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The Most Predictive Red Flags for Suspecting Cardiac Amyloidosis in Patients with Heart Failure with Preserved Ejection Fraction

Korunmuş Ejeksiyon Fraksiyonlu Kalp Yetersizliği Olan Hastalarda Kardiyak Amiloidoz Şüphesi için En Belirleyici Kırmızı Bayraklar

ABSTRACT

Objective: Cardiac amyloidosis (CA) is a cardiomyopathy characterized by amyloid infiltration in the myocardium. Transthyretin cardiac amyloidosis (TTR-CA), commonly presenting as heart failure with preserved ejection fraction (HFpEF), was the focus of our study, which aimed to identify red flags that heighten suspicion of CA in HFpEF patients.

Methods: We prospectively included patients diagnosed with HFpEF. All patients were assessed for TTR-CA red flag features, cardiac and extra-cardiac, as outlined in the "Diagnosis and Treatment of Cardiac Amyloidosis: A Position Statement of the European Society of Cardiology." Technetium-99m pyrophosphate (99mTc-PYP) cardiac scintigraphy was performed in 167 HFpEF patients suspected of having TTR-CA. Patients testing positive and negative for TTR-CA were compared based on these red flag features.

Results: Out of 167 HFpEF patients, 19 (11.3%) were diagnosed with TTR-CA. In the TTR-CA group, 17 (89.5%) patients were 65 years or older. The presence of three or more red flags differentiated the TTR-CA positive and negative groups (P = 0.040). Features such as low voltage and pseudo infarct patterns were more prevalent in the TTR-CA group (P < 0.001 and P < 0.048, respectively). Left ventricular global longitudinal strain (LV-GLS) was lower in the TTR-CA positive group (P < 0.001). Multivariate analysis identified four variables—older age, pseudo infarct pattern, low/decreased QRS voltage, and LV-GLS—as strong, independent predictors of TTR-CA, with significant odds ratios (ORs) of 7.8, 6.8, 16.9, and 1.2, respectively.

Conclusion: In this study, TTR-CA etiology occurs in approximately one in every ten HFpEF patients. The presence of three or more red flags increases the likelihood of TTR-CA. Older age, pseudo infarct pattern, low/decreased QRS voltage, and reduced LV-GLS are the most significant red flags indicating TTR-CA in HFpEF patients.

Keywords: Cardiac amyloidosis, heart failure, red flags

ÖZET

Amaç: Kardiyak amiloidoz (KA), kalpte amiloid infiltrasyonu ile karakterize miyokardiyal bir hastalıktır. Transtiretin kardiyak amiloidozun (TTR-KA) en sık klinik başvuru şekli, korunmuş ejeksiyon fraksiyonlu kalp yetersizliğidir (KEFKY). Bu çalışmanın amacı, KEFKY hastalarında KA şüphesini arttıran kırmızı bayrakları (red flag) değerlendirmektir.

Yöntem: Çalışmaya; KEFKY tanılı hastalar prospektif olarak dahil edildi. Avrupa Kardiyoloji Derneği'nin kardiyak amiloidozun tanı ve tedavisi raporu temel alınarak; tüm hastalar TTR-KA'nın kardiyak ve ekstra-kardiyak kırmızı bayrak özellikleri açısından değerlendirildi. TTR-KA şüphesi olan 167 KEFKY hastasına teknesyum-99m pirofosfat (99mTc-PYP) sintigrafisi yapıldı. TTR-KA pozitif olan hastalar ile negatif olan hastalar kırmızı bayrak özellikleri açısından karşılaştırıldı.

Bulgular: Çalışmamızda 167 hastanın 19'una (%11,3) TTR-KA tanısı konuldu. TTR-KA tanısı konulan hastaların 17'si (%89,5) ≥ 65 yaş idi. Red flag sayısı 3 ve daha fazla olanlarda TTR-KA olma olasılığı daha fazla idi (P = 0,040). Red flagler içinde; düşük voltaj ve psödo infarkt paterni TTR-KA olan grupta TTR-KA olmayan gruba göre istatistiksel olarak anlamlı derecede daha fazla görüldü (sırasıyla P < 0,001 ve P < 0,048). Sol ventrikül (SV) global longitudinal strain ise, TTR-KA grubunda, TTR-KA tanısı olmayanlara göre daha düşüktü (P < 0,001). Multivariate analiz sonuçları, red flagler içinden özellikle dört tanesinin KA'yı öngördüren güçlü ve bağımsız belirleyiciler olduğunu ortaya koydu; ileri yaş, psödoinfarkt paterni, LV duvar kalınlığı ile orantısız QRS voltajı ve düşük SV global longitudinal strain. Bu dört değişkenin odds ratio (OR) oranları ise sırasıyla 7.8, 6.8, 16.9 ve 1.2 idi.

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Sonuç: Bu çalışmanın sonuçları, yaklaşık her on KEFKY hastasından birinde TTR-KA etiyolojisinin bulunduğunu göstermektedir. Üç ve daha fazla red flag bulunması TTR-KA olasılığını arttırmaktadır. Ayrıca bu çalışma ileri yaş, psödo infarkt paterni, SV duvar kalınlığı ile orantısız QRS voltajı ve düşük SV global longitudinal strain'in TTR-KA'yı öngördüren en güçlü red flagler olduğunu ortaya koymaktadır.

Anahtar Kelimeler: Kardiyak amiloidoz, kalp yetersizliği, red flag

Cardiac amyloidosis (CA) is a type of cardiomyopathy characterized by high mortality and morbidity due to amyloid fibril deposition in the myocardium. There are two main types of amyloidosis associated with cardiac involvement: immunoglobulin light chain amyloidosis (AL-CA) and transthyretin amyloidosis (TTR-CA). TTR-CA itself is subdivided into two forms: wild type (wtTTR-CA) and mutant (mTTR-CA).[1] Patients with cardiac amyloidosis often exhibit heart failure symptoms, and recognition of its role, especially in heart failure with preserved ejection fraction (HFpEF), has grown significantly in recent years.

In clinical practice, the identification of certain cardiac and extracardiac red flags can heighten suspicion of TTR-CA in patients with HFpEF, aiding in early diagnosis.[1] This study investigates the presence and significance of these red flags to enhance clinical awareness and facilitate early detection.

Materials and Methods

This prospective, observational study adhered to the Declaration of Helsinki and received approval from Eskişehir Osmangazi University Ethics Committee (Approval Number: E-25403353-050.99-120847, Date: 10.12.2020). All participants provided written informed consent. Artificial intelligence (AI)-assisted technologies (such as Large Language Models [LLM], chatbots, or image creators) were not utilized in the production of this study.

Study Population and Data Collection

From 2020 to 2022, 207 patients diagnosed with HFpEF were evaluated, based on current guidelines.[2,3] Forty of the patients (19.3%) did not undergo the Technetium-99m pyrophosphate (99mTc-PYP) scintigraphy procedure due to the absence of clinical red flags for CA, withdrawal of consent, or death prior to the scheduled procedure. Consequently, 167 patients who underwent 99mTc-PYP cardiac scintigraphy with suspected CA were included. All data were collected during admission.

ABBREVIATIONS

99mTc-PYP	Technetium-99m pyrophosphate
AL-CA	Immunoglobulin light chain amyloidosis
CA	Cardiac amyloidosis
ECG	Electrocardiogram
HFpEF	Heart failure with preserved ejection fraction
LA	Left atrial
LASr	LA reservoir strain
LAVI	LA volume index
LV	Left ventricular
LV-GLS	Left ventricular global longitudinal strain
NT-proBNP	N-terminal pro b-type natriuretic peptide
RV	Right ventricular
SPECT	Single-Photon Emission Computed Tomography
TTR-CA	Transthyretin cardiac amyloidosis

Electrocardiogram

A standard 12-lead electrocardiogram (ECG) was obtained from each patient during evaluation. The heart rate, PR interval, and QRS voltage were analyzed. Low QRS voltages were defined as a QRS amplitude ≤ 0.5 mV in all limb leads, or ≤ 1 mV amplitude in all precordial leads.[4] A pseudo infarct pattern was defined as the presence of pathological Q waves in at least two adjacent leads without evidence of obstructive coronary artery disease or a history of myocardial infarction.[5]

Echocardiography

Comprehensive echocardiography was performed using a commercially available system (EPIQ 7C, X5-1 transducer, Philips Medical Systems, Andover, MA, USA). The echocardiographic data were stored digitally as DICOM (Digital Imaging and Communications in Medicine) files and transferred for offline analysis to a workstation equipped with Philips QLAB software. Measurements of left atrial (LA) and left ventricular (LV) dimensions and mass followed the joint guidelines of the American Society of Echocardiography and the European Association of Cardiovascular Imaging.[6,7] Left ventricular global longitudinal strain (LV-GLS) was measured from the three apical views. The relative apical sparing index was calculated using the formula: average apical longitudinal strain (LS) / (average basal LS + mid-LS).[7]

LA volume was assessed using four-chamber and two-chamber views and calculated with the biplane area-length method.[4] LA volume was indexed to body surface area (BSA), and the LA volume index (LAVI) was calculated. For LA strain analysis, an LA-focused apical four-chamber view was obtained. We performed offline analysis to calculate the LA reservoir strain (LASr) using the onset of the QRS complex as the zero-reference point. LASr was defined as the peak LA strain during the cardiac cycle.[8]

All measurements of leaflet thickness are expressed in millimeters. Using echocardiography, the thickness of the mitral valve leaflets was measured from the parasternal long-axis and four-chamber views.[9] Aortic valve thickness was measured in a zoomed two-dimensional parasternal long-axis view at end-diastole. Abnormal leaflet thickness was defined as thickness greater than 2 mm for the aortic valve and greater than 3 mm for the mitral valves.[10] The maximum thickness of the interatrial septum was measured in an apical four-chamber view during the end-diastolic phase with zoom enhancement. An interatrial septum thickness exceeding 5 mm was classified as thickening.[11] Right ventricular (RV) wall thickness was assessed from subcostal views, with a thickness greater than 5 mm indicating RV hypertrophy.[6,12]

Cardiac 99mTc-PYP Scintigraphy

We performed 99mTc-PYP cardiac scintigraphy to diagnose TTR-CA, following the protocol recommended by current

guidelines.[13-15] After injecting 99mTc-PYP, we obtained planar images and quantitative Single-Photon Emission Computed Tomography (SPECT) images at both 1 and 3 hours post-intravenous injection.[13,14] The analysis included two methods:

1. Semi-Quantitative Visual Scoring: We evaluated cardiac uptake in the 3-hour planar images relative to bone (rib) uptake. The grading system was as follows:
   - Grade 0: No cardiac uptake with normal rib uptake;
   - Grade 1: Cardiac uptake less than rib uptake;
   - Grade 2: Cardiac uptake equal to rib uptake;
   - Grade 3: Cardiac uptake greater than rib uptake with mild or absent rib uptake.[13,14]
2. Quantitative Analysis: We calculated the heart-to-contralateral lung (H/CL) ratio by comparing the mean counts of the heart regions of interest (ROI) to the mean counts of the contralateral chest ROI at 1 hour.[13,14]

Concurrently with the scintigraphy, we performed serum free light chain assays, along with serum and urine protein electrophoresis with immunofixation. The criteria for a positive diagnosis of TTR-CA included negative serum free light chains, negative serum and urine immunofixation, myocardial uptake graded 2 to 3, and an H/CL ratio of ≥ 1.5.

Definitions of Red Flags

In our study, we identified specific cardiac and extra-cardiac symptoms and signs indicative of cardiac amyloidosis, which are classified as red flags. These were organized into two categories—cardiac and extra-cardiac—based on the guidelines from the "Diagnosis and Treatment of Cardiac Amyloidosis: A Position Statement of the European Society of Cardiology".[1]

Extra-cardiac clinical red flags identified in our study include polyneuropathy, carpal tunnel syndrome, dysautonomia, biceps tendon rupture, and lumbar spinal stenosis. Polyneuropathy was considered if the patient's medical history included peripheral nervous system involvement, such as neuropathic pain, sensory loss, or motor loss.[16] Orthostatic hypotension was classified under dysautonomia.[17] Additionally, renal insufficiency and proteinuria were identified as extra-cardiac laboratory red flags.

Cardiac red flags included clinical, electrocardiographic, echocardiographic, and laboratory indicators. Among the clinical red flags, hypotension or intolerance to antihypertensive treatment were highlighted. Hypotension was symptomatically defined as a systolic blood pressure below 90 mm Hg, intolerance to β-blockers/angiotensin-converting enzyme inhibitors, or the onset of normotension or hypotension in a patient previously diagnosed with hypertension.[1,18] Electrocardiographic red flags included atrioventricular (AV) conduction abnormalities, low or decreased QRS voltage, or a pseudo-infarct pattern on the ECG. A disproportionately elevated N-terminal pro b-type natriuretic peptide (NT-proBNP) was defined as a cardiac laboratory red flag, specifically identified as an exaggerated NT-proBNP elevation disproportionate to LV mass.[19] Cardiac echocardiographic red flags included increased valve thickness, granular sparkling appearance of the myocardium, presence of pericardial effusion, increased RV wall thickness, and reduced LV-GLS with apical sparing.[1] TTR-CA positive and negative groups were compared based on the presence of these red flags. The details of the evaluated red flags are presented in Table 1.

Statistical Analysis

Continuous variables were presented as means with standard deviations (SD) and compared using t-tests when the data

Table 1. Cardiac and Extracardiac Red Flags of Cardiac Amyloidosis

Extracardiac Red Flags	**Clinical Red Flags** • Polyneuropathy • Dysautonomia • Macroglossia • Bilateral carpal tunnel syndrome • Ruptured biceps tendon • Lumbar spinal stenosis • Family history **Laboratory Red Flags** • Renal insufficiency • Proteinuria
Cardiac Red Flags	**Clinical Red Flag** • Hypotension or normotensive if previously hypertensive **ECG Red Flags** • Pseudo infarct pattern • Low or decreased QRS voltage relative to LV thickness • AV conduction disease **Laboratory Red Flag** • Disproportionally elevated NT-proBNP relative to HF severity **Echocardiogram Red Flags** • Granular sparkling of the myocardium • Increased right ventricular wall thickness • Increased valve thickness • Pericardial effusion • Reduced longitudinal strain with apical sparing pattern

AV, Atrioventricular; ECG, Electrocardiogram; HF, Heart Failure; LV, Left Ventricular; NT-proBNP, N-Terminal Pro B-type Natriuretic Peptide.

Table 2. Characteristics of HFpEF Patients with and without Transthyretin Cardiac Amyloidosis

Variables	Total (n = 167)	TTR-CA Negative (n = 148)	TTR-CA Positive (n = 19)	*P*
Age, years, mean ± SD	68.1 ± 10.1	67.7 ± 10.2	71.63 ± 9.2	0.117
Male Sex, n (%)	64 (38.3)	56 (37.8)	8 (42.1)	0.451
≥ 65 years, n (%)	109 (65.3)	92 (62.2)	17 (89.5)	0.013
Hypertension, n (%)	124 (74.3)	110 (74.3)	14 (73.7)	0.573
Diabetes, n (%)	56 (33.5)	51 (34.5)	5 (26.3)	0.334
Coronary Artery Disease, n (%)	53 (31.7)	45 (30.4)	8 (42.1)	0.218
Atrial Fibrillation, n (%)	67 (40.1)	58 (39.2)	9 (47.4)	0.328
Chronic Kidney Disease, n (%)	54 (32.3)	47 (31.8)	7 (36.8)	0.417
Anemia, n (%)	77 (46.1)	67 (45.3)	10 (52.6)	0.358
Creatinine, mg/dL, mean ± SD	1.2 ± 0.7	1.17 ± 0.74	1.29 ± 0.61	0.624
Hemoglobin, gr/dL, mean ± SD	12.6 ± 2.1	12.6 ± 2.2	12.7 ± 1.8	0.829
NT-proBNP, pg/mL, median (IQR)	1100 (553-2545)	1087.5 (535-2397.7)	1501 (820-2613)	0.058

HFpEF, Heart Failure with Preserved Ejection Fraction; IQR, Interquartile Range; NT-proBNP, N-Terminal Pro B-type Natriuretic Peptide; SD, Standard Deviation; TTR-CA, Transthyretin Cardiac Amyloidosis.

were normally distributed. For non-normally distributed data, variables were presented as medians with interquartile ranges (IQR) and compared using the Mann-Whitney U test. Analyses were performed using IBM Statistical Package for the Social Sciences (SPSS) Statistics 21.0 software (IBM Corp., released in 2012, Armonk, NY, USA). A p-value less than 0.05 was considered statistically significant. The power of red flags and other important variables in predicting CA was assessed through both univariate and multivariate regression analyses. The odds ratio (OR) and its 95% confidence interval (CI) were calculated.

Results

Baseline Characteristics

The study included 167 patients who underwent cardiac 99mTc-PYP scintigraphy under suspicion of CA. The mean age was 68.1 years (SD = 10.1), with 38.3% of the participants being male. The mean LV wall thickness (LVWT) was 14.1 mm (SD = 3.6), and the median NT-proBNP level was 1100 pg/ml (IQR = 553-2545) (Table 2).

Prevalence of Transthyretin Cardiac Amyloidosis

Out of the 167 scintigraphy studies conducted, 23 (13.7%) were positive for TTR-CA with grade 2 to 3 myocardial uptake and a heart-to-contralateral lung (H/CL) ratio of ≥ 1.5. Four patients with positive 99mTc-PYP scintigraphy results were deemed false positive. One of these patients was diagnosed with AL amyloidosis following simultaneous immunofixation tests. The other 3 patients were re-evaluated as grade 1 due to low suspicion. Consequently, 19 (11.3%) patients were diagnosed with CA, including 18 with wild-type TTR-CA (wtTTR-CA) and 1 with mutant TTR-CA (mTTR-CA). Serum and urine immunofixation and free light chain tests were normal in all these patients.

Comparison of Patients Positive and Negative for TTR-CA

No differences were observed between the TTR-CA positive and negative groups in terms of age and gender (P = 0.117, P = 0.451). Within the TTR-CA positive group, 17 (89.5%) patients were aged 65 years or older. There was also no difference in comorbidities between the groups (Table 2).

Regarding ECG features, low voltage was more frequent in the TTR-CA positive group compared to the negative group (26.3% vs. 2.7%, P = 0.001), as was the pseudo-infarct pattern (21.1% vs. 6.8%, P = 0.005). Although the difference in the incidence of AV block was not statistically significant, it occurred more frequently in the TTR-CA positive group (10.5% vs. 1.4%, P = 0.064) (Table 3).

Among all participants (n = 167), 126 (75.4%) patients had LVWT ≥ 12 mm on echocardiography. All patients diagnosed with TTR-CA had a LVWT ≥ 12, indicating that left ventricular hypertrophy was more common in the TTR-CA positive group (100% vs. 72.3%, P = 0.003). The LV-GLS was lower in the TTR-CA positive group (-12.0 ± 3.8 vs. -14.8 ± 2.8; P < 0.001). Additionally, interatrial septal thickening was more frequent in the TTR-CA positive group (P = 0.020). In a more comprehensive echocardiographic evaluation, there was no difference in LAVI between the two groups (P = 0.841); however, the LASr was lower in the TTR-CA positive group (13.2 ± 6.0 vs. 19.7 ± 9.4; P = 0.005) (Table 3).

Red Flag Features in Patients with Transthyretin Cardiac Amyloidosis

In this study, red flags were analyzed in various categories as indicators of CA. We assessed the frequency and differences in cardiac and extra-cardiac red flags between the TTR-CA positive and negative groups. Among the participants, 73.7% of those with TTR-CA positive and 54.7% of those with TTR-CA negative exhibited extra-cardiac red flags (P = 0.091). No differences were observed between the groups regarding extra-cardiac clinical and laboratory red flags (P = 0.191 and P = 0.213, respectively).

Cardiac red flags were identified in 73.7% of TTR-CA positive patients and 81.1% of TTR-CA negative patients (P = 0.311).

Table 3. Electrocardiographic and Echocardiographic Features of Patients

Variables	Total (n = 167)	TTR-CA Negative (n = 148)	TTR-CA Positive (n = 19)	*P*
LV Ejection Fraction, %, mean ± SD	60.9 ± 5.3	61.1 ± 5.4	59.3 ± 4.1	0.152
LV End-Diastolic Diameter, mm, mean ± SD	47.5 ± 6.4	47.5 ± 6.5	47.4 ± 5.9	0.937
IVSd, mm, median ± SD	14.1 ± 3.6	14.0 ± 3.6	15.1 ± 3.1	0.206
IVS Thickness ≥12 mm, n (%)	126 (75.4)	107 (72.3)	19 (100)	0.003
LAVI, ml/m^2, mean ± SD	39.0 ± 15.3	38.6 ± 15.6	39.4 ± 15.4	0.841
Septal E' Wave, cm/s, mean ± SD	6.4 ± 2.0	6.5 ± 2.07	5.7 ± 1.8	0.134
sPAP, mmHg, mean ± SD	41.6 ± 15.8	41.5 ± 15.9	41.9 ± 15.0	0.928
LA Dilatation, n (%)	141 (84.4)	125 (84.5)	16 (84.2)	0.598
Aortic Valve Thickness, n (%)	26 (15.6)	17 (11.5)	9 (47.4)	<0.001
LAVI > 34 ml/m^2, n (%)	105 (62.9)	92 (62.2)	13 (68.4)	0.397
Peak TR Velocity > 2.8 m/s, n (%)	85 (50.9)	76 (51.4)	9 (47.4)	0.467
Right Ventricular Hypertrophy, n (%)	23 (13.8)	19 (12.8)	4 (21.1)	0.253
Interatrial Septum Hypertrophy, n (%)	6 (3.6)	3 (2.0)	3 (15.8)	0.020
LV-GLS, %, mean ± SD	-14.5 ± 3.0	-14.8 ± 2.8	-12.0 ± 3.8	<0.001
Apical/(Mid + Basal) LS Ratio, mean ± SD	0.99 ± 0.3	0.95 ± 0.28	1.4 ± 0.63	<0.001
Left Atrial Reservoir Strain, %, mean ± SD	18.9 ± 9.3	19.7 ± 9.4	13.2 ± 6.0	0.005
Right Ventricular Free Wall Strain, %, mean ± SD	-19.2 ± 5.8	-19.6 ± 5.5	-15.2 ± 6.8	0.005
Heart Rate, beats per minute, mean ± SD	78.5 ± 18.0	78.5 ± 17.6	82.8 ± 20.8	0.277
PR Interval, ms, mean ± SD	152.5 ± 39.9	149.0 ± 37.8	184.0 ± 46.9	0.008
Low QRS, n (%)	9 (5.4)	4 (2.7)	5 (26.3)	0.001
AV Block, n (%)	4 (2.4)	2 (1.4)	2 (10.5)	0.064
Pseudoinfarct Pattern, n (%)	14 (8.4)	10 (6.8)	4 (21.1)	0.048

AV, Atrioventricular; GLS, Global Longitudinal Strain; IVS, Interventricular Septum; IVSd, Interventricular Septum Diameter; LA, Left Atrium; LAVI, Left Atrial Volume Index; LS, Longitudinal Strain; LV, Left Ventricular; sPAP, Systolic Pulmonary Artery Pressure; SD, Standard Deviation; TR, Tricuspid Regurgitation; TTR-CA, Transthyretin Cardiac Amyloidosis.

The specific cardiac clinical red flag of 'hypotension or becoming normotensive after previously being hypertensive' was significantly more prevalent in the TTR-CA positive group (21.1% vs. 0.7%; *P* = 0.001). Electrocardiographically, the presence of low or decreased QRS voltage was significantly higher in the TTR-CA positive patients (26.3% vs. 2.7%; *P* = 0.001). Echocardiographically, granular sparkling of the myocardium (31.6% vs. 0.7%; *P* < 0.001) and reduced LV-GLS with an apical sparing pattern (29.4% vs. 2.7%; *P* = 0.001) were more common in TTR-CA positive patients. The details of red flags observed across all patients are detailed in Tables 4 and 5. Furthermore, Figure 1 illustrates the distribution of red flags among all HFpEF patients, as well as between TTR-CA positive and negative groups.

Multivariate regression analysis identified several red flags as strong and independent predictors of TTR-CA diagnosis in HFpEF patients. These included age ≥ 65 years (OR: 7.8, *P* = 0.023), pseudo infarct pattern (OR: 6.85, *P* = 0.024), low or decreased QRS voltage (OR: 16.92, *P* = 0.027), and lower LV-GLS (OR: 1.23, *P* = 0.023) (Table 6).

Discussion

This study has highlighted specific red flags that strongly suggest CA in patients diagnosed with HFpEF. Key findings from our analysis include:

1. Prevalence of TTR-CA: Our results indicate that 11.3% of HFpEF patients had TTR-CA as the underlying etiology.
2. Strong Predictors of TTR-CA: The most significant predictors for diagnosing TTR-CA in HFpEF patients were older age, the presence of a pseudo infarct pattern on an electrocardiogram, low or decreased QRS voltage, and reduced LV-GLS.
3. Diagnostic Value of Red Flags: The presence of three or more red flags supported the likelihood of a TTR-CA diagnosis.

TTR-CA is a significant underlying etiological cause in HFpEF.[1-3] There is a critical need for greater recognition of diagnostic 'red flags' to facilitate the early detection of HFpEF patients with a TTR-CA etiology. These red flags encompass a range of indicators including cardiac and extra-cardiac clinical findings, demographic characteristics, electrocardiographic and echocardiographic features, and various laboratory findings, all of which raise suspicion for the diagnosis of CA in patients with HFpEF.

Table 4. Presence of Red Flags and Comparison Between Groups

Variables (n, %)	Total (n=167)	TTR-CA Negative (n = 148)	TTR-CA Positive (n = 19)	*P*
Peripheral Polyneuropathy	16 (9.6%)	12 (8.1%)	4 (21.1%)	0.090
Dysautonomia	7 (4.2%)	5 (3.4%)	2 (10.5%)	0.182
Macroglossia	-	-	-	-
Bilateral Carpal Tunnel Syndrome	2 (1.2%)	0 (0%)	2 (10.5%)	-
Ruptured Biceps Tendon	-	-	-	-
Lumbar Spinal Stenosis	-	-	-	-
Family History	-	-	-	-
Renal Insufficiency (GFR < 60 ml/min/1.73 m^2)	69 (41.3%)	62 (41.9%)	7 (36.8%)	0.436
Proteinuria	24 (14.4%)	19 (12.8%)	5 (26.3%)	0.113
Hypotension or Normotensive if Previously Hypertensive	5 (3%)	1 (0.7%)	4 (21.1%)	0.001
Pseudo-Infarct Pattern	14 (8.4%)	10 (6.8%)	4 (21.1%)	0.050
Low/Decreased QRS Voltage to Degree of LV Thickness	9 (5.4%)	4 (2.7%)	5 (26.3%)	0.001
AV Conduction Disease	4 (2.4%)	2 (1.4%)	2 (10.5%)	0.064
Disproportionately Elevated NT-proBNP	9 (5.4%)	5 (3.4%)	4 (21.1%)	0.022
Granular Sparkling of the Myocardium	7 (4.2%)	1 (0.7%)	6 (31.6%)	<0.001
Increased Right Ventricular Wall Thickness	23 (13.8%)	19 (12.8%)	4 (21.1%)	0.253
Increased Valve Thickness	126 (75.4%)	107 (72.3%)	19 (100%)	0.003
Interatrial Septum Hypertrophy	6 (3.6%)	3 (2.0%)	3 (15.8%)	0.020
Pericardial Effusion	14 (8.4)	13 (8.8)	1 (5.3%)	0.508
Reduced LS with Apical Sparing Pattern	9 (5.5%)	4 (2.7%)	5 (29.4%)	0.001

AV, Atrioventricular; GFR, Glomerular Filtration Rate; NT-proBNP, N-Terminal Pro B-type Natriuretic Peptide; LS, Longitudinal Strain; LV, Left Ventricular; SD, Standard Deviation; TTR-CA, Transthyretin Cardiac Amyloidosis.

Table 5. Red Flag Categories in All Patients

Variables	Total (n=167)	TTR-CA Negative (n = 148)	TTR-CA Positive (n = 19)	P
Extra-Cardiac Red Flags				
Extra-Cardiac Clinical, n (%)	28 (16.8)	23 (15.5)	5 (26.3)	0.191
Extra-Cardiac Laboratory, n (%)	78 (46.7)	67 (45.3)	11 (57.9)	0.213
Cardiac Red Flags				
Clinical, n (%)	5 (3)	1 (0.7)	4 (21.1)	0.001
Electrocardiogram, n (%)	23 (13.8)	15 (10.1)	8 (42.1)	0.001
Laboratory, n (%)	10 (6.0)	6 (4.1)	4 (21.1)	0.016
Echocardiography, n (%)	126 (75.4)	112 (75.7)	14 (73.7)	0.522
Red Flag Numbers				
Total RF per Patient	2.0 ± 1.3	1.85 ± 1.0	3.26 ± 2.4	0.001
≥ 2 RFs	109 (65.3)	94 (63.5)	15 (78.9)	0.140
≥ 3 RFs	17 (10.2)	11 (7.4)	6 (31.9)	0.040

RF, Red Flag; TTR-CA, Transthyretin Cardiac Amyloidosis.

