Assessment of clinical characteristics of cardiac amyloidosis as a potential underlying etiology in patients diagnosed with heart failure with preserved ejection fraction

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ABSTRACT

Background: Heart failure with preserved ejection fraction (HFpEF) is heterogeneous clinical syndrome. Transthyretin cardiac amyloidosis (CA) is an underdiagnosed cause of HFpEF. Red flags are extremely useful for suspecting CA.

Aims: We aimed to evaluate the frequency of cardiac and extracardiac manifestations of CA in HFpEF patients based on red flags.

Methods: Baseline characteristics of 85 patients were recorded during admission. Electrocardiogram and echocardiography were performed. All patients were examined for red flags. Cardiac scintigraphy was performed in 85 patients.

Results: The mean (standard deviation [SD]) age of the study group was 67.9 (9.8) years, and 52 (61.2%) patients were female. At least 1 red flag was observed in 67% of HFpEF patients. Only 4 of the patients had more than 3 red flags. The mean number of red flags in a patient with HFpEF was 1.3. Extracardiac clinical red flags were observed in only 9 (10.5%) patients. Cardiac clinical red flags were extremely rare. An electrocardiographic red flag was detected in 2 out of 10 patients and an echocardiographic red flag in 4 out of 10 patients with HFpEF. Scintigraphy showed that 17.6% of all patients have had a grade 2 or 3 cardiac uptake. The patients with wild-type transthyretin CA had twice as many red flags as those without.

Conclusion: The results of the study showed that patients diagnosed with HFpEF had an average of 1.3 red flags suggestive of CA. In real life, extracardiac red flags are rare, while electrocardiographic and echocardiographic red flags are more common in patients with HFpEF.

Key words: cardiac amyloidosis, diastolic heart failure, heart failure with preserved ejection fraction, red flags, transthyretin

INTRODUCTION

Heart failure (HF) with preserved ejection fraction (HFpEF) is a heterogeneous clinical syndrome with multiple underlying causes with increased prevalence in the elderly population and women. Furthermore, it is more associated with comorbidities such as hypertension (HT), diabetes (DM), obesity, and chronic kidney disease (CKD) [1]. Recently, it has been established that cardiac amyloidosis (CA) is an important cause of HFpEF than previously thought [2, 3]. The disease has two main subtypes: transthyretin CA (ATTR-CA) and immunoglobulin light chain CA (AL-CA). ATTR-CA is further subdivided into wild-type (ATTRwt-CA) and mutant (ATTRm-CA) [4]. Gonzalez-Lopez et al. [5] reported that 13.3% of patients with HFpEF with left ventricular hypertrophy (LVH) showed uptake of 99mTc3,3-diphosphono-1,2-propanodicarboxylic acid scintigraphy, which suggested cardiac involvement of ATTRwt-CA. However, diagnosis of CA remains a frequent clinical challenge, especially in the early stages, and

WHAT'S NEW?

Data from the present study showed that at least one red flag for cardiac amyloidosis was observed in almost 70% of the patients with heart failure with preserved ejection fraction (HFpEF). The mean number of red flags in a patient with HFpEF was 1.3. Extracardiac and cardiac clinical red flags were extremely rare in patients. Approximately, an electrocardiographic red flag was detected in 2 out of 10 patients, and an echocardiographic red flag was observed in 4 out of 10 patients with HFpEF. What is more, HFpEF patients with wild-type transthyretin cardiac amyloidosis had twice as many red flags as HFpEF patients without cardiac amyloidosis.

CA is still under-diagnosed [6]. Red flags have been defined as a set of cardiac and extracardiac signs and symptoms, which are extremely useful for suspecting the disease in CA [4, 7]. In this study, we evaluated the frequency of cardiac and extracardiac manifestations of ATTR-CA in patients with HFpEF and aimed to identify red flags that would further alert clinicians to the diagnosis of CA in real-life.

METHODS

We conducted a prospective, observational, single-center study. The study was approved by our institutional ethics committee. All participants provided written informed consent.

Study population

A total of 100 patients diagnosed with HFpEF who were admitted to the Department of Cardiology of Eskisehir Osmangazi University were screened between October 2020 and July 2021. The diagnosis of HFpEF was based on the European Society of Cardiology guidelines [8]. Patients with severe valvular heart disease, previous myocardial infarction, sarcomeric hypertrophic cardiomyopathy, or myocardial storage diseases were excluded. Finally, 85 patients who underwent cardiac scintigraphy with the clinician's suspicion of CA were included in the study.

Study design, data collection, and definition

Demographic characteristics, comorbidities, laboratory findings, and medications were collected during admission. CKD was defined as the presence of an estimated glomerular filtration rate (eGFR) of ≤60 ml/min/1.73 m^2. N-terminal pro-brain natriuretic peptide (NT-proBNP) and the serum or urine monoclonal proteins results were evaluated. Comprehensive transthoracic echocardiography (ECHO) was performed and electrocardiograms (ECG) were recorded. Extracardiac clinical red flags including polyneuropathy, dysautonomia, history of carpal tunnel syndrome (CTS), biceps tendon rupture or lumbar spinal stenosis, positive family history, macroglossia, and cardiac red flags, including hypotension or intolerance to β-blockers/angiotensin-converting enzyme inhibitors, low-voltage or pseudoinfarct pattern or atrioventricular (AV) conduction anomalies on ECG were investigated. Findings including granular sparkling of the myocardium, increased right ventricular (RV) wall thickness, increased valve thickness, pericardial effusion, and reduced longitudinal strain with the apical sparing pattern were investigated as ECHO red flags. 99mTechnetium-pyrophosphate (99mTc-PYP) cardiac scintigraphy was performed in 85 patients. Transthyretin (TTR) gene sequencing was performed in positive patients to identify the mutant type. Also, these patients were evaluated for AL-CA with serum-free light chains and immunofixation electrophoresis.

Echocardiography and electrocardiography

Comprehensive ECHO was performed by a physician using a commercially available system (EPIQ 7C, X5-1 transducer, Philips Medical Systems, Andover, MA, US). Echocardiographic raw data were stored digitally as digital imaging and communications in medicine (DICOM) and transferred for offline analysis to a workstation with the Philips QLAB software. All dimensions were obtained from 2D imaging according to the recommendations of the guidelines [9, 10]. Global longitudinal strain (GLS) was measured in the three apical views. The relative apical sparing index was defined using the equation: average apical LS/(average basal LS + mid-LS) [11]. A standard 12-lead ECG was recorded.

Cardiac scintigraphy

For the primary analysis, which was based on myocardial tracer uptake, two methods were used: (1) semi-quantitative visual scoring of cardiac retention (0–1–2–3) at 3 hours; and (2) quantitative analysis of heart retention was calculated by drawing a region of interest (ROI) over the heart in the standard manner at 1 hour. The fraction of mean counts in the heart ROI-to-contralateral chest ROI was calculated as the heart to contralateral lung (H/CL) ratio [12, 13]. In the absence of monoclonal protein in the serum and urine, grade 2 to 3 myocardial uptake or a H/CL ratio of ≥1.5 were considered positive for ATTR-CA. Grade 2–3 uptake with a H/CL ratio ≥1.5 or grade 0–1 uptake with a H/CL ratio <1.5 were considered concordant results. Grade 2–3 uptake with a semi-quantitative score of 1 or H/CL ratio 1–1.5 were considered equivocal [12, 13].

Statistical analysis

Continuous variables were presented as means (standard deviation [SD]) and compared using t-tests if they were normally distributed and described using medians (interquartile ranges [IQR]) if they were not; the Mann–Whitney

U test was used for comparisons. Poisson regression analysis was used to evaluate the distribution of RF incidences in the ATTR-CA positive/negative groups. We expressed descriptive data as number (%) for categorical variables and compared them *via* the χ^2 test or Fisher exact test. A $P<0.05$ was considered statistically significant. IBM SPSS Statistics 21.0 software (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY, US; IBM Corp.) was used in the analyses.

RESULTS

The mean (SD) age of the study group was 67.9 (9.8) years and 52 (61.2%) were female. Overall, 20 (23.5%) patients were in New York Heart Association (NYHA) class III–IV, and median (IQR) NT-proBNP was 1000 (433.5–2040.5) pg/ml. Other baseline features are summarized in Table 1.

Echocardiographic and electrocardiographic findings

Mean (SD) left ventricular ejection fraction (LVEF) was 59.7 (4) %, mean LV-GLS was –14.3 (2.5)%. The number of patients with left ventricular wall thickness (LVWT) ≥15 mm, 12–14 mm, and ≤11 mm was 27 (31.8%), 29 (34.1%), and 29 (34.1%), respectively. Reduced LV-GLS with the apical sparing pattern was detected in 9 (10.5%) patients and granular sparkling of myocardium in 2 (2.3%) patients. According to the ECG findings, 2 (2.3%) patients had low/decreased QRS voltage to degree of LVWT, 5 (5.8%) patients had pseudoinfarct pattern, and 3 (3.5%) patients had AV conduction disease. Other ECHO and ECG findings are summarized in Table 2.

