Original Article

Cardiac Amyloidosis in South India: A Tertiary Care Centre Experience

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Abstract

Background: Cardiac amyloidosis (CA), a rare entity, is underappreciated as a cause of common cardiac diseases. Most of the data in India focuses on the amyloid light chain (AL) type of amyloidosis. The amyloid transthyretin (ATTR) type is not well recognized. **Materials and Methods:** This study aimed to highlight the clinical characteristics, diagnostic approach, and type of CA from the retrospective analysis of electronic medical records (EMR) of 31 patients. EMRs of the patients diagnosed with CA at a tertiary care Centre in South India between 2015 and 2022 were retrospectively analyzed. **Results:** The mean age is 64.5 ± 12.51 years, with a male preponderance. Heart failure was the most common cardiac presentation. Forty-five percent had heart failure with preserved ejection fraction, and 29% had heart failure with reduced ejection fraction. Arrhythmias were present in 48%, of which two-thirds had atrial arrhythmias. Extracardiac manifestations of amyloidosis included hepatic dysfunction, peripheral polyneuropathy, and macroglossia. Orthostatic hypotension was seen in 22.5%. Electrocardiogram findings included low-voltage QRS complexes and a pseudo-infarct pattern. Bi-atrial involvement (41.9%), Myocardial speckle appearance (32.2%), and abnormal global longitudinal strain (GLS) with apical sparing (87.5%) on echocardiography favored CA. The median GLS is -9.6%. Cardiac magnetic resonance imaging reported characteristic late gadolinium enhancement in 38.4%. ^{99m}Tc Pyrophosphate scans demonstrated positive pyrophosphate uptake in 20 patients. Rectal, pericardial, lingual, and gastric biopsies confirmed the diagnosis in one-fifth of patients. Plasma cell dyscrasias in bone marrow biopsy confirmed light chain amyloidosis. ATTR type was the most common type, confirmed in 41.9% (13) patients, followed by AL type in 32.2% (10) patients. Our study showed that 9.6% (three) patients were positive for hematological tests and demonstrated scintigraphy Grades 2 and 3 uptakes in ^{99m}Tc Pyrophosphate scan. Chemotherapy for plasma dyscrasias was administered to 34.2% of patients. One out of 13 ATTR types received tafamidis. **Conclusions:** The diagnosis of CA is challenging as it frequently presents nonspecific signs and symptoms. The emerging diagnostic modalities, including advances in cardiac imaging favoring early diagnosis and the growing availability of disease-modifying drugs, especially specific therapies targeting transthyretin amyloidosis, may improve this entity's prognosis.

Keywords: Cardiac amyloidosis, AL amyloidosis, ATTR amyloidosis, transthyretin, diagnosis

Key Message: The awareness of cardiac amyloidosis can enable its early diagnosis and help improve the survival and prognosis with timely initiated chemotherapy.

Introduction

Cardiac amyloidosis (CA) is characterized by extracellular deposition of the misfolded precursor proteins as fibrillary amyloid deposits in cardiac tissues. More than 98% of CA results from fibrils composed of monoclonal immunoglobulin amyloid light chains (AL) or amyloid transthyretin (ATTR). CA, secondary to chronic inflammatory and infectious diseases (AA) is less frequent.[1] Cardiac amyloid is an uncommon cause of restrictive cardiomyopathy (RCMP) in India and is usually fatal. Forty percent of the patients with cardiac involvement

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die from heart failure or rhythm disturbances.[2] Data on cardiac amyloid from India is lacking.

The aim of the study was to discuss the clinicopathological and investigational features of 31 patients who presented with CA in a tertiary care center in South India.