Table 6. Univariate and Multivariate Analysis of Red Flags in Predicting Cardiac Amyloidosis in HFpEF Patients

Variables	Univariate OR (95% CI)	*P*	Multivariate OR (95% CI)	*P*
≥ 65 Years	14.2 (1.352-149.9)	0.027	**7.80 (1.32-46.06)**	**0.023**
Pseudo-Infarct Pattern	15.07 (1.34-169.2)	0.028	**6.85 (1.29-36.21)**	**0.024**
Low/Decreased QRS Voltage to Degree of LV Thickness	5.77 (0.262-127.4)	0.267	**16.92 (2.45-11.9)**	**0.027**
LV Global Longitudinal Strain	0.86 (0.613-1.217)	0.401	**1.23 (1.02-1.45)**	**0.023**
Peripheral Polyneuropathy	0.72 (0.061-8.558)	0.798		
Dysautonomia	0.00 (0.000-0.001)	0.999		
Bilateral Carpal Tunnel Syndrome	0.00 (0.000-0.001)	1.000		
Renal Insufficiency (GFR < 60 ml/min/1.73 m^2)	0.45 (0.094-2.160)	0.319		
Proteinuria	2.57 (0.351-18.84)	0.353		
Hypotension or Normotensive if Previously Hypertensive	1.15 (0.000-0.001)	0.998		
AV Conduction Disease	0.00 (0.000-0.001)	1.000		
Disproportionately Elevated NT-proBNP	0.00 (0.000-0.001)	0.999		
Granular Sparkling of the Myocardium	3.17 (0.000-0.001)	0.997		
Increased Right Ventricular Wall Thickness	1.05 (0.072-15.45)	0.970		
Increased Valve Thickness	1.33 (0.165-10.85)	0.784		
Interatrial Septum Hypertrophy	0.00 (0.000-0.001)	0.998		
Pericardial Effusion	0.81 (0.076-8.58)	0.861		
Reduced Longitudinal Strain with Apical Sparing Pattern	0.00 (0.000-0.001)	0.999		
IVS Thickness ≥12 mm	2.52 (0.309-20.69)	0.387		
Right Ventricular Free Wall Strain	1.05 (0.887-1.242)	0.572		
Left Atrial Reservoir Strain	0.98 (0.886-1.104)	0.843		

AV, Atrioventricular; GFR, Glomerular Filtration Rate; IVS, Interventricular Septum; LV, Left Ventricular; NT-proBNP, N-Terminal Pro B-type Natriuretic Peptide.

Primarily, the key factors linked to the diagnosis of CA in patients with HFpEF are older age and male gender.[1] Research has shown that TTR-CA becomes more prevalent with advancing age and is an important underlying cause of HFpEF in patients aged 65 years and older.[20] In our study, the average age of patients in the TTR-CA positive group was 71.6 (± 9.2) years. Additionally, 89.5% of the patients in this group were aged 65 years or older, a proportion significantly higher than in the TTR-CA negative group (*P* = 0.013). Another important aspect of TTR-CA prevalence relates to gender differences. wtTTR-CA is typically reported to have a significant male predominance.[21] However, our study revealed some deviations from this trend in terms of gender distribution among TTR-CA positive HFpEF patients. One of the notable findings in our study was that the proportion of male patients in the TTR-CA positive HFpEF group was lower than expected, with only 42% of these patients being male. Typically, wtTTR-CA occurs predominantly in men, as documented in previous research.[22,23] However, in our study, over 60% of the TTR-CA positive patients were female. This female gender predominance of the study population may have influenced the results. Additionally, it is hypothesized that the lower observed frequency of the disease in women compared to men may be due to underdiagnosis in female patients.[24]

Secondly, echocardiography serves as an initial imaging modality for evaluating many cardiac red flags, and it often reveals numerous echocardiographic red flags in HFpEF patients suspected of having TTR-CA. A previously published study with a smaller cohort of HFpEF patients reported that echocardiographic red flags were detected in six out of every ten patients with TTR-CA.[25] Among these red flags, unexplained left ventricular hypertrophy (LVH) is one of the most important findings, as it raises the clinician's suspicion of TTR-CA during the echocardiographic evaluation of a patient with HFpEF. Previous studies have reported that the prevalence of TTR-CA in patients with LVH ranges between 13% and 19%.[25-28] While LVH is recognized as an important finding, a recent study found that the prevalence of CA in HFpEF patients without LVH was 5.2%.[24] In contrast, our study did not obtain any grade 2 or 3 99mTc-PYP scintigraphy results in HFpEF patients lacking LVH, and none of these patients were diagnosed with TTR-CA. In the present study, all patients diagnosed with TTR-CA exhibited increased LVWT. Additionally, LV-GLS is valuable in detecting myocardial dysfunction in CA.[30] In our study, reduced LV-GLS was one of the red flags that effectively predicted TTR-CA in HFpEF patients, with 29.4% of TTR-CA patients exhibiting reduced LV-GLS with apical sparing. Relative apical sparing is believed to result from complex interactions among amyloid infiltration, myocardial structure, and adaptation. Consistent with the findings of our study, it has been reported that one-third of CA patients exhibit apical sparing.[31]

