CA. The apical sparing parameter proposed by Phelan et al. was also investigated in the study, but yielded a markedly low sensitivity of 37.5% in that sample population, utilizing the proposed cut-off values [36]. The study also confirmed that EFSR displays low inter-observer variability, being a standardized parameter, and demonstrably retains its high diagnostic value in populations with either increased wall thickness or preserved EF. Figure 2 is representative of echocardiographic findings in CA.

One of the recent developments is the clinical implementation of three-dimensional (3D) echocardiography and 3D speckle tracking (3DST) technique. In one of the first studies, LV regional dyssynchrony was measured via a 16-segment dyssynchrony index in AL patients and was found significantly impaired compared to control subjects [37]. In addition, very recent studies used deformation and rotational 3DST parameter in order to differentiate CA patients from patients with other forms of myocardial hypertrophy [37]. One of the studies has further confirmed with the use of 3DST that the basal rotational strain was significantly reduced compared to apical rotational strain, a finding that could efficiently differentiate CA patients from patients suffering from HCM [38]. However, it is important to mention that 3D echocardiography is still not widely used compared to 2D echocardiography in clinical routine. Further developments and clinical studies are needed in order to develop measures and techniques that could offer a significant additive value compared to 2D echocardiography.

Cardiac MRI

Cardiac Magnetic Resonance (CMR) is considered a very sensitive and specific diagnostic modality for both ATTR and AL, although it is more time-consuming and

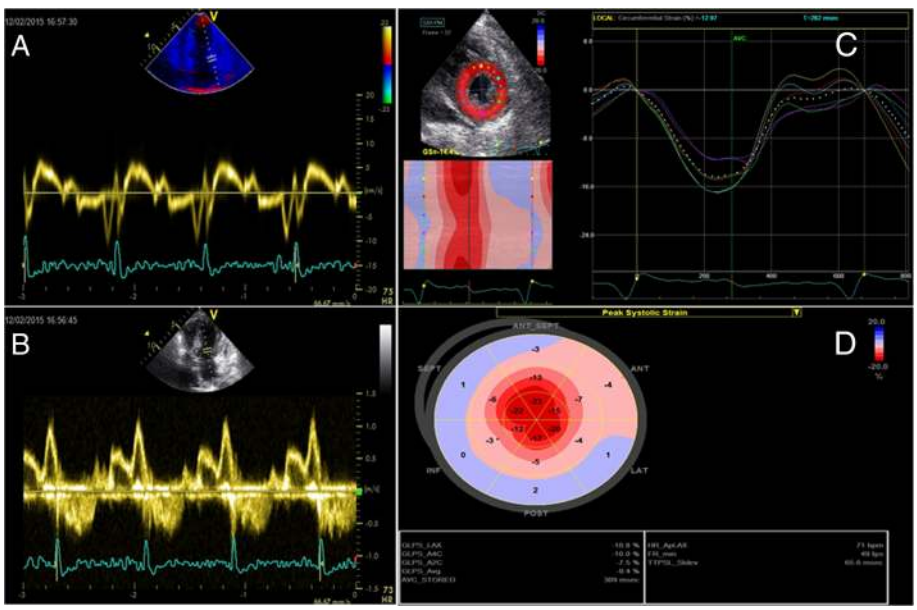

Fig. 2 Mitral valve inflow pulsed wave Doppler (**a**) and Tissue Doppler Imaging of the mitral valve annulus (**b**) of a patient with CA demonstrating an early diastolic dysfunction pattern. Circumferential (**c**) and longitudinal deformation by 2D strain imaging (**c** and **d**) mainly shows an impairment of global longitudinal deformation. In patients with CA, an impaired deformation in basal segments compared to apical segments could be found

expensive when compared to cardiac ultrasound [39, 40]. CMR demonstrated high sensitivity in diagnosing further diseases, such as in myocardial iron overload [41], although cardiac ultrasound remains the first choice as it is easy to use and widely available, as demonstrated in studies which compared the sensitivity of normal echocardiography compared to CMR [42, 43]. The deposition of amyloid in the heart leads to an increase in myocardial extracellular volume (ECV). This increase is readily detected by CMR through the Late Gadolinium Enhancement (LGE) test. Gadolinium-based contrasts rapidly extravasate are not absorbed by healthy cardiomyocytes and is rapidly removed from the circulation, while any in the elimination of contrast indicates an increase in ECV, and it is this tissue that shows up positive in LGE tests CA characteristically leads to diffuse subendothelial LGE in the left ventricle as well as the atria [44].During the disease progression, LGE expands transmurally and gradually to all chambers of the heart tissue [45].

CMR with LGE demonstrated 80% sensitivity and 90% specificity in detecting cardiac involvement in amyloidosis [46]. Since then its predictive value has improved even further [47], in great part thanks to the development of phase-sensitive inversion recovery (PSIR). This technique, which allows the use of different inversion times, alleviates some previous technical problems of LGE CMR, which would cause discrepancies in LGE measurement, leading to an underestimation of LGE extent and severity in cases where the majority of cardiac tissue would be affected [48]. Based on the increasing accuracy CMR findings, many clinicians actually forgo the step of confirming the diagnosis through endomyocardial biopsy (EMB), when a typical LGE pattern is detected and no other causes of focal increase in cardiac ECV, such as myocarditis, are likely. Although it is difficult to assess the implications of this approach, the inclusion of CA patients in studies whose diagnosis has not been confirmed through EMB has been contested [39]. Furthermore, it has been claimed that CMR can also differentiate between ATTR and AL, due to differences in the pattern of LGE [49], although further investigation is necessary.

CMR's role in the differential diagnosis between amyloidosis and other diseases such as Fabry disease, and HCM has also been examined. Specifically, while HCM shows a patchy LGE pattern mainly located in the middle of the hypertrophic wall and Fabry disease shows a more located LGE pattern in the basal segment of the LV, CA shows atypical signal intensity related to the amyloid deposition pattern and faster clearance of gadolinium [50]. Due to this faster clearance of gadolinium, CA patients also present a diminished T1 difference between myocardium and blood pool. However, because of the reduced specificity of CMR in distinguishing between the aforementioned diseases in some cases, the simultaneous examination of LGE and the relative apical strain sparing was necessary to yield the best results, being capable of very reliably detecting CA patients (Fig. 3) [51]. A technique that attempts to quantify the LGE findings, the Look-Locker magnetic resonance sequence, was tested in real-life patient series and yielded mixed results [52]. Higher T1 inversion times (roughly the time it takes for T1 signals to drop to pre-contrast levels) correlated with amyloid load but not patient prognosis.

Non-contrast T1 CMR imaging constitutes a very promising technique with a reported 92% accuracy in detecting cardiac involvement in amyloidosis. Notably, it is safe for patients with renal failure, which is a common problem among patients with amyloidosis [53, 54]. Efforts to quantify amyloid load using T1 images have yielded several techniques that boast reliable detection of increased ECV, which is tied to higher amyloid load in EMB specimens and worse patient outcome in small studies [55–57].

Nuclear imaging

Nuclear imaging of the heart pertains to the intravenous administration of radioactive substances and the interpretation its absorption throughout cardiac tissues by measuring the emitted radiation. Radio-labeled phosphonates, generally referred to as bone tracers, such as [99mTc]-DPD show strong affinity for TTR amyloid fibrils in cardiac tissue. This has been extensively utilized in the CA diagnostic process [58, 59]. The exact mechanism of [99mTc]-DPD binding to the amyloid fibrils is yet to be elucidated, although the higher calcium content of the TTR fibrils may play a decisive role [60]. [99mTc]-DPD scans showed a surprisingly high sensitivity and specificity approaching 100% for ATTR CA whilst being capable of very reliably excluding AL CA [61]. This latter finding has been somewhat contested, as AL amyloid deposits exhibiting uptake have been reported [62]. Its sensitivity in asymptomatic patients has also been challenged [63], potentially limiting [99mTc]-DPD use to assessing cardiac involvement in patients already diagnosed with ATTR amyloidosis.

Similar claims have been made about another radio-labeled compound, [99mTc]-PYP. Bokhari et al. proved in a study, which included 25 patients, that [99mTc]-PYP imaging could efficiently discern between ATTR and AL CA [64]. They also developed a standardized [99mTc]-PYP protocol for the diagnosis of ATTR CA [65]. However, larger studies reported significant absorption in patients suffering from AL CA as well. Further studies concerning both tracers would definitely shed some light on their potential use [4].

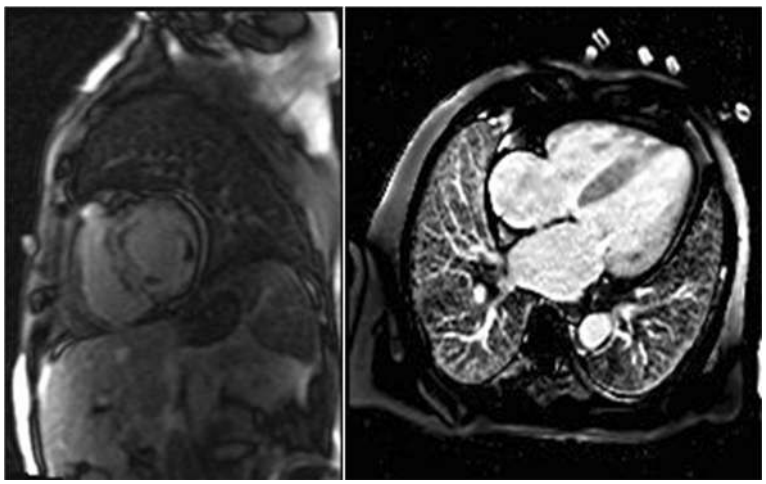

Fig. 3 Cardiac magnetic resonance (CMR) images of patients with cardiac amyloidosis. Amyloid fibril deposition pattern mainly affects subendocardial CMR imaging, leading to a shortened T1 relaxation time and a diffuse LGE of the left ventricular endocardium

PET scans with 18F-florbetapir, a tracer originally developed for amyloid imaging in the brain, also represent a promising tool for early diagnosis of cardiac amyloidosis, as well as quantification of cardiac amyloid and extracardiac amyloid load [66]. It must be noted that 18F-florbetapir binds to both AL and ATTR deposits, although a higher affinity for AL amyloid was reported in vitro studies [67]. ^{18}F-FDG PET/CT scans are a mainstay of clinical oncology and have also been examined as a potential imaging tool for detecting ATTR and AL amyloidosis. Unfortunately, many organs, including the heart, demonstrated variable avidity to the tracer. This fact limited the scan's sensitivity of detecting cardiac involvement to 62.5%. ^{11}C-Labelled Pittsburgh compound B (^{11}C-PiB) is a radio-labeled derivative of thioflavin-T that has been thoroughly used to detect Aβ amyloid deposition in Alzheimer's disease [68]. The potential application of ^{11}C-PiB PET scans in ATTR and AL amyloid imaging was explored, with promising results. The findings of ^{11}C-PiB PET tomography correlated well with post-mortem histopathological samples [68]. Further studies are definitely needed to confirm and build upon this work, but the ability to image amyloidosis with ^{11}C-PiB would greatly increase PET's accessibility, as this is a relatively common tracer.

Finally, 123I-MIBG scintigraphy has the capability of detecting cardiac sympathetic denervation in amyloidosis patients with cardiac involvement [69]. Specifically in the case of ATTR CA, 123I-MIBG can return positive results before echocardiographic evidence of disease [70]. Although the increased likelihood of lethal arrhythmias has been proven in the setting of denervation of viable myocardium in patients' post-myocardial infarction, scarce data exists, with regard to amyloidosis patients. Such a finding would imply that positive 123I-MIBG findings place the patient at heightened risk of arrhythmias.

Fat ultrasonography

Misumi et al. introduces fat ultrasonography, a novel tool for the screening and diagnosis of ATTR amyloidosis. The reported sensitivity is 85.1% and the specificity is 97.1%, under ideal imaging conditions [71]. Although the sample size and constitution is not ideal, this study serves as a proof of concept for a technique that constitutes both a potential screening tool a promising research field.

Biomarkers

Cardiac involvement biomarkers

Serum troponin and NT-proBNP, biomarkers classically associated with detecting and evaluating heart failure from causes such as coronary heart disease [72], have proven successful in assessing myocardial involvement in amyloidosis.

Cardiac Troponin T (cTnT) is a reliable marker of cardiomyocyte death and has proven itself a strong negative prognostic factor for overall survival in AL and ATTR amyloidosis [73, 74]. The introduction of a new, high sensitivity assay for measuring cTnT, hs-cTnT, was thought that could improve the staging of AL amyloidosis. It has been shown that although the use of hs-cTnT does not improve the classic Mayo Staging System, it can render NT-ProBNP testing unnecessary, as models indicate that the Staging System retains its strength without it, when hs-cTnT is utilized [73–75].

The Brain Natriuretic Peptide (BNP) and the protein that results from the N-terminal cleavage of BNP's prohormone, titled NT-proBNP, have been consistently shown to be reliable prognostic markers for cardiac amyloidosis, regardless of the nature of the amyloid (AL or ATTR) [76]. For this reason, NT-proBNP levels have been included in the Mayo Amyloidosis Staging System,

which is widely used for the staging of AL amyloidosis [77]. The logarithm of NT-proBNP levels is an independent prognostic factor of mortality [78]. According to the Transthyretin Amyloidosis Outcomes Survey (THAOS), patients with elevated BNP and NT-ProBNP levels at the time of diagnosis demonstrated poorer prognosis, mainly attributed to renal insufficiency and worsened functional status [79].

AL amyloidosis-specific biomarkers

Serum and urine immunofixation electrophoresis (IFE), coupled with quantitative free light chain (FLC) measurements, boast an impressive sensitivity in diagnosing monoclonal gammopathies and have become a mainstay in the diagnosis of AL amyloidosis [80]. Recent data suggest that serum IFE alone, combined with FLC only misses 0.5% of monoclonal gammopathy cases with abnormal urinary results [81].

It is of note, that positive FLC and IFE findings in patients with confirmed amyloid deposition, whether through EMB or imaging studies, do not definitively confirm the diagnosis of AL amyloidosis, as cases of older patients with ATTRwt amyloidosis and concomitant MGUS are repeatedly reported throughout the literature. In patients with risk factors for both diseases, diagnostic modalities with the capacity to objectively discern amyloid composition are necessary [82].

dFLC is defined as the difference between the serum levels of κ an λ Free Light Chains. It is a major independent prognostic factor in AL amyloidosis, as well as several other plasma cell disorders such as the multiple and smoldering myeloma [83]. The pathophysiological reasoning is that increased dFLC values reflect more available free light chains, accelerating fibril formation. Increased dFLC levels are associated with higher likelihood and severity of heart disease, as well as worse response to therapy, whilst a reduction post-therapy has been tied to better outcomes [84].

The currently preferred staging system in AL amyloidosis is the Mayo Amyloidosis Staging System that utilizes the aforementioned biomarkers cTNT, NT-proBNP and dFLC to stratify disease severity in patients with AL (Table 1) [77].

ATTR amyloidosis-specific biomarkers

The V122I variant of the TTR protein is being increasingly recognized as an underdiagnosed cause of heart failure in elderly African American patients, 3–4% of which appear to carry the gene [85]. Arvanitis et al. discovered that Retinol Binding Protein 4 (RBP4) levels in ATTRm amyloidosis patients with the V122I mutation have been found significantly diminished [86]. By combining ultrasound measurements (LVEF, IVSD) and ECG parameters such as the mean QRS alongside with serum RBP4 levels, the authors proposed a clinical score with significant diagnostic accuracy [87].

Table 1 AL Staging according to the revised Mayo AL staging tool [55]

Number of abnormal laboratory tests	Stage (according to revised staging system)	Median Overall Survival (months)	5-year Survival
0	I	94.1	59%
1	II	40.3	42%
2	III	14	20%
3	IV	5.8	14%

(Laboratory tests: cTnT ≥0.025 ng/mL, NT-ProBNP ≥1800 pg/mL, dFLC≥18 mg/dL)

A very similar staging system to that used in AL amyloidosis has been proposed for ATTR-wt amyloidosis, incorporating cTnT and NT-proBNP values to stratify patients in three stages, depending on the number of the aforementioned lab values exceeding a certain cut-off value [88].