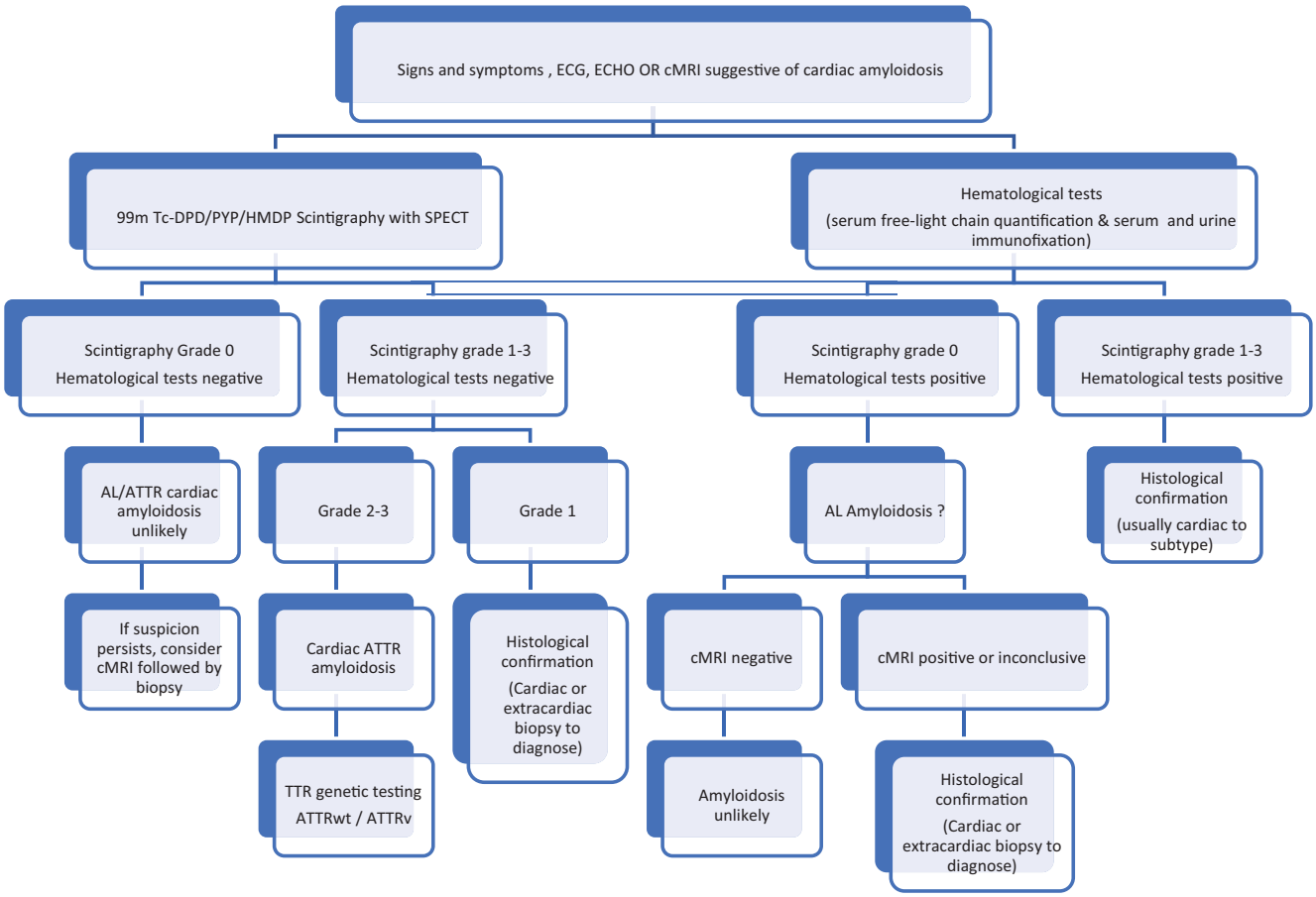
Methods and Materials

This is a retrospective study that was conducted at a tertiary care center in South India, covering the period from 2015 to 2022. The study included 31 cases of histopathologically diagnosed CA. Institutional ethics committee clearance was obtained. After informed verbal consent from the eligible patients, electronic medical records were accessed to retrieve the clinical and investigational data. The data were analyzed using SSPS IBM software version 25 (IBM SPSS Statistics for Windows, Version 25.0., manufactured by Armonk, NY: IBM Corporation).

CA was suspected based on clinical signs and symptoms of heart failure. The high values of N-terminal pro-B-type natriuretic peptide, persistent troponin elevation, and disproportionally low QRS voltage in electrocardiogram (ECG) despite left ventricular hypertrophy (LVH) in ECHO or early conduction system disease are the red flag signs that could cling to the diagnosis of CA.[1] In our patients, ECG was screened for arrhythmias and voltage waveforms. Detailed echocardiography with tissue Doppler, speckled tracking, and 3D echocardiography were reviewed for ventricular wall hypertrophy and function, valvular thickening, diastolic dysfunction (DD), myocardial speckle appearance, and GLS. Cardiac magnetic resonance imaging (cMRI) (available for 13 cases) was reviewed for late gadolinium enhancement (LGE), and nuclear imaging with ^{99m}Tc PYP scan (available for 22 cases) was reviewed for scintigraphy uptake of Grades 2 and 3.

The proposed diagnostic algorithm [Flowchart 1] was focused on identifying the amyloid subtypes by incorporating the initial use of 99mTc-PYP, DPD, or HMDP scintigraphy along with assessment for monoclonal proteins by SPIE, UPIE, and quantification of serum free light chains. The results of these tests had four possible scenarios:

(1) Scintigraphy didn't show cardiac uptake and assessments for monoclonal proteins were negative—these



Flowchart 1: Showing Diagnostic algorithm for CA as per Garcia-Pavia *et al.*[1] in an ESC myocardial working group position paper (Abbreviations: AL—light-chain amyloidosis, ATTR—transthyretin amyloidosis, ATTRv—hereditary transthyretin amyloidosis, ATTRwt—wild-type transthyretin amyloidosis, cMRI—cardiac magnetic resonance imaging, ECG—electrocardiogram, SPECT—single photon emission computed tomography, TTR—transthyretin)

suggested a very low probability of CA, and therefore an alternative diagnosis was to be considered. However, in case of suspicion, cMRI followed by cardiac or extracardiac biopsy was recommended.

(2) Scintigraphy showed cardiac uptake and assessments for monoclonal proteins were negative—if cardiac uptake was Grade 2 or 3, ATTR CA was confirmed, and they were advised for genetic testing to differentiate between ATTRv and ATTRwt forms. If cardiac uptake was Grade 1, an invasive diagnosis with histological confirmation of amyloid deposits (cardiac or extracardiac) was required.

(3) Scintigraphy didn't show cardiac uptake and at least one of the monoclonal protein tests was abnormal—this group was suspected of light-chain amyloidosis, and cMRI was performed to confirm the cardiac involvement. Negative cMRI ruled out CA. In case of positive or inconclusive cMRI, cardiac or extracardiac histological demonstration of amyloid deposits was required to confirm AL CA. A cardiac or other clinically affected organ biopsy was done. If cMRI could not be performed, direct biopsy was performed.

(4) Scintigraphy showed cardiac uptake, and at least one of the monoclonal protein tests was abnormal—the differentials included transthyretin amyloidosis with concomitant MGUS (or any hematological disorder that produces FLC), AL amyloidosis, or coexistence of both AL and ATTR amyloidosis. The confirmation of the diagnosis of CA warranted histology with amyloid typing, usually via endomyocardial biopsy (EMB).

In our study, histopathological diagnosis was achieved with rectal, pericardial, lingual, and gastric biopsy in one case each, bone marrow biopsy in 14 cases, and additional EMB in 1 case. The data were classified for amyloid distribution based on hematoxylin and eosin staining and Congo red staining of the interstitial and vascular deposits.[1]

The diagnosis and treatment of CA were based on the invasive and noninvasive diagnostic criteria proposed by Garcia-Pavia *et al.*[1] in an ESC myocardial working group position paper. Among the different methods proposed to prognosticate CA, the biomarker-based Mayo staging system developed by Kumar *et al.*[3] was used.

Results

The data of 31 patients were analyzed. The majority of the patients were males (51.6%). The age range was 40–91 years of age. The mean age is 64.5 ± 12.51 years. Among the associated chronic comorbidities, 38.7% had hypertension, 32.3% had diabetes mellitus, 12.9% had dyslipidemia, 25.8% had coronary artery disease, 16.1% had chronic kidney disease on hemodialysis, 9.7% had bronchial asthma, 3.2% had a previous history of stroke. Two had a previous history of pulmonary TB. Overall, 25.8% (n = 8) were diagnosed to have an associated tumor. None of them had any history of amyloidosis in family members.

Blood pressure measurement on presentation revealed that 22.6% (n = 7) had orthostatic hypotension (OH), and 16.1% (n = 5) cases who were previously hypertensive were found to be normotensive.

Ninety percent patients presented with cardiac manifestations, heart failure being the most common manifestation. Forty-two percent (n = 13) presented with heart failure with preserved ejection fraction (HFpEF), and 25.8% (n = 8) presented with heart failure with reduced ejection fraction (HFrEF). Arrhythmias were present in 48.4% (n = 15) of patients. One patient presented with infective endocarditis. Three patients did not have cardiac symptoms but had presented with extracardiac manifestations, and their echocardiographic features were suggestive of restrictive physiology, whose further workup led to the diagnosis of AL amyloidosis with multiple myeloma in two patients and equivocal ATTR in one patient. Extracardiac manifestations of amyloidosis were seen in 71% (n = 22) patients, which included renal involvement, gastrointestinal (GI) involvement with hepatic dysfunction, peripheral polyneuropathy, and macroglossia. Among the thyroid abnormalities, 5.2% (n = 14) had hypothyroidism, and 6.5% (n = 2) had hyperthyroidism [Table 1].

Among the electrocardiographic findings, ECG abnormalities were seen in 67.7% of cases. QTc prolongation (QTc interval greater than 440 ms in men and greater than 460 ms in women) was the most common finding in 45.2% (n = 14). Other ECG features seen were low voltage QRS complexes, pseudo infarct pattern, and bundle branch blocks (QRS greater than 120 ms). 12.9% (n = 4) had atrioventricular (AV) blocks, of which

Table 1: Cardiac and extracardiac manifestations in patients

Cardiac manifestations n = 28 (90.3%)	Number of patients, n (%)
HFpEF	13 (41.9%)
HFrEF	8 (25.8%)
Infective endocarditis	1 (3.2%)
Arrythmias	15 (48.4%)
Extracardiac manifestations, n = 22 (71%)	**Number of patients, n (%)**
Hypothyroidism	14 (45.2%)
Hyperthyroidism	2 (6.5%)
Renal amyloid	3 (9.7%)
GI amyloid with hepatic dysfunction	9 (29%)
Peripheral polyneuropathy	2 (6.5%)
Macroglossia	1 (3.2%)
Periorbital ecchymosis	0 (0%)

GI: gastrointestinal, HFpEF: heart failure with preserved ejection fraction, HFrEF: heart failure with reduced ejection fraction

Table 2: Analysis of ECG data

ECG features	Number of patients, *n* (%)
ECG abnormalities	21 (67.7%)
QTc prolongation	14 (45.2%)
Low voltage QRS complexes	5 (16.1%)
Pseudo-infarct pattern	5 (16.1%)
Arrhythmias	15 (48.4%)
Atrial fibrillation	10 (32.3%)
Atrial flutter	2 (6.5%)
Frequent VPCs	2 (6.5%)
Ventricular bigeminy	1 (3.2%)
VT	1 (3.2%)
AV conduction defects	4 (12.9%)
First-degree AV block	3 (9.7%)
Second-degree AV block	1 (3.2%)
LBBB	5 (16.1%)
RBBB	2 (6.5%)

ECG: electrocardiogram, QTc: corrected QT interval, VPCs: ventricular premature beats, VT: ventricular tachycardia, AV: atrioventricular, LBBB: left bundle branch block, RBBB: right bundle branch block

Table 3: Analysis of trans-thoracic echocardiographic data

TTE features	Number of patients, *n* (%)
Ventricular hypertrophy	27 (87.0%)
Isolated LVH (LVWT >12 mm)	15 (48.3%)
Isolated RVH (RVFWT >5 mm)	4 (12.9%)
BVH	9 (29%)
Decreased LVEF (<50%)	10 (32.2%)
Decreased RV function (FAC <35%)	5 (16.1%)
Isolated LA enlargement	4 (12.9%)
Isolated RA enlargement	1 (3.2%)
Bi-atrial enlargement (BAE)	13 (41.9%)
Thickened IAS	6 (19.4%)
Thickened AV valves	3 (9.7%)
AV sclerosis	6 (19.4%)
Myocardial speckle appearance	10 (32.3%)
LV diastolic dysfunction (DD)	29 (93.5%)
Elevated LV filling pressures (E/e'>15)	20 (64.5%)
Abnormal GLS (<-15%) with Apical sparing	14 out of 16 available data (87.5%) (median -9.3%)
Pulmonary artery hypertension	11 (35.4%)
Pericardial effusion (PE)	15 (48.3%)
LV thrombus	1 (3%)
RA apical obliteration	11 (35.5%)

