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Results of a Screening Program for Diagnosis of Amyloid Cardiomyopathy Among Patients with Left Ventricular Hypertrophy: PAPCAT Cardiac Amyloidosis Türkiye Survey

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ABSTRACT

Background: Cardiac amyloidosis (CA) is an increasingly recognized disease. Several recent advanced imaging techniques and parameters have been introduced into the diagnosis of CA. However, the first step in using those techniques is clinical suspicion. Left ventricular hypertrophy (LVH) is the main entity in rising the suspicion of CA in routine echocardiography, although it is not a diagnosis for CA. The aim of this study is to investigate the prevalence of CA and its subtypes and predictive value of clinical and echocardiographic red flags of CA among consecutive adult patients with LVH identified during routine echocardiographic examination in 25 tertiary institutions in Türkiye.

Methods: This was a prospective observational multicenter, national registration study. Patients with LVH (interventricular septum thickness ≥13 mm or >15 mm in those with hypertension) were screened for CA stepwise. The first step was a clinical questionnaire for the red flags of CA. Those having ≥2 red flags were further analyzed by detailed echocardiography, blood tests, Tc-pyrophosphate (PYP) bone scintigraphy, and histopathological examination if needed. Parameters associated with CA were evaluated via univariate and multivariate analyses. Wild-type transthyretin (wTTR) vs. mutant-type TTR (mTTR), CA discriminators were also evaluated in the same manner.

Results: A total of 420 patients meeting these criteria were included in the study. With a standardized algorithmic approach, 27.1% (114) of patients received a CA diagnosis. Among these patients with CA, 50.8% (58) were diagnosed with immunoglobulin free chain (AL) CA, 38.6% (44) with wTTR CA, and 7% (8) with mTTR CA. Left ventricular apical sparing pattern and restrictive type LV filling on echocardiography, low QRS voltage on ECG, bilateral carpal tunnel syndrome, low blood pressure, right ventricular diameter, and an increased basal heart rate (HR) were independent predictors for CA diagnosis. When it comes to diagnosis of wTTR CA; advanced age (age >75), lower troponin values, absence of pericardial effusion and absence of proteinuria were the independent predictors.

Conclusion: Cardiac amyloidosis is highly prevalent in a patient population with LVH and >2 red flags who underwent a standardized algorithmic approach, in which apical sparing, restrictive filling pattern, low QRS voltage, carpal tunnel syndrome, low blood pressure, and increased HR are the highly suggestive signs of CA. Among this pool of newly diagnosed CA patients in Türkiye, AL-CA constituted 50.8%, wTTR CA 38.6%, and mTTR CA 7%, emphasizing that approximately 1 in 2 patients diagnosed with CA may have TTR CA.

Keywords: Amyloidosis, cardiac amyloidosis, left ventricular hypertrophy, transthyretin cardiac amyloidosis

INTRODUCTION

Systemic amyloidosis is a clinical condition referring to a heterogenous group of disorders that are characterized by deposition of amyloid fibrils in the extracellular space. Cardiac amyloidosis (CA) is the most significant contributor to morbimortality in systemic amyloidosis; its most common forms include immunoglobulin free chain (AL) or transthyretin (TTR) amyloidosis. Early diagnosis plays a pivotal role in determining prognosis for both AL and TTR forms. However, due to nonspecific symptoms related to systemic involvement and lack of awareness among

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physicians, patients often receive a late diagnosis. The emergence of new therapeutic agents that change the course of the disease in both AL and TTR forms has further increased the importance of early diagnosis. Recent data on the high prevalence of wild-type TTR (wTTR) CA in general population further emphasize the importance of this matter. Recent data from various studies indicate that TTR CA was present in 25% of cardiac autopsies in patients over 75 years old,[1] 13% of those with preserved ejection fraction (EF) heart failure (HF),[2] 16% of patients with Alzheimer's disease undergoing transcatheter aortic valve implantation,[3] 5% of patients with chronic decompensated HF,[4] and 1-2% of individuals who underwent DPD/PYP bone scintigraphy for other reasons.[5]

A notable development in this field involves the demonstration that cardiac uptake on DPD/PYP bone scintigraphy has high specificity and sensitivity for diagnosis of TTR-type CA. This eliminated the necessity of biopsy for diagnosis, significantly simplifying the diagnostic process. However, all these developments have not yet been fully reflected in routine practice, with awareness of both the clinical manifestations and screening methods of CA remaining suboptimal. Additionally, existing prevalence data on CA have not been derived from studies designed to represent the general population. There are very different prevalence data in the literature, varying significantly depending on the characteristics of the study population and the study design.

Genetic mutations responsible for mTTR amyloidosis vary significantly according to geographical regions.[6] The prevalance of wTTR amyloidosis varies depending on parameters such as demographic characteristics of the population and endemic factors in the geographical region.

Prevalence data in both TTR amyloidosis and AL amyloidosis are directly related to the availability and accessibility of healthcare services and disease awareness.

Given these considerations, it is essential to investigate data on the prevalance of CA and the characteristics of patients with CA in Türkiye. This study aimed to elucidate data on the prevalence of CA and patient characteristics in Türkiye using an appropriate diagnostic algorithm in individuals with echocardiographic evidence of cardiac hypertrophy, the first sign of CA.

METHODS

This was a prospective observational multicenter registration study. The study involved 25 tertiary sites located across various geographical parts of Türkiye. Patients with suspected CA due to the presence of cardiac hypertrophy and clinical findings were consecutively included in the study if they met the inclusion and exclusion criteria.

HIGHLIGHTS

- Cardiac amyloidosis is highly prevalent in a patient population with LVH and >2 red flags who underwent a standardized algorithmic approach; 1 in 4 patients reached a final diagnosis of CA with this approach. This standardized algorithm may be a guide for the clinicians for whom to perform a full CA diagnostic work-up.
- As long as the study was conducted as a multicenter national registry, the results give insights about the prevalence rates of CA subtypes in Türkiye. In this aspect, this is the first study in literature, representing a general profile of CA patients in Türkiye. In the whole CA population, AL-CA constituted 50.8%, wTTR CA 38.6%, and mTTR CA 7%, emphasizing that approximately 1 in 2 patients diagnosed with CA may have TTR CA in Türkiye.
- The results of this study holds importance for precise analysis of routine physical examinations, ECGs, blood and urine tests, and echocardiographic data in diagnosis of CA and its subtypes. Apical sparing and restrictive filling pattern on echocardiography, low QRS voltage, carpal tunnel syndrome, low blood pressure, and increased HR are the highly suggestive signs of CA. Wild-type TTR CA patients represented a subgroup with an isolated cardiac involvement and a favorable clinical profile compared to AL CA patients.

Table 1. Screenning Questionnaire for Cardiac Amyloidosis

1. Finding or history of peripheral neuropathy with numbness in the hands and feet	Yes No
2. GI symptoms such as weight loss, diarrhea-constipation episodes, abdominal bloating	Yes No
3. Clinical findings consistent with restrictive cardiomyopathy (neck venous distention, ascites, peripheral edema, signs of low-output heart failure.)	Yes No
4. Disproportionately low voltage on ECG	Yes No
5. Unexplained chronic pleural-pericardial effusion	Yes No
6. Bundle branch block of unknown cause on ECG	Yes No
7. Family history of amyloidosis	Yes No Unknown
8. Chronic, unexplained moderate troponin elevation	Yes No Unknown
9. Chronic natriuretic peptide elevation (BNP>100, NT-proBNP>300 pg/ml)	Yes No Unknown
10. Presence of proteinuria without diabetes or hypertension	Yes No Unknown
11. Signs of senile type cardiac amyloidosis: Any of the following cardiac findings in patients over 70 years of age:	
• Low flow severe aortic stenosis	Yes No
• Persistent atrial fibrillation	Yes No
• Heart failure with preserved EF or mid-range EF (in patients without a restrictive pattern, ischemic or with no other known etiology)	Yes No
• Microvascular angina	Yes No
12. Autonomic neuropathy findings	
• Normotension in a previously hypertensive patient or hypotension	Yes No
• Orthostatic Hypotension on physical examination	Yes No
• Intolerance to Beta Blockers and ACE inhibitors	Yes No
• History of syncope	Yes No
• Other findings of Autonomic Neuropathy (erectile dysfunction, sweating disorders..)	Yes No
13. Findings of amyloid soft tissue deposition	
• Carpal Tunnel Syndrome	Yes No Unknown
• Macroglossia	Yes No Unknown
• Spinal stenosis	Yes No Unknown
• Biceps tendon rupture	Yes No Unknown
• Periorbital ecchymosis	Yes No Unknown
14. Typical imaging findings of cardiac amyloidosis	
• Biventricular hypertrophy with granular pattern on ECHO	Yes No
• Apical preservation pattern in strain imaging	Yes No
• Difficulty distinguishing null point in cardiac MRI/ late enhancement/increase in extracellular volume	Yes No
• Typical cardiac involvement in PYP/DPD/HDMP bone scintigraphy performed for another reason	Yes No

Inclusion Criteria

Patients were included in the study if they met the following criteria:

- 18 years old or older,
- Informed about the study and provided informed consent,
- Presented with left ventricular hypertrophy (LVH): this included all patients with LVH (IVS ≥13 mm) without pressure or volume overload; and those diagnosed with hypertension and aortic stenosis having an IVS >15 mm,
- Clinical suspicion of CA: a screening questionnaire for evidence of CA red flags was created and patients with at least 2 positive findings in different categories were included in the study (Table 1).
- Fullfilment of all the above criteria.

Exclusion Criteria

- Patients with conditions other than aortic stenosis and arterial hypertension that caused left ventricular pressure or volume overload (other valvular diseases, chronic renal failure, congenital heart disease, other hypertrophic cardiomyopathies proven by genetic or clinical findings, or known CA).

Patient Population

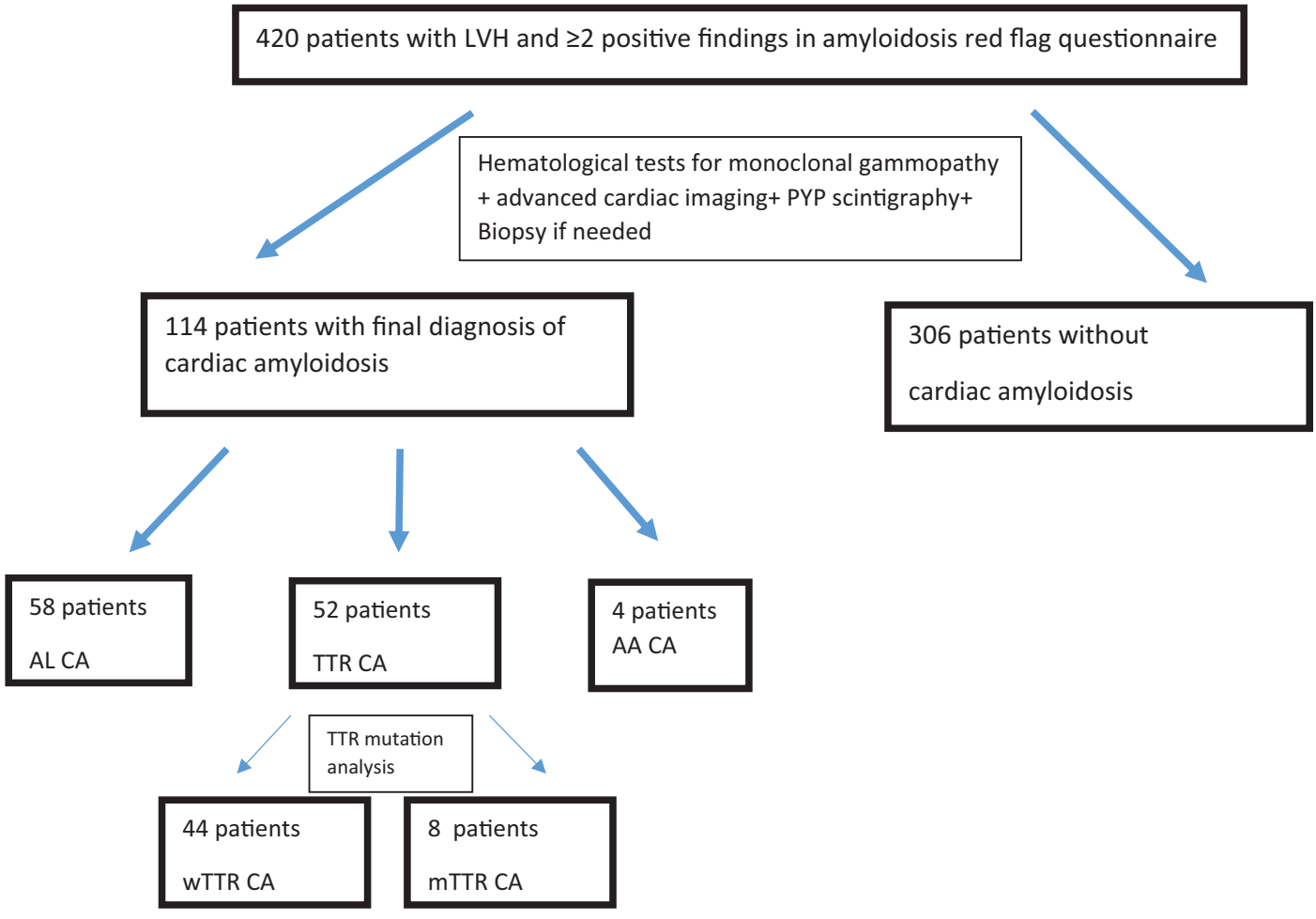
A total of 420 patients meeting these criteria were included in the study between September 17, 2020, and December 23, 2022. These patients underwent assessment for the presence of CA in accordance with the CA diagnostic algorithm outlined in the guideline, with all findings meticulously documented.[7-9] Their medical history, demographic data, ECG data, physical examination outcomes, baseline blood tests, and questionnaire data related to CA features were all

recorded. Blood and urine analysis, ECG evaluation, echocardiographic measurements, Tc-PYP scintigraphy, genetic analysis, and histopathological evaluation used in the diagnostic algorithm of CA were performed in accordance with the guidelines.[7]

All of the patients underwent clinical evaluation, blood and urine tests, and scintigraphy with bone tracer. Diagnosis of TTR CA was made in the presence of grade 2 or 3 myocardial uptake of 99mTc-pyrophosphate (PYP) cardiac scintigraphy and absence of clonal dyscrasia with blood and urine tests, according to the latest European Society of Cardiology position statement.[7] Discrimination of wild-type and mutant-type TTR-CA was made according to the mutation analysis. In the presence of grade 1 myocardial uptake of radiotracer, cardiac magnetic resonance (CMR), and/or histological analysis were performed to rule out or confirm the diagnosis of CA and, eventually, to determine the subtype. All patients with AL-CA were histologically proven.

Data Analysis

Data analysis was performed using JASP 17.3 (open source software with structural support from the University of Amsterdam) and R Programme 4.1.0. (free software environment for statistical computing and graphics). Continuous data were presented as means and standard deviations. Categorical data were shown as counts and percentages. Significance assessment of the continuous data with 2 independent groups were analyzed with robust 2independent groups *t*-test (Yuen's Method with 1000 bootstrap replicatesyuenbt). Fligner-Killeen test was performed to assess the test of homogeneity of variances. Continuous data with more than 2 independent groups were analyzed with robust 1-way ANOVA (Welch's method with 1000 bootstrap



LVH: left ventricular hypertrophy, AL CA: AL type cardiac amyloidosis, TTR CA: transthyretin cardiac amyloidosis

wTTR CA: wild type transthyretin cardiac amyloidosis, mTTR CA: mutant type transthyretin cardiac amyloidosis

Figure 1. Study flowchart and distribution of the patients with cardiac amyloidosis and amyloidosis subtypes in the whole study population.

replicates—t1waybt). For significance test of the contingency tables either chi-Square or Exact Test of Goodness-of-fit test was used in accordance with appropriate criteria. Multiple stepwise logistic regression analysis was utilized in order to determine predictors for CA diagnosis. Prior to the logistic regression analysis, predictors to be analyzed were selected according to their significance level from univariate analyses. Variables with $P < .1$ were considered to be candidates. One final check before the analysis was to check for autocorrelation. Variables which were highly correlated ($r > 0.80$) were dropped from multiple regression analysis in advance. All statistical tests with P-values less than .05 were considered as significant.

Artificial intelligence (AI)–assisted technologies (such as Large Language Models [LLMs], chatbots, or image creators) were not used in the production of submitted work.

RESULTS

The study enrolled 420 patients with LVH and clinical suspicion of CA. The mean age of the participants was 65.5 years (ranging from 20 to 93 years), with 60.2% being male and 39.8% female. After 420 patients underwent diagnostic evaluation in parallel with the algorithm recommended in the study protocol but "*as required on a patient-by-patient basis,*" 114 patients were diagnosed with CA. Of these 114 patients diagnosed with CA, 58 had AL CA, 44 had wTTR CA, 8 had mTTR CA, and 4 had AA CA (Figure 1).

Data were analyzed in 2 phases. The aim was to determine the parameters predicting the diagnosis of CA in the first phase, and the parameters predicting wTTR CA in the second phase. Due to the limited number of cases with mTTR CA, no analysis was performed for mTTR CA. As wTTR and mTTR CA have a diverse presentation, course and pathopyhsiology, an analysis for whole TTR was not preferred. Therefore, predictors of wTTR were assessed by comparing wTTR CA and AL CA patients. The analysis of both CA and wTTR CA predictors excluded Tc-PYP bone scintigraphy, biopsy, and monoclonal antibody data. As both scintigraphy and biopsy are the final diagnostic tests used for definitive diagnosis in current guidelines, the authors focused on the predictive value of routine basal tests for diagnosing CA and wTTR CA.

Comparison between patients diagnosed with CA and those without CA showed no differences in age, sex, and past medical history. Systolic and diastolic blood pressure values were significantly lower in CA patients. (Table 2).

Analysis of the parameters from the screening questionnaire indicated that all but 2 parameters described in the questionnaire were significantly higher in the CA group (Table 2). The parameters showing no difference between groups with and without a diagnosis of CA, were the presence of bundle branch block on ECG and family history of amyloidosis.

An analysis of the ECG findings revealed a significantly higher heart rate in CA patients. As expected, disproportionate low voltage and a pseudoinfarct pattern were significantly more prevalent in CA patients (Table 2).

Baseline blood and urinary parameters analysis showed that CA patients had significantly lower hemoglobin, albumin, sodium, total cholesterol, and LDL-cholesterol levels, while levels of troponin, BNP/NT pro-BNP, GGT, and spot urine proteins were significantly higher (Table 2).

Comparison of baseline echocardiographic data between the groups showed that CA patients had lower left ventricular EF and left ventricular diastolic diameter, while left ventricular posterior wall thickness, right ventricular free wall thickness, right ventricular basal diameter, systolic pulmonary artery pressure, presence of IVC plethora, presence of pericardial-pleural effusion, and presence of left ventricular restrictive filling were significantly higher in the CA group (Table 2).

In a multiple logistic regression analysis for all parameters with significant differences between the groups with and without CA, the most effective independent predictors for CA diagnosis included left ventricular apical sparing pattern on echocardiography (OR = 10.42, $P < .001$, 95% CI = 4.25-25.22), low voltage on ECG (OR = 5.31, $P = .005$, 95% CI = 1.61-12.54), restrictive LV filling pattern (OR = 3.52, $P = .001$, 95%, CI = 1.64-7.61), bilateral carpal tunnel syndrome (OR = 4.62, $P = .008$, 95% CI = 1.44-14.43), systolic blood pressure (OR = 0.90, $P < .001$, 95% CI = 0.93-0.97), right ventricular basal diameter (OR= 1.24, $P = .013$, 95% CI = 1.02-1.22), and heart rate on ECG (OR = 1.12, $P = .001$, 95% CI = 1.06-1.21) (Table 3).

In the second phase of the study, the authors' objective was to identify predictors of wTTR CA in contrast to AL CA. Analysis of baseline patient characteristics showed that the mean age was significantly higher in wTTR patients (72.2 ± 14.2 vs. 63.1 ± 10.1, $P = .006$). There was no difference between the 2 groups in terms of gender distribution, with a similar male predominance in wTTR and AL CA patients (63.6% vs. 62.0%, $P = .87$). The prevalence of hypertension and diabetes in medical history was notably higher in wTTR patients (61.3% vs. 37.9%, $P = .019$, and 36.3% vs. 12.0%, $P = .004$, respectively). Systolic blood pressure values were lower in the AL-CA group (111.4 ± 20.1 mm Hg vs. 119.4 ± 12.8, $P = .010$). Among patients with a history of HF, the proportion of those classified as NYHA FC 3-4 was significantly lower in wTTR CA patients (32.3% vs. 72.2%, $P = .004$) (Table 4).

Analysis of the questionnaire data indicated no significant difference in the frequency of peripheral neuropathy and carpal tunnel syndrome between wTTR CA and AL CA patients. However, gastrointestinal system findings, low voltage on ECG, chronic pleural/pericardial effusion, chronic troponin elevation, proteinuria, autonomic dysfunction findings, granular pattern and biventricular hypertrophy on transthorasic echocardiography , apical sparing pattern were significantly higher in AL patients. Persistent atrial fibrillation was significantly more common in wTTR patients (Table 4).

When wTTR and AL CA patients were compared in terms of ECG data, AL CA patients exhibited a significantly higher prevalence of sinus rhythm, disproportionate low voltage,

Table 2. Baseline Characteristics, Laboratory Exams, and Echocardiographic Findings of Patients Who Received the Final Diagnosis of Amyloid Cardiomyopathy and Those in Whom the Diagnosis of Amyloid Cardiomyopathy Were Excluded

	Cardiac Amyloidosis (n = 114)	Non-Cardiac Amyloidosis (n = 306)	*P*
Clinical Features			
Sex (male%)	73 (64.0)	180 (58.8)	.332
Age (years)	63.9 ± 14.4	63.1 ± 12.7	.619
BMI (kg/m^2)	26.3 ± 4.5	27.7 ± 4.6	**.006**
Heart rate (beats/min)	82.6 ± 12.9	77.3 ± 14.8	**<.001**
Systolic BP (mm Hg)	114.2 ± 17.4	125.9 ± 18.1	**<.001**
Diastolic BP (mm Hg)	70.9 ± 12.4	77.6 ± 11.8	**<.001**
Arterial hypertension (%)	51 (44.7)	167 (54.5)	.070
Heart failure (%)	76 (66.7)	186 (60.8)	.268
Coronary artery disease (%)	24 (21.1)	81 (26.5)	.254
Diabetes Mellitus (%)	24 (21.1)	75 (24.5)	.458
Chronic kidney disease (%)	29 (25.4)	77 (25.2)	.954
Pacemaker (%)	4 (4.2)	11 (3.8)	.767
CA-red flag features			
Peripheral neuropathy (%)	53 (46.5)	105 (34.3)	**.022**
GIS symptoms (%)	51 (44.7)	67 (21.9)	**<.001**
Orthostatic hypotension (%)	32 (28.1)	40 (13.1)	**<.001**
Carpal Tunnel syndrome (%)	23(20.2)	21 (6.9)	**<.001**
Family history (%)	4 (3.5)	2 (0.6)	.099
Electrocardiography			
Sinus Rhythm (%)	90 (78.9)	226 (73.9)	.282
Low voltage (%)	61 (53.5)	111 (36.3)	**.001**
Bundle branch block (%)	22 (19.3)	75 (24.5)	.260
Pseudo-infarct pattern (%)	53 (46.5)	60 (19.6)	**<.001**
Echocardiography			
Interventricular septum thickness (mm)	17.0 ± 2.6	17.2 ± 3.3	.412
Posterior wall thickness (mm)	15.3 ± 2.7	14.2 ± 2.7	**<.001**
LV systolic dimension (mm)	31.0 ± 6.7	31.3 ± 7.4	.657
LV diastolic dimension (mm)	44.7 ± 6.6	46.5 ± 6.5	**.013**
LA dimension (mm)	44.2 ± 6.8	44.5 ± 6.5	.765
LV EF (%)	52.4 ± 11.7	55.9 ± 10.6	**.013**
RV basal dimension (mm)	37.4 ± 6.6	35.4 ± 5.1	**.009**
RV wall thickness (mm)	7.7 ± 4.9	6.0 ± 4.4	**.003**
sPAP (mm Hg)	41.7 ± 12.6	36.0 ± 15.5	**<.001**
Diffuse hypertrophy with granular pattern (%)	90 (78.9)	158 (51.6)	**<.001**
LV apical sparing (%)	64 (60.9)	36 (12.6)	**<.001**
Restrictive LV filling features (%)	59 (51.8)	51 (16.7)	**<.001**
Pericardial effusion (%)	57 (50.0)	63 (20.6)	**<.001**
Pleural effusion (%)	43 (37.7)	56 (18.3)	**<.001**
IVC plethora (%)	54 (47.4)	73 (23.9)	**<.001**
Serum and urine biomarkers			
Troponin T (ng/mL)	129.6 ± 99.6	43.0 ± 32.5	**.008**
Nt pro BNP (pg/mL)	7327 ± 2506	3926 ± 1922	**.003**
Hemoglobin	12.3 ± 2.1	13.1 ± 2.2	**<.001**
Glucose (g/dL)	110.8 ± 39	116.5 ± 48.4	.217
Creatinine (mg/dL)	1.31 ± 1.02	1.23 ± 0.94	.483
AST (unit/L)	26.6 ± 15.3	22.4 ± 12.8	**.017**
ALT (unit/L)	25.8 ± 20.5	20.8 ± 16.6	**.028**
GGT (IU/L)	86.4 ± 87.9	42.6 ± 38.2	**.005**
Sodium (mEq/L)	137.9 ± 4.1	139.5 ± 3.9	**.017**
LDL (mg/dL)	100.8 ± 41.0	117.6 ± 44.2	**.017**
Triglycerides (mg/dL)	119.9 ± 53.2	150.1 ± 117.9	.055
Albumin (g/dL)	4.12 ± 2.06	4.44 ± 3.61	**.011**
CRP (mg/L)	18.8 ± 37.9	8.9 ± 13.0	.084
Proteinuria (%)	59 (51.8)	59 (19.7)	**<.001**

Continuous data are shown as median (interquartile range) and means ± 95% CI upper and lower mean values when appropriate. BMI, body mass index; CRP, c-reactive protein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; NYHA FC, New York Heart Association functional class; sPAP, systolic pulmonary artery pressure. Bold values express the parameters which have statistically significant difference.

Table 3. Multiple Logistic Regression Analysis for Diagnosis of Amyloid Cardiomyopathy in Patients with Left Ventricular Hypertrophy

Clinical Variables	OR	95% CI	*P*
LV apical sparing	10.42	4.25-25.22	<.001
Low QRS voltage	5.31	1.61-12.54	.005
Restrictive filling	3.52	1.64-7.61	.001
Bilateral carpal tunnel syndrome	4.62	1.44-14.43	.008
RV basal diameter	1.24	1.02-1.22	.013
Systolic blood pressure	0.90	0.93-0.97	<.001
Heart rate	1.12	1.06-1.21	.001

pseudoinfarct pattern, and longer corrected QT inteval (QTc) duration (Table 4).

Analysis of blood and urine parameters revealed that NT pro BNP, troponin, indirect bilirubin, ALT and AST were higher in AL CA patients, whereas serum glucose and potassium levels were significantly elevated in wTTR CA patients (Table 4).

When wTTR and AL CA patients were compared in terms of echocardiographic data, left ventricular and right ventricular diameters were significantly smaller in AL CA patients. Although left atrial diameters were higher in wTTR patients, the difference was not statistically significant (43.4 ± 6.6 vs. 46.0 ± 7.1, $P = .06$).

There were no significant differences between the groups in terms of ınterventricular septum and right ventricular wall thickness values; however, left ventricular posterior wall thickness wass slightly higher in AL CA patients. Pericardial effusion and restrictive type of filling were significantly higher in the AL CA group (Table 4).

When all the factors showing a significant difference between wTTR and AL CA in patients with CA were evaluated by multiple logistic regression analysis, the most effective independent predictors for wTTR CA diagnosis were pericardial effusion (OR = 0.19, $P < .001$, 95% CI = 0.08-0.43), proteinuria (OR = 0.23, $P < .001$, 95% CI = 0.09-0.41), advanced age (age >75 OR = 4.31, $P = .08$, 95% CI = 1.52-13.21), and high troponin values (OR = 0.13, $P = .006$, 95% CI = 0.03-0.57). The parameters except the advanced age were negative predictors of wTTR CA diagnosis (Table 5).

DISCUSSION

This study presents the findings from the analysis of the screening phase of the PAPCAT study, which is the first multicenter, prospective-observational study on CA in Türkiye. These analyses yielded the following outcomes:

1. When a standardized algorithmic approach was applied in patients with LVH (interventricular septum thickness ≥13 mm or >15 mm in those with hypertension) and clinical suspicion of amyloidosis (≥2 evidence of red flags for amylodosis in the questionnaire), 27.1% of patients received a CA diagnosis. Among these patients with CA, 50.8% were diagnosed with AL CA, 38.6% with wTTR CA, and 7% with mTTR CA. These findings hold significance as they offer the initial data on the proportion of TTR CA within the CA spectrum, which has never been described before in Türkiye.
2. Three parameters used in the screening questionnaire emerged as robust independent predictors for CA diagnosis. These parameters include left ventricular apical sparing pattern and restrictive LV filling on echocardiography, low voltage on ECG, and bilateral carpal tunnel syndrome. In addition to these parameters, low blood pressure, a larger right ventricular diameter and high heart rate were other independent predictors for CA diagnosis. These findings underscore the diagnostic value of simple physical examination findings such as low blood pressure and high heart rate in hypertrophic patients. They also highlight the importance of monitoring the right ventricle in a patient with hypertrophic left ventricle, suggesting that a preserved diameter despite of a hypertrophic-restrictive right ventricle should prompt consideration for CA diagnosis in hypertrophic patients.
3. Wild-type TTR CA represents a form of CA characterized by isolated cardiac involvement. In this study, the following parameters were defined as independent factors predicting wTTR in the group diagnosed with CA: advanced age (age>75), lower troponin values , absence of pericardial effusion and absence of proteinuria. All of the echocardiographic, laboratory and clinical parameters pointed a better clinical profile in wTTR CA group compared to AL-CA group.

Until the recent emergence of data on the prevalence of TTR CA, CA was deemed a rare disease, with available data predominantly based on AL-CA statistics. The annual prevalence of AL-CA was reported as 8 patients per 1 million people. However, over the past decade, significant advancements have occured concerning TTR CA, revealing much higher prevalence rates within the elderly population. The advent of noninvasive TTR CA diagnosis via scintigraphic methods and the introduction of drugs such as Tafamidis that alter the disease trajectory, have made CA an important, popular and relevant topic for the general public. Nevertheless, studies on the prevalence of the disease have yielded varied results. For instance, a prospective study in patients with preserved EF HF detected TTR-CA in 13% of hypertrophic patients by Tc-DPD scintigraphy.[2] Three years later, a similar group of patients but with retrospective screening and Tc-PYP scintigraphy revealed a 19% TTR-CA diagnosis rate.[10] In 2021, a single-center retrospective study identified CA in 34.3% of patients following etiologic evaluation of patients with LVH.[11] Another population screening study, based on medical record data, reported a prevalence rate of CA as 6.3% upon systematic screening in the HF population with preserved EF.[12] However, this study also adopted a retrospective design. In a recent retrospective registry study, a prevalence rate was obtained by extrapolating all patients diagnosed with TTR-CA over a 2-year period in the Kumamoto region of Japan to the regional population. Accordingly, the annual prevalence rate was defined as 33/1

Table 4. Baseline Characteristics, Laboratory Exams, and Echocardiographic Findings of Patients with AL Type and Wild-type Transthyretin Amyloid Cardiomyopathy