Recently, Gillmore et al. devised a novel staging tool that can be used for both ATTRwt and ATTRm amyloidosis (Table 2). They validated its capability to predict median survival in a study consisting of 869 patients. This staging tool assesses eGFR and NT-proBNP, which both correlate well with overall survival [89]. This approach elicited mixed results from the research community. It has been lauded for its simplicity and reproducibility, but criticized for the omission of cTnT from the risk stratification, as well as the inclusion of eGFR. In an insightful editorial, Singh and Falk pointed out that a reduced eGFR in ATTR CA patients is mostly a byproduct of either age-related comorbidities or renal hypoperfusion secondary to heart failure, thus not a good independent prognostic factor of mortality [90]. They also hint towards the general trend of machine learning-based clinical prediction models [91, 92], and their potential application to ATTR patients.

Conclusion

Cardiac amyloidosis is the main cause of morbidity and mortality in AL and ATTR amyloidosis. Heart failure is almost inevitable during the course of the disease [93–95],

Table 2 Proposed ATTR staging utilizing the staging tool proposed by Gillmore et al. [67]

Number of abnormal laboratory tests	Stage (according to revised staging system)	Median Overall Survival (months)	5-year Survival
0	I	69.2	63%
1	II	46.7	37%
2	III	24.1	19%

(Laboratory tests: eGFR< 45 ml/min/1.73 m2, NT-proBNP > 3000 ng/L)

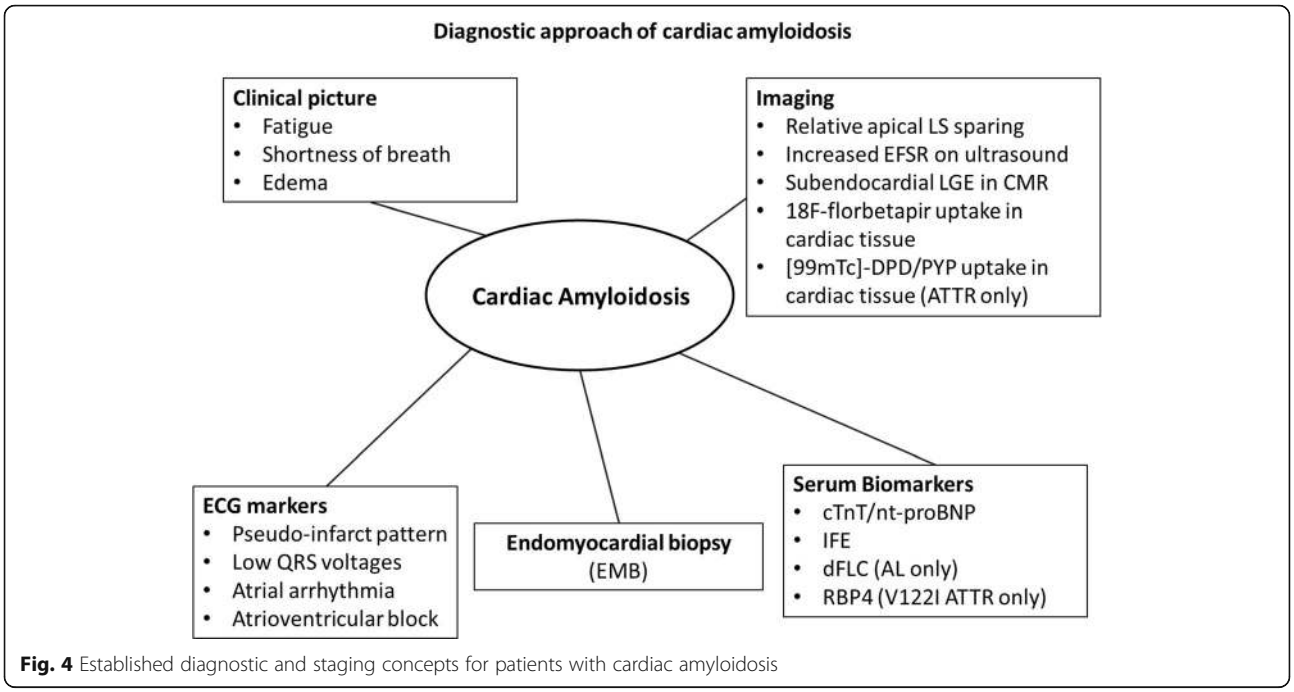

Fig. 4 Established diagnostic and staging concepts for patients with cardiac amyloidosis