TTE: trans-thoracic echocardiography, BAE: bi-atrial enlargement, LV: left ventricle, RV: right ventricle, LVH: left ventricular hypertrophy, RVH: right ventricular hypertrophy, LVWT: left ventricle wall thickness, RVFWT: right ventricle free wall thickness, BVH: biventricular hypertrophy, LVEF: left ventricular ejection fraction, FAC: fractional area change, IVS: interventricular septum, IAS: interatrial septum, AV: atrio-ventricular, GLS: global longitudinal strain, DD: diastolic dysfunction, PE: pericardial effusion, LA: left atrium, RA: right atrium

three patients had 1st-degree AV block with PR interval greater than 200 ms, and one patient had a 2:1 AV block. Arrhythmias were present in 48.4% (n = 15) patients, of which 38.8% had atrial arrhythmias and 12.9% had ventricular arrhythmias. Among the atrial arrhythmias, atrial fibrillation with a fast ventricular rate was most common, seen in 32.3% of patients requiring electrical cardioversion [Table 2].

The echocardiographic findings suggestive of restrictive physiology were present in 93.5% (n = 29) patients in our study. These included: 48.3% (n = 15) had unexplained LVH, and 12.9% (n = 4) had increased right ventricular free wall thickness (RVFWT). Left and right ventricular systolic dysfunction was seen in 32.2% (n = 10) and 17.1% (n = 6), respectively. Of the LV dysfunction, mild and moderate LV dysfunction was seen in 16.1% (n = 5) each; the rest patients had normal LV function. Pulmonary artery hypertension (PAH) was seen in 35.4% (n = 11), of which eight had mild, one had moderate, and two had severe PAH. Atrial involvement was seen in 58% (n = 18) of patients, of which bi-atrial dilatation was the most common (41.3%, n = 13). Other restrictive features on ECHO included elevated LV filling pressures and higher grades of DD (grade III DD in 29%, n = 9 patients; grade IV DD in 6.45%, n = 2 patients). Myocardial speckle appearance was seen in 32.3% (n = 10) patients. Abnormal global longitudinal strain (GLS < -15%) with apical sparing (Cherry on top appearance) was evident in 87.5% (n = 14 out of 16 available data). Median GLS being -9.3%. Other echocardiographic features included pericardial effusion and thickening of the interatrial septum (IAS) and AV valves. Anterior mitral leaflet thickening was the most common, followed by aortic valve sclerosis [Table 3, Figure 1].

Among the biochemical findings, 25.8% (n = 8) had renal insufficiency (defined by KDIGO); however, proteinuria was demonstrated in 54.8% (n = 17). A serum-free light chain assay revealed elevated lambda and kappa light chains in 67.8% (n = 19 out of 28 available data). Serum immunofixation (SIFE) was positive in 37.9% (n = 11 out of 29 available data), demonstrating IgG lambda monoclonal gammopathy in most cases. Urine immunofixation was positive in only 16.6% (n = 5 out of 30 available data). Beta 2 microglobulin was elevated in 1 case. Among the cardiac markers, NTproBNP levels more than 1800 pg/l were seen in 63.1% (n = 12 out of 19 available data), and elevated high sensitive troponin I level (HsTrop I > 40 ng/l) was seen in 30.7% (n = 4 out of 13 available data).

The MRI was performed in 13 out of 31 patients, revealing atrial and ventricular dilatation, concentric LV hypertrophy, and subendocardial LGE in LV, RV in 38.4% (n = 5 out of 13) [Figure 2].

The ^{99m}Tc Pyrophosphate scan data was available for 22 out of 31 patients, demonstrating positive pyrophosphate (PYP) uptake of Grade 2 in 31.8% (n = 7) and Grade 3 in

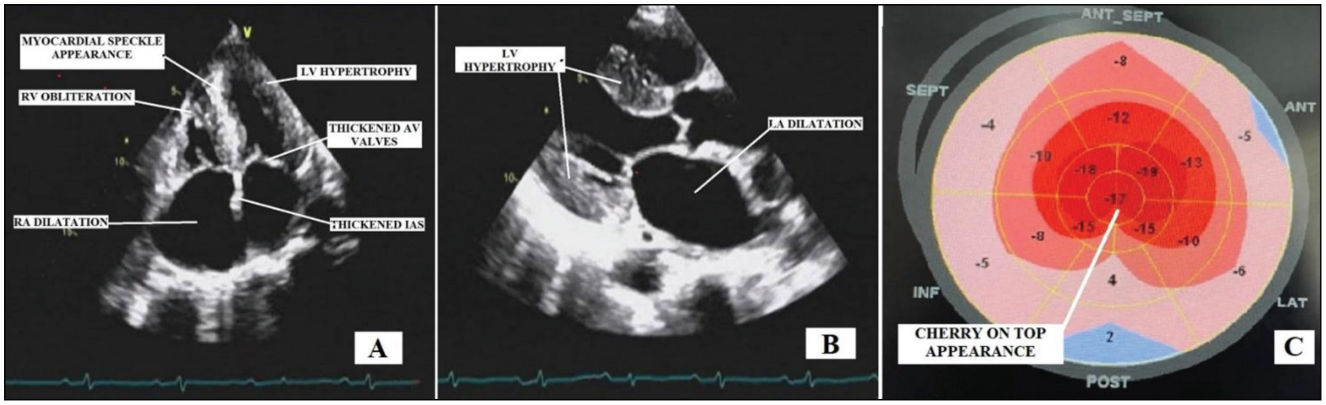


Figure 1: Two-dimensional trans-thoracic echocardiography (A) apical four-chamber view showing LVH, thickened IAS and AV valves, right atrial dilatation, and RV apical obliteration (single arrows). (B) Parasternal long axis view showing LVH (red arrow), LA dilatation. (C) Strain rate imaging of LV showing abnormal GLS with apical sparing—"Cherry on top" appearance. Abbreviations: LV: left ventricle, LA: left atrium, RA: right atrium, RV: right ventricle, IVS: interventricular septum, IAS: interatrial septum, AV: atrio-ventricular

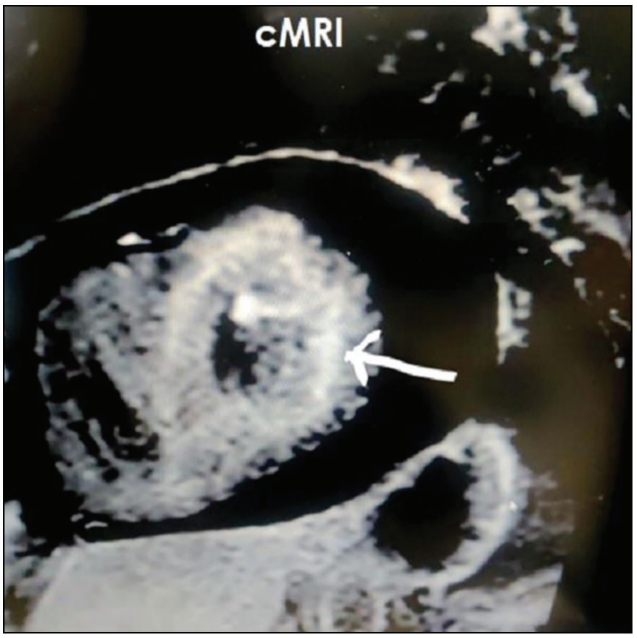


Figure 2: cMRI showing subendocardial LGE of LV, RV, and concentric LVH (single white arrow). Abbreviations: cMRI: cardiac magnetic resonance imaging, LV: left ventricle, RV: right ventricle

36.6% (n = 8) out of 22 patients, confirming the diagnosis of ATTR type of amyloidosis. Five patients (16.1%) were equivocal for ATTR with Grade 1 PYP uptake [Table 4, Figure 3].

Extracardiac tissue biopsy to confirm amyloid deposits included pericardial (n = 1), rectal (n = 1), renal (n = 5), gastric (n = 2), and lingual (n = 1) biopsy. EMB was positive for amyloid deposit in one patient, demonstrating predominant interstitial deposition. Bone marrow aspiration and bone marrow biopsy were performed in 14 out of 31 patients, demonstrating plasmacytosis and amyloid deposits in 85.7% (n = 12 out of 14 patients). Serum protein electrophoresis confirmed the diagnosis of multiple myeloma in 85.7% (n = 12) patients [Figure 4].

Table 4: Type of amyloidosis and Prognosis by Mayo Clinic staging of amyloidosis

Type of amyloidosis	Number of patients, *n* (%)
ATTR amyloidosis	13 (41.9%)
AL amyloidosis	10 (32%)
AL + ATTR amyloidosis	3 (9.6%)
Equivocal for ATTR	5 (16.1%)
Prognosis by Mayo Clinic staging of amyloidosis	**Number of patients, *n* (%) (data available for 10 patients only)**
Stage I	2 (20%)
Stage II	2 (20%)
Stage III	5 (50%)
Stage IV	1 (10%)

The most common type of amyloidosis in our study was the ATTR type, confirmed in 41.9% (n = 13) patients, followed by the AL type, confirmed in 32.2% (n = 10) patients. However, 9.6% (n = 3) patients were positive for the immunofixation test as well as demonstrated by scintigraphy Grades 2–3 uptake in 99mTc pyrophosphate scan, they were advised EMB to confirm the amyloid type, but they were not willing for the same. 16.1% (n = 5) were equivocal for ATTR. In these cases, histological confirmation of amyloid deposits either via cardiac or extracardiac biopsy was recommended; however, it could not be accomplished since two patients were not willing for invasive testing, and three were lost to follow-up [Table 4].

All the patients diagnosed with AL type of amyloidosis with associated multiple myeloma were started on CyBorD (cyclophosphamide, bortezomib, and dexamethasone) regimen, whereas patients diagnosed with ATTR amyloidosis were initiated on conservative management. One of the patients with ATTR amyloidosis received Tafamidis therapy. The prognosis of patients (those with will all the available data, n - 10) was assessed by the Mayo Clinic staging of amyloidosis.[1] The assessment showed that 50% (5 out of 10) were in stage III [Table 4].

