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ORIGINAL ARTICLE

First report of the clinical characteristics and outcomes of cardiac amyloidosis in Saudi Arabia

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Abstract

Aims Cardiac amyloidosis (CA) is a potentially fatal multisystemic disease that remains significantly underdiagnosed, particularly in the Middle East. This study aims to evaluate the prevalence and clinical characteristics of CA in a high-risk population at a tertiary centre in Saudi Arabia.

Methods This cross-sectional, retrospective, single-centre study was conducted at a tertiary hospital in Riyadh, Saudi Arabia. We reviewed the medical records of heart failure patients seen between August 2018 and July 2022 who exhibited red flags for CA and subsequently underwent CA screening. Red flags that prompted the workup included at least two of the following factors: the presence of unilateral or bilateral carpal tunnel syndrome, a family history of transthyretin amyloid (ATTR) amyloidosis and specific electrocardiographic features (relative/absolute low QRS voltage, pseudoinfarct pattern and atrioventricular/interventricular conduction abnormalities). Echocardiographic red flags included mainly increased wall thickness (≥12 mm), significant diastolic dysfunction, reduced left ventricular (LV) longitudinal function, right ventricular (RV) dysfunction and elevated right atrial (RA)/pulmonary artery (PA) pressure. Cardiac magnetic resonance (CMR) red flags included aspects similar to those in an echocardiogram as well as a subendocardial or transmural late gadolinium enhancement (LGE) pattern. These patients were assessed for CA through technetium-99m pyrophosphate ([^{99m}Tc]Tc-PYP) bone scintigraphy, serum and urine protein electrophoresis with immunofixation and a serum-free light chain assay.

Results A total of 177 patients were screened, of which 21.0 (11.9%) patients were diagnosed with transthyretin amyloid CA (ATTR-CA) and 13 (7.3%) patients were diagnosed with light chain CA (AL-CA). Compared with patients with negative/equivocal [^{99m}Tc]Tc-PYP scans (grades 0–1), patients with positive [^{99m}Tc]Tc-PYP scans (grades 2–3) were older (78.0 vs. 68.0 years, $P < 0.001$), had higher levels of troponin ($P = 0.003$) and N-terminal pro-brain natriuretic peptide (NT-proBNP) ($P < 0.001$), had a higher LV mass index ($P < 0.001$), displayed a more depressed global longitudinal strain (GLS) ($P < 0.001$) with a greater prevalence of a relative apical sparing pattern ($P < 0.001$) and demonstrated a higher incidence of first-degree atrioventricular block ($P = 0.008$) and low voltage patterns on electrocardiography ($P < 0.001$). Patients with ATTR-CA and AL-CA were more likely to have a subendocardial or transmural LGE pattern on CMR ($P < 0.001$) and had a significantly lower overall survival ($P < 0.001$) when compared with other heart failure aetiologies.

Conclusions This is the first study to describe the clinical characteristics and outcomes of CA in the Middle East and Saudi Arabia. The prevalence of CA among screened heart failure patients here aligns with major international studies, suggesting significant underdiagnosis in the region. Therefore, larger multicentric studies and regional screening programmes are urgently needed to accurately characterize the epidemiology and outcomes of CA in the Middle East.

Keywords cardiac amyloidosis; heart failure; heart failure with preserved ejection fraction; light chain; restrictive cardiomyopathies; transthyretin

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Introduction

Cardiac amyloidosis (CA) is characterized by the misfolding of soluble precursor proteins, resulting in the extracellular deposition of amyloid fibrils in the myocardium.[1] CA generally arises as a consequence of either misfolded monoclonal immunoglobulin light chains (AL) due to plasma cell dyscrasia or the misfolding of transthyretin (TTR) protein resulting in transthyretin amyloid (ATTR) cardiomyopathy.[2] Furthermore, ATTR can be further classified into an acquired subtype underpinned by the deposition of wild-type transthyretin protein (ATTRwt) and a hereditary subtype depicted by pathogenic variants in the TTR gene (ATTRv).[1,2] Clinically, CA manifests as a restrictive or hypertrophic cardiomyopathy resulting in heart failure with preserved ejection fraction (HFpEF) or heart failure with mildly reduced ejection fraction (HFmrEF), and the disease is thought to account for 5%–15% of total HFpEF/HFmrEF cases.[3] Moreover, CA may also be associated with aortic stenosis, often with low flow and a low gradient, accounting for approximately 8%–15% of severe aortic stenosis presentations.[4]

CA represents a disease with a high morbidity and mortality burden, and it is associated with a 5 year mortality rate of approximately 44%–65%.[5] Several screening studies published over the past decade, particularly in western nations, have indicated that the prevalence of CA is higher than previously expected.[6] A recent prospective, population-based cohort study emerging from the United States has identified a prevalence rate of 6.3% in a cohort sample with HFpEF that was systematically screened for CA.[7] The emergence of non-invasive diagnostic imaging modalities coupled with the use of novel therapeutics has increased interest among physicians in identifying and screening patients for transthyretin amyloid CA (ATTR-CA).[8] Moreover, recent advances in plasma cell-targeted immunotherapy have improved the survival outcomes of patients with AL.[9] Despite these advances, the diagnosis and management of CA remain challenging, with significant diagnostic delays as well as misdiagnosis and underdiagnosis of the disease.[10] Limited information exists regarding the epidemiology and clinical features of CA in the Middle East, particularly in Saudi Arabia. CA remains an unexplored entity within this region, with most patients remaining undiagnosed. Recent studies have highlighted significant shortcomings in awareness of the diagnostic and therapeutic modalities associated with CA in the Middle East region.[11] To our knowledge, there are no published studies reporting the epidemiology and clinical characteristics of CA within the region. Herein, we report the findings of the first CA screening programme established at a tertiary centre in Saudi Arabia.

Methods

Study design and patient enrolment

This is a cross-sectional, retrospective, single-centre study conducted at a tertiary hospital in Riyadh, Saudi Arabia. We

Table 1 Red flag features that warranted screening for cardiac amyloidosis.

Criteria	Features
Clinical	Age ≥ 65 years
	Excessive fatigue/weight loss/yellow skin pigmentation/macroglossia
	Unilateral or bilateral carpal tunnel syndrome
	Familial history of ATTR amyloidosis
	Unexplained neuropathic symmetrical paraesthesia
Laboratory	Raised NT-proBNP ≥ 1285 pg/mL
	Chronically elevated high-sensitivity troponin T ≥ 53 ng/L
ECG	Relative/absolute low QRS voltage
	Pseudoinfarct pattern in precordial leads
	Atrioventricular or intraventricular conduction disturbances
Echocardiogram	Increased LV wall thickness (≥12 mm)
	Systolic LV dysfunction irrespective of LV ejection fraction
	Evidence of diastolic dysfunction with elevated LV filling pressures
	Severely reduced mitral annular tissue Doppler velocities
	Reduced global longitudinal strain with relative apical sparing
	Increased LV and RV filling pressures
	Biatrial enlargement
	Dilated inferior vena cava/increased RA pressure
	Significant systolic pulmonary hypertension
	RV systolic dysfunction
	Increased RV free wall thickness
	Small pericardial effusion
CMR	Evidence of restrictive and/or 'hypertrophic' cardiomyopathy as described by echo (similar morphological abnormalities)
	Subendocardial or transmural LGE

Abbreviations: ATTR, transthyretin amyloid; CMR, cardiac magnetic resonance; ECG, electrocardiogram; LGE, late gadolinium enhancement; LV, left ventricular; NT-proBNP, N-terminal pro-brain natriuretic peptide; RA, right atrial; RV, right ventricular.

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enrolled patients at our centre over a 4 year period spanning from August 2018 up until July 2022. Patients with clinical symptoms of heart failure and at least two red flag clinical, laboratory, electrocardiographic, echocardiographic and/or cardiac magnetic resonance (CMR) features suggestive of CA, as outlined in Table 1, were screened and included in the study. All patients that fit the aforementioned criteria underwent serum-free light chain assay, immunofixation electrophoresis of serum and urine and cardiac technetium-99m pyrophosphate ([^{99m}Tc]Tc-PYP) bone scintigraphy. CMR imaging and endomyocardial/extracardiac biopsy were performed in selected patients if considered necessary by the treating physician. Patients excluded from screening were those under 18 years, those with a confirmed aetiology of other types of cardiomyopathies (dilated, ischaemic and/or hypertrophic sarcomeric familial cardiomyopathy), those with heart failure due to severe valvular mitral stenosis or regurgitation, those with heart failure due to severe aortic regurgitation and those with confirmed constrictive pericarditis. In addition, patients without available echocardiogram data were excluded from the study. The study was approved by the institutional review board at King Faisal Specialist Hospital and Research Center under Approval Number 2231255. The requirement for written informed consent was waived by the ethics committee due to the retrospective nature of the study. All methods were carried out in accordance with relevant guidelines, including the 'Declaration of Helsinki'.

Data collection

All patients who met the inclusion criteria and had undergone appropriate investigations were retrospectively analysed. Baseline clinical characteristics and outcome measures were collected from the patient's electronic medical records on admission. Electrocardiogram (ECG) measures were based on standard definitions, utilizing the first ECG available at admission. Low voltage criteria were defined as QRS amplitudes of $\leq$0.5 mV in all limb leads or $\leq$1 mV in all precordial leads. The classification of heart failure subtypes was conducted in accordance with the 2021 European Society of Cardiology (ESC) guidelines for the diagnosis and treatment of acute and chronic heart failure.[12] Transthoracic echocardiograms (TTEs) were performed using the Vivid E95 by General Electric. Chamber and left ventricular (LV) ejection fraction (LVEF) quantification was based on standard recommendations.[13] Left atrial diameter, interventricular septum thickness at end-diastole (IVSd) and LV posterior wall thickness at end-diastole (LVPWd) were measured in the parasternal long-axis view. Global longitudinal strain (GLS) by speckle tracking echocardiography was measured manually in a 17-segment LV model as the average segmental value based on three apical imaging planes. LV mass and LV mass index (LVMI) were assessed through the Cube formula.[13] Relative wall thickness was calculated as the ratio of 2 × posterior wall thickness at end-diastole over LV end-diastolic diameter (LVEDd). The relative apical sparing pattern was calculated by determining the ratio of the average apical strain segments to the average of the basal segments and the average of the middle segments, in concordance with other reported studies.[14] The LV mass-to-strain ratio was evaluated by calculating the ratio of LV mass to LV GLS, whereas the ejection fraction (EF)-to-strain ratio was assessed by calculating the ratio of the LVEF to the LV GLS, as reported.[15,16]

Diagnosis of ATTR-CA and AL-CA

Echocardiographic, electrocardiographic and/or CMR red flags consistent with CA were used to screen patients prior to undergoing [^{99m}Tc]Tc-PYP bone scintigraphy.

ATTR-CA and AL-CA were diagnosed in line with pre-existing guidelines and recommendations.[8,17] ATTR-CA was diagnosed in patients on the basis of the following criteria: (i) grade 2 or 3 myocardial uptake with [^{99m}Tc]Tc-PYP bone scintigraphy; (ii) negative urine/serum immunofixation and negative serum-free light chain assays; and (iii) CMR or echocardiographic imaging displaying LV wall thickness consistent with ATTR-CA. Patients with a positive [^{99m}Tc]Tc-PYP scan (grades 2–3) underwent genetic analysis to differentiate between ATTRwt-CA and ATTRv-CA. DNA was extracted from whole blood and amplified by a polymerase chain reaction (PCR) assay. The whole coding region of the TTR gene was sequenced using next-generation sequencing (NGS) on the NovaSeq 6000 platform from Illumina. For patients with a family history of ATTRv-CA, only the specific mutation associated with their family history was tested for. Key variants identified were validated using Sanger sequencing. AL-CA was diagnosed on the basis of the following criteria: (i) CMR or echocardiographic imaging displaying red flags consistent with AL cardiac involvement irrespective of [^{99m}Tc]Tc-PYP; (ii) monoclonal protein component presence in urine and serum immunofixation in addition to a positive serum-free light chain assay; and (iii) a tissue biopsy with Congo red staining confirming the presence of amyloid fibrils. As AL amyloidosis may present with a positive [^{99m}Tc]Tc-PYP scan in 10%–20% of cases, all 177 patients were evaluated using serum and urine protein electrophoresis, immunofixation and free light chain assays. Any patient with monoclonal gammopathy underwent a tissue biopsy with Congo red staining to confirm the presence and type of amyloid fibrils, regardless of the [^{99m}Tc]Tc-PYP scan outcome.

Scintigraphy protocol

The bone scintigraphy protocol was in accordance with American Society of Nuclear Cardiology (ASNC) 2021

guidelines.[18] Planar imaging followed by single-photon emission computed tomography with computed tomography (SPECT/CT) imaging of the chest with a dual-headed camera (Philips Healthcare) was performed. Patients received 10–20 mCi (370–740 MBq) of [^{99m}Tc]Tc-PYP. With patients in a supine position, anterior and lateral planar images were acquired at 1 and 3 h post-injection using a low-energy, high-resolution collimator with an energy window set at 126–154 keV. With the patient's heart positioned in the centre field of view, images were acquired for a total of 750 000 counts with a 256 × 256 matrix and a 1.46 zoom factor.

For patients showing myocardial uptake of [^{99m}Tc]Tc-PYP on planar images, SPECT/CT imaging was conducted 3 h post-injection in step-and-shoot mode with 40 views per detector and 20 s per stop. Images were acquired at a matrix size of 128 × 128, with a magnification factor of 1.46. The photopeak was set at 140 keV, and a scatter window of 120–140 keV was used. For CT acquisition, the voltage setting was 120 kV with a slice thickness of 2.5 mm.

Either of two methods were used to assess myocardial tracer uptake. The first method involved a quantitative analysis of planar imaging at 1 h, where circular target regions of interest (ROIs) were drawn over the heart and mirrored over the contralateral chest to account for background and rib interference. Total and absolute mean counts were measured in each ROI, and a heart-to-contralateral lung (H/CL) ratio was calculated by dividing the mean counts in the heart ROI by the mean counts in the contralateral chest ROI. The second method was a semi-quantitative analysis with the following grading system devised by Perugini *et al*. regardless of H/CL ratio: grade 0 = absent cardiac uptake; grade 1 = mild uptake less than bone; grade 2 = moderate uptake equal to bone; and grade 3 = high uptake greater than bone.[19] SPECT imaging was necessary to confirm that tracer uptake within the myocardium was greater than that within the blood pool.

CMR protocol

CMR was performed on a 1.5 Tesla CMR (Siemens Medical Solutions). Imaging sequences included retrospectively gated cine imaging to assess cine function. Two-chamber, three-chamber, four-chamber and short-axis stack cine images were acquired. A gadolinium-based contrast agent was used at a dose of 0.1–0.2 mmol/kg. Late gadolinium enhancement (LGE) images were acquired 10 min post-contrast injection using phase-sensitive inversion recovery (PSIR) sequences in two-chamber, three-chamber, four-chamber and short-axis views. LGE was defined categorically based on the presence or absence of a typical CA pattern, specifically global subendocardial or transmural enhancement.[18]

Statistical analysis

Numerical variables were described with their medians and ranges, whereas categorical variables were described with their relative frequencies and percentages. The Mann–Whitney *U* test was used to compare numerical variables between two groups, assuming that the data are independent and that the distributions of the two groups are similar in shape. Categorical variables were compared using Pearson's χ^2 test, assuming that the variables are categorical and mutually exclusive. Specifically, comparisons were made between

- patients with [^{99m}Tc]Tc-PYP grade 0/1 versus patients with [^{99m}Tc]Tc-PYP grade 2/3 and
- patients diagnosed with ATTR-CA versus patients diagnosed with AL-CA.

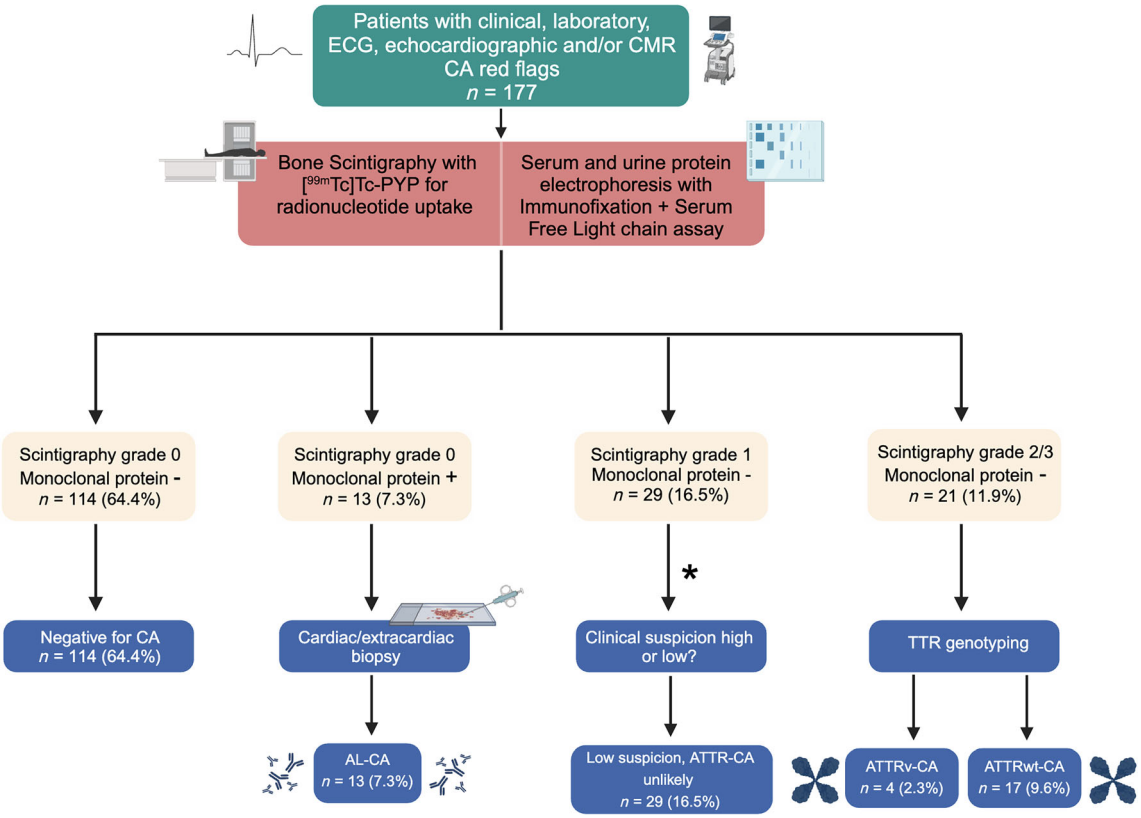
The Kaplan–Meier method was utilized to conduct survival analysis and estimate overall survival (OS). OS was defined as the incidence of death from any cause during the follow-up period. The log-rank test was used to compare survival between groups. The Cox proportional hazards model was utilized for multivariate survival analysis. Two-sided *P* values < 0.05 were considered significant. We encountered missing data due to echocardiographic technical issues: 5 out of 177 patients (2.8%) had missing GLS values, and 11 out of 177 patients (6.2%) had missing pulmonary artery pressure (PAP) values, all from the [^{99m}Tc]Tc-PYP grade 0 scan group. Little's missing completely at random (MCAR) test showed that these missing values can be assumed to be missing completely at random. Therefore, we performed complete case analyses, excluding the patients with missing values, resulting in sample sizes of 172 for GLS and 166 for PAP analyses.[20] All other variables were available for all 177 patients. All statistical analysis was conducted using Version 27.0.01 of IBM SPSS Statistics. Data handling followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines.[21]

Results

Overview of the study cohort

Figure 1 outlines the study flowchart. Between August 2018 and July 2022, a total of 177 patients underwent systematic screening for CA, with an average of 44 patients screened per year (2018: 9, 2019: 32, 2020: 44, 2021: 57 and 2022: 35). Of which, 21 (11.9%) patients had a positive [^{99m}Tc]Tc-PYP scan (grades 2–3), 29 (16.5%) patients had an equivocal [^{99m}Tc]Tc-PYP scan (grade 1) and 127 (71.6%) patients had a negative [^{99m}Tc]Tc-PYP scan (grade 0). A total of 21 (11.9%) patients were diagnosed with ATTR-CA, with 17 (9.6%) patients diagnosed with ATTRwt and 4 (2.3%) diagnosed with

Figure 1 Study flowchart. Flowchart representing the distribution of the study cohort. A total of 177 patients underwent systematic screening for cardiac amyloidosis (CA) through technetium-99m pyrophosphate ([^{99m}Tc]Tc-PYP) bone scintigraphy, serum and urine protein electrophoresis with immunofixation and a serum-free light chain assay. *Ideally, patients with a grade 1 [^{99m}Tc]Tc-PYP scan should undergo biopsy for histological confirmation of CA; however, as some patients in our cohort refused the procedure, we had to rely on clinical suspicion and statistical analyses to determine the likelihood of CA in this group. AL-CA, light chain CA; ATTR-CA, transthyretin amyloid CA; ATTRv-CA, variant transthyretin amyloid CA; ATTRwt-CA, wild-type transthyretin amyloid CA; CMR, cardiac magnetic resonance; ECG, electrocardiogram; TTR, transthyretin. Created using Biorender.com.



hereditary ATTR (ATTRh). Moreover, 13 (7.3%) patients were diagnosed with AL-CA. Extracardiac biopsies for AL amyloidosis confirmation were obtained from the following sites: bone marrow (n = 2), kidney (n = 3), bowel (n = 7) and salivary gland (n = 1).

Baseline demographics and clinical characteristics

Table 2 displays the comparison of baseline demographics and clinical characteristics between patients with ATTR-CA (i.e., [^{99m}Tc]Tc-PYP grades 2–3) and patients with a negative/equivocal [^{99m}Tc]Tc-PYP scan (grades 0–1). The median age of the cohort was 68 years (range 17–95), with males comprising 54.8% of study participants. Patient age was significantly higher in individuals with ATTR-CA with a median of 78 years when compared with patients with a negative/equivocal [^{99m}Tc]Tc-PYP scan in which the median age was 66 years ($P < 0.001$). The median body mass index (BMI) was significantly lower in the ATTR-CA group compared with the negative/equivocal [^{99m}Tc]Tc-PYP group (24.2 vs. 28.0 kg/m^2, P = 0.011). Troponin levels were significantly higher among individuals with ATTR-CA when compared with those with a negative/equivocal [^{99m}Tc]Tc-PYP scan (74.0 vs. 28.5 ng/L, P = 0.003). Similarly, patients with ATTR-CA had a significantly higher N-terminal pro-brain natriuretic peptide (NT-proBNP) level when compared with subjects with a negative/equivocal [^{99m}Tc]Tc-PYP scan (5489.0 vs. 1094.0 pg/mL, $P < 0.001$). Additionally, patients with ATTR-CA had a significantly lower median systolic blood pressure when compared with subjects with a negative/equivocal [^{99m}Tc]Tc-PYP scan (127.0 vs. 134.0 mmHg, P = 0.035). A significantly higher proportion of patients with ATTR-CA had carpal tunnel syndrome when compared with those with negative/equivocal [^{99m}Tc]Tc-PYP scans (28.6% vs. 0.7%, $P < 0.001$). Finally, the incidence of deaths was significantly higher among patients with ATTR-CA (42.9%) when compared with the negative/equivocal group (11.5%) ($P < 0.001$).

Table 3 outlines the comparison of the baseline demographics and clinical characteristics between patients with

Table 2 Comparison of baseline demographics and clinical characteristics between patients with a positive [^{99m}Tc]Tc-PYP scan and those with a negative/equivocal scan.

Characteristic	ATTR amyloidosis $n = 21$	[^{99m}Tc]Tc-PYP negative/equivocal (grades 0–1) $n = 156$	Total $n = 177$	*P* value
Median age, years (range)	78.0 (59.0–95.0)	66.0 (17.0–91.0)	68.0 (17.0–95.0)	<**0.001**
Sex (%)				0.812
Male	11.0 (52.4)	86.0 (55.1)	97.0 (54.8)	
Median BMI, kg/m^2 (range)	24.2 (19.3–40.3)	28.0 (16.0–61.6)	27.9 (16.0–61.6)	**0.011**
Heart failure subtypes (%)				0.194
HFpEF	10.0 (47.6)	101.0 (69.7)	111.0 (66.9)	
HFmrEF	4.0 (19.0)	19.0 (13.1)	23.0 (13.9)	
HFrEF	7.0 (33.3)	24.0 (16.6)	31.0 (18.7)	
Median troponin, ng/L (range)	74.0 (17.0–758.0)	28.5 (4.0–1345.0)	31.0 (4.0–1345.0)	**0.003**
Median NT-proBNP, pg/mL (range)	5489.0 (44.0–70 000.0)	1094.0 (19.0–35 221.0)	1274.5 (19.0–70 000.0)	<**0.001**
Median systolic BP, mmHg (range)	127.0 (90.0–160.0)	134.0 (88.0–198.0)	133.0 (88.0–198.0)	**0.035**
Median diastolic BP, mmHg (range)	68.0 (50.0–85.0)	73.0 (39.0–105.0)	72.0 (39.0–105.0)	0.051
Median creatinine, μmol/L (range)	116.0 (39.0–374.0)	103.0 (27.0–964.0)	103.5 (27.0–964.0)	0.746
eGFR (%)				0.773
>60 mL/min	10.0 (47.6)	79.0 (51.0)	89.0 (50.6)	
<60 mL/min	11.0 (52.4)	76.0 (49.0)	87.0 (49.4)	
Presence of carpal tunnel syndrome (%)	6.0 (28.6)	1.0 (0.7)	7.0 (4.1)	<**0.001**
Positive CA LGE pattern on CMR	2.0 (50.0)[a]	6.0 (17.6)[b]	8.0 (21.1)	0.062
Deaths (%)	9.0 (42.9)	18.0 (11.5)	27.0 (15.3)	<**0.001**

Abbreviations: [^{99m}Tc]Tc-PYP, technetium-99m pyrophosphate; ATTR, transthyretin amyloid; BMI, body mass index; BP, blood pressure; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LGE, late gadolinium enhancement; NT-proBNP, N-terminal pro-brain natriuretic peptide. P values <0.05 are shown in bold.
[a]The values are based on the four patients who underwent CMR.
[b]The values are based on the 34 patients who underwent CMR.

ATTR-CA and those with AL-CA. Patients with ATTR-CA were significantly older at diagnosis when compared with patients with AL-CA (78 vs. 63 years, $P < 0.001$). The median time from symptoms to diagnosis was significantly longer in patients with ATTR-CA: 52 months when compared with 8 months for patients with AL amyloidosis ($P = 0.002$), indicating a significant delay in diagnosis for ATTR-CA.

Echocardiographic and ECG data

Table 4 displays the comparison of echocardiographic and ECG data between patients with ATTR-CA (i.e., [^{99m}Tc]Tc-PYP grades 2–3) and patients with a negative/equivocal [^{99m}Tc]Tc-PYP (grades 0–1). The median LVEF was significantly lower among patients with ATTR-CA compared with patients with negative/equivocal [^{99m}Tc]Tc-PYP (42.5% vs. 55.0%, $P < 0.001$). Moreover, the stroke volume (SV) index was significantly lower among patients with ATTR-CA compared with those with a negative/equivocal scan (24.0 vs. 34.0 mL/m^2, $P < 0.001$). The median GLS was significantly worse between both groups, as patients with ATTR-CA had a median GLS of −9.9% compared with −15.0% among patients with negative/equivocal scans ($P < 0.001$). Patients with a positive [^{99m}Tc]Tc-PYP scan also demonstrated a significantly higher median IVSd at 14.0 mm compared with 12.0 mm among patients with negative/equivocal scans ($P < 0.001$). The LVPWd was significantly higher among patients with positive [^{99m}Tc]Tc-PYP scans (13.0 vs. 11.0 mm, $P < 0.001$), whereas the LVEDd was significantly lower among individuals with a positive [^{99m}Tc]Tc-PYP scan (39.0 vs. 44.0 mm, $P = 0.002$). ATTR-CA patients had a significantly greater LVMI compared with patients with negative/equivocal [^{99m}Tc]Tc-PYP scans (116.6 vs. 97.4 g/m^2, $P = 0.017$). Moreover, the relative apical sparing pattern ($P < 0.001$) and the relative wall thickness ($P < 0.001$) were significantly different among both groups. Additionally, both the LV mass-to-strain ratio ($P < 0.001$) and the EF-to-strain ratio ($P = 0.011$) were significantly different between the groups. A significantly higher proportion of patients in the positive [^{99m}Tc]Tc-PYP group displayed evidence of moderate and severe right ventricular systolic dysfunction ($P < 0.001$). Patients in the [^{99m}Tc]Tc-PYP positive group also demonstrated significantly higher PAPs when compared with individuals with negative/equivocal [^{99m}Tc]Tc-PYP scans (45.0 vs. 35.0 mmHg, $P = 0.013$).

Regarding ECG data, patients with ATTR-CA had a significantly higher incidence of low voltage patterns, of 61.9% among ATTR-CA individuals compared with 12.9% among those with [^{99m}Tc]Tc-PYP negative/equivocal scans ($P < 0.001$). Additionally, patients in the ATTR-CA group demonstrated an increased incidence of first-degree atrioventricular conduction block (33.3% vs. 11.8%, $P = 0.008$), due to a significant increase in PR interval duration (198.0 vs. 174.0 ms, $P = 0.016$).

Table 5 displays the comparison of echocardiographic and ECG data between patients with ATTR-CA and those with AL-

Table 3 Comparison of baseline demographics and clinical characteristics between patients with ATTR and AL cardiac amyloidosis.

Characteristic	ATTR amyloidosis $n = 21$	AL amyloidosis $n = 13$	Total $n = 34$	P value
Median age, years (range)	78.0 (59.0–95.0)	63.0 (45.0–73.0)	70.0 (45.0–95.0)	**<0.001**
Sex (%)				0.217
Male	11.0 (52.4)	4.0 (30.8)	15.0 (44.1)	
Median BMI, kg/m^2 (range)	24.2 (19.3–40.3)	27.0 (18.3–41.4)	25.0 (18.3–41.4)	0.06
Median time from symptoms to diagnosis, months (range)	52.0 (1.0–120.0)	8.0 (1.0–56.0)	24.0 (1.0–120.0)	**0.002**
Heart failure subtypes (%)				0.933
HFpEF	10.0 (47.6)	7.0 (53.8)	17.0 (50.0)	
HFmrEF	4.0 (19.0)	2.0 (15.4)	6.0 (17.6)	
HFrEF	7.0 (33.3)	4.0 (30.8)	11.0 (32.4)	
Median troponin, ng/L (range)	74.0 (17.0–758.0)	52.0 (18.0–375.0)	68.0 (17.0–758.0)	0.589
Median NT-proBNP, pg/mL (range)	5489.0 (44.0–70 000.0)	3815.0 (1610.0–17 000.0)	4532.0 (44.0–70 000.0)	0.699
Median systolic BP, mmHg (range)	127.0 (90.0–160.0)	117.0 (91.0–160.0)	122.5 (90.0–160.0)	0.381
Median diastolic BP, mmHg (range)	68.0 (50.0–85.0)	69.0 (51.0–80.0)	68.5 (50.0–85.0)	0.529
Median haemoglobin, g/L	115.0 (41.0–166.0)	105.0 (37.0–142.0)	114.0 (37.0–166.0)	0.246
Median creatinine, μmol/L (range)	116.0 (39.0–374.0)	88.0 (55.0–590.0)	92.0 (39.0–590.0)	0.780
eGFR (%)				0.429
>60 mL/min	10.0 (47.6)	8.0 (61.5)	18.0 (52.9)	
Comorbidities				
Ischaemic heart disease	8.0 (61.5)	5.0 (38.5)	15.0 (44.1)	0.601
Diabetes	12.0 (57.1)	6.0 (46.2)	18.0 (52.9)	0.533
Hypertension	13.0 (61.9)	6.0 (46.2)	19.0 (55.9)	0.369
Presence of carpal tunnel syndrome (%)	6.0 (28.6)	0.0 (0.0)	6.0 (17.6)	**0.034**
Positive CA LGE pattern on CMR	2.0 (50.0)[a]	4.0 (80.0)[b]	6.0 (66.7)	0.166
Deaths (%)	9.0 (42.9)	5.0 (38.5)	14.0 (41.2)	0.800

Abbreviations: AL, light chain; ATTR, transthyretin amyloid; BMI, body mass index; BP, blood pressure; CA, cardiac amyloidosis; CMR, cardiac magnetic resonance; eGFR, estimated glomerular filtration rate; HFmrEF, heart failure with mildly reduced ejection fraction; HFpEF, heart failure with preserved ejection fraction; HFrEF, heart failure with reduced ejection fraction; LGE, late gadolinium enhancement; NT-proBNP, N-terminal pro-brain natriuretic peptide. P values <0.05 are shown in bold.
[a]The values are based on the four patients who underwent CMR.
[b]The values are based on the five patients who underwent CMR.

CA. Echocardiographic parameters were nearly identical between both groups, with the only statistically significant parameter being the median GLS, as patients in the ATTR group had a median GLS of −9.9% compared with −15.4% in the AL group (P = 0.035). Similarly, electrocardiographic data were similar between groups, with the only significant parameter being the median PR interval duration, as it was significantly greater in the ATTR group when compared with the AL group (198.0 vs. 154.0 ms, P = 0.013).

Overview of survival analysis and comparison of survival outcomes

Figure 2 outlines the Kaplan–Meier curve for survival for the study cohort as stratified by CA subtype. During the follow-up period, all patients with AL-CA were treated with current guideline-recommended therapies, including daratumumab, dexamethasone, bortezomib and cyclophosphamide.[22] Conversely, none of the patients with ATTR-CA were treated with tafamidis, as it was not available in our hospital yet. Survival among patients as stratified by CA was significantly different among patient groups ($P < 0.001$). Patients with AL-CA had the lowest median OS time of 31 months [95% confidence interval (CI) 6.5–55.5], while patients with ATTR-CA had a median OS time of 38 months (95% CI 18.9–57.1). Patients with other heart failure aetiologies had a median OS time of 106 months (95% CI 100.2–112.8). In a multivariate model after adjusting for age and gender, CA subtype remained a critical indicator of survival, as AL-CA was associated with a hazard ratio of 10.5 (95% CI 3.4–32.0, $P < 0.001$), whereas ATTR-CA was associated with a hazard ratio of 7.9 (95% CI 2.9–21.0, $P < 0.001$).

Discussion

We conducted a cross-sectional, retrospective, single-centre study of a novel CA screening programme and have systematically screened 177 patients for the diagnosis of ATTR or AL amyloidosis. To our knowledge, this is the first study to describe the clinical characteristics and outcomes of CA in the Middle East and Saudi Arabia. The pertinent findings of this study are the following: (i) The prevalence of ATTR-CA among heart failure patients screened in this study was 11.9%, which is comparable to findings from major studies in other populations, indicating that the disease is significantly underdiagnosed in the region; (ii) patients with CA have distinct demographic, clinical and imaging features when compared with other heart failure aetiologies; and (iii) CA carries

Table 4 Comparison of echocardiographic and electrocardiogram data between patients with a positive [^{99m}Tc]Tc-PYP scan and those with a negative/equivocal scan.

Parameter	ATTR amyloidosis n = 21	[^{99m}Tc]Tc-PYP negative/equivocal (grades 0–1) n = 156	Total n = 177	P value
Echocardiogram features				
Presence of aortic stenosis (%)	4.0 (19.0)	20.0 (13.1)	24.0 (13.8)	0.647
TAVR (%)	2.0 (9.5)	15.0 (9.9)	17.0 (9.8)	0.960
Median LVEF, % (range)	42.5 (25.0–70.0)	55.0 (22.5–75.0)	55.0 (22.5–75.0)	**<0.001**
Median SV index, mL/m^2 (range)	24.0 (12.0–53.0)	34.0 (12.0–65.0)	32.0 (12.0–65.0)	**<0.001**
Median GLS, % (range)	−9.9 (−18.4 to −6.2)	−15.0 (−24.3 to −3.1)	−14.8 (−24.3 to −3.1)	**<0.001**
Median IVSd, mm (range)	14.0 (10.0–21.0)	12.0 (7.0–18.0)	12.0 (7.0–21.0)	**<0.001**
Median LVPWd, mm (range)	13.0 (5.0–23.0)	11.0 (4.7–19.0)	11.0 (4.7–23.0)	**<0.001**
Median LVEDd, mm (range)	39.0 (30.0–51.0)	44.0 (29.0–64.0)	43.0 (29.0–64.0)	**0.002**
Median left ventricular mass index, g/m^2 (range)	116.6 (49.1–211.6)	97.4 (41.7–235.5)	98.7 (41.7–235.5)	**0.017**
Median relative apical sparing pattern (range)	1.1 (0.4–1.6)	0.8 (0.5–1.6)	0.8 (0.4–1.6)	**<0.001**
Median relative wall thickness (range)	0.6 (0.3–1.3)	0.5 (0.2–0.9)	0.5 (0.2–1.3)	**<0.001**
Median left ventricular mass-to-strain ratio (range)	−20.5 (−48.7 to −6.0)	−10.8 (−49.2 to −3.7)	−11.5 (−49.2 to −3.7)	**<0.001**
Median EF-to-strain ratio (range)	−3.8 (−6.9 to −2.8)	−3.38 (−7.0 to −2.2)	−3.5 (−7.0 to −2.2)	**0.011**
Presence of RV dilation (%)	10.0 (47.6)	44.0 (28.4)	54.0 (30.7)	0.185
Presence of RV systolic dysfunction (%)	12.0 (60.0)	43.0 (28.3)	55.0 (32.0)	**<0.001**
Presence of LA dilation (%)	14.0 (66.7)	57.0 (36.5)	71.0 (40.6)	**<0.001**
Median pulmonary artery pressure, mmHg	45.0 (25.0–85.0)	35.0 (25.0–75.0)	35.0 (25.0–85.0)	**0.013**
Pericardial effusion (%)	4.0 (19.0)	25.0 (16.1)	29.0 (16.5)	0.735
Electrocardiogram features				
Rhythm (%)				0.318
Sinus	15.0 (71.4)	122.0 (80.8)	137.0 (79.7)	
Atrial fibrillation	6.0 (28.6)	29.0 (19.2)	35.0 (20.3)	
Low voltage QRS (%)	13.0 (61.9)	20.0 (12.9)	33.0 (18.8)	**<0.001**
1st-degree AV block (%)	7.0 (33.3)	18.0 (11.8)	25.0 (14.4)	**0.008**
Median PR interval, ms (range)	198.0 (142.0–280.0)	174.0 (94.0–286.0)	174.0 (94.0–286.0)	**0.016**
Median QRS interval, ms (range)	110.0 (70.0–182.0)	92.0 (62.0–286.0)	92.0 (62.0–286.0)	0.098

Abbreviations: [^{99m}Tc]Tc-PYP, technetium-99m pyrophosphate; ATTR, transthyretin amyloid; AV, atrioventricular; EF, ejection fraction; GLS, global longitudinal strain; IVSd, interventricular septum thickness at end-diastole; LA, left atrial; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall thickness at end-diastole; RV, right ventricular; SV, stroke volume; TAVR, transcatheter aortic valve replacement. P values <0.05 are shown in bold.

a high morbidity and mortality rate that is significantly higher than that of other heart failure aetiologies.

Among 177 patients with heart failure systematically screened for CA, 21 patients had received a diagnosis of ATTR-CA, corresponding to a prevalence rate of 11.9%. This finding highlights the significant presence of CA within our patient cohort and provides a comparison point with other international studies. For instance, a landmark US study prospectively enrolled 108 HFpEF patients for endomyocardial biopsies, finding a 14% prevalence of CA: 6.4% with ATTRwt, 3.6% with ATTRh and 2.7% with AL-CA.[23] Furthermore, a single-centre study conducted at a tertiary hospital in Spain has reported a 13.0% prevalence of ATTR-CA among HFpEF patients screened using [99mTc]Tc-PYP bone scintigraphy.[3] Most recently, a multicentre prospective Japanese study reported a prevalence of 14.2% for ATTR-CA among patients with HFpEF.[24] The prevalence rate in our study is largely concordant with the aforementioned studies; hence, this suggests that the disease has a similar epidemiological landscape within our region yet remains significantly underdiagnosed. In addition, we conducted a recent survey that included 85 cardiologists in the Middle East and revealed that many participants believed the prevalence of CA to be unknown, some were not aware of the red flags for suspecting the disease and most of them were unaware of the role of bone scintigraphy in diagnosing ATTR-CA, often opting for a cardiac biopsy or cardiac CT scan instead.[25] Therefore, this cohort study not only sheds novel insights into the epidemiology of CA in Saudi Arabia but also serves an educational purpose. By highlighting the red flags for suspicion and emphasizing the diagnostic utility of bone scintigraphy, we aim to improve awareness and diagnostic practices among physicians in the region.

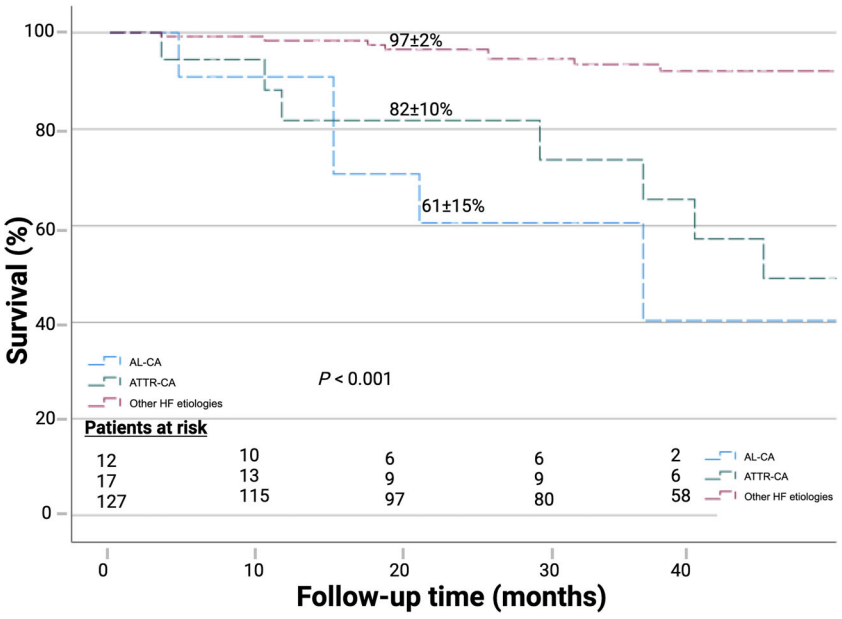
Of the 21 patients diagnosed with ATTR-CA in our study, 4 (19%) were found to have ATTRh after undergoing genetic analysis for mutations in the TTR gene. Recent studies emerging from western countries have highlighted that the prevalence rates of ATTRh tend to differ categorically between different regions.[26] The prevalence of ATTRh within our study does indeed provide novel insights into the epidemiology of ATTRh within our region, highlighting that its prevalence may be higher than in other regions around the world. Within

Table 5 Comparison of echocardiographic and electrocardiogram parameters between patients with ATTR and AL cardiac amyloidosis.

Parameter	ATTR amyloidosis $n = 21$	AL amyloidosis $n = 13$	Total $n = 34$	P value
Echocardiogram features				
Aortic stenosis (%)	4.0 (19.0)	0.0 (0.0)	4.0 (11.8)	0.094
TAVR (%)	2.0 (9.5)	0.0 (0.0)	2.0 (5.9)	0.251
Median LVEF, % (range)	42.5 (25.0–70.0)	52.5 (32.5–65.0)	43.0 (25.0–70.0)	0.138
Median SV index, mL/m^2 (range)	24.0 (12.0–53.0)	33.0 (16.0–47.0)	26.0 (12.0–53.0)	0.137
Median GLS, % (range)	−9.9 (−18.4 to −6.2)	−15.4 (−20.4 to −5.8)	−11.0 (−20.4 to −5.8)	**0.035**
Median IVSd, mm (range)	14.0 (10.0–21.0)	14.0 (10.0–18.0)	14.0 (10–21.0)	0.807
Median LVPWd, mm (range)	13.0 (5.0–23.0)	11.5 (6.0–18.0)	13.0 (5.0–23.0)	0.365
Median LVEDd, mm (range)	39.0 (30.0–51.0)	43.0 (34.0–52.0)	39.5 (30.0–52.0)	0.120
Median left ventricular mass index, g/m^2 (range)	116.6 (49.1–211.6)	111.2 (41.7–178.4)	116.3 (41.7–211.6)	0.130
Median relative apical sparing pattern (range)	1.1 (0.4–1.6)	1.0 (0.7–1.6)	1.0 (0.4–1.6)	0.164
Median relative wall thickness (range)	0.6 (0.3–1.3)	0.6 (0.2–0.9)	0.6 (0.2–1.3)	0.385
Median left ventricular mass-to-strain ratio (range)	−20.5 (−48.7 to −6.0)	−13.7 (−49.2 to −6.0)	−16.8 (−49.2 to −6.0)	0.130
Median EF-to-strain ratio (range)	−3.8 (−6.9 to −2.8)	−3.5 (−6.5 to −2.5)	−3.6 (−6.9 to −2.5)	0.136
RV dilation (%)	10.0 (47.6)	7.0 (53.8)	17.0 (50.0)	0.896
RV systolic dysfunction (%)	12.0 (60.0)	8.0 (61.5)	20.0 (60.6)	0.668
Severe LA dilation (%)	14.0 (66.7)	11.0 (84.6)	25.0 (73.5)	0.518
Median pulmonary pressure, mmHg	45.0 (25.0–85.0)	45.0 (25.0–60.0)	45.0 (25.0–85.0)	0.598
Pericardial effusion (%)	4.0 (19.0)	1.0 (7.7)	5.0 (14.7)	0.364
Electrocardiogram features				
Rhythm (%)				0.549
Sinus	15.0 (71.4)	8.0 (61.5)	23.0 (67.6)	
Atrial fibrillation	6.0 (28.6)	5.0 (38.5)	11.0 (32.4)	
Low voltage QRS (%)	13.0 (61.9)	7.0 (53.8)	20.0 (58.8)	0.643
1st-degree AV block (%)	7.0 (33.3)	1.0 (7.7)	8.0 (23.5)	0.087
Median PR interval, ms (range)	198.0 (142.0–280.0)	154.0 (134.0–214.0)	186.0 (134.0–280.0)	**0.013**
Median QRS interval, ms (range)	110.0 (70.0–182.0)	102.0 (74.0–144.0)	105.0 (70.0–182.0)	0.400

Abbreviations: AL, light chain; ATTR, transthyretin amyloid; AV, atrioventricular; EF, ejection fraction; GLS, global longitudinal strain; IVSd, interventricular septum thickness at end-diastole; LA, left atrial; LVEDd, left ventricular end-diastolic diameter; LVEF, left ventricular ejection fraction; LVPWd, left ventricular posterior wall thickness at end-diastole; RV, right ventricular; SV, stroke volume; TAVR, transcatheter aortic valve replacement. P values <0.05 are shown in bold.

Figure 2 Kaplan–Meier curve for overall survival. This figure illustrates the Kaplan–Meier curve for overall survival in the study cohort. Survival among patients with cardiac amyloidosis (CA) was significantly different between patients with light chain CA (AL-CA), transthyretin amyloid CA (ATTR-CA) and other heart failure (HF) aetiologies.



our cohort, three patients had a c.239C>T (p.Thr80Ile) variant, whereas one patient had a c.1746T>A (p.Tyr582Ter) variant. The c.239C>T (p.Thr80Ile) variant has been validated as a rare pathogenic variant in the context of ATTRv, whereas the c.1746T>A (p.Tyr582Ter) variant represents a novel variant.[27] Indeed, these findings suggest that the genotype of ATTRh in our region is largely unexplored and is likely different from findings from other regions around the world. A recent genetic study conducted at our centre was the first to provide insights into the prevalence of TTR mutations in the region.[27] The study analysed 13 906 exomes from Saudi Arabian subjects and utilized data mining to identify three TTR variants known to be associated with ATTR-CA in addition to three novel potentially pathogenic variants. These findings indicate that ATTRh within our region likely possesses unique epidemiological and genetic characteristics. Thus, larger population-based studies are required to characterize the epidemiological and genetic landscape of ATTRh within our region.

This study has also identified and reinforced demographic, clinical and imaging characteristics that provide clues towards the diagnosis of CA when compared with other heart failure aetiologies. Patients with ATTR-CA within our study had significantly higher levels of troponin and NT-proBNP when compared with patients with negative/equivocal [^{99m}Tc]Tc-PYP scans. A recent study of 1149 patients from the United Kingdom, France and Italy reported that high-sensitivity troponin T and NT-proBNP have diagnostic utility in patients with suspected CA, indicating that these biomarkers may be utilized to effectively rule out the disease among patients with predefined levels.[28] Additionally, NT-proBNP is a critical marker in diagnosing AL amyloidosis. Our study found that the median NT-proBNP in the AL-CA cohort was 3815 pg/mL, significantly above a diagnostic cut-off of 1285 pg/mL that has shown high sensitivity and specificity in identifying amyloid heart dysfunction in AL amyloidosis.[29] Moreover, NT-proBNP also serves as a strong indicator of disease burden and prognosis in both AL-CA and ATTR-CA. The median NT-proBNP levels in our ATTR-CA and AL-CA cohorts significantly exceeded the thresholds indicative of a poorer prognosis as outlined in several staging systems, including the Mayo and UK staging systems for ATTR-CA and the Mayo 2004 and Mayo 2012 staging systems for AL-CA.[22] Moreover, our study has reinforced the characteristic demographic, echocardiographic and ECG features associated with CA, including older age, lower BMI, increased interventricular septum thickness, increased LVMI, increased relative wall thickness, increased relative apical sparing pattern, more depressed GLS, increased incidence of atrioventricular conduction blocks and a predominance of low voltage patterns on the ECG. In addition, patients with ATTR-CA and AL-CA were more likely to have diffuse subendocardial or transmural LGE on CMR compared with patients without CA [66% (6/9) vs. 18% (6/34), respectively; $P < 0.001$]. These findings are largely concordant with those of other multicentric studies characterizing the clinical features of ATTR-CA around the globe.[23,30,31] However, while international studies suggest that CA is more prevalent in patients with HFpEF, our cohort showed that 19% and 33% of ATTR-CA patients had HFmrEF and heart failure with reduced ejection fraction (HFrEF), respectively, and 15% and 31% of AL-CA patients had HFmrEF and HFrEF, respectively. Given that the median time from symptom onset to diagnosis was 52 months for ATTR-CA and 8 months for AL-CA, and considering the rapid progression of AL-CA, we hypothesize that the high prevalence of reduced EF is likely due to CA reaching advanced stages, where reduced EF is common.[17,32] Interestingly, despite their validation in other international studies, the LV mass-to-strain ratio, the EF-to-strain ratio and the relative apical sparing pattern failed to differentiate between ATTR-CA and AL-CA, with the GLS being the only echocardiographic parameter that was significantly different among both CA subtypes.[15,16,33]

This study reinforces the concept that CA is a progressive disease that is associated with a poor outcome along with a significant morbidity and mortality burden. Within our study, AL-CA had the worst prognosis, closely followed by ATTR-CA, whereas patients with other heart failure aetiologies had significantly superior survival. In concordance with our findings, a comprehensive study of 2251 heart failure patients concluded that amyloid cardiomyopathy was an independent poor prognostic factor when compared with other heart failure aetiologies.[34] Moreover, AL-CA was associated with significantly lower survival when compared with ATTR-CA in the study. In addition, a recent study found that patients with CA were at a greater risk of mortality after acute decompensated heart failure compared with patients without CA.[35] However, the development of TTR-targeting therapeutics, particularly the TTR tetramer stabilizer tafamidis, has been shown to provide an incremental increase in survival of 3.88 years for ATTR-CA compared with standard-of-care therapy.[36] Additionally, advancements in chemotherapies and immunotherapies for the treatment of AL amyloidosis have shown promising findings in relation to improving patient outcomes and slowing disease progression.[8] Hence, it is apparent that the treatment landscape of CA is rapidly evolving, and the disease is increasingly becoming a treatable entity.

Our results ought to be interpreted in light of some limitations. First, our study included 29 patients with Perugini grade 1 cardiac tracer uptake who did not undergo histological confirmation. This limitation may result in an underestimation of the true prevalence of ATTR-CA, as emphasized by Garcia-Pavia *et al*. and Gillmore *et al*.[8,37] The absence of biopsies was due to patient and family refusals, primarily due to concerns about the risks associated with invasive procedures in these elderly patients. AL-CA was ruled out in these patients as all of them had a negative screening for monoclonal gammopathy. Furthermore, statistical analyses

suggested that these patients with a grade 1 [^{99m}Tc]Tc-PYP scan are less likely to have ATTR amyloidosis, as their clinical variables did not differ significantly and were similar to patients with a grade 0 [^{99m}Tc]Tc-PYP scan. Consequently, as the suspicion of amyloidosis was low in these patients with a grade 1 scan, we combined the grade 0 and grade 1 groups for comparisons with grade 2/3 patients. Nevertheless, future studies should prioritize histological confirmation for these equivocal cases to ensure an accurate diagnosis. Moreover, the retrospective nature of our study is subject to inherent limitations, such as potential missing data and incomplete medical records. In addition, the single-centre nature of our study limits the sample size and demographic distribution of our study, hindering its applicability to a general population. Furthermore, the small sample size of our study impedes our ability to conduct multivariate analysis to determine independent predictors of mortality.

To our knowledge, this is the first study to describe the clinical characteristics and outcomes of CA in the Middle East and Saudi Arabia. The prevalence of CA among heart failure patients screened in this study is comparable to findings from major studies in other nations, indicating that the disease is significantly underdiagnosed in the region. Further larger multicentre prospective studies are required within the region in order to accurately depict the burden of CA within the region. Moreover, a need emerges for the establishment of region-wide screening programmes to enhance diagnostic efforts and contribute to the limited knowledge regarding the epidemiology and outcomes of CA in the region.

Conflict of interest statement

D. M. reports grants from Pfizer Inc. during the conduct of the study and personal fees from Pfizer Inc. and Novartis, outside the submitted work. T. D. reports personal fees from Akcea Therapeutics, Inc., Alnylam Pharmaceuticals, AstraZeneca, Neurimmune, Novo Nordisk AS and Pfizer Inc., outside the submitted work. I. A. reports personal fees from Pfizer during the conduct of the study.

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