	AL Cardiac Amyloidosis (n = 58)	wTTR Cardiac Amyloidosis (n = 44)	*P*
Clinical features			
Sex (male%)	36 (62.1)	28 (63.6)	.871
Age (years)	63.1 ± 10.1	72.2 ± 14.2	**.006**
BMI (kg/m^2)	25.7 ± 3.8	27.5 ± 5.3	.131
Heart rate (beats/min)	83.9 ± 12.0	82.4 ± 14.1	.567
Systolic BP (mm Hg)	111.4 ± 20.1	119.5 ± 12.8	**.010**
Diastolic BP (mm Hg)	70.3 ± 14.6	72.5 ± 10.0	.376
Arterial hypertension (%)	22 (37.9)	27 (61.4)	**.019**
Heart failure (%)	36 (62.1)	34 (77.3)	.101
NYHA FC 3-4 symptoms	26 (72.2)	11 (32.3)	**.004**
Coronary artery disease (%)	12 (20.7)	11 (25.0)	.606
Diabetes mellitus (%)	7 (12.1)	16 (36.4)	**.004**
Chronic kidney disease (%)	13 (22.4)	13 (29.5)	.413
CA-red flag features			
Peripheral neuropathy (%)	25 (43.1)	18 (40.9)	.824
GIS symptoms (%)	32 (55.2)	13 (29.5)	**.010**
Orthostatic hypotension (%)	22 (37.9)	9 (20.5)	**.050**
Carpal tunnel syndrome (%)	11 (19.0)	9 (20.5)	.973
Electrocardiography			
Persistent atrial fibrillation(%)	8 (14.3)	14 (33.3)	**.025**
Low voltage (%)	46 (79.3)	14 (31.8)	**<.001**
Bundle branch block (%)	9 (15.5)	9 (20.5)	.517
Pseudo-infarct pattern (%)	39 (67.2)	9 (20.5)	**<.001**
QTc (ms)	445.8 ± 32.2	416.6 ± 73.1	**.032**
Echocardiography			
Interventricular septumthickness (mm)	17.0 ± 2.8	16.7 ± 2.3	.593
Posterior wall thickness (mm)	15.7 ± 2.7	14.5 ± 2.5	**<.014**
LV systolic dimension (mm)	29.6 ± 5.6	32.5 ± 7.3	**.034**
LV diastolic dimension (mm)	42.6 ± 5.6	46.9 ± 7.2	**<.001**
LA dimension (mm)	43.4 ± 6.6	46.0 ± 7.1	.063
LV EF (%)	53.0 ± 9.7	52.6 ± 13.0	.867
RV basal dimension (mm)	36.2 ± 5.9	39.1 ± 6.7	**.027**
RV wall thickness (mm)	7.9 ± 4.0	7.7 ± 6.5	.856
sPAP (mm Hg)	40.2 ± 11.1	43.2 ± 13.8	.244
Diffuse hypertrophy withgranular pattern (%)	51 (87.9)	27 (61.4)	**.002**
LV apical sparing (%)	39 (75.0)	19 (46.3)	**.005**
Restrictive LV filling features(%)	38 (65.5)	14 (31.8)	**<.001**
Pericardial effusion (%)	40 (69.0)	13 (29.5)	**<.001**
Pleural effusion (%)	25 (43.1)	15 (34.1)	.356
IVC plethora (%)	30 (51.7)	22 (50.0)	.863
Serum and urine biomarkers			
Troponin T (ng/mL)	128.4 ± 88.2	69.61 ± 25.2	**.032**
Nt pro BNP (pg/mL)	9234 ± 2033	4905.3 ± 1045	**.019**
Hemoglobin (g/dL)	12.1 ± 1.9	12.6 ± 2.6	.204
Glucose (mg/dL)	106.6 ± 33.6	121.3 ± 49.0	**.050**
Creatinine (mg/dL)	1.3 ± 0.9	1.2 ± 0.8	.714
AST (unit/L)	31.7 ± 17.9	20.5 ± 9.3	**.002**
ALT (unit/L)	30.8 ± 24.6	19.5 ± 11.2	**.009**
GGT (unit/L)	94.0 ± 98.6	82.6 ± 78.0	.681
Indirect bilirubin (mg/dL)	0.6 ± 0.4	0.4 ± 0.3	**.039**
Sodium (mEq/L)	137.9 ± 4.9	137.5 ± 3.5	.757
Potassium (mEq/L)	4.1 ± 0.59	4.5 ± 0.75	**.035**
LDL (mg/dL)	106.9 ± 41.7	97.0 ± 45.4	.410
Triglycerides (mg/dL)	116.8 ± 52.6	132.1 ± 57.4	.352
Albumin (g/dL)	4.4 ±3.4	4.3 ± 3.1	.160
CRP (mg/L)	21.4 ± 36.8	20.4 ± 44.4	.084
Proteinuria (%)	42 (72.4)	12 (27.3)	**<.001**

Continuous data are shown as median (interquartile range) and means ± 95% CI upper and lower mean values when appropriate. BMI, body mass index; CRP, c-reactive protein; IVC, inferior vena cava; LA, left atrium; LV, left ventricle; NYHA FC, New York Heart Association functional class; sPAP, systolic pulmonary artery pressure; wTTR, wild-type TTR. Bold values express the parameters which have statistically significant difference.

Table 5. Multiple Logistic Regression Analyses for Prediction of Wild-type Subtype in Patients with a Diagnosis of Amyloid Cardiomyopathy

Clinical Variables	OR	95% CI	*P*
Age >75	4.31	1.52-13.21	.008
High troponin values	0.137	0.03-0.57	.006
Pericardial effusion	0.193	0.08-0.43	<.001
Proteinuria	0.232	0.09-0.41	<.001

000 000 in the whole population and 1/10 000 in the age group over 65 years. These prevalence studies underscore wide ranging results, spanning from 34.3% to 33/1 000 000.[13] The primary reason behind such discrepancies is the variance in study designs and populations. Another inherent limitation in all of these studies lies in the biased patient referral tendency in the centers. Given that most of the centers are tertiary facilities, the screened patients have minimal potential to represent the broader population. Indeed, the challenges outlined here are major hurdles encountered in prevalence studies for rare diseases and for conditions that require complex screening. Consequently, due to similar limitations, the authros were unable to provide clear and reliable data on prevalence values for CA and TTR-CA in Türkiye.

However, the high rate (27.1%) of CA diagnosis upon standardized screening in 25 experienced tertiary centers, underscore the efficiency of the screening process used in this study.

In our study, out of 114 patients diagnosed with CA, 58 had AL CA, 44 had wTTR CA, 8 had mTTR CA and 4 had AA CA. These findings represent the initial data on the rates of amyloid subtypes among newly diagnosed CA patients in Türkiye. Contrary to what is expected in the general literature, the proportion of wTTR CA was lower than of AL CA. This result can be explained in 3 ways, including high referral rate of AL-CA patients with more experience and awareness by other related departments, insufficient hospital referral of the elderly patient group in which wTTR CA is prevalent, and potential error rates due to insufficient experience in the diagnostic process of wTTR CA. Although the study sites were experienced tertiary centers, many centers utilized Tc-PYP scintigraphy for the first time for this purpose. Since there was no central laboratory in the study, it was impossible to exclude the technical margins of error in these centers. However, despite these limitations, the comparable rates of AL (51.3%) and TTR CA (46%) suggest that the diagnosis of TTR CA should be considered in approximately one out of every 2 patients with a diagnosis of CA.

The most pivotal stage in the diagnosis of CA is known as clinical suspicion. Therefore, it is very important to standardize the definition of *clinical suspicion of CA and not let* it to remain as a subjective definition. A critical aspect of our study was that; all hypertrophic patients were administered a standardized questionnaire for CA red flag findings. In all hypertrophic patients, findings involving 14 different categories in the questionnaire were recorded. Of these 14 parameters, all but 2 were significantly higher in patients diagnosed with CA. These 2 questionnaire parameters were the presence of bundle branch block on ECG and family history of amyloidosis. Conduction abnormalities on ECG may have been underrepresented in our CA population because it is a relatively late finding of the disease. As long as, our CA patients were diagnosed as a part of screening project they may represent an earlier period of the disease. Additionally, the small size of the mTTR CA group may also explain the low rate of positive family history.

Upon evaluating findings predicting CA diagnosis in the entire screening process via multivariate analysis, independent predictors were identified as left ventricular apical sparing pattern on echocardiography , bilateral carpal tunnel syndrome , low voltage on ECG, restrictive LV filling pattern , right ventricular basal diameter ,heart rate on ECG and systolic blood pressure . Given the early restrictive physiology observed in CA patients, hypotension and tachycardia are more prevalent compared to other hypertrofic patients. Therefore, low blood pressure and high resting heart rate in a patient with hypertrophic left ventricle should suggest a diagnosis of CA.

While patchy involvement has been reported in CA, diffuse hypertrophy is seen in the majority of patients.[14] At this stage, hypertrophy of the right ventricle, valves and interatrial septum is quite typical in CA. However, in our study, in addition to right ventricular hypertrophy, right ventricular diameter was found to be higher in patients with CA than in patients without CA. When comparing 2 patients with CA and non-CA having similar degrees of hypertrophy, those with CA exhibit significantly higher pulmonary artery pressure, potentially explaining why the right ventricle is more dilated in patients with CA than in those without CA.

Wild-type TTR CA is characterized by isolated cardiac involvement, often in the absence of systemic amyloidosis. Spinal stenosis and carpal tunnel syndrome are other findings associated with amyloid deposition in these patients. It is typically known as an advanced age male disease.[15] In this study, although older age was found to be a predictor for wTTR CA, no difference was found in terms of gender. Although this gender-related finding is contrary to general literature, it may be a finding reflecting a unique aspect of the Turkish population. In line with the general literature, almost all of the findings of systemic amyloidosis were more common in AL-CA. The 2 exceptions were peripheral neuropathy and carpal tunnel syndrome, which were found at similar rates in both groups. In terms of carpal tunnel syndrome, this finding is consistent with the literature.[15] As for the peripheral neuropathy, the data is based on a questionnaire and suggests that it may be influenced by factors like diabetes and advanced age, which are more common in wTTR CA.

In our study, wTTR-CA patients displayed higher systolic blood pressures, lower NYHA functional classes, and lower BNP and troponin levels compared to AL CA patients. On echocardioghraphy, left ventricular diameters were larger,

and restrictive type filling and pericardial effusion were significantly less. All these data suggest that wTTR-CA has a better prognosis than AL-CA. AL amyloidosis is worse than TTR CA, because it has a direct toxic effect on myocytes causing higher BNP and higher troponin values. In TTR CA, extracellular amyloid deposits causes hypertrophy and small amount of restrictive physiology, however myocyte toxicity in cellular level is not usually present. Only the frequency of persistent atrial fibrillation and left atrial diameter were higher in wTTR-CA than in AL-CA; however, these findings may be explained by the advanced age of the patients. Regarding the independent predictors that differentiated wTTR-CA from AL-CA, 4 parameters including advanced age (age >75 years), lower troponin values, absence of pericardial effusion, and absence of proteinuria. The persistence of pericardial effusion as an independent predictor may be related to the fact that it is a final hemodynamic outcome in restrictive processes.

In summary, in hypertrophic heart patients with preserved EF HF, wTTR CA should be kept in mind in the presence of older age, low ECG voltage without systemic manifestations of CA and in those with a favorable clinical profile compared to AL CA patients.

Study Limitations

The main limitation of this study lies in the bias concerning patient referrals to the centers. Since these centers are tertiary centers, they may represent a more specific group of patients with hypertrophic left ventricle. This bias could also extend to AL-CA patients. The fact that there is more available experience in this area suggests that these patients may have been over-represented in this study. This may cause the proportion of AL-CA patients to be higher than usual. Another limitation was the absence of a central laboratory for Tc-PYP scintigraphy, and histopathological evaluations used for definitive diagnosis of CA. Particularly in Tc-PYP scintigraphy, where experience may be limited, it was not possible to completely rule out technical errors of the health centers. Number of patients with mTTR CA was extremely low that the authors couldn't make any analysis in this group of patients. Lower troponin values had emerged as an independent predictor for wTTR CA patients among CA population. However, the authors couldn't identify a cut-off troponin value to rule out wTTR CA because of our limited number of wTTR CA patients.

CONCLUSION

Cardiac amyloidosis presents a significant and treatable form of disease in patients with LVH. By employing a standardized evaluation of CA's systemic manifestations and utilizing a diagnostic algorithm effectively, it is possible to detect CA patients at an early stage. This necessitates precise analysis of routine physical examinations, ECGs, blood and urine tests and echocardiographic data. This study holds importance for providing insight into the accurate interpretation of these fundamental tests. Among this pool of newly diagnosed CA patients in Türkiye, AL-CA constituted 50.8%, wTTR CA 38.6% and TTR CA 7%, emphasizing that approximately 1 in 2 patients diagnosed with CA may have TTR CA.

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