Scintigraphy results

Scintigraphy showed that 15 (17.6%) patients had a grade 2 or 3 cardiac uptake; the H/CL ratio was ≥1.5, and concordance was positive. In the absence of monoclonal protein in the serum and urine, positive bone scintigraphy is considered diagnostic for ATTR-CA. All patients with a positive scan underwent genetic testing of the TTR gene, and no mutations were found.

Frequency of cardiac and extracardiac amyloidosis red flags in patients with HFpEF

At least 1 red flag was observed in 57 (67%) of the 85 patients with HFpEF. The mean number of red flags in a patient with HFpEF was 1.3. Only 4 (4.7%) patients had more than 3 red flags. Extracardiac clinical red flags were observed in only 9 (10.5%) patients. Among all patients, 31 (36.4%) patients had extracardiac laboratory red flags. Cardiac clinical red flags were extremely rare and were observed in only one of the 85 patients. Approximately, an ECG red flag was detected in 1 out of 10 patients and an ECHO red flag in 4 out of 10 patients with HFpEF. The presence of disproportionately elevated NT-proBNP to degree of HF was present in 8 (9.4%) patients. Patients with ATTR-CA had twice as many red flags as those without (2.46 vs. 1.04). However, ATTR-CA diagnosis was more common in patients with 2 or more red flags (Tables 3 and 4).

Table 1. Baseline clinical characteristics

Variable	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
Age, years, mean (SD)	66.8 (10.0)	72.1 (8)	0.046
≥65 years, n (%)	39 (55.7)	12 (80)	0.05
Male sex, n (%)	27 (38.6)	6 (40)	0.56
BMI, kg/m^2, mean (SD)	30.4 (5.62)	30.2 (4.0)	0.90
Hypertension, n (%)	55 (78.6)	12 (80)	0.60
Diabetes, n (%)	31 (44.3)	3 (20)	0.07
Coronary artery disease, n (%)	22 (31.4)	6 (40)	0.36
Atrial fibrillation, n (%)	23 (32.9)	8 (53.3)	0.11
Chronic kidney disease, n (%)	30 (42.9)	3 (20)	0.08
NYHA class I, n (%)	1 (1.4)	0	0.61
NYHA class II, n (%)	51 (72.9)	13 (86.7)	
NYHA class III, n (%)	13 (18.6)	2 (13.3)	
NYHA class IV, n (%)	5 (7.1)	0	
SBP, mm Hg, mean (SD)	127.8 (17.7)	123.7 (19.5)	0.42
Heart rate, bpm, mean (SD)	77.5 (18.3)	79.3 (24.4)	0.75
Creatinine, mg/dl, median (IQR)	0.96 (0.77–1.3)	0.89 (0.80–1.10)	0.28
NT-proBNP, pg/ml, median (IQR)	966.5 (425.5–2037.7)	1113.0 (768.0–2385.0)	0.37
β-blocker, n (%)	53 (75.7)	12 (80)	0.51
Calcium channel blockers, n (%)	18 (25.7)	5 (33.3)	0.38
ACEI/ARB, n (%)	37 (52.8)	7 (46.6)	0.41
Furosemide, n (%)	40 (57.1)	10 (66.7)	0.35
MRA, n (%)	16 (22.9)	6 (40)	0.15

Abbreviations: ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; MRA, mineralocorticoid receptor antagonists; NT-proBNP, N-terminal pro-B-type natriuretic peptide; NYHA, New York Heart Association; SBP, systolic blood pressure; TTR-CA, transthyretin cardiac amyloidosis

Table 2. Baseline echocardiographic and electrocardiographic features

Variable	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
LV ejection fraction, %, mean (SD)	60.0 (4.14)	58.6 (3.76)	0.22
LV end-diastolic diameter, mm, mean (SD)	47.6 (3.72)	48.4 (3.65)	0.47
IVSd, mm, median (IQR)	12.8 (11.0–15.0)	13.0 (11.0–16.0)	0.78
Posterior wall thickness, mm, median (IQR)	12.0 (10.0–13.0)	12.0 (11.0–14.0)	0.40
IVS thickness ≥12 mm, n (%)	45 (64.3)	11 (73.3)	0.78
RWT, median (IQR)	0.48 (0.42-0.53.5)	0.47 (0.46-0.60)	0.44
Right ventricular wall thickness, mm, median (IQR)	4.0 (3.0-4.5)	4.0 (3.0-5.0)	0.97
LV mass index, g/m^2, median (IQR)	115.5 (100.0–145.5)	129.0 (104.0–159.0)	0.52
LA diameter, mm, mean (SD)	43.7 (5.85)	45.9 (5.83)	0.20
LA area (cm^2), median (IQR)	19.5 (16.5–24.0)	21.0(20.0–26.0)	0.15
LAVI, ml/m^2, median (IQR)	34.0 (26.0–45.0)	37 (32.0–49.0)	0.24
LAVI >34 ml/m^2, n (%)	34 (48.6)	10 (66.7)	0.16
GLS, %, mean (SD)	–14.7 (2.37)	–12.5 (2.78)	0.003
Apical/(mid + basal) LS ratio, median (IQR)	0.90 (0.84–0.95)	1.08 (0.85–1.49)	0.006
Peak TR velocity> 2.8 m/s, n (%)	28 (40)	5 (33.3)	0.43
sPAP, mm Hg, median (IQR)	35.0 (27.7–50.0)	35.0 (32.0–48.0)	0.78
E-wave, cm/s, mean (SD)	81.8 (21.0)	77.9 (27.2)	0.53
E/e' lat, means (SD)	11.6 (3.01)	12.6 (2.98)	0.22
E/e'≥15 E/e' 9–14	12 (17.1) 47 (67.1)	4 (26.7) 10 (66.7)	0.52
TAPSE, mm, mean (SD)	18.1 (2.78)	16.7 (2.19)	0.08
Right ventricular hypertrophy, n (%)	8 (11.4)	2 (13.3)	0.56
Interatrial septum hypertrophy, n (%)	2 (2.9)	1 (6.7)	0.45
Low QRS, n (%)	—	2 (13.3)	0.03
PR interval, ms, median (IQR)	150.0 (120.0–160.0)	160.0 (160.0–200.0)	0.048
AV block (first degree), n (%)	2 (2.9)	1 (6.7)	0.44
BBB, n (%)	17 (24.3)	2 (13.3)	0.29
Pseudo-infarct pattern, n (%)	2 (2.9)	3 (20)	0.04

Abbreviations: AF, atrial fibrillation; AV, atrioventricular; BBB, bundle branch block; GLS, global longitudinal strain; IVS, interventricular septum; IVSd, interventricular septal dimension; LA, left atrium; LAVI, left atrial volume index; LV, left ventricle; LVH, left ventricular hypertrophy; RWT, relative wall thickness; sPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion; TR, tricuspid regurgitation; other — see Table 1

Table 3. Details of the presence of red flags in patients with HFpEF

Variables	Total (n = 85)	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
Extracardiac red flags				
Extracardiac clinical, n (%)	8 (9.4)	5 (7.1)	3 (20)	0.14
Extracardiac laboratory, n (%)	40 (47.1)	34 (48.6)	6 (40)	0.38
Cardiac red flags				
Clinical, n (%)	1(1.2)	0	1 (6.7)	0.18
Electrocardiogram, n (%)	9 (10.5)	5 (7.1)	4 (26.7)	0.048
Laboratory, n (%)	8 (9.4)	3 (4.3)	5 (33.3)	0.004
Echocardiography, n (%)	32 (37.6)	22 (31.4)	10 (66.7)	0.013
Total number of RF	110	73	37	0.013
Patients with 0–1 RF number, n (%)[a]	55 (64.7)	51 (72.9)	4 (26.7)	0.002
Patients with 2–7 RF number, n (%)[a]	30 (35.2)	19 (27.1)	11 (73.3)	0.001
RF number/patients number ratio	1.3	1.04	2.46	<0.001

[a]Patients with 0–1 RF number vs. patients with 2–7 RF number *P*-value: 0.001

Abbreviations: RF, red flag; other — see Tables 1 and 2

DISCUSSION

The results of this prospective study demonstrated that (1) 67% of patients with HFpEF had at least one of the red flags; (2) HFpEF patients with ATTR-CA had twice as many red flags as those without; (3) extracardiac clinical red flags are rarely seen in patients. We concluded that the presence of ECHO red flags and disproportionately elevated NT-proBNP are more common warnings to suspect CA.

ATTRwt-CA has been increasingly recognized as an underdiagnosed cause of HFpEF. It is valuable to recognize clinical findings for the underlying etiology in patients with HFpEF at an early stage. In previous studies, the prevalence of ATTR-CA was reported to be between 13% and 19% in patients with unexplained LVH with HFpEF [5, 14, 15]. Also, in a study conducted on patients with HFpEF without LVH, it was reported that ATTR-CA was detected in 5% of

Table 4. Frequency of cardiac and extracardiac amyloidosis red flags in patients with HFpEF

Variable	TTR-CA negative (n = 70)	TTR-CA positive (n = 15)	*P*-value
Polyneuropathy, n (%)	4 (4.3)	2 (13.3)	0.21
Dysautonomia, n (%)	2 (2.9)	1 (6.7)	0.45
Macroglossia, n (%)	—	—	—
Bilateral carpal tunnel syndrome, n (%)	—	—	—
Ruptured biceps tendon, n (%)	—	—	—
Lumbar spinal stenosis, n (%)	—	—	—
Family history, n (%)	—	—	—
Renal insufficiency (GFR <60 ml/min/1.73 m^2), n (%)	30 (42.8)	3 (20)	0.28
Proteinuria, n (%)	12 (17.1)	3 (20)	0.52
Hypotension or normotensive if previous hypertensive, n (%)	—	1 (6.7)	0.18
Pseudoinfarct pattern, n (%)	2 (2.9)	3 (20)	0.04
Low/decreased QRS voltage to degree of LV thickness, n (%)	0	2 (13.3)	0.03
AV conduction disease, n (%)	2 (2.9)	1 (6.7)	0.44
Disproportionately elevated NT-proBNP, n (%)	3 (4.3)	5 (33.3)	0.004
Granular sparkling of the myocardium, n (%)	0	2 (13.3)	0.03
Increased right ventricular wall thickness, n (%)	8 (11.4)	2 (13.3)	0.56
Increased valve thickness, n (%)	14 (20)	6 (40)	0.09
Pericardial effusion, n (%)	3 (4.3)	3 (20)	0.06
Reduced LS with apical sparing pattern, n (%)	1 (1.5)	8 (57.1)	<0.001

Abbreviations: GFR, glomerular filtration rate; HF, heart failure; LS, longitudinal strain; other — see Tables 1–3

these patients [2]. In our study, 65.9% of patients had LVH, of which approximately one-third was unexplained LVH. Patients with HFpEF were included in our study regardless of age and LVMT. Although it is frequently reported that ATTR-CA is seen in the elderly and men [16], reports show that it also affects wider age ranges and younger and female patients [17]. Our study included a different patient population than the "elderly male" profile usually included in studies about CA. This reflects the HFpEF patient profile that we encounter in daily practice.

Extracardiac and cardiac clinical red flags

Extracardiac and cardiac clinical red flags are less frequent in patients with HFpEF. Orthostatic hypotension (OH) affecting an estimated 40%–60% of patients with ATTRm-CA is a manifestation of autonomic dysfunction [18]. Orthostatic hypotension is diagnosed in 5-11% of middle-aged adults and approximately 20%–30% of people 65 years and older, but the incidence of OH in the HF population is not clear [19, 20]. However, a recent review showed that the incidence of OH in HF varies from 8% to 83% [21]. Also, there is often accompanying neurological involvement such as sensorimotor polyneuropathy in CA, but purely neurological manifestations are rare (4%) [22]. In addition, ATTRwt-CA is known to be associated with CTS, lumbar spinal stenosis, and ruptured biceps tendon [4]. Carpal tunnel syndrome is the most frequent focal peripheral neuropathy in the general population and has been shown to have a prevalence ranging from 0.2% to 4% [23]. In cases of CA, its frequency varies in relation to variables such as amyloid subtypes, duration of the disease, male sex, and age. CTS is present in about 25% of patients and can occur years before diagnosis [24]. Besides, in patients with a history of HT, "spontaneous" resolution of HT over the preceding few months is a valuable history for the diagnosis of CA and has been identified as a cardiac clinical red flag [4, 25]. In the present study, 3% of the patients with HFpEF had autonomic dysfunction findings, and 6% had polyneuropathy. While 2 patients had unilateral CTS, there was no patient with bilateral CTS. The absence of bilateral CTS may be related to the small size of our patient population. "Spontaneous" resolution of HT was observed in only one patient, and this patient was positive on scintigraphy.

Proteinuria and CKD are characterized as extracardiac clinical red flags, these conditions are already common in the HFpEF population. Although the prevalence of proteinuria and CKD varies depending on the age and comorbidities of the patient population included in the studies, it has been reported that 30%–41% of patients with HfpEF have proteinuria [26–28], and 26%–49% have CKD [29]. Similar to previous studies, in our study population, we observed proteinuria in 15 (17.6%) patients (8 with CKD, 7 without CKD) and CKD in 33 (38.8%) patients. Also, there were no patients planned for kidney transplantation. The most common reasons for the increase in the number of red flags were the presence of CKD and/or proteinuria.

ECG, ECHO, and laboratory red flags

Electrocardiographic abnormalities in HF with reduced ejection fraction are widely described and guide medical and device therapy. However, other than a high prevalence of atrial fibrillation, little is known about ECG features associated with HFpEF. ECG variables can help predict the etiology in patients with HFpEF but are very heterogeneous. It has been reported that 10-30% of patients with HFpEF have electrocardiographic LVH. ECG abnormalities reported in patients with HFpEF include atrial fibrillation (prevalence 12%–46%), long PR interval (11%–20%), pathological Q

waves (11%–18%), and left bundle branch block (0%–8) [30]. In our study population, 27% of patients had electrocardiographic LVH, 5 (5.8%) had a pseudo-infarct pattern, and 3 (3.5%) had AV conduction disease. In addition, there were two patients with low voltage on ECG in the limb leads inconsistent with LV wall thickness and these patients were ATTR-CA positive. Analysis of easy-to-assess ECG variables in patients with HFpEF can be of substantial help in the diagnostic workup of ATTRwt-CA.

Besides, ECHO is essential for the initial evaluation of patients with suspected and diagnosed of HFpEF. In addition, it has been reported that cardiac magnetic resonance imaging is a valuable tool in determining the etiology in patients with HFpEF [31]. Diastolic dysfunction, LA enlargement, LVH, RV enlargement, and elevated pulmonary artery systolic pressure were common in patients with HFpEF. Apart from these findings, RV hypertrophy, thickening of cardiac valves and interatrial septum, granular appearance of the myocardium, and pericardial effusion are common in patients with CA. In the present study, the most common finding among ECHO red flags was thickening of cardiac valves, but there was no difference between the two groups (P >0.05). Another "classical" ECHO features of CA were the "granular sparkling and reduced LS with apical sparing pattern", which were significantly higher in the patients with ATTRwt-CA. The results of this study were similar to the results of previous studies for echocardiographic red flags [4].

NT-proBNP is a marker of neurohormonal activation that is useful in the diagnosis and prognosis of HF. Previous studies comparing NT-proBNP levels in different forms of amyloid cardiomyopathy suggested that NT-proBNP values are lower in ATTR-CA than in AL-CA, besides increased ventricular wall thickness [32]. In addition, NT-proBNP levels that are disproportionate to the degree of HF are suggestive of ATTRwt-CA [33]. It has even been reported that some patients with suspected hypertrophic cardiomyopathy, with LVH and normal NT-proBNP levels, may have undiagnosed ATTR-CA [34]. In this study, there was no significant difference in NT-proBNP levels between HFpEF patients with and without CA. However, "the presence of disproportionately elevated NT-proBNP to degree of HF" was significantly higher in patients with ATTRwt-CA.

Study limitations

The presence of persisting elevated troponin could not be evaluated as a cardiac laboratory red flag. Cardiac magnetic resonance imaging findings that were part of the red flag assessment were not evaluated. Another limitation is that endomyocardial biopsies were not performed in this study. Diagnostic tests were performed for storage diseases and hypertrophic cardiomyopathy in clinically suspected patients, but not routinely in all patients.

CONCLUSION

The results of the study showed that patients diagnosed with HFpEF had an average of 1.3 red flags suggestive of CA. Extracardiac and cardiac clinical red flags were extremely rare in patients. Approximately, an electrocardiographic red flag was detected in 2 out of 10 patients and an echocardiographic red flag in 4 out of 10 patients with HFpEF. Furthermore, red flags were twice as common in HFpEF patients with CA than in HFpEF patients without CA.

Article information

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REFERENCES

1. McDonagh T, Metra M, Adamo M, et al. Corrigendum to: 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: Developed by the Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC) with the special contribution of the Heart Failure Association (HFA) of the ESC. Eur Heart J. 2021; 42(36): 3599–3726, doi: 10.1093/eurheartj/ehab368, indexed in Pubmed: 34447992.
2. Devesa A, Camblor Blasco A, Pello Lázaro AM, et al. Prevalence of transthyretin amyloidosis in patients with heart failure and no left ventricular hypertrophy. ESC Heart Fail. 2021; 8(4): 2856–2865, doi: 10.1002/ehf2.13360, indexed in Pubmed: 33963812.
3. Izumiya Y, Hayashi H, Ishikawa H, et al. How to identify transthyretin cardiac amyloidosis at an early stage. Intern Med. 2021; 60(1): 1–7, doi: 10.2169/internalmedicine.5505-20, indexed in Pubmed: 32713926.
4. Garcia-Pavia P, Rapezzi C, Adler Y, et al. Diagnosis and treatment of cardiac amyloidosis. A position statement of the European Society of Cardiology Working Group on Myocardial and Pericardial Diseases. Eur J Heart Fail. 2021; 23(4): 512–526, doi: 10.1002/ejhf.2140, indexed in Pubmed: 33826207.
5. González-López E, Gallego-Delgado M, Guzzo-Merello G, et al. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J. 2015; 36(38): 2585–2594, doi: 10.1093/eurheartj/ehv338, indexed in Pubmed: 26224076.
6. Lane T, Fontana M, Martinez-Naharro A, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. Circulation. 2019; 140(1): 16–26, doi: 10.1161/CIRCULATIONAHA.118.038169, indexed in Pubmed: 31109193.
7. Witteles RM, Bokhari S, Damy T, et al. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail. 2019; 7(8): 709–716, doi: 10.1016/j.jchf.2019.04.010, indexed in Pubmed: 31302046.
8. Ponikowski P, Voors A, Anker S, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure [article in Polish]. Kardiol Pol. 2016; 74(10): 1037–1147, doi: 10.5603/kp.2016.0141, indexed in Pubmed: 27748494.
9. Lang RM, Badano LP, Mor-Avi V, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. J Am Soc Echocardiogr. 2015; 28(1): 1–39.e14, doi: 10.1016/j.echo.2014.10.003, indexed in Pubmed: 25559473.
10. Devereux RB, Alonso DR, Lutas EM, et al. Echocardiographic assessment of left ventricular hypertrophy: comparison to necropsy findings. Am J Cardiol. 1986; 57(6): 450–458, doi: 10.1016/0002-9149(86)90771-x, indexed in Pubmed: 2936235.
11. Phelan D, Collier P, Thavendiranathan P, et al. Relative apical sparing of longitudinal strain using two-dimensional speckle-tracking echocardiography is both sensitive and specific for the diagnosis of cardiac amyloido-

sis. Heart. 2012; 98(19): 1442–1448, doi: 10.1136/heartjnl-2012-302353, indexed in Pubmed: 22865865.
12. 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 1 of 2-evidence base and standardized methods of imaging. J Nucl Cardiol. 2019; 26(6): 2065–2123, doi: 10.1007/s12350-019-01760-6, indexed in Pubmed: 31468376.
13. 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. J Nucl Cardiol. 2020; 27(2): 659–673, doi: 10.1007/s12350-019-01761-5, indexed in Pubmed: 31468377.
14. Lo Presti S, Horvath SA, Mihos CG, et al. Transthyretin Cardiac Amyloidosis as Diagnosed by 99mTc-PYP Scanning in Patients with Acute Heart Failure and Preserved Ejection Fraction. Crit Pathw Cardiol. 2019; 18(4): 195–199, doi: 10.1097/HPC.0000000000000183, indexed in Pubmed: 31725511.
15. Hahn VS, Yanek LR, Vaishnav J, et al. Endomyocardial biopsy characterization of heart failure with preserved ejection fraction and prevalence of cardiac amyloidosis. JACC Heart Fail. 2020; 8(9): 712–724, doi: 10.1016/j.jchf.2020.04.007, indexed in Pubmed: 32653448.
16. Connors LH, Sam F, Skinner M, et al. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. Circulation. 2016; 133(3): 282–290, doi: 10.1161/CIRCULATIONAHA.115.018852, indexed in Pubmed: 26660282.
17. Ochi Y, Kubo T, Baba Y, et al. Wild-Type transthyretin amyloidosis in female patients — consideration of sex differences. Circ Rep. 2021; 3(8): 465–471, doi: 10.1253/circrep.CR-21-0067, indexed in Pubmed: 34414336.
18. Palma JA, Gonzalez-Duarte A, Kaufmann H. Orthostatic hypotension in hereditary transthyretin amyloidosis: epidemiology, diagnosis and management. Clin Auton Res. 2019; 29(Suppl 1): 33–44, doi: 10.1007/s10286-019-00623-x, indexed in Pubmed: 31452021.
19. Saedon NI, Pin Tan M, Frith J. The prevalence of orthostatic hypotension: a systematic review and meta-analysis. J Gerontol A Biol Sci Med Sci. 2020; 75(1): 117–122, doi: 10.1093/gerona/gly188, indexed in Pubmed: 30169579.
20. Feldstein C, Weder AB. Orthostatic hypotension: a common, serious and underrecognized problem in hospitalized patients. J Am Soc Hypertens. 2012; 6(1): 27–39, doi: 10.1016/j.jash.2011.08.008, indexed in Pubmed: 22099697.
21. Gorelik O, Feldman L, Cohen N, et al. Factors associated with prevention of postural hypotension by leg compression bandaging. Blood Press. 2014; 23(4): 248–254, doi: 10.3109/08037051.2013.871787, indexed in Pubmed: 24460143.
22. Ihne S, Morbach C, Sommer C, et al. Amyloidosis-the diagnosis and treatment of an underdiagnosed disease. Dtsch Arztebl Int. 2020; 117(10): 159–166, doi: 10.3238/arztebl.2020.0159, indexed in Pubmed: 32295695.
23. Boyle RP, Sharan J, Schwartz G. Carpal tunnel syndrome in transthyretin cardiac amyloidosis: implications and protocol for diagnosis and treatment. Cureus. 2021; 13(4): e14546, doi: 10.7759/cureus.14546, indexed in Pubmed: 34017661.
24. Yilmaz A, Bauersachs J, Bengel F, et al. Diagnosis and treatment of cardiac amyloidosis: position statement of the German Cardiac Society (DGK). Clin Res Cardiol. 2021; 110(4): 479–506, doi: 10.1007/s00392-020-01799-3, indexed in Pubmed: 33459839.
25. Falk RH. Diagnosis and management of the cardiac amyloidoses. Circulation. 2005; 112(13): 2047–2060, doi: 10.1161/CIRCULATIONAHA.104.489187, indexed in Pubmed: 16186440.
26. Miura M, Shiba N, Nochioka K, et al. Urinary albumin excretion in heart failure with preserved ejection fraction: an interim analysis of the CHART 2 study. Eur J Heart Fail. 2012; 14(4): 367–376, doi: 10.1093/eurjhf/hfs001, indexed in Pubmed: 22298637.
27. Benjamin EJ, Blaha MJ, Chiuve SE, et al. Heart disease and stroke statistics-2017 update: a report from the American Heart Association. Circulation. 2017; 135(10): e146–e603, doi: 10.1161/CIR.0000000000000485, indexed in Pubmed: 28122885.
28. Oeun B, Hikoso S, Nakatani D, et al. Prognostic significance of dipstick proteinuria in heart failure with preserved ejection fraction: insight from the PURSUIT-HFpEF registry. BMJ Open. 2021; 11(9): e049371, doi: 10.1136/bmjopen-2021-049371, indexed in Pubmed: 34526341.
29. Ter Maaten JM, Damman K, Verhaar MC, et al. Connecting heart failure with preserved ejection fraction and renal dysfunction: the role of endothelial dysfunction and inflammation. Eur J Heart Fail. 2016; 18(6): 588–598, doi: 10.1002/ejhf.497, indexed in Pubmed: 26861140.
30. Nikolaidou T, Samuel NA, Marincowitz C, et al. Electrocardiographic characteristics in patients with heart failure and normal ejection fraction: A systematic review and meta-analysis. Ann Noninvasive Electrocardiol. 2020; 25(1): e12710, doi: 10.1111/anec.12710, indexed in Pubmed: 31603593.
31. Ojrzyńska-Witek N, Marczak M, Mazurkiewicz Ł, et al. Role of cardiac magnetic resonance in heart failure of initially unknown etiology: A 10-year observational study. Kardiol Pol. 2022; 80(3): 278–285, doi: 10.33963/KP.a2021.0186, indexed in Pubmed: 34936084.
32. Perfetto F, Bergesio F, Grifoni E, et al. Different NT-proBNP circulating levels for different types of cardiac amyloidosis. J Cardiovasc Med (Hagerstown). 2016; 17(11): 810–817, doi: 10.2459/JCM.0000000000000349, indexed in Pubmed: 26765991.
33. Maurer MS, Bokhari S, Damy T, et al. Expert Consensus Recommendations for the Suspicion and Diagnosis of Transthyretin Cardiac Amyloidosis. Circ Heart Fail. 2019; 12(9): e006075, doi: 10.1161/CIRCHEARTFAILURE.119.006075, indexed in Pubmed: 31480867.
34. Petkow-Dimitrow P, Rajtar-Salwa R, Holcman K, et al. From hypertrophic cardiomyopathy to transthyretin amyloidosis: an unusual case and challenging diagnosis. Pol Arch Intern Med. 2020; 130(2): 153–154, doi: 10.20452/pamw.15140, indexed in Pubmed: 31933485.