Differences in the characteristics and contemporary cardiac outcomes of patients with light-chain versus transthyretin cardiac amyloidosis

Osnat Itzhaki Ben Zadok1,2*, Mordehay Vaturi1,2, Iuliana Vaxman2,3, Zaza Iakobishvili2,4, Noa Rhurman-Shahar2,5, Ran Kornowski1,2, Ashraf Hamdan1,2

1 Department of Cardiology, Rabin Medical Center, Petah Tikva, Israel, 2 Sackler Faculty of Medicine, Tel Aviv University, Tel Aviv, Israel, 3 Davidoff Cancer Center, Institute of Hematology, Rabin Medical Center, Petah-Tikva, Israel, 4 Clalit Health Services, Tel-Aviv District, Israel, 5 Raphael Recanati Genetic Institute, Rabin Medical Center, Petah Tikva, Israel

* osnat.itzhaki@gmail.com

Abstract

Aims
To compare the baseline cardiovascular characteristics of immunoglobulin light-chain (AL) and amyloid transthyretin (ATTR) cardiac amyloidosis (CA) and to investigate patients’ contemporary cardiac outcomes.

Methods
Single-center analysis of clinical, laboratory, echocardiographic and cardiac magnetic resonance imaging (CMRI) characteristics of AL and ATTR-CA patients’ cohort (years 2013–2020).

Results
Included were 67 CA patients of whom 31 (46%) had AL-CA and 36 (54%) had ATTR-CA. Patients with ATTR-CA versus AL-CA were older (80 (IQR 70, 85) years versus 65 (IQR 60, 71) years, respectively, p < 0.001) with male predominance (p = 0.038). Co-morbidities in ATTR-CA patients more frequently included diabetes mellitus (19% versus 3.0%, respectively, p = 0.060) and coronary artery disease (39% versus 10%, respectively, p = 0.010). By echocardiography, patients with ATTR-CA versus AL-CA had a trend to worