Clinical Clues and Diagnostic Workup of Cardiac Amyloidosis

SAJAN S. GILL, MD
ERIC FELLIN, BS
LISA STAMPKE, BS
YUNAZI ZHAO, MD, PhD
AHMAD MASRI, MD, MS

ABSTRACT

Cardiac amyloidosis is increasingly recognized as an underlying cause of left ventricular wall thickening, heart failure, and arrhythmia with variable clinical presentation. Due to the subtle cardiac findings in early transthyretin cardiac amyloidosis and the availability of therapies that can modify but not reverse the disease progression, early recognition is vital. In light chain amyloidosis, timely diagnosis and treatment can significantly improve survival. In this manuscript, we review the clinical, imaging, and electrocardiographic clues that should raise suspicion for cardiac amyloidosis and provide a simplified diagnostic workup algorithm that ensures an accurate diagnosis. The evolution of the noninvasive diagnosis of cardiac amyloidosis has significantly influenced our understanding of disease prevalence, presentations, and outcomes. However, clinical recognition of clues and red flags remains the most important factor in advancing the care of patients with cardiac amyloidosis.

CORRESPONDING AUTHOR:
Ahmad Masri, MD, MS
Knight Cardiovascular Institute,
Oregon Health & Science University School of Medicine,
Portland, Oregon, US
masria@ohsu.edu

KEYWORDS:
cardiac amyloidosis; systemic amyloidosis; immunoglobulin light chain; transthyretin;
left ventricular hypertrophy; heart failure; aortic stenosis; bone scintigraphy; cardiac magnetic resonance imaging; endomyocardial biopsy

TO CITE THIS ARTICLE:
Gill SS, Fellin E, Stampke L, Zhao Y, Masri A. Clinical Clues and Diagnostic Workup of Cardiac Amyloidosis. Methodist DeBakey Cardiovasc J. 2022;18(2):36-46. doi: 10.14797/mdcvj.1061

*Author affiliations can be found in the back matter of this article
INTRODUCTION

Systemic amyloidosis is caused by the extracellular deposition of misfolded protein in multiple organs and systems. The two most prevalent amyloid types with common cardiac involvement are immunoglobulin light chain and transthyretin (ATTR) amyloidosis. These can overlap in presentation but differ in diagnostic pathway and therapeutic approaches; hence, it is crucial to identify the underlying subtype of cardiac amyloidosis. In this review, we discuss the clinical clues that should raise suspicion for cardiac amyloidosis (CA) in patients presenting in outpatient settings, and we provide a patient-centered diagnostic workup that ensures an accurate diagnosis (Figure 1).

Light chain amyloidosis (AL-CA) is caused by sporadic deposition of kappa or lambda light chains in tissue and therefore does not follow any known inheritance pattern. The disease is one of the plasma cell dyscrasias and found in 10% of patients with multiple myeloma. AL-CA is relatively uncommon, with an incidence of 3 to 9 per million person-years. Across all forms of amyloidosis, misfolded proteins are often more prevalent in older individuals, possibly due to the changes in physiological microenvironments seen with aging. The age at diagnosis varies, although the mean age of AL-CA diagnosis is approximately 57 years old. AL-CA is historically more readily recognized compared to ATTR, often with a wide-ranging presentation depending on which organ is involved. Symptoms may include heart failure, weight loss, nephrotic syndrome, macroglossia, and GI disturbances, among others.

Transthyretin is a thyroxine and retinol transport protein predominantly produced in the liver, choroid plexus, and retina and is found circulating in plasma and cervical spinal fluid. ATTR amyloidosis can result from an amino acid change, leading to variants (ATTRv) that precipitate transthyretin tetramer instability, or can occur despite having normal protein structure, as in wild type ATTR (ATTRwt). These two types are closely related in pathophysiology, both showing deposition of fibrils in

Figure 1 Simplified diagnostic algorithm for suspected cardiac amyloidosis. EKG: electrocardiogram; AL: immunoglobulin light chain; Heme: hematology; CMR: cardiac magnetic resonance imaging; Tc-99m PYP: technetium-99m pyrophosphate; SPECT: single-photon emission computed tomography; MGUS: monoclonal gammopathy of undetermined significance; ATTR/TTR: transthyretin; NT-proBNP: N-terminal prohormone of brain natriuretic peptide
different organs and systems, but the distinction comes in their presentation and currently available therapies.

As the name suggests, ATTRwt is a sporadic disease of older individuals, most often seen in White males, with prevalence increasing significantly (12-25%) in people over 80 years.\(^9\) ATTRwt predominantly presents as heart failure with features of restrictive and infiltrative cardiomyopathy, with additional history clues including orthopedic manifestations such as prior carpal tunnel release, spinal stenosis, and neuropathy.\(^10\) ATTRv is inherited through an autosomal dominant pattern with over 100 different associated variants.\(^11\) The severity, age of onset, and symptomology of the disease is dependent on the particular variant and geographical location.\(^12\) In ATTRv, early onset is considered before the age of 50, and incidence varies geographically in endemic versus nonendemic areas.\(^13,14\) In the United States, there is a higher prevalence of the p.Val142Ile mutation among people of African and Afro-Caribbean ancestry but with variable penetrance.\(^15\) This mutation is of particular interest given its prevalence and predominantly cardiac phenotype.\(^16,17\) Overall, ATTRv has a rather heterogeneous presentation depending on the underlying variant and can emerge with a polyneuropathy phenotype, cardiomyopathy phenotype, or mixed.\(^6,18\)

Due to the varying and at times nonspecific symptomatology in patients with amyloidosis, it is important to pay attention to minor clues in a patient’s history, such as previous orthopedic or neurological conditions that were present years prior to presentation, and carefully evaluate left ventricular hypertrophy (LVH) even in the presence of hypertension. Table 1 summarizes extracardiac symptoms and disease manifestations that should alert the clinician to consider amyloidosis in the differential.\(^19-21\)

**CARDIAC PHENOTYPE (HEART FAILURE)**

In the cardiac phenotype, amyloidosis can cause a wide range of presentations; however, the classic presentation is often cardiomyopathy with restrictive hemodynamics and heart failure.\(^22\) The cardiac phenotype typically starts with subclinical extracellular deposition of amyloid fibrils, with progressive increase in ventricular wall thickness, atrial dilatation, arrhythmias, and conduction system abnormalities.\(^20,21\) The cardiac phenotype is the leading cause of mortality, with varying survival rates depending on the stage of cardiac involvement.\(^24\) For example, in untreated advanced AL-CA, the mean survival is less than 6 months after development of heart failure.\(^25\) Early recognition of cardiac involvement in amyloidosis is vital given the high morbidity and mortality coupled with

| PRESENTATION                        | AL AMYLOID | ATTR AMYLOID |
|-------------------------------------|------------|--------------|
| Foamy urine                         | ✓          | --           |
| Hepatosplenomegaly                   | ✓          | --           |
| Macroglossia                        | ✓          | --           |
| Purpura (periorbital, neckline)      | ✓          | --           |
| Arthropathy                         | ✓          | --           |
| Skin bruising                       | ✓          | --           |
| Autonomic dysfunction (intestinal motility/orthostatic hypotension) | ✓ | ✓* |
| Dysesthesia                         | ✓          | --           |
| Carpal tunnel syndrome (often bilateral) | --       | ✓            |
| Biceps tendon rupture                | --         | ✓            |
| Lumbar spinal stenosis              | --         | ✓            |
| Trigger finger                      | --         | ✓            |
| Vitreous deposits                   | --         | ✓            |
| Constipation/diarrhea               | ✓          | ✓            |
| Unexplained weight loss (dysphagia, malabsorption) | ✓ | ✓ |
| Polyneuropathy                      | ✓          | ✓*           |

*Table 1* Extracardiac findings in amyloidosis that should prompt workup in patients presenting with heart failure.\(^19-21\)

*More common in this subtype*
therapeutics that frequently halt the progression of disease but do not reverse it.\textsuperscript{22}

Perhaps the most important aspect is developing a systematic approach to evaluating systemic signs, symptoms, and diagnostic findings that could provide clues to the diagnosis, which, in the era of electronic medical record systems, can be integrated as a systematic checklist for every new patient with heart failure. Table 2 provides some clues from cardiac involvement in amyloidosis.\textsuperscript{17,19,20,26-32}

While the sensitivity and specificity of electrocardiograms for cardiac amyloidosis diagnosis is low, the combination of red flags from the patient’s history and electrocardiogram, in the setting of LV hypertrophy, should prompt an evaluation for cardiac amyloidosis.\textsuperscript{33,34} A history of hypertension should not discourage such an evaluation since hypertension is common in patients with a history of ATTR.\textsuperscript{35} Once clinical suspicion is raised, pretest probability should drive targeted evaluation.

### AORTIC STENOSIS

Coexistent aortic stenosis (AS) and ATTR cardiomyopathy (ATTR-CM) is a relatively recent finding, and there are no mechanistic studies to directly explain the high prevalence of ATTR-CM in AS.\textsuperscript{30,36} The coexistence of these conditions represents a unique challenge since AS can also lead to increased LV wall thickness and abnormal strain pattern. However, this also represents a unique opportunity to apply screening for red flags in patients presenting with AS, akin to those presenting with heart failure, to identify those with

| CLINICAL FINDINGS |
|-------------------|
| Proteinuria (AL)  |
| Hepatosplenomegaly (AL) |
| Syncope           |
| Unexplained weight loss, fatigue, cachexia |
| Orthostatic hypotension |
| Progressive decline of blood pressure, or the need for less anti-hypertensive medications over time |
| Inability to tolerate standard heart failure therapies (BB, ACEi/ARB, ARNI) or rate control strategy in atrial fibrillation |

| ECHOCARDIOGRAPHIC FINDINGS |
|-----------------------------|
| Left ventricular hypertrophy particularly when associated with relative apical sparing pattern on global longitudinal strain analysis |
| Restrictive diastolic filing pattern |
| Left ventricular ejection fraction to global longitudinal strain ratio (LVEF/GLS) > 4.1 |
| Aortic stenosis |
| Mitral annular tissue Doppler S’ < 6 cm/s |
| Left ventricular ejection fraction 50% ± 5% |
| Low QRS voltage to LV mass ratio |
| Thickening of aortic and mitral valves and intra-atrial septum |
| Pericardial effusions |
| Average apical/basal longitudinal strain ratio > 2 |
| Atrial enlargement |
| Normal/small LV cavity size |

| EKG FINDINGS |
|--------------|
| Low voltage (QRS < 1 mV in precordial and < 0.5 mV in extremity leads) |
| Pseudoinfarct patterns without known prior MI (QS waves in any two consecutive leads) |

Table 2 Clinical, echocardiographic, and EKG clues to cardiac amyloidosis.\textsuperscript{17,19,20,26-32} AL: amyloid light chain; BB: beta blocker; ACEi: angiotensin converting enzyme inhibitor; ARB: angiotensin receptor blocker; ARNI: angiotensin receptor npeprilysin inhibitor; LVEF: left ventricular ejection fraction; GLS: global longitudinal strain; EKG: electrocardiogram; LV: left ventricle; MI: myocardial infarction
underlying ATTR-CM (Table 2). This is especially important given the comparable mortality between AS patients who underwent transcatheter aortic valve replacement (TAVR) and patients with AS and ATTR-CM who underwent TAVR without other treatments for ATTR-CM.52 Nilsche et al. recently reported on a clinical risk score that can be used to identify ATTR-CM by narrowing down red flags, which include carpal tunnel syndrome, right bundle branch block, ≥ 85 years of age, elevated high sensitivity troponin T ≥ 20 ng/L, having an interventricular septum thickness ≥ 18 mm, E/A ratio ≥ 1.4, and, when feasible to perform, a Sokolow index < 1.9 millivolt.38 Ultimately, the message is to recognize that ATTR-CM coexists with AS, and an evaluation for ATTR-CM red flags in all patients with AS is necessary to improve the care of such patients, especially given the availability of therapeutics.

LABORATORY EVALUATION

Currently, no single laboratory test can definitively rule in or out cardiac amyloidosis. When used within the clinical context, elevated N-terminal prohormone of brain natriuretic peptide (NT-proBNP) in patients with stable symptoms in the nonacute setting can be a red flag when it is discrepant with New York Heart Association (NYHA) class. Similarly, chronically elevated troponin is a marker of subclinical myocardial injury and, in the absence of other explanation, should prompt workup for amyloidosis in the presence of LVH.39,40 These markers, in addition to glomerular filtration rate, are the backbone of prognostic models in both AL-CA and ATTR-CM.41-45

Additionally, with the overlap between AL and ATTR presentation, it is important to rule out AL-CA via laboratory studies early in the evaluation, although at times, for practicality purposes, ruling out AL and obtaining technetium-99m pyrophosphate (Tc-99m PYP) in patients with undifferentiated LVH or appear to be at low to intermediate suspicion of CA, CMR is the appropriate next step in evaluating LVH. In patients who have clear high pretest probability for ATTR-CM based on clinical and echocardiographic evaluation, bone scintigraphy is used to confirm ATTR-CM after ruling out AL amyloid cardiomyopathy.35

CARDIAC MAGNETIC RESONANCE IMAGING

CMR provides a wealth of cardiac data including anatomy, function, and tissue characterization, with the constellation of findings being highly sensitive and specific for detecting CA.56 Aside from the typical features that can be seen, two main CMR sequences provide diagnostic and mechanistic understanding into the underlying burden of disease.

Late gadolinium enhancement imaging (LGE)

In amyloidosis, LGE is reflective of amyloid fibrils occupying the extracellular space and the associated subendocardial fibrosis.57 The presence and pattern of LGE provides important diagnostic clues to the extent of CA. The main LGE patterns are diffuse subendocardial LGE and transmural LGE. A common issue when performing LGE imaging is abnormal gadolinium kinetics, where the myocardium and blood T1 values are similar because of high myocardial uptake and fast blood pool washout, which makes it harder to null the myocardium for acquisition of phase-
sensitive inversion recovery sequences. Although abnormal gadolinium kinetics can provide diagnostic clues, it can cause confusion in interpreting the images due to poor LGE technique (Figure 2A-F). Routine use of native T1 mapping and extracellular volume (ECV) quantification can rescue these shortcomings (Figure 2G).

**T1 mapping and ECV**

Progressive amyloid fiber deposition leads to progressive expansion of the extracellular space, which can be estimated using CMR. Native T1 mapping can offer clues regarding the presence of CA without using gadolinium. ECV, which requires both native and post-gadolinium T1 map, can also be used as a surrogate for total amyloid mass in the myocardium. Rarely, certain early amyloidosis phenotypes, especially in patients with hereditary ATTR, can present without significant LVH and with minimal or absent LGE but with elevated T1 mapping and ECV (Figure 3). Hence, one should always attempt to acquire these sequences in patients referred with LVH or suspicion for CA.