Other echocardiographic red flags for CA include granular sparkling, increased valve thickness, interatrial septum hypertrophy, and increased RV wall thickness.[1] In our study population, while no difference was observed in RV wall thickness between the TTR-CA positive and negative groups, the frequency of interatrial septum hypertrophy and valve thickness was significantly higher in the TTR-CA positive group. Additionally, while granular sparkling observed in echocardiography is characteristic, it is not specific to the diagnosis of CA. However, this feature has a reported sensitivity of 87% and a specificity of 81%.[32] In our study, the presence of granular sparkling was found in 31% of TTR-CA positive patients, significantly higher than in those who were TTR-CA negative.

Thirdly, electrocardiographic findings play a crucial role in raising suspicion of CA. These findings include low voltage on the ECG, a "pseudo infarct" pattern, and AV conduction abnormalities, which may indicate the presence of underlying CA. Particularly, the diagnosis of CA should be considered when there is a notable discrepancy between ECG voltage and LVWT observed on echocardiography.[33] Previous studies have documented an overall prevalence of low voltage in TTR-CA from 25% to 40%.[34] Furthermore, low voltage has been significantly associated with markers of advanced disease and has demonstrated prognostic significance.[35-39] In our study, the incidence of low QRS voltage in the TTR-CA positive group was 26.3%, which was significantly higher than in the TTR-CA negative group. Additionally, the current study identified that both a pseudo infarct pattern on the electrocardiogram and low/decreased QRS voltage are strong and independent predictors of TTR-CA diagnosis in patients with HFpEF. Another frequent manifestation associated with TTR-CA is atrial fibrillation (AF); prior studies have indicated that it occurs in approximately 70% of patients with wtTTR-CA.[40] In our study, the rate of AF was 47.4% in the TTR-CA positive group, and there was no difference in the rate of AF between the TTR-CA positive and negative groups ($P = 0.328$). According to the literature, both older age and advanced stages of TTR-CA are linked with the occurrence and frequency of AF in patients with TTR-CA.[41] The slightly lower prevalence of AF in our study compared to others may be attributed to differences in demographic characteristics, the degree of diastolic dysfunction, variations in LA structure and function, and the stage of the disease among the study populations.[41] Additionally, we did not perform Holter monitoring on all patients, which may have resulted in underreporting of occult AF occurrences.

Finally, extra-cardiac coexisting findings that should alert clinician to consider CA in patients presenting with HFpEF include autonomic dysfunction, peripheral neuropathy, carpal tunnel syndrome, biceps tendon rupture, and lumbar spinal stenosis.[1] In a study examining both extra-cardiac and cardiac findings in CA, it was reported that initial extra-cardiac findings as the first historical symptoms occurred in 46% to 63% of patients with wtTTR-CA.[42] In our study, 73.7% of TTR-CA positive patients exhibited extra-cardiac red flags. None of our patients presented with TTR-CA red flags such as carpal tunnel syndrome or lumbar spinal stenosis, which may be attributed to the small size of our patient cohort. The most common extra-cardiac findings in our study were renal failure, proteinuria, and polyneuropathy. Although renal failure is a common comorbidity in patients with HFpEF, there is a gap in understanding how renal failure and proteinuria are associated with TTR-CA in this patient population. Increased awareness and knowledge of both extra-cardiac clinical manifestations and cardiac features are essential to enhance early diagnosis of this condition.

Limitations

Our study has certain limitations. One significant limitation is the relatively small number of patients, which may explain the absence of certain TTR-CA red flags such as carpal tunnel syndrome and lumbar spinal stenosis in our findings. Another limitation is the lack of evaluation of cardiac magnetic resonance imaging findings, which, while not essential for diagnosis, are an important part of the red flag evaluation for TTR-CA. Nevertheless, we believe that our study can impact clinical practice by identifying the most important red flags for predicting TTR-CA.

Conclusion

TTR-CA is associated with several distinct clinical features, commonly referred to as red flags. Recognizing these red flags is crucial for the early diagnosis of CA. Our study found that 11.3% of patients with HFpEF had TTR-CA as the underlying etiology. Older age, a pseudo infarct pattern on the electrocardiogram, low or decreased QRS voltage, and reduced LV-GLS are prominent red flags that strongly suggest the presence of TTR-CA in patients with HFpEF.

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