greatly limiting therapeutic options. A timely diagnosis is thus critical [96] but frequently proves difficult, as the symptoms are rarely indicative of the disease. The low cost, simplicity and lack of radiation render ultrasonographic protocols an almost ideal tool to "rule in" amyloidosis as a likely cause of congestive heart failure. Less readily available and more expensive tools such as cardiac MRI and nuclear imaging are better used to confirm and quantify cardiac involvement or to screen for it in patients already diagnosed with amyloidosis. Both diagnostic tools have yielded quantitative values (ECV fraction and myocardial retention index respectively) that appear to detect cardiac involvement in amyloidosis patients, so their inclusion in the current staging systems is an interesting avenue of research. These staging systems currently stratify patients solely through the use of biomarkers, whose role in CA is constantly re-evaluated. Current research aims at rendering existing tools more effective and sensitive, in addition to discovering novel disease biomarkers, such as RBP4.

In summary, several novel diagnostic and staging concepts have been established for cardiac amyloidosis in recent years (Fig. 4). Research is now focusing on validating these novel concepts using larger patient groups and better adjusting them for clinical practice. The validation of diagnostic algorithms that use simplified and cost-effective means of ruling in the diagnosis and sensitive tools to confirm the disease and to quantify amyloid load are key elements to shortening the time to diagnosis and improving patients' prognosis.

Abbreviations

[99mTc]-PYP: Tc-99 m-pyrophosphate; 123I-MIBG: 123I-metaiodobenzylguanidine; 2D: Two-dimensional; 2DST: Two-dimensional speckle tracking; 3D: Three-dimensional; 3DST: Three-dimensional speckle tracking; A: amyloidosis; AL: Light chain amyloidosis; ANP: Atrial Natriuretic Peptide; ATTRm: Mutant Transthyretin amyloidosis; ATTRwt: Wild-type Transthyretin amyloidosis; BNP: Brain Natriuretic Peptide; CA: Cardiac amyloidosis; CMR: Cardiac Magnetic Resonance; cTnT: Cardiac Troponin T; dFLC: Difference in κ and λ light chain concentrations; ECV: Extracellular Volume; EF: Ejection Fraction; EFSR: Ejection Fraction Strain Ratio; eGFR: Estimated Glomerular Filtration Rate; EMB: Endomyocardial biopsy; FLC: Free light chains; GLS: Global Longitudinal Strain; HCM: Hypertrophic Cardiomyopathy; HFpEF: Heart failure with preserved ejection fraction; hs-cTnT: High sensitivity cardiac Troponin T; IFE: Immunofixation electrophoresis; IVSd: Interventricular septal end diastole; LGE: Late Gadolinium Enhancement; LS: Longitudinal strain; LVEF: Left ventricular ejection fraction; LVH: Left ventricular hypertrophy; MRI: Magnetic Resonance Imaging; NT-proBNP: N-terminal pro-Brain Natriuretic Peptide; PSIR: Phase-Sensitive Inversion Recovery; RALS: Relative Apical Longitudinal Strain; RBP4: Retinol binding protein 4; TDI: Tissue Doppler Imaging; THAOS: Transthyretin Amyloidosis Outcomes Survey; TTR: Transthyretin; TTR: Transthyretin[99mTc]-DPD Tc-99 m-3,3-diphosphono-1,2-propanodicarboxylicacid

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Availability of data and materials

As described in the methods section.

Authors' contributions

PG, DM, TA and CB drafted the manuscript. AR, MN and VV revised it critically for important intellectual content, made substantial contributions to concept and design and gave final approval of the version to be published. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Consent for publication
Not applicable.

Competing interests
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