It is worth noting that CMR cannot differentiate between subtypes of CA. Based on the recent multisocietal expert consensus recommendations for multimodality imaging in CA, typical imaging findings of CA on CMR should be accompanied by either histological confirmation (cardiac or extra-cardiac) or by bone scintigraphy and laboratory studies for AL-CA.

**BONE SCINTIGRAPHY**

The resurrection of Tc-99m PYP scintigraphy and a subsequent multicenter study in 2016 have revolutionized the approach to diagnosing ATTR-CM. While planar imaging has been historically used, recent advances have shown how myocardial single-photon emission computed tomography (SPECT) imaging is essential to define myocardial involvement and exclude false positive scans due to blood pooling of the tracer. In addition, SPECT/computed tomography in particular provides excellent anatomical landmarks that help differentiate blood pooling versus myocardial uptake in milder and regional forms of tracer uptake. Despite its limitations, in a population with a high clinical pre-test probability for ATTR-CM, grades 2 to 3 on planar imaging combined with a negative serum evaluation for AL-CA yield a 100% positive predictive value. The use of Tc-99m PYP with SPECT can be a successful strategy in making a nontissue diagnosis of ATTR-CM when clear diffuse uptake of the tracer is present. In all other atypical imaging findings, supportive evidence should be sought from other imaging tests or tissue biopsy to avoid misdiagnosis of ATTR-CM.

**TISSUE AND ENDOMYOCARDIAL BIOPSY**

Historically, endomyocardial biopsy was required to diagnose and subtype cardiac amyloidosis. With advances...
in diagnostic imaging and evaluation of CA, endomyocardial biopsy is not required routinely for ATTR-CM patients. Biopsy in ATTR-CM is indicated in the following cases: (1) when one cannot reliably differentiate between AL and ATTR-CM, such as abnormal monoclonal protein workup in elderly individuals who are at risk for ATTR-CM or in conjunction with abnormal bone scintigraphy; (2) when imaging has atypical findings, such as borderline or negative nuclear scintigraphy in suspected patients with ATTR-CM; or (3) to evaluate for other less common forms of amyloidosis. In AL-CA, endomyocardial biopsy is more frequently required in the absence of histological confirmation from an extracardiac site. The demonstration of Congo red stained extracellular amorphous material in the presence of an amyloid clinical phenotype is diagnostic of the disease, with mass spectroscopy providing unique capabilities of subtyping the amyloid protein.67

**TRANSTHYRETIN GENE SEQUENCING**

In patients deemed to have ATTR-CM, transthyretin gene sequencing is essential to differentiate ATTRv-CM from ATTRwt-CM. It is vital to differentiate between the two subtypes because there are implications with regard to understanding disease severity, family screening, and
utilization of approved therapies. If a patient is genotype positive for a pathogenic variant, it is vital to provide genetic counseling and assess family members either for the phenotype or via cascade genetic screening. ATTRv has an autosomal dominant inheritance pattern that is age dependent with variable penetrance. Each pathogenic variant has its own unique biochemical effects and phenotype. Generally, it is recommended to start genetic testing at least 10 years prior to the onset of clinical disease in a family member or earlier if signs of clinical disease appear.

**CONCLUSION**

Cardiac amyloidosis, particularly ATTR-CM, is common in elderly patients with heart failure. Red flags exist and can be systematically incorporated into one’s own practice as simple screening tools to improve the pretest probability. It is essential to differentiate ATTR-CM from AL-CA given the vastly different treatment approach. As the noninvasive diagnosis of CA continues to evolve, improvement in the diagnosis rate of ATTR-CM with less reliance on endomyocardial biopsy as well as availability of novel therapeutics promise a better future for patients living with ATTR-CM.

**KEY POINTS**

- Transthyretin cardiac amyloidosis (CA) is a common cause of heart failure in elderly patients. Enhancing pretest probability by clinical screening of red flags improves diagnostic yield of testing.
- Transthyretin amyloid cardiomyopathy coexists with aortic stenosis.
- Light chain amyloidosis should be ruled out in all patients with CA phenotype using serum free light chain assay and direct serum and urine immunofixation electrophoresis.
- A modern approach to the noninvasive diagnosis of transthyretin CA using bone scintigraphy requires imaging with single-photon emission computed tomography.
- Cardiac magnetic resonance imaging has diverse roles in the imaging cascade of patients with left ventricular hypertrophy including CA.

**CME CREDIT OPPORTUNITY**

Houston Methodist designates this enduring material for a maximum of .25 AMA PRA Category 1 Credit™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Click to earn CME credit: [https://cvent.me/01meWq](https://cvent.me/01meWq).

**COMPETING INTERESTS**

Ahmad Masri receives research grants from Pfizer, Ionis, Akcea, and Ultromics and fees from Eidos, Pfizer, Ionis, Akcea, Alnylam, Cytokinetics, BMS, Tenaya and Attralus. There are no other disclosures.

