Am J Cardiovasc Dis 2024;14(6):384-395
www.AJCD.us /ISSN:2160-200X/AJCD0160832

Original Article

Prevalence of transthyretin cardiac amyloidosis in patients with aortic stenosis

Rozana SadrAldin[1], Jamal Ahmed[1], Fahmi Alkaf[1], Mohammed K Ahmed[2], Zakaria Bin Mousa[2], Saad A AlQahtani[3], Hussein Farghaly[3], Zahra AlAsiri[4], Raneem Alodhaib[4], Shehana Bin Shigair[1], Abdullah Alqarni[3], Hussein AlAmri[5], Abdulrahman Almoghairi[5], Saeed Alahmari[2], Abeer Bakhsh[1,6]

[1]Prince Sultan Cardiac Centre, Heart Function Unit, Department of Adult Cardiology, Riyadh, Saudi Arabia; [2]Prince Sultan Cardiac Centre, Division of Echocardiography, Department of Adult Cardiology, Riyadh, Saudi Arabia; [3]Prince Sultan Military Medical City, Department of Nuclear Medicine, Riyadh, Saudi Arabia; [4]Prince Sultan Cardiac Centre, Department of Nursing, Riyadh, Saudi Arabia; [5]Prince Sultan Cardiac Centre, Division of Interventional Cardiology, Department of Adult Cardiology, Riyadh, Saudi Arabia; [6]King Abdullah Medical City, Department of Adult Cardiology, Makkah, Saudi Arabia

Received September 28, 2024; Accepted December 13, 2024; Epub December 15, 2024; Published December 30, 2024

Abstract: Background: Transthyretin cardiac amyloidosis (ATTRCA) is a prevalent disease, and it can be associated with heart failure (HF), left ventricle hypertrophy (LVH), atrial fibrillation (AF), and aortic stenosis (AS). Aim: The study aims to detect the prevalence of ATTRCA in the symptomatic AS population. Method: A single-center prospective study screening for ATTRCA in patients diagnosed with symptomatic severe AS undergoing aortic valve (AV) intervention. Results: A total of 27 patients were enrolled, of which 15 (56%) were men. The mean age was 72.8 ± 10.5 years. HF symptoms were present in 11 (40.7%) patients at New York Heart Association (NYHA) class II, while 15 (55.6%) patients had NYHA class III symptoms. AF was present in 6 (22.2%) patients. The mean left ventricle ejection fraction (LVEF) was 49.4 ± 9.75%, and the mean stroke volume (SV) was 37.4 ± 8.7 ml/m^2. The interventricular septal thickness (IVS) was 1.2 ± 0.18 cm. The AS mean gradient was 46 ± 12 mmHg, and the aortic valve area (AVA) was 0.69 ± 0.16 cm^2. The ATTRCA was diagnosed by bone scintigraphy in 5 (18.5%) AS patients. Perugini scores of 2 and 3 were considered positive for ATTRCA with the heart/contralateral lung (H/CL) ratio of 1.48 ± 0.35. There was no difference in LVEF between patients with ATTRCA and those without ATTRCA 50 ± 9.8% vs 47 ± 9.3%; *p*-value 0.55. The ATTRCA had a lower SV of 33.9 ± 6.9 ml/m^2 compared to patients without ATTRCA 37.5 ± 8.8 ml/m^2; *p*-value of 0.34. There was no significant difference in LVH or IVS thickness between the patients with ATTRCA and those without ATTRCA. The left ventricle (LV) mass index in ATTRCA was 87 ± 21 g/m^2 compared to patients without ATTRCA 98.7 ± 26 g/m^2, with a *p*-value 0.38, and the IVS thickness was 1.1 ± 0.22 cm compared to patients without ATTRCA 1.2 ± 0.18 cm; *p*-value 0.17. The left atrial (LA) volumes were significantly higher in the ATTRCA group 55.5 ± 25.6 ml/m^2 compared to patients without ATTRCA 37.5 ± 10.9 ml/m^2 with a significant *p*-value 0.028. The mean AV gradient was lower in ATTRCA patients at 40.8 ± 8.4 mmHg, compared to patients without ATTRCA at 46.1 ± 12.1 mmHg; it did not reach a statistical significance *p*-value 0.3. There was a significant difference in LV relative longitudinal strain (LS) between patients with ATTRCA 11.8 ± 3.2 and those without ATTRCA 63.3 ± 22.6 with a significant *p*-value 0.001. Conclusion: ATTRCA is prevalent in AS patients; bone scintigraphy is recommended for screening AS patients for ATTRCA.

Keywords: Aortic stenosis, low flow-low gradient aortic stenosis, cardiac amyloidosis, ATTRCA, TAVR, heart failure, HFpEF, carpal tunnel syndrome

Introduction

Amyloidosis is a multisystem disease characterized by the deposition of misfolded protein into the extracellular tissue [1-5]. Several proteins have been identified as causing amyloidosis. The most common type of amyloidosis is the amyloid light chain (AL), a myeloma-type protein caused by plasma cell disorders [4]. Moreover, transthyretin amyloidosis is the second most common type, which can be hereditary or wild-type related to age [4]. Cardiac

https://doi.org/10.62347/HJHT9161

deposition of amyloid protein is known to increase mortality and morbidity. The median survival of AL amyloidosis after the onset of heart failure is less than six months [6]. Patients with ATTRCA have twofold higher mortality rates compared to HF patients [7].

ATTRCA is a common yet underrecognized disorder. The prevalence of ATTRCA is thought to be higher in men; however, the disease is increasingly recognized in women and in heart failure with a preserved ejection fraction (HFpEF). In patients hospitalized with HFpEF, 13% have ATTRCA [8]. Moreover, 35% of hypertensive heart disease have ATTRCA, 5% are misdiagnosed as hypertrophic cardiomyopathy, and 25% of the elderly patients who have asymmetrical hypertrophy have ATTRCA [9-11]. Carpal tunnel syndrome is associated with ATTRCA in around 5% of patients, and it predates cardiac involvement by 5 to 15 years [12].

Both AS and ATTRCA are prevalent conditions in elderly patients [13]. The co-occurrence of AS and ATTRCA is identified in 13-16% of patients who underwent transcatheter aortic valve replacement (TAVR) [14, 15]. Other studies have shown that ATTRCA may present with a low-flow/low-gradient AS [13]. The exact pathophysiological mechanisms underlying AS and ATTRCA are not completely understood. It has been hypothesized that an increased afterload on the left ventricular myocardium may prime for amyloid deposition [16]. Furthermore, the presence of ATTRCA with severe AS was associated with significantly higher mortality than severe AS alone, 56% vs 20% at 1-year, *p*-value < 0.0001 [17, 18]. The factors associated with poor prognosis in AS patients with the presence of ATTRCA are LVEF < 50%, restrictive filling pattern, and severely reduced global longitudinal strain (GLS) [13].

The ATTRCA should be suspected if the echocardiography (ECHO) reveals increased LV wall thickness, LV apical sparing pattern on GLS imaging, and high LA volume as a marker for diastolic dysfunction [14, 19]. The Tissue Doppler (TD) is highly sensitive for diagnosing amyloidosis when the mitral and tricuspid annular velocities are reduced and the E/e' ratio is elevated [20].

Bone scintigraphy using tracers, such as Technetium labeled pyrophosphate (^{99MTc}PYP), offers a novel imaging modality for the noninvasive diagnosis of ATTRCA. It has > 99% sensitivity and 86% specificity for detecting transthyretin amyloid deposits in the myocardium in conjunction with a negative serum free light chain assay [2, 20, 21]. Non-invasive bone scintigraphy tests with either ^{99MTc}PYP or Tc-99m-diphosphono-1,2-propanodicarboxylic acid (^{Tc99m}DPD) are approved to screen patients for ATTRCA [21, 22]. The diagnosis is made by Perugini visual grading as grade 2 and 3 uptake are consistent with ATTRCA [1]. The semi-quantitative ratio H/CL > 1.3 at 3-hour post tracer uptake is highly specific for ATTRCA [20, 23-25]. The ^{99MTc}PYP scintigraphy has a positive predictive value with a H/CL ratio > 1.6 [23]. The recognition of ATTRCA is progressing due to the increased use of cardiac scintigraphy as a non-invasive diagnostic test [26]. Moreover, cases with Perugini 1 should be evaluated for AL-type cardiac amyloidosis by serum protein electrophoresis and serum-free light chain [1, 27]. The early ATTRCA can present with Perugini 1, which requires further evaluation by alternative imaging such as cardiac magnetic resonance imaging (MRI), histological confirmation, and genetic testing [1, 27].

There is growing evidence in Saudi Arabia regarding the diagnosis of ATTRCA among the population. This study aims to examine the burden of ATTRCA in AS patients in the Saudi population.

Methods

Study design

A Single-center prospective study was conducted at Prince Sultan Cardiac Center to evaluate the prevalence of ATTRCA in patients with severe symptomatic AS undergoing aortic valve intervention. The patients were enrolled over 1-year from 2022 to 2023. After obtaining informed consent, patients were screened for ATTRCA by ^{99TM}PYP bone scintigraphy.

Sample size

The sample size calculation was not performed for the study; thus, the study is underpowered. The sample size is not powered for cardiovascular outcomes.

Inclusion criteria

The study inclusion criteria were patients with symptomatic severe AS defined by ECHO crite-

ria with a mean transvalvular gradient ≥ 40 mmHg and AVA ≤ 1.0 cm^2, with degenerative etiology.

Exclusion criteria

The study excluded patients with congenital aortic valve disease, such as bicuspid and rheumatic aortic valve disease. The patients were identified for the study during the hospitalization episode for aortic valve intervention.

Study protocol

Baseline investigation: All patients had an electrocardiogram (ECG) and ECHO study. Serum levels of N-terminal pro-brain natriuretic peptide (NT-proBNP), troponin T, and renal profile were collected. AL-type amyloidosis was ruled out by obtaining serum protein electrophoresis and serum free light chain. The ECG was reviewed to determine the presence or absence of arrhythmia, conduction disease, or bundle branch block. Low voltage criteria were defined as all limb leads with an amplitude of 0.5 mV.

ECHO parameters: Detailed ECHO was performed for every patient using Phillips EPIQ 7C with S5/X5 probe, including 2-dimensional (2D) imaging, color and tissue Doppler, and speckle tracking strain imaging. All ECHO measurements were performed according to the most recent American Society of Echocardiography (ASE) guidelines [28, 29]. These include the LV ejection fraction (LVEF), calculated using Simpson's biplane method. Relative wall thickness was defined as (2× posterior wall thickness)/(LV internal diameter at end-diastole). Diastolic dysfunction was assessed with an E/A ratio of the mitral inflow, deceleration time, and TD of the medial and lateral mitral annulus (s', e', and a'). The LV GLS was performed using Tomtec software. Relative apical strain ratio was calculated using the formula (Apical LS/average of mid and basal LS). SV was calculated using the left ventricular outflow tract (LVOT) diameter and velocity time integral (VTI) with the formula (LVOT VTI × cross-sectional area of the LVOT).

Assessment of AS: The AS was assessed by the peak jet velocity of the aortic valve (AV), mean transvalvular gradient, and the AVA by the continuity equation (AVA = cross-sectional area of the LVOT × VTI LVOT/VTI AV) [30]. The AV Doppler velocity index (DVI) is calculated using the formula (velocity LVOT/velocity AV). The criteria for severity of AS were defined by peak jet velocity ≥ 4.0 m/s, mean transvalvular gradient ≥ 40 mmHg, and AVA < 1.0 cm^2 [30].

Nuclear study: Bone scintigraphy was performed using a General Electric (GE) Discovery 670 hybrid gamma camera with ^{99MTc}PYP tracer injection. Planar images were obtained at 1 hour, and planar and single photon emission computed tomography/computed tomography (SPECT/CT) at 3 hours after intravenous injection of 10-20 mCi (370-740 MBq) ^{99MTc}PYP. Images interpretation was performed based on the latest expert consensus recommendations for cardiac amyloidosis imaging and using Perugini semiquantitative visual grading when there is diffuse myocardial ^{99MTc}PYP uptake, confirmed by reviewing the SPECT/CT images to diagnose ATTRCA [24, 25]. The Perugini grade 2 and grade 3 uptakes are consistent with ATTRCA if a monoclonal plasma cell dyscrasia is excluded. Grade 0 or 1 uptakes are considered negative for ATTRCA. To estimate the ratio radionuclide activity for the H/CL ratio, a circle is drawn over the region of interest (ROI) on the heart in the anterior planar images and mirrored ROI over the contralateral chest. An H/CL ratio is calculated as the fraction of heart ROI mean counts to contralateral lung ROI mean counts. The reporting nuclear medicine physician was blinded to the ECHO findings.

Statistical analysis

The data analysis was performed using XLSTAT version 2021.2.2 Life-Science. The baseline characteristics for all the patients were reported as median and [interquartile range (IQR)] or mean ± standard deviation (SD) for quantitative variables. Categorical variables are presented as numbers and percentages (%) as appropriate. The patients were divided into groups based on the bone scintigraphy result, into ATTRCA positive and ATTRCA negative groups. The correlation analysis was performed using chi-square, Fisher exact test, and logistic regression as appropriate. The level of significance is defined as a p-value < 0.05. The Kaplan-Meier curve is used for survival rate analysis.

Table 1. Baseline characteristics of the study population

	All (27)	ATTRCA$^-$ (22)	ATTRCA$^+$ (5)	*p*-value
Demographic				
Age	72.8 ± 10.5	72.2 ± 8.5	75.2 ± 18.9	0.59
Gender (%)	Male 15 (56) Female 12 (44)	Male 12 (54.5) Female 10 (45.5)	Male 3 (60) Female 2 (40)	0.78
Co-morbidities				
Diabetes	17 (62.9)	14 (63.6)	3 (60)	0.72
Hypertension	20 (74)	17 (77.1)	3 (60)	0.43
Dyslipidemia	7 (25.9)	5 (22.7)	2 (40)	0.43
Coronary Disease	13 (48)	11 (50)	2 (40)	0.68
Stroke	2 (7.4)	2 (9.1)	0	0.48
Atrial Fibrillation	6 (22.2)	2 (9.1)	4 (80)	0.001
HF symptoms				
NYHA I	1 (3.7)	1 (4.5)	0	0.46
NYHA II	11 (40.7)	10 (45.5)	1 (20)	
NYHA III	15 (55.6)	11 (50)	4 (80)	
NYHA IV	0	0	0	
Carpal Tunnel Syndrome	1 (3.7)	0	1 (20)	0.03
Weight loss	1 (3.7)	1 (4.5)	0	0.41
Bleeding	2 (7.4)	2 (9.1)	0	0.48
ECG				
QRS duration ms	100 [94-135]	100 [91-135]	115 [98-131]	0.51
Low Voltage	0	0	0	
Heart Block	0	0	0	
Biomarkers				
Troponin T mcg/L*	0.055 ± 0.064	0.057 ± 0.07	0.047 ± 0.036	0.78
Pro-BNP ng/L**	8116 ± 18298	7676 ± 19799	10055 ± 14015	0.8
Intervention				
TAVR	23 (85)	19 (86.4)	4 (80)	0.71
SAVR	2 (7.4)	1 (4.5)	1 (20)	0.23
No Intervention	2 (7.4)	2 (9)	0	

HF, Heart Failure; NYHA, New York Heart Association; ECG, electrocardiogram; NT-Pro-BNP, N-terminal pro-brain natriuretic peptide; TAVR, transcatheter aortic valve replacement; SAVR, surgical aortic valve replacement. *Troponin T normal value < 0.05; **NT-Pro-BNP Cutoff for HF < 125 ng/L.

Results

Baseline characteristics

Patients diagnosed with symptomatic severe AS were screened for ATTRCA. Patients were identified during the admission for aortic valve intervention. The total number of patients reviewed was 52, and 27 (51.9%) agreed to consent to ATTRCA screening. Patients enrolled had a mean age of 72.8 ± 10.5 years; men were 15 (56%), and women were 12 (44%). Hypertension was present in 20 (74%), and diabetes in 17 (62.9%). History of ischemic heart disease and cerebrovascular disease was present in 13 (48%) and 2 (7.4%), respectively. The clinical presentation of HF with NYHA Class II and III symptoms occurred in 11 (40.7%) and 15 (55.6%) patients, respectively. AF was present in 6 (22%). The serum level of NT-proBNP was high in all patients with a mean of 8116 ± 18298 ng/L, while Troponin-T levels were not significantly elevated 0.055 ± 0.064 mcg/L. There were no conduction disease or low voltage criteria on ECG in any of the patients enrolled in the study.

Prevalence of ATTRCA in AS

ATTRCA was detected in 5 (18.5%) cases of severe AS by bone scintigraphy scan. ATTRCA patients had a mean age of 75.2 ± 18.9 years.

Table 2. ECHO characteristics for patients with AS

ECHO	All (27)	ATTRCA$^-$ (22)	ATTRCA$^+$ (5)	*p*-value
LV Dimensions				
LV Systolic Diameter (cm)	3.6 ± 0.8	3.4 ± 0.68	4.2 ± 1.2	0.072
LV Diastole Diameter (cm)	4.9 ± 0.8	4.8 ± 0.62	5.3 ± 1.4	0.3
LV Systolic Function				
LVEF (%)	49.4 ± 9.75	50 ± 9.8	47 ± 9.3	0.55
Stroke Volume Indexed (ml/m^2)	37.4 ± 8.7	37.5 ± 8.8	33.9 ± 6.9	0.34
LV Hypertrophy				
LV Mass index (g/m^2)	97 ± 25.6	98.7 ± 26	87 ± 21	0.38
Interventricular Septal Thickness (cm)	1.2 ± 0.18	1.2 ± 0.16	1.1 ± 0.22	0.17
Posterior Wall Thickness (cm)	0.9 ± 0.18	0.9 ± 0.17	1.1 ± 0.21	0.17
Relative Wall Thickness (cm)	0.4 ± 0.13	0.4 ± 0.1	0.44 ± 0.18	0.47
Diastolic Function				
E wave velocity (cm/sec)	92 ± 34.4	95 ± 25	144 ± 33	0.16
A wave velocity (cm/sec)	75.5 ± 32	84 ± 22	90 ± 28	0.68
E/A ratio	1.7 ± 2	1.8 ± 2.2	1.2 ± 0.4	0.6
Deceleration time (sec)	188 ± 59	190 ± 64	177 ± 39	0.7
e' Medial (sec)	4.9 ± 1.6	4.9 ± 1.7	4.9 ± 1.2	0.98
e' Lateral (sec)	5.4 ± 2.3	6.3 ± 2.3	5.8 ± 1.8	0.7
E/e' ratio	19.4 ± 6.8	18.3 ± 5.9	25 ± 7.8	
Mitral annular s' medial (sec)	5.2 ± 1.1	5.1 ± 1	5.8 ± 1.4	0.25
Mitral annular s' lateral (sec)	6.1 ± 1.3	5.9 ± 1.1	6.8 ± 1.6	0.25
Right Ventricle s' (sec)	11.8 ± 2.3	11.6 ± 2	12.8 ± 3.3	0.36
LA volume (ml/m^2)	41 ± 16.5	37.5 ± 10.9	55.5 ± 25.6	0.028
Strain				
Mid longitudinal strain (%)	52.4 ± 20.7	54.8 ± 20.2	34.6 ± 15.2	0.12
Basal longitudinal strain (%)	57.1 ± 27	63.3 ± 22.6	11.8 ± 3.2	0.001
Apical longitudinal strain (%)	46.2 ± 18.8	44.8 ± 19.3	56.4 ± 9	0.33
Global longitudinal strain (%)	10.4 ± 3.1	10.5 ± 3.1	9.7 ± 2.4	0.69
Relative LS apical/basal and mid	0.54 ± 0.4	0.43 ± 0.24	1.3 ± 0.3	< 0.0001
Pericardial effusion	3 (11%)	3 (13.6%)	0	0.85

LV, Left Ventricle; LA, Left Atrium; LS, Longitudinal Strain.

In the ATTRCA group, symptomatic HF with NYHA II was noted in 1 (20%) patient, and NYHA III was noted in 4 (80%) patients. AF was present in 4 (80%) of ATTRCA patients compared to 2 (9.1%) in the ATTRCA negative group; *p*-value 0.001. Carpal Tunnel syndrome was present in 1 (20%) patient with ATTRCA positive scan; *p*-value 0.03. There was no significant difference in the NT-proBNP and Troponin T levels between the patients with ATTRCA compared to patients without ATTRCA. The details of baseline characteristics are described in **Table 1**.

Echocardiography

LV systolic and diastolic function: In AS patients, the mean LVEF was 49.4 ± 9.75%, and the mean SV was 37.4 ± 8.7 ml/m^2. The LVH was mild in all patients, with an LV mass index of 97 ± 25.6 g/m^2 and an IVS of 1.2 ± 0.18 cm. The diastolic function was impaired, and the TD was decreased at the medial wall e' 4.9 ± 1.6 cm/s, lateral wall e' 5.4 ± 2.3 cm/s, and the E/e' was 19.4 ± 6.8. The medial mitral annular s' was 5.2 ± 1.1 cm/s, and the lateral mitral annular s' was 6.1 ± 1.3 cm/s. The LA volume was increased to 41 ± 16.5 ml/m^2 (**Table 2**).

There was no difference in LVEF between patients with ATTRCA and those without ATTRCA. The LVEF was 50 ± 9.8% in the ATTRCA group compared to the LVEF of 47 ± 9.3% in the ATTRCA negative group with a non-significant

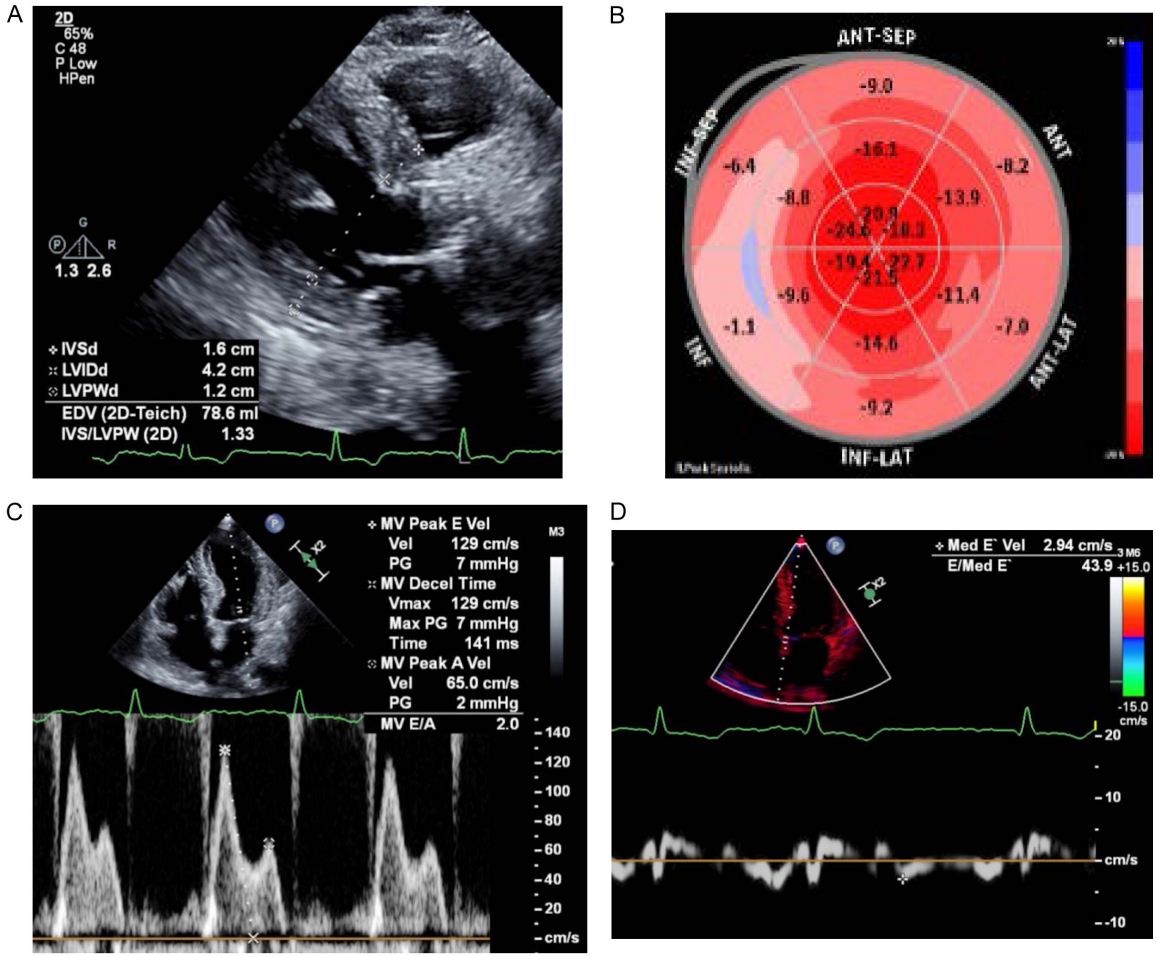

Figure 1. ECHO cardiography finding in ATTRCA patient. A. Long axis view of left ventricle hypertrophy, interventricular wall thickness, posterior wall thickness. B. Strain image representing apical sparing, low strain at basal level. C. Mitral inflow velocity represents restrictive physiology and short deceleration time. D. Tissue Doppler image shows suppressed lateral e' of the mitral annulus waves and a high E/e' ratio.

p-value 0.55. The ATTRCA had a lower SV of 33.9 ± 6.9 ml/m^2 compared to the ATTRCA negative group of 37.5 ± 8.8 ml/m^2 with a non-significant *p*-value of 0.34. In the ATTRCA, the LV mass index was 87 ± 21 g/m^2 compared to the ATTRCA negative group 98.7 ± 26 g/m^2 with a non-significant *p*-value of 0.38. The IVS thickness was 1.1 ± 0.22 cm compared to the ATTRCA negative group of 1.2 ± 0.18 cm with a non-significant *p*-value of 0.17 (**Table 2**).

In ATTRCA, the inflow velocity of the E wave was higher at 144 ± 33 cm/s vs 95 ± 25 cm/s in the ATTRCA negative group with a non-significant *p*-value 0.16. There was no significant difference in the E/A ratio between both groups, the E/A 1.2 ± 0.4 in the ATTRCA group vs 1.8 ± 2.2 in the ATTRCA negative group; *p*-value 0.6. The two groups had no significant difference in the TD medial and lateral walls or the mitral annulus. This is likely due to low patient volume. However, the LA volumes were significantly higher in the ATTRCA group 55.5 ± 25.6 ml/m^2 compared to 37.5 ± 10.9 ml/m^2 in the ATTRCA negative group with a significant *p*-value 0.028; this may be due to a higher AF burden in the ATTRCA group (**Table 2**; **Figure 1**).

LV global longitudinal strain: The LV GLS in the AS population was 10.4 ± 3.1. There was no difference in LV GLS in ATTRCA 9.7 ± 2.4 compared to the ATTRCA negative group 10.5 ± 3.1 with a non-significant *p*-value of 0.69. There was no difference in LV strain at the apical segment between the ATTRCA 56.4 ± 9 and ATTRCA negative group 44.8 ± 19.3 with a non-

Table 3. The aortic valve ECHO measurements

Aortic valve	All (27)	ATTRCA^{-} (22)	ATTRCA^{+} (5)	*p*-value
LVOT diameter (cm)	2.1 ± 0.24	2.1 ± 0.2	2.2 ± 0.37	0.4
LVOT VTI (cm)	90 ± 17	89.7 ± 16.4	93.4 ± 21	0.7
Peak AV velocity (cm/sec)	437 ± 53	422.7 ± 99	427.6 ± 35	0.7
Mean AV gradient (mmHg)	46 ± 12	46.1 ± 12.1	40.8 ± 8.4	0.3
AV DVI	0.21 ± 0.04	0.2 ± 0.06	0.17 ± 0.09	0.7
AV Area (cm^2)	0.69 ± 0.16	0.69 ± 0.16	0.7 ± 0.19	0.9

LVOT, Left ventricle outflow tract; VTI, velocity time integral; AV, aortic valve; DVI, dimensional velocity index.

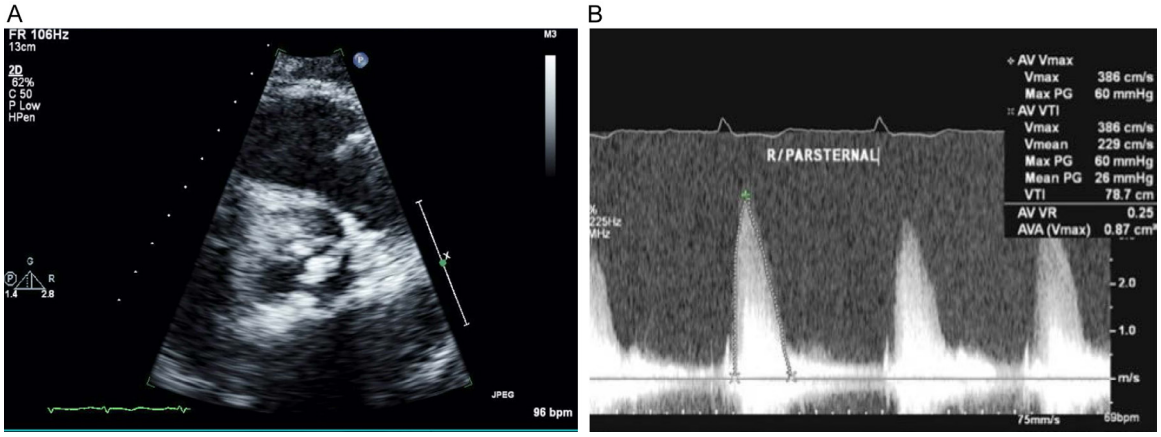

Figure 2. Aortic Valve severity assessment. A. Stenotic aortic Valve on 2D ECHO. B. The aortic valve continuous wave Doppler velocity shows high peak velocity and mean AV gradient.

Table 4. The Nuclear Scintigraphy findings for both groups

NM PYP scan	All (27)	ATTRCA -ve	ATTRCA +ve	*p*-value
Perugini				
Grade 0	15 (55.6)	15 (68)	0	< 0.0001
Grade 1	7 (25.9)	7 (31.8)	0	
Grade 2	2 (7.4)	0	2 (40)	
Grade 3	3 (11)	0	3 (60)	
H/CL ratio	1.09 ± 0.25	1 ± 0.06	1.48 ± 0.35	< 0.0001

NM, nuclear medicine; ^{99MTc}PYP, Technetium labeled pyrophosphate; ATTRCA, Transthyretin Cardiac Amyloidosis; H/CL, Heart/contralateral lung.

significant *p*-value of 0.33. However, there was a significant difference in LV relative LS (Apical LS/average of mid and basal LS) between the ATTRCA group 11.8 ± 3.2 and the ATTRCA negative group 63.3 ± 22.6 with a significant *p*-value of 0.001.

Aortic stenosis: The AS patients had a peak aortic velocity of 437 ± 53 cm/s, and a mean gradient of 46 ± 12 mmHg. The AVA was 0.69 ± 0.16 cm^2. There was no difference between patients with ATTRCA and those without ATTRCA in peak aortic velocity. The peak aortic velocity in the ATTRCA group was 427.6 ± 35 cm/s compared to the ATTRCA negative group 422.7 ± 99 cm/s with a non-significant *p*-value 0.7. The mean AV gradient was lower in ATTRCA patients at 40.8 ± 8.4 mmHg compared to patients without ATTRCA at 46.1 ± 12.1 mmHg, with a non-significant *p*-value 0.3. The AVA was 0.7 ± 0.19 cm^2 in ATTRCA patients compared to 0.69 ± 0.16 cm^2 in patients without ATTRCA with a non-significant *p*-value 0.9 (**Table 3**; **Figure 2**).

Nuclear scintigraphy

Out of 27 patients, a Perugini score of 0 was reported in 15 (55.6%) patients, and a Perugini score of 1 was reported in 7 (25.9%) patients, which are considered negative for ATTRCA. The H/CL ratio in $^{Tc\text{-}99m}$PYP negative scans is 1 ± 0.06. All patients with negative $^{Tc\text{-}99m}$PYP scan have a final diagnosis of "negative for ATTRCA". A Perugini score of 2 was reported in 2 (7.4%)

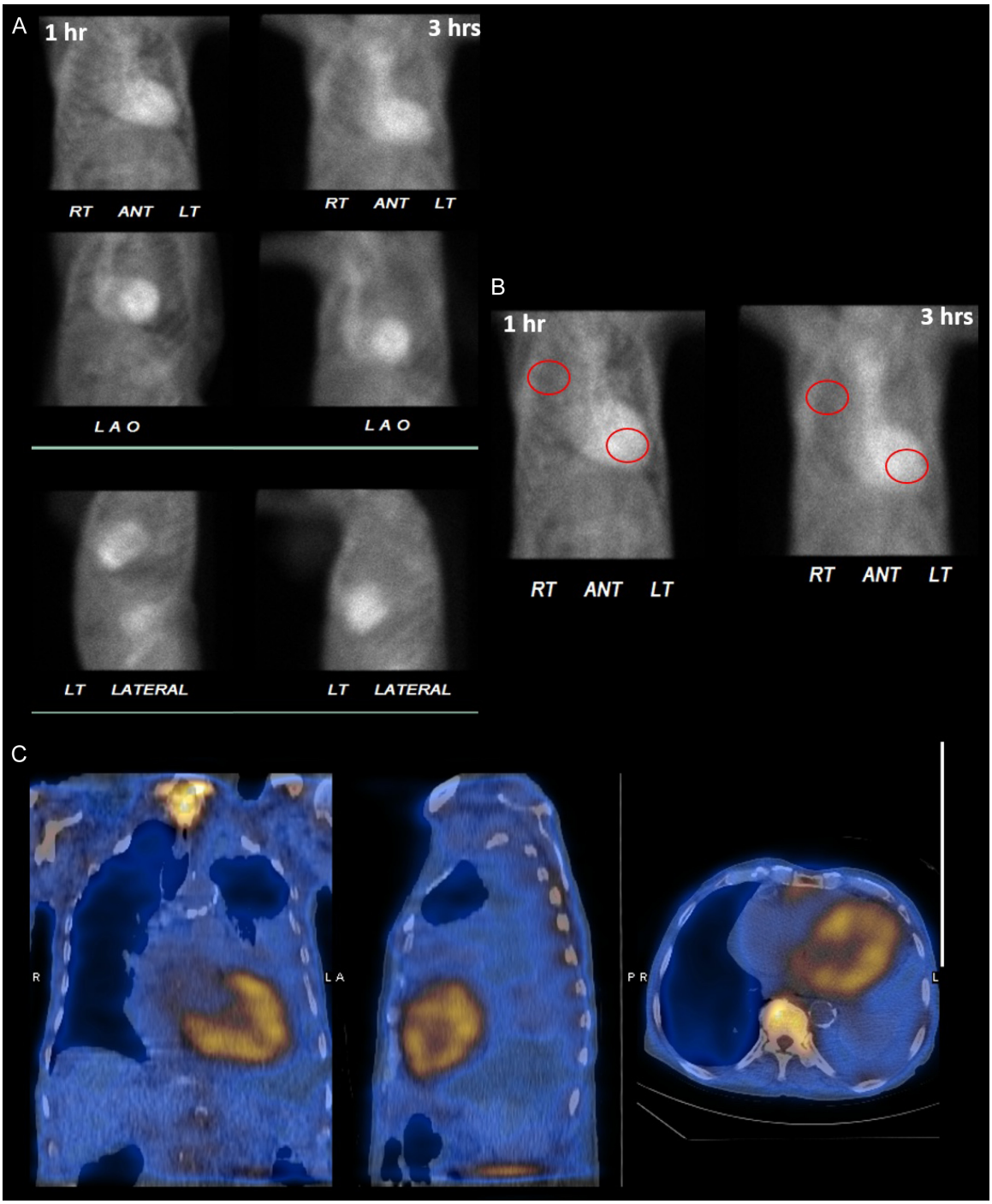

Figure 3. Images from ^{99m}Tc-PYP bone scintigraphy and single photon emission tomography (SPECT-CT) for patients with ATTRCA. A. Planner images at 1-hour and 3-hour uptake on ^{99m}Tc-PYP bone scintigraphy representing myocardial Perugini grade 3 uptakes at 1 and 3 hours. ANT, anterior; LAO, Left anterior oblique. B. Heart to contralateral lung (H/CL) ratio at 1 and 3 hours. C. SPECT-CT showed diffuse high myocardial at 3 hours more than rib uptake (Perugini grade 3).

patients, and a Perugini score of 3 was reported in 3 (11%) patients, which are considered positive for ATTRCA. The H/CL ratio in $^{Tc\text{-}99m}$PYP positive scans is 1.48 ± 0.35. All patients with positive $^{Tc\text{-}99m}$PYP scans have a final diagnosis of "positive for ATTRCA" (**Table 4** and **Figure 3**).

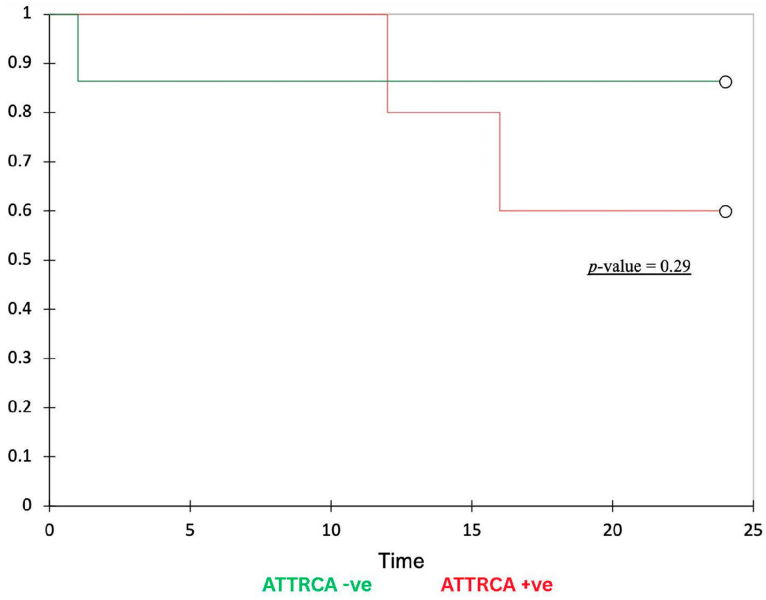

Figure 4. Kaplan-Meier curve for outcome of patients with AS with or without ATTRCA.

Intervention and follow-up

The patient was enrolled between 2022-2023. The follow-up in the clinic was as per standards of care. This study is not powered for cardiovascular outcomes. Patients who underwent percutaneous aortic valve replacement (TAVR) were 23 (85%), and those who had surgical aortic valve replacement (SAVR) were 2 (7.4%), and the other 2 (7.4%) patients did not undergo intervention. The baseline characteristics are summarized in **Table 1**. The treatment with Tafamidis was started in one patient with ATTRCA. Patients who required further hospitalization in the enrolled cohort 4 (14.8%), only one patient diagnosed with ATTRCA required hospitalization for HF. The survival rate for the study cohort was 95.8% at 1-year post-enrollment. The survival rate for ATTRCA was 80% at 1-year and 75% at 2-year (**Figure 4**).

Discussion

The prevalence of ATTRCA in Saudi Arabia has not been previously investigated. This is the first study to evaluate ATTRCA in Saudi patients with severe AS. Previous studies of ATTRCA prevalence in AS reported around 12% to 16% [14]. Our data showed a significant prevalence of 18.5% of ATTRCA in patients with severe AS, which is higher than reported in the literature [13]. This higher prevalence can be attributed to the low number of patients screened.

The resemblance of the clinical symptoms of AS and ATTRCA makes the diagnosis more challenging. Both diseases share symptoms of shortness of breath, orthopnea, dizziness, general fatigue, high cardiac biomarkers, and renal impairment [27, 31, 32]. The ECG is an essential diagnostic test for identifying ATTRCA. Low voltage on limb leads, pseudo-infarct pattern, and atrioventricular block are seen in ATTRCA [1, 15, 33]. The disproportionate ECG finding of low voltage and LVH on ECHO can be one of the diagnostic clues [1, 15, 33].

Studies had identified ECHO red flags for ATTRCA such as LVH, reduced GLS, myocardial granular appearance, thickness of the atrioventricular valves, and pericardial effusion [1, 15, 33]. European Society of Cardiology (ESC) ATTRCA Guideline highlights an ATTRCA initial suspicion by the presence of LVH with at least one of the ECHO red flag features [1, 15, 33]. The similarity of ECHO features of ATTRCA and severe AS is an obstacle that leads to the under-recognition of ATTRCA. The fact that severe AS is one of the known causes of LVH makes predicting ATTRCA more difficult. However, patients with AS and concomitant ATTRCA are more likely to present with low-flow, low-gradient AS and GLS impairment with apical sparing [1, 15, 33]. The current trial did not show a difference in GLS impairment in both groups. However, the relative LS significantly differed in ATTRCA 11.8 ± 3.2 and ATTRCA negative group 63.3 ± 22.6 with the *p*-value 0.001. The ATTRCA patients had a lower AS gradient of 40.8 ± 8.4 mmHg with the *p*-value 0.3, not reaching statistical significance. The AF was significantly higher in ATTRCA patients 80%, leading to higher LA volumes in these patients at 55.5 ± 25.6 ml/m^2. In women, the diagnostic value of IVS thickness is lower than in men for suspecting ATTRCA, making the diagnostic benefit of screening with ^{99MTc}PYP nuclear scan is high [34].

Bone scintigraphy has a higher specificity, 86%, in diagnosing ATTRCA [2, 20, 21]. The diagnostic criteria for ATTRCA are semiquantitative visual grading by Perugini > 2 and the H/CL ratio > 1.3 [31]. Bone scintigraphy should be conducted in all patients with severe AS to diagnose ATTRCA.