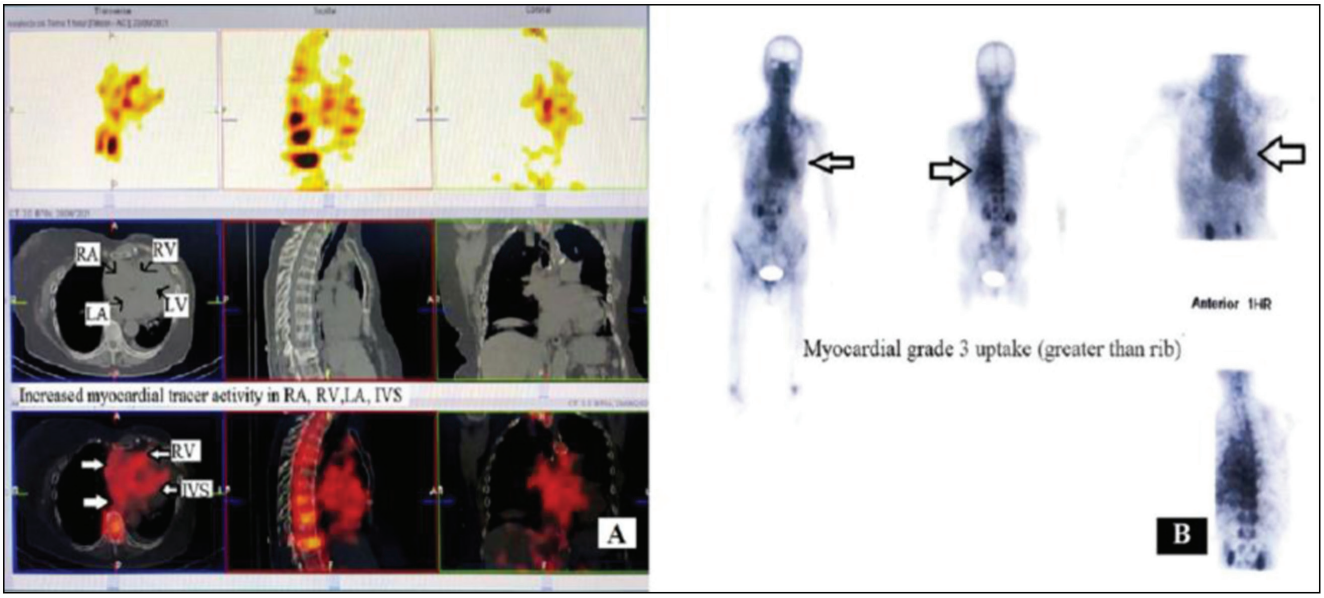


Figure 3: ^{99m}Tc Pyrophosphate scintigraphy for cardiac amyloidosis (A) SPECT-CT showing increased myocardial tracer activity in the RA, LA, RV, and IVS (solid white arrows), (B) Semiquantitative visual grading of myocardial ^{99m}Tc PYP uptake in comparison to rib uptake—grade 3 (more than rib) (black arrows). Abbreviations: LV: left ventricle, LA: left atrium, RA: right atrium, RV: right ventricle, IVS: interventricular septum, SPECT-CT: single photon emission computed tomography

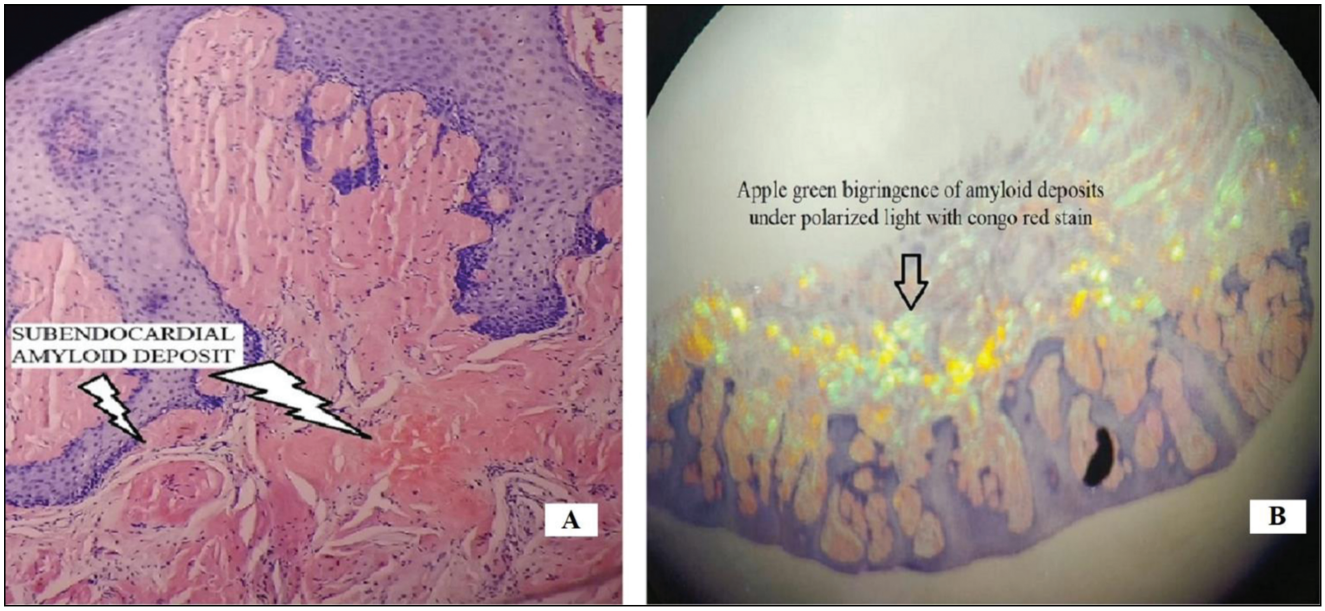


Figure 4: Histopathological section: (A) subendocardial deposits of amyloid material (H and E) (solid white arrows), (B) apple green birefringence of amyloid deposits on polarized microscopy on Congo red stain (black arrow)

Discussion

CA is an uncommon cause of restrictive cardiomyopathy, which is difficult to diagnose and treat. The delay in recognition and treatment further adds to its poor prognosis. Its diagnosis is difficult due to diverse manifestations leading to the patients presenting to different specialties, lack of clinical suspicion, non-availability of uniform recommendations to guide diagnosis and interpretation of CA, and financial constraints in a developing country like India for procuring specific therapies like Tafamidis.

In this retrospective clinicopathological study, we have described the findings of 31 CA patients diagnosed using the algorithm of diagnostic criteria proposed by Garcia-Pavia *et al.*[1] in an ESC myocardial working group position paper. Most presented with heart failure symptoms and low ECG voltages, although LV or biventricular

hypertrophy on echocardiogram raised clinical suspicion. Most had preserved LV function but abnormal GLS with apical sparing on TTE.

Our cardiac amyloid patients could not be subcharacterized into subtypes, but the most common type of cardiac amyloid reported was transthyretin amyloidosis, whereas the AL type was less common. Similar results were reported by Griffin *et al.*[4] and Kapoor *et al.*[5] However, our results were contrary to those reported by Raut *et al.*[6] and Agarwal *et al.*[2] The true incidence of wild-type ATTR is probably underestimated. Owing to the rising age demographic and recent developments in cMRI and PYP scans, there has been immense improvement in the detection rate of cardiac amyloid during life, suggesting that wild-type ATTR is more common than previously thought. Our case series is the second largest data on CA from our country, but the first one to report ATTR type as the most common CA in South India and also the first of its kind to highlight the importance of a PYP scan in diagnosing ATTR amyloidosis.

Both AL and the wild-type ATTR and ATTR due to Val122Ile are diseases of more than 60-year age group,[6,7] AL being most common in the 6th and 7th decade, but ATTR can occur as early as the third or fourth decade.[7] In our series, the youngest patient was 40 years, the age range was 40–91, and the mean age was 64.5 ± 12.51 years. AL was most reported in the 6th and 7th decades. In contrast, a bimodal distribution was seen in the ATTR type involving the 4th decade and age group more than 70 years, which is similar to the Western data by Ochi *et al.*[8] as well as that by Banypersad *et al.*[7] However, the patient population in the case series reported by Raut *et al.*[6] and Agarwal *et al.*[2] was younger than our study (median age is 51 years and 53 years, respectively).

Cardiac amyloid distribution in our study showed a strong female preponderance, similar to that found in a study by Ochi *et al.*[8] and a Spanish and Italian cohort study by González-López *et al.*[9] However, a strong male predominance in wild-type ATTR (ATTRwt) was reported by other Indian case series[2,6,7] and some Western series.[10,11] These differences in clinical features may have resulted from a bias in patient cohorts from referral tertiary centers or community-based medical facilities. Furthermore, the use of noninvasive diagnostic modalities, including 99 mTc-labeled scintigraphy, in the present study and the studies by Ochi *et al.*[8] and González-López *et al.*[9] have increased the rate of diagnosis of female ATTRwt patients.

Twenty-six percent of our CA patients presenting with anginal chest pain were labeled as CAD on conventional or 640-slice CT coronary angiography. Among them, the majority (75%, n = 6) had insignificant/mild CAD on medical management, and only 25% (n = 2) required revascularization. Michelle *et al.*[12] reported that patients with CA experiencing anginal pain have no significant atherosclerotic epicardial coronary stenosis. Dorbala *et al.*,[13] postulated three major mechanisms of chest pain in amyloidosis. First, structural: accumulation of amyloid within the walls of the small coronary arteries and no amyloid deposition in the epicardial coronary arteries. Obstruction of these small coronary arteries may lead to myocardial ischemia. Second, extravascular: perivascular and interstitial amyloid deposits may lead to extramural compression and reduced diastolic perfusion time. Third, functional: coronary microvascular dysfunction is highly prevalent in subjects with CA, even in the absence of epicardial CAD, and may explain their anginal symptoms. The subgroup analysis of our study showed that CAD was equally prevalent in patients with ATTR and AL amyloidosis (30.7% versus 30%, respectively). Michelle *et al.*[12] reported exertional anginal pain in 15% of patients with AL amyloidosis.

In this study, HFpEF, or atrial arrhythmia, raised the suspicion of CA. Reduced ejection fraction was uncommon.

One-third of our patients presented with OH. OH, defined as a drop of 20 mmHg or more in SBP or 10 mmHg or more in DBP when standing up after sitting or lying down, in CA, may manifest likely due to a combination of low cardiac output and reduced vascular tone due to autonomic dysfunction. Its clinical signs and symptoms include light-headedness, dizziness, blurred vision, confusion, or fainting after standing up. In our study, OH was more commonly seen in AL amyloidosis than ATTR type (42.8% [n = 3] versus 14.2% [n = 1]). The study by Kyle *et al.*[14] reported OH in 7.9% of primary systemic amyloidosis. OH has been reported as a symptom of ATTR amyloidosis in 11.7% of the THAOS registry.[15]

Wild-type ATTR is predominantly a cardiac disease, and its only significant extracardiac feature is carpal tunnel syndrome, often preceding heart failure by 3–5 years[7] (which was not seen in the present study) and autonomic dysfunction causing significant postural hypotension as was observed in our seven cases. Subtle clues raised the possibility of AL amyloidosis—6% of the patients had peripheral neuropathy. Symmetrical sensory neuropathy is a common presentation. Macroglossia was seen in one patient (3.2%). Periorbital bruising in the setting of heart failure, although not seen in our study, is pathognomic of amyloidosis.[1,7]

Various ECG changes were observed, including QTc prolongation, low voltage QRS complex, pseudo infarction pattern, atrial arrhythmias, and AV block. These reflect the generalized infiltrative nature of this entity and are well-known in the literature.[1]

Although echocardiography provides crucial information, the images should be interpreted in the context of clinical pictures and other investigations. A comprehensive TTE

involving M mode, 3D, tissue Doppler, and speckled tracking should be performed. LVH in the absence of systemic hypertension is the commonest finding. The RVFWT is also increased. These can be explained by the pathological process involving myocardial infiltration and should not be interpreted as hypertrophy.[6] A thickened IVS with a speckled or granular (sparkling) appearance (32.3%) and thickened IAS (19.4%) strongly favored CA in this study. A grossly thickened IAS has 100% specificity for diagnosing CA and is usually seen in an advanced stage of the disease.[16] Other features helpful in diagnosis include atrial enlargement, thickened AV valves, and PE. All patients had a restrictive pattern on mitral inflow assessment, DD of higher grades, and elevated filling pressures. Speckle tracking, tissue Doppler and 3D imaging demonstrated abnormal GLS with apical sparing.

In recent years, 99mTc-PYP scintigraphy imaging has become a standard-of-care diagnostic tool to help clinicians identify transthyretin amyloidosis. A PYP scan is considered positive when the heart-to-contralateral lung ratio is greater than or equal to 1.5, with a visual Grade of 2 or 3, with confirmation by SPECT imaging.[17] Our study reported 68% PYP uptake in Grades 2 and 3.

cMRI, due to its superior tissue characterization, facilitates timely diagnosis and assists in the subclassification of CA. MRI demonstrated the following characteristic features of CA—a subendocardial pattern of LGE within the atrial and ventricular myocardium, expanded extracellular volume fraction, elevated T1 signal, and failure in nulling the myocardium following gadolinium injection, all these owing to diffuse fibrosis.[1] The subendocardial pattern and scoring of LGE help in the differentiation of CA subtypes. Subendocardial LGE is more prevalent in the AL variety, whereas trans-mural is more prevalent in the ATTR type.[18]

The combination of SPIE, UPIE, and quantification of serum FLC demonstrate a sensitivity of 99% for identifying abnormal pro-amyloidotic precursors in AL amyloidosis. It is important that serum and urine protein electrophoresis should always be performed in conjunction with immunofixation to increase the sensitivity of the assays for detecting monoclonal proteins.[1]

The combination of plasma cell dyscrasias with atypical echocardiographic features, with or without cMRI imaging, highly suggests AL amyloidosis. However, the definitive diagnosis requires a tissue biopsy demonstrating amyloid deposits with apple-green birefringence when stained with Congo red. The biopsy can be performed on any affected organ. In this study, Rectal, pericardial, renal, gastric, and lingual biopsy proved extremely useful. Endo-myocardial biopsy was done in one patient. The AL subtype was diagnosed in 67.8% by detecting free light chain abnormal protein using SIFE.

Treatment is classified as supportive (heart failure therapy, antiarrhythmias) and targeted therapies that suppress the production of respective amyloid fibril precursor protein. Specific pharmacologic treatments for ATTR amyloidosis include stabilizing molecules (tafamidis) and genetic silencers (patisiran and inotersen). Tafamidis is currently the only drug that has shown efficacy in patients with ATTRwt and ATTRv (variant) with cardiomyopathy and should be considered in patients with reasonably expected survival.[1] One of our patients diagnosed with ATTR CA received Tafamidis. Chemotherapy that targets the underlying plasma cell dyscrasia consists of bortezomib (proteasome inhibitor), cyclophosphamide, and dexamethasone, which cause remission and extends survival by a few years.[6] Bortezomib was well tolerated in our patients without any cardiotoxicity. Standard heart failure therapy is of limited benefit or even detrimental due to low blood pressure and arrhythmias. Pacemakers and other devices provide limited benefits. A cardiac transplant for AL amyloidosis has been performed, but the outcome depends on an extremely careful selection of patients. The role of antibodies to induce the removal of tissue amyloid deposits and genetic editing treatments are still under investigation.[1]

CA has a poor prognosis. The prognostic assessment in our study done by Mayo Clinic staging showed that 50% were in stage III. A study of six patients demonstrated the death of four (66%) within a short period. The reported median survival from the onset of heart failure is approximately 6 months.[6]

The limitations of our study were; first, it was a single-center study and did not include the follow-up of the patients and the subsequent survival analysis. Second, the data pertaining to GLS in TTE, cardiac biomarkers, light chain assay, cMRI, and nuclear imaging was unavailable for all the patients, which can be attributed to financial constraints. Moreover, for the same reasons, the patients with ATTR amyloidosis could not be subjected to genetic testing for TTR mutations. Thirdly, ^{99m} Tc PYP scanning with a visual score Grade 2 with planar imaging alone often gives false positive results. To prevent misdiagnosis in such cases, it is recommended to add SPECT to positive planar imaging.

Since our study was a single-center study with a small sample size, it warrants a large-scale, multicentric study to determine its prevalence. We also recommend widespread training for cMRI and PYP nuclear imaging in referral centers to enable earlier diagnosis and translate into improved survival.

Conclusion

Our study demonstrated that the most common type of amyloidosis prevalent in South India is the ATTR type.

The presence of HFpEF, atrial arrhythmias, low ECG voltages despite LVH in ECHO, restrictive features on echocardiography including the cherry on top appearance, abnormal light chain assay, and awareness of the red flag signs helped us keep a high index of suspicion for CA. The algorithm of diagnostic criteria used in our study incorporated the utilization of noninvasive cMRI and 99mTc PYP imaging techniques and invasive cardiac or extracardiac histological demonstration of amyloid deposits, thereby helping in the early recognition of the amyloid type and prompt initiation of specific targeted therapy.

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Conflicts of interest

There are no conflicts of interest.

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