**AUTHOR AFFILIATIONS**

Sajan S. Gill, MD  
ocid.org/0000-0002-9156-7103  
Knight Cardiovascular Institute, Oregon Health & Science University School of Medicine, Portland, Oregon, US

Eric Fellin, BS  
Oregon Health & Science University School of Medicine, Portland, Oregon, US

Lisa Stampke, BS  
Oregon Health & Science University School of Medicine, Portland, Oregon, US

Yunazi Zhao, MD, PhD  
Knight Cardiovascular Institute, Oregon Health & Science University School of Medicine, Portland, Oregon, US

Ahmad Masri, MD, MS  
ocid.org/0000-0002-6390-6526  
Knight Cardiovascular Institute, Oregon Health & Science University School of Medicine, Portland, Oregon, US

**REFERENCES**

1. Garcia-Pavia P, Rapezi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J. 2021 Apr 21;42(16):1554-1568. doi: 10.1093/eurheartj/ehab072

2. Hasserjian RP, Goodman HJB, Lachmann HJ, Muzikansky A, Hawkins PN. Bone marrow findings correlate with clinical outcome in systemic AL amyloidosis patients. Histopathology. 2007 Apr;50(5):567-73. doi: 10.1111/j.1365-2559.2007.02658.x

3. Muchtar E, Buadi FK, Dispensieri A, Gertz MA. Immunoglobulin Light-Chain Amyloidosis: From Basics to New Developments in Diagnosis, Prognosis and Therapy. Acta Haematol. 2016;135(3):172-90. doi: 10.1159/000443200

4. Eirin A, Irazabal MV, Gertz MA, et al. Clinical features of patients with immunoglobulin light chain amyloidosis (AL) with vascular-limited deposition in the kidney. Nephrol Dial Transplant. 2012 Mar;27(3):1097-101. doi: 10.1093/ndt/gfr381
5. McCausland KL, White MK, Guthrie SD, et al. Light Chain (AL) Amyloidosis: The Journey to Diagnosis. Patient. 2018 Apr;11(2):207-216. doi: 10.1007/s40271-017-0273-5

6. Nienhuis HLA, Bijjzet J, Hazenberg BPC. The prevalence and management of systemic amyloidosis in Western Countries. Kidney Dis (Basel). 2016 Apr;2(1):10-9. doi: 10.1159/000444206. Epub 2016 Feb 25. doi: 10.1159/000444206

7. Purkey HE, Dorrell MJ, Kelly JW. Evaluating the binding selectivity of transthyretin amyloid fibril inhibitors in blood plasma. Proc Natl Acad Sci U S A. 2001 May 8;98(10):5566-71. doi: 10.1073/pnas.091431798

8. Merlini G, Bellotti V. Molecular mechanisms of amyloidosis. N Engl J Med. 2003 Aug 7;349(6):583-96. doi: 10.1056/NEJMra023144

9. Nakagawa M, Sekijima Y, Yazaki M, et al. Carpal tunnel syndrome: a common initial symptom of systemic wild-type ATTR (ATTRwt) amyloidosis. Amyloid. 2016;23(1):58-63. doi: 10.3109/13506129.2015.1135792

10. Aus dem Siepen F, Hein S, Prestel S, et al. Carpal tunnel syndrome and spinal canal stenosis: harbingers of transthyretin amyloid cardiomyopathy? Clin Res Cardiol. 2019 Dec;108(12):1324-1330. doi: 10.1007/s00392-019-01467-1

11. Parman Y, Adams D, Obici L, et al. Sixty years of transthyretin familial amyloid polyneuropathy (TTR-FAP) in Europe: where are we now? A European network approach to defining the epidemiology and management patterns for TTR-FAP. Curr Opin Neurol. 2016 Feb;29 Suppl 1(Suppl 1):S3-S13. doi: 10.1097/WCO.0000000000000288

12. Moriani L-L, Lozeron P, Théaudin M, et al. Genotype-phenotype correlation and course of transthyretin familial amyloid polyneuropathies in France. Ann Neurol. 2015 Dec;78(6):901-16. doi: 10.1002/ana.24519

13. Woddington-Cruz M, Ackermann EJ, Polydefkis M, et al. Hereditary transthyretin amyloidosis: baseline characteristics of patients in the NEURO-TTR trial. Amyloid. 2018 Sep;25(3):180-188. doi: 10.1080/13506129.2018.1503593

14. Russo M, Obici L, Bartolomei I, Cappelli F, Luigetti M, Fenu S, et al. ATTRv amyloidosis. Curr Heart Fail Rep. 2016 Dec;13(6):267-272. doi: 10.1007/s11897-016-0311-y

15. Shah KB, Mankod AK, Castano A, et al. Transthyretin Cardiac Amyloidosis in Black Americans. Circ Heart Fail. 2016 Jun;9(6):e002558. doi: 10.1161/CIRCHEARTFAILURE.115.002558

16. Siddiqi OK, Ruberg FL. Cardiac amyloidosis: An update on pathophysiology, diagnosis, and treatment. Trends Cardiovasc Med. 2018 Jan;28(1):10-21. doi: 10.1016/j.tcm.2017.07.004

17. Perlini S, Mussinelli R, Salinaro F. New and Evolving Concepts Regarding the Prognosis and Treatment of Cardiac Amyloidosis. Curr Heart Fail Rep. 2018 Dec;15(6):267-272. doi: 10.1007/s11897-016-0311-y

18. Ihne S, Morbach C, Sommer C, Geier A, Knop S, Störk S. Amyloidosis: the Diagnosis and Treatment of an Underdiagnosed Disease. Dtsch Arztebl Int. 2020 Mar 6;117(10):159-166. doi: 10.3238/arztebl.2020.0159

19. Martinez-Naharro A, Hawkins PN, Fontana M. Cardiac amyloidosis. Clin Med (Lond). 2018 Apr;18(1):s30-s35. doi: 10.7861/clinmedicine.18-2-s30

20. Dispensieri A, Gertz MA, Buodi F. What do I need to know about immunoglobulin light chain (AL) amyloidosis? Blood. 2012 Jul;26(4):137-54. doi: 10.1016/j.bild.2012.03.001

21. Maurer MS, Schwartz JH, Gundapaneni B, et al. Tafamidis Treatment for Patients with Transthyretin Amyloid Cardiomyopathy. N Engl J Med. 2018 Sep 13;379(11):1007-1016. doi: 10.1056/NEJMoa1805689

22. Falck RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005 Sep 27;112(13):2047-60. doi: 10.1161/CIRCULATIONAHA.104.489187

23. Ruberg FL, Berk JL. Transthyretin (TTR) cardiac amyloidosis. Circulation. 2012 Sep 4;126(10):1286-300. doi: 10.1161/CIRCULATIONAHA.111.078915

24. Pennell DJ, Maceira AM. Magnetic resonance imaging in cardiac amyloidosis. JACC Cardiovasc Imaging. 2009 Dec;12(12):1378-80. doi: 10.1016/j.jcmg.2009.10.001

25. Dispensieri A, Merlini G. Immunoglobulin Light Chain Systemic Amyloidosis. Cancer Treat Res. 2016;169:273-318. doi: 10.1007/978-3-319-40320-5_15

26. Rahman JE, Helou EF, Gelzer-Bell R, et al. Noninvasive diagnosis of biopsy-proven cardiac amyloidosis. J Am Coll Cardiol. 2004 Feb 4;43(3):410-5. doi: 10.1016/j.jacc.2003.08.043

27. Papathanasiou M, Carpinteiro A, Rischpler C, Hagenacker T, Rassaf T, Luedike P. Diagnosing cardiac amyloidosis in every-day practice: A practical guide for the cardiologist. Int J Cardiol Heart Vasc. 2020 Apr 27;28:100519. doi: 10.1016/j.ijcha.2020.100519

28. Pagourelis ED, Mirea O, Duchenne J, et al. Echo Parameters for Differential Diagnosis in Cardiac Amyloidosis: A Head-to-Head Comparison of Deformation and Nondeformation Parameters. Circ Cardiovasc Imaging. 2017 Mar;10(3):e005588. doi: 10.1161/CIRCIMAGING.116.005588

29. Castaño A, Narotsky DL, Hamid N, et al. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J. 2017 Oct 7;38(38):2879-2887. doi: 10.1093/eurheartj/ehx350

30. Carroll JD, Goasch WH, McAdam KP. Amyloid cardiomyopathy: characterization by a distinctive voltage/
mass relation. Am J Cardiol. 1982 Jan;49(1):9-13. doi: 10.1016/0002-9149(82)90270-3

32. Murtagh B, Hammill SC, Gertz MA, Kyle RA, Tajik AJ, Grogan M. Electrocardiographic findings in primary systemic amyloidosis and biopsy-proven cardiac involvement. Am J Cardiol. 2005 Feb 15;95(4):535-7. doi: 10.1016/j.amjcard.2004.10.028

33. Cyrille NB, Goldsmith J, Alvarez J, Maurer MS. Prevalence and prognostic significance of low QRS voltage among the three main types of cardiac amyloidosis. Am J Cardiol. 2014 Oct 1;114(7):1089-93. doi: 10.1016/j.amjcard.2014.07.026

34. Mussinelli R, Salinaro F, Allegna A, et al. Diagnostic and prognostic value of low QRS voltages in cardiac AL amyloidosis. Ann Noninvasive Electrocardiol. 2013 May;18(3):271-80. doi: 10.1111/ane.12036

35. Dungu JN, Papadopoulou SA, Wykes K, et al. Afro-Caribbean Heart Failure in the United Kingdom: Cause, Outcomes, and ATTR V122I Cardiac Amyloidosis. Circ Heart Fail. 2016 Sep;9(9):e003352. doi: 10.1161/CIRCHEARTFAILURE.116.003352

36. Treibel TA, Fontana M, Gilbertson JA, et al. Occult Transthyretin Cardiac Amyloid in Severe Calcific Aortic Stenosis: Prevalence and Prognosis in Patients Undergoing Surgical Aortic Valve Replacement. Circ Cardiovasc Imaging. 2016 Aug;9(8):e005066. doi: 10.1161/CIRCIMAGING.116.005066

37. Rosenblum H, Masri A, Narotsky DL, et al. Unveiling outcomes in coexisting severe aortic stenosis and transthyretin cardiac amyloidosis. Eur J Heart Fail. 2016 Feb;23(2):250-258. doi: 10.1002/ehj.1974

38. Nitsche C, Scully PR, Patel KP, et al. Prevalence and Outcomes of Concomitant Aortic Stenosis and Cardiac Amyloidosis. J Am Coll Cardiol. 2021 Jan 19;77(2):128-139. doi: 10.1016/j.jacc.2020.11.006

39. Takashio S, Yamamuro M, Izumiya Y, et al. Diagnostic utility of cardiac troponin T level in patients with cardiac amyloidosis. ESC Heart Fail. 2018 Mar;25(1):62-67. doi: 10.1002/ejhf.1043

40. Donnelly JP, Hanna M. Cardiac amyloidosis: An update on diagnosis and treatment. Cleve Clin J Med. 2017 Dec;84(12 Suppl 3):12-26. doi: 10.3949/ccjm.2017.0007

41. Natural History of Wild-Type Transthyretin Cardiac Amyloidosis and Risk Stratification Using a Novel Staging System. J Am Coll Cardiol. 2016 Sep 6;68(10):1014-20. doi: 10.1016/j.jacc.2016.06.033

42. Kreussler MM, Volz MJ, Knop B, et al. A novel risk score to predict survival in advanced heart failure due to cardiac amyloidosis. Clin Res Cardiol. 2020 Jun;109(6):700-713. doi: 10.1007/s00392-019-01559-y

43. Dispenzieri A, Gertz MA, Kyle RA, et al. Serum cardiac troponins and N-terminal pro-brain natriuretic peptide: a staging system for primary systemic amyloidosis. J Clin Oncol. 2004 Sep 15;22(18):3751-7. doi: 10.1200/JCO.2004.03.029

44. Gillmore JD, Damy T, Fontana M, et al. A new staging system for cardiac transthyretin amyloidosis. Eur Heart J. 2018 Aug;39(30):2799-2806. doi: 10.1093/eurheartj/ehx589

45. Bonderman D, Püzl G, Ablasser K, et al. Diagnosis and treatment of cardiac amyloidosis: an interdisciplinary consensus statement. Wien Klin Wochenschr. 2020 Dec;132(23-24):742-761. doi: 10.1007/s00508-020-01781-z

46. Palladini G, Russo P, Bosoni T, et al. Identification of amyloidogenic light chains requires the combination of serum-free light chain assay with immunofixation of serum and urine. Clin Chem. 2009 Mar;55(3):499-504. doi: 10.1373/clinchem.2008.117143

47. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin Amyloid Cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol. 2019 Jun 11;73(22):2872-2891. doi: 10.1016/j.jacc.2019.04.003

48. Phull P, Sanchorawala V, Connors LH, et al. Monoclonal gammapathy of undetermined significance in systemic transthyretin amyloidosis (ATTR). Amyloid. 2018 Mar;25(1):62-67. doi: 10.1080/13506129.2018.1436048

49. Singh G. Serum Free Light Chain Assay and κ/λ. Ratio Performance in Patients Without Monoclonal Gammapathies: High False-Positive Rate. Am J Clin Pathol. 2016 Aug;146(2):207-14. doi: 10.1093/ajcp/qqw099

50. Abadie JM, van Hoeven KH, Wells JM. Are renal reference intervals required when screening for plasma cell disorders with serum free light chains and serum protein electrophoresis? Am J Clin Pathol. 2009 Feb;131(2):166-71. doi: 10.1309/AJCPR2MEUVNHLGM

51. Marshall G, Tate J, Mollee P. Borderline high serum free light chain kappa/lambda ratios are seen not only in dialysis patients but also in non-dialysis-dependent renal impairment and inflammatory states. Am J Clin Pathol. 2009 Aug 13;132(2):309. doi: 10.1309/AJCPBVOT5TVLAAQBO

52. Hansson JLS, Arvanitis M, Koch CM, et al. Use of Serum Transthyretin as a Prognostic Indicator and Predictor of Outcome in Cardiac Amyloid Disease Associated With Wild-Type Transthyretin. Circ Heart Fail. 2018 Feb;11(2):e004000. doi: 10.1161/CIRCHEARTFAILURE.117.004000

53. Saith SE, Gamino D, Teruya S, et al. Factors associated with changes in serum transthyretin after treatment with tafamidis and outcomes in transthyretin cardiac amyloidosis. Amyloid. 2021 Dec;28(4):267-268. doi: 10.1080/13506129.2021.1904390

54. Arvanitis M, Koch CM, Chan GG, et al. Identification of Transthyretin Cardiac Amyloidosis Using Serum Retinol-Binding Protein 4 and a Clinical Prediction Model. JAMA Cardiol. 2017 Mar 1;2(3):305-313. doi: 10.1001/jamacardio.2016.5864
55. Gillmore JD, Maurer MS, Falk RH, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016 Jun 14;133(24):2404-12. doi: 10.1161/CIRCULATIONAHA.116.021612

56. Brownrigg J, Lorenzini M, Lumley M, Elliott P. Diagnostic performance of imaging investigations in detecting and differentiating cardiac amyloidosis: a systematic review and meta-analysis. ESC Heart Fail. 2019 Oct;6(5):1041-1051. doi: 10.1002/ehf2.12511

57. Pucci A, Aimo A, Musetti V, et al. Amyloid Deposits and Fibrosis on Left Ventricular Endomyocardial Biopsy Correlate With Extracellular Volume in Cardiac Amyloidosis. J Am Heart Assoc. 2021 Oct 19;10(20):e020358. doi: 10.1161/JAHA.120.020358

58. Maceira AM, Joshi J, Prasad SK. Cardiovascular magnetic resonance in cardiac amyloidosis. Circulation. 2005 Jan 18;111(2):186-93. doi: 10.1161/01.CIR.0000152819.97857.9D

59. Baggiano A, Boldrini M, Martínez-Naharro A, et al. Noncontrast Magnetic Resonance for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovasc Imaging. 2020 Jan;13(1 Pt 1):69-80. doi: 10.1016/j.jcmg.2019.03.026

60. Martínez-Naharro A, Treibel TA, Abdel-Gadir A, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. J Am Coll Cardiol. 2017 Jul 25;70(4):466-477. doi: 10.1016/j.jacc.2017.05.053

61. Dorbala S, Ando Y, Bokhari S, et al. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI Expert Consensus Recommendations for Multimodality Imaging in Cardiac Amyloidosis: Part 2 of 2-Diagnostic Criteria and Appropriate Utilization. Circ Cardiovasc Imaging. 2021 Jul;14(7):e000030. doi: 10.1161/CIRCIMAGING.119.010249

62. Bokhari S, Castaño A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging. 2013 Mar;6(2):195-201. doi: 10.1161/CIRCIMAGING.112.000132

63. Poterucha TJ, Elias P, Bokhari S, et al. Diagnosing Transthyretin Cardiac Amyloidosis by Technetium Tc 99m Pyrophosphate: A Test in Evolution. JACC Cardiovasc Imaging. 2021 Jun;14(6):1221-1231. doi: 10.1016/j.jcmg.2020.08.027

64. Alexander KM, Masri A. Recipe for Success in Transthyretin Cardiomyopathy: Monoclonal Protein Rule Out, SPECT Imaging, and Genetic Testing. JACC Cardiovasc Imaging. 2021 Jun;14(6):1232-1234. doi: 10.1016/j.jcmg.2020.09.009

65. Masri A, Bukhari S, Ahmed S, et al. Efficient 1-Hour Technetium-99 m Pyrophosphate Imaging Protocol for the Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Cardiovasc Imaging. 2020 Feb;13(2):e010249. doi: 10.1161/CIRCIMAGING.119.010249

66. Duvall WL, Goday Rivas C, Elsadany M, Hobocan M, Mcmahon S. The use of a novel method for SPECT/CT quantification of 99m-Tc-PYP uptake in the evaluation of ATTR cardiac amyloidosis. Eur Heart J Cardiovasc Imaging. 2021 Jul 20;22(Suppl 3). doi: 10.1093/ehjci/jeab111.075

67. Dasari S, Theis JD, Vrana JA, et al. Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples. Mayo Clin Proc. 2020 Sep;95(9):1852-1864. doi: 10.1016/j.mayocp.2020.06.029

68. Adams D, Gonzalez-Duarte A, O’Riordan WD, et al. Patisiran, an RNAi Therapeutic, for Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):11-21. doi: 10.1056/NEJMoa1716153

69. Benson MD, Waddington-Cruz M, Berk JT, et al. Inotersen Treatment for Patients with Hereditary Transthyretin Amyloidosis. N Engl J Med. 2018 Jul 5;379(1):22-31. doi: 10.1056/NEJMoa1716793

TO CITE THIS ARTICLE:
Gill SS, Fellin E, Stampke L, Zhao Y, Masri A. Clinical Clues and Diagnostic Workup of Cardiac Amyloidosis. Methodist DeBakey Cardiovasc J. 2022;18(2):36-46. doi: 10.14797/mdcvj.1061

Submitted: 12 November 2021 Accepted: 10 February 2022 Published: 14 March 2022

COPYRIGHT:
© 2022 The Author(s). This is an open-access article distributed under the terms of the Attribution-NonCommercial 4.0 International (CC BY-NC 4.0), which permits unrestricted use, distribution, and reproduction in any noncommercial medium, provided the original author and source are credited. See https://creativecommons.org/licenses/by-nc/4.0/.
Methodist DeBakey Cardiovascular Journal is a peer-reviewed open access journal published by Houston Methodist DeBakey Heart & Vascular Center.