Conclusion

The prevalence of ATTRCA is found to be 18.5% in severe symptomatic AS patients in Saudi Arabia. The age and clinical presentation were similar in patients with and without ATTRCA. The AF was present in patients with ATTRCA. The degree of LVH and IVS thickness was similar between patients with ATTRCA and patients without ATTRCA in the AS population. ATTRCA patients are found to have lower mean AV gradients and lower mean SV. The GLS was similar in all patients; however, the difference in relative LS between the apex and mid to basal was statistically significant between both groups. Screening is advised for these patients by ^{99m}Tc PYP bone scintigraphy to rule out ATTRCA.

Limitation

The small number of patients screened limits the generalizability of our data to the AS population; patients with moderate AS or asymptomatic severe AS are not included. Patients with moderate AS and HF need to be studied, as the severity of AS could be underestimated in the presence of myocardial disease. Further study with a larger number of participants is needed.

Recommendation

Routine screening is advised for AS patients by ^{99m}Tc PYP bone scintigraphy to rule out ATTRCA.

Acknowledgements

This study was funded by Pfizer Global Research Grant (#70163957).

Disclosure of conflict of interest

None.

Address correspondence to: Dr. Abeer Bakhsh, King Abdullah Medical City, Department of Adult Cardiology, 24246 Al Mashair, Makkah 21955, Saudi Arabia. E-mail: Bakhsh.A5@KAMC.med.sa

References

[1] Garcia-Pavia P, Rapezzi C, Adler Y, Arad M, Basso C, Brucato A, Burazor I, Caforio ALP, Damy T, Eriksson U, Fontana M, Gillmore JD, Gonzalez-Lopez E, Grogan M, Heymans S, Imazio M, Kindermann I, Kristen AV, Maurer MS, Merlini G, Pantazis A, Pankuweit S, Rigopoulos AG and Linhart A. Diagnosis and treatment of cardiac amyloidosis: a position statement of the ESC Working Group on Myocardial and Pericardial Diseases. Eur Heart J 2021; 42: 1554-1568.

[2] Writing Committee; Kittleson MM, Ruberg FL, Ambardekar AV, Brannagan TH, Cheng RK, Clarke JO, Dember LM, Frantz JG, Hershberger RE, Maurer MS, Nativi-Nicolau J, Sanchorawala V and Sheikh FH. 2023 ACC expert consensus decision pathway on comprehensive multidisciplinary care for the patient with cardiac amyloidosis: a report of the American College of Cardiology Solution Set Oversight Committee. J Am Coll Cardiol 2023; 81: 1076-1126.

[3] Donnelly JP and Hanna M. Cardiac amyloidosis: an update on diagnosis and treatment. Cleve Clin J Med 2017; 84 Suppl 3: 12-26.

[4] Banypersad SM, Moon JC, Whelan C, Hawkins PN and Wechalekar AD. Updates in cardiac amyloidosis: a review. J Am Heart Assoc 2012; 1: e000364.

[5] Griffin JM, Rosenblum H and Maurer MS. Pathophysiology and therapeutic approaches to cardiac amyloidosis. Circ Res 2021; 128: 1554-1575.

[6] Tahir UA, Doros G, Kim JS, Connors LH, Seldin DC and Sam F. Predictors of mortality in light chain cardiac amyloidosis with heart failure. Sci Rep 2019; 9: 8552.

[7] Lauppe R, Liseth Hansen J, Fornwall A, Johansson K, Rozenbaum MH, Strand AM, Vakevainen M, Kuusisto J, Gude E, Smith JG and Gustafsson F. Prevalence, characteristics, and mortality of patients with transthyretin amyloid cardiomyopathy in the Nordic countries. ESC Heart Fail 2022; 9: 2528-2537.

[8] Gonzalez-Lopez E, Gallego-Delgado M, Guzzo-Merello G, de Haro-Del Moral FJ, Cobo-Marcos M, Robles C, Bornstein B, Salas C, Lara-Pezzi E, Alonso-Pulpon L and Garcia-Pavia P. Wild-type transthyretin amyloidosis as a cause of heart failure with preserved ejection fraction. Eur Heart J 2015; 36: 2585-2594.

[9] Damy T, Costes B, Hagege AA, Donal E, Eicher JC, Slama M, Guellich A, Rappeneau S, Gueffet JP, Logeart D, Plante-Bordeneuve V, Bouvaist H, Huttin O, Mulak G, Dubois-Rande JL, Goossens M, Canoui-Poitrine F and Buxbaum JN. Prevalence and clinical phenotype of hereditary transthyretin amyloid cardiomyopathy in

patients with increased left ventricular wall thickness. Eur Heart J 2016; 37: 1826-1834.
[10] Witteles RM, Bokhari S, Damy T, Elliott PM, Falk RH, Fine NM, Gospodinova M, Obici L, Rapezzi C and Garcia-Pavia P. Screening for transthyretin amyloid cardiomyopathy in everyday practice. JACC Heart Fail 2019; 7: 709-716.
[11] Ruberg FL, Grogan M, Hanna M, Kelly JW and Maurer MS. Transthyretin amyloid cardiomyopathy: JACC State-of-the-Art Review. J Am Coll Cardiol 2019; 73: 2872-2891.
[12] Westin O, Fosbol EL, Maurer MS, Leicht BP, Hasbak P, Mylin AK, Rorvig S, Lindkaer TH, Johannesen HH and Gustafsson F. Screening for cardiac amyloidosis 5 to 15 years after surgery for bilateral carpal tunnel syndrome. J Am Coll Cardiol 2022; 80: 967-977.
[13] Ternacle J, Krapf L, Mohty D, Magne J, Nguyen A, Galat A, Gallet R, Teiger E, Cote N, Clavel MA, Tournoux F, Pibarot P and Damy T. Aortic stenosis and cardiac amyloidosis: JACC Review Topic of the Week. J Am Coll Cardiol 2019; 74: 2638-2651.
[14] Shimoni S, Zikri M, Haberman D, Livschitz S, Tshori S, Fabricant Y, Meledin V, Gandelman G, Goland S and George J. Transthyretin cardiac amyloidosis in patients after TAVR: clinical and echocardiographic findings and long term survival. ESC Heart Fail 2021; 8: 4549-4561.
[15] Castano A, Narotsky DL, Hamid N, Khalique OK, Morgenstern R, DeLuca A, Rubin J, Chiuzan C, Nazif T, Vahl T, George I, Kodali S, Leon MB, Hahn R, Bokhari S and Maurer MS. Unveiling transthyretin cardiac amyloidosis and its predictors among elderly patients with severe aortic stenosis undergoing transcatheter aortic valve replacement. Eur Heart J 2017; 38: 2879-2887.
[16] Maleszewski JJ. Cardiac amyloidosis: pathology, nomenclature, and typing. Cardiovasc Pathol 2015; 24: 343-350.
[17] Cavalcante JL, Rijal S, Abdelkarim I, Althouse AD, Sharbaugh MS, Fridman Y, Soman P, Forman DE, Schindler JT, Gleason TG, Lee JS and Schelbert EB. Cardiac amyloidosis is prevalent in older patients with aortic stenosis and carries worse prognosis. J Cardiovasc Magn Reson 2017; 19: 98.
[18] Treibel TA, Fontana M, Gilbertson JA, Castelletti S, White SK, Scully PR, Roberts N, Hutt DF, Rowczenio DM, Whelan CJ, Ashworth MA, Gillmore JD, Hawkins PN and Moon JC. Occult transthyretin cardiac amyloid in severe calcific aortic stenosis: prevalence and prognosis in patients undergoing surgical aortic valve replacement. Circ Cardiovasc Imaging 2016; 9: e005066.
[19] Geenty P, Sivapathan S, Stefani LD, Zada M, Boyd A, Richards D, Kwok F and Thomas L. A novel echocardiographic risk score for light-chain amyloidosis. Eur Heart J Open 2023; 3: oead040.
[20] Dorbala S, Cuddy S and Falk RH. How to image cardiac amyloidosis: a practical approach. JACC Cardiovasc Imaging 2020; 13: 1368-1383.
[21] Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F and Maurer MS. (99m)Tc-pyrophosphate scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidoses. Circ Cardiovasc Imaging 2013; 6: 195-201.
[22] Masri A, Bukhari S, Ahmad S, Nieves R, Eisele YS, Follansbee W, Brownell A, Wong TC, Schelbert E and Soman P. Efficient 1-hour technetium-99 m pyrophosphate imaging protocol for the diagnosis of transthyretin cardiac amyloidosis. Circ Cardiovasc Imaging 2020; 13: e010249.
[23] Castano A, Haq M, Narotsky DL, Goldsmith J, Weinberg RL, Morgenstern R, Pozniakoff T, Ruberg FL, Miller EJ, Berk JL, Dispenzieri A, Grogan M, Johnson G, Bokhari S and Maurer MS. Multicenter study of planar technetium 99m pyrophosphate cardiac imaging: predicting survival for patients with ATTR cardiac amyloidosis. JAMA Cardiol 2016; 1: 880-889.
[24] Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, Fontana M, Gheysens O, Gillmore JD, Glaudemans AWJM, Hanna MA, Hazenberg BPC, Kristen AV, Kwong RY, Maurer MS, Merlini G, Miller EJ, Moon JC, Murthy VL, Quarta CC, Rapezzi C, Ruberg FL, Shah SJ, Slart RHJA, Verberne HJ and Bourque JM. 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. Circ Cardiovasc Imaging 2021; 14: e000029.
[25] Dorbala S, Ando Y, Bokhari S, Dispenzieri A, Falk RH, Ferrari VA, Fontana M, Gheysens O, Gillmore JD, Glaudemans AWJM, Hanna MA, Hazenberg BPC, Kristen AV, Kwong RY, Maurer MS, Merlini G, Miller EJ, Moon JC, Murthy VL, Quarta CC, Rapezzi C, Ruberg FL, Shah SJ, Slart RHJA, Verberne HJ and Bourque JM. ASNC/AHA/ASE/EANM/HFSA/ISA/SCMR/SNMMI expert consensus recommendations for multimodality imaging in cardiac amyloidosis: part 2 of 2-diagnostic criteria and appropriate utilization. Circ Cardiovasc Imaging 2021; 14: e000030.

[26] Nazir T and Nuffati M. Cardiac amyloidosis-an underdiagnosed cause of heart failure in the elderly. J Saudi Heart Assoc 2020; 32: 98-102.
[27] Rauf MU, Hawkins PN, Cappelli F, Perfetto F, Zampieri M, Argiro A, Petrie A, Law S, Porcari A, Razvi Y, Bomsztyk J, Ravichandran S, Ioannou A, Patel R, Starr N, Hutt DF, Mahmood S, Wisniowski B, Martinez-Naharro A, Venneri L, Whelan C, Roczenio D, Gilbertson J, Lachmann HJ, Wechalekar AD, Rapezzi C, Serenelli M, Massa P, Caponetti AG, Ponziani A, Accietto A, Giovannetti A, Saturi G, Sguazzotti M, Gagliardi C, Biagini E, Longhi S, Fontana M and Gillmore JD. Tc-99m labelled bone scintigraphy in suspected cardiac amyloidosis. Eur Heart J 2023; 44: 2187-2198.
[28] Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, Flachskampf FA, Gillebert TC, Klein AL, Lancellotti P, Marino P, Oh JK, Alexandru Popescu B and Waggoner AD; Houston, Texas; Oslo, Norway; Phoenix, Arizona; Nashville, Tennessee; Hamilton, Ontario, Canada; Uppsala, Sweden; Ghent and Liege, Belgium; Cleveland, Ohio; Novara, Italy; Rochester, Minnesota; Bucharest, Romania; and St. Louis, Missouri. Recommendations for the evaluation of left ventricular diastolic function by echocardiography: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Eur Heart J Cardiovasc Imaging 2016; 17: 1321-1360.
[29] Nishimura RA, Otto CM, Bonow RO, Carabello BA, Erwin JP 3rd, Fleisher LA, Jneid H, Mack MJ, McLeod CJ, O'Gara PT, Rigolin VH, Sundt TM 3rd and Thompson A. 2017 AHA/ACC focused update of the 2014 AHA/ACC guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Task Force on clinical practice guidelines. J Am Coll Cardiol 2017; 70: 252-289.
[30] Baumgartner H, Hung J, Bermejo J, Chambers JB, Edvardsen T, Goldstein S, Lancellotti P, LeFevre M, Miller F Jr and Otto CM. Recommendations on the echocardiographic assessment of aortic valve stenosis: a focused update from the European Association of Cardiovascular Imaging and the American Society of Echocardiography. J Am Soc Echocardiogr 2017; 30: 372-392.
[31] Brito D, Albrecht FC, de Arenaza DP, Bart N, Better N, Carvajal-Juarez I, Conceicao I, Damy T, Dorbala S, Fidalgo JC, Garcia-Pavia P, Ge J, Gillmore JD, Grzybowski J, Obici L, Pinero D, Rapezzi C, Ueda M and Pinto FJ. World heart federation consensus on transthyretin amyloidosis cardiomyopathy (ATTR-CM). Glob Heart 2023; 18: 59.
[32] Bruno M, Castano A, Burton A and Grodin JL. Transthyretin amyloid cardiomyopathy in women: frequency, characteristics, and diagnostic challenges. Heart Fail Rev 2021; 26: 35-45.
[33] Longhi S, Lorenzini M, Gagliardi C, Milandri A, Marzocchi A, Marrozzini C, Saia F, Ortolani P, Biagini E, Guidalotti PL, Leone O and Rapezzi C. Coexistence of degenerative aortic stenosis and wild-type transthyretin-related cardiac amyloidosis. JACC Cardiovasc Imaging 2016; 9: 325-327.
[34] Ochi Y, Kubo T, Baba Y, Sugiura K, Ueda M, Miyagawa K, Noguchi T, Hirota T, Hamada T, Yamasaki N and Kitaoka H. Wild-type transthyretin amyloidosis in female patients-consideration of sex differences. Circ Rep 2021; 3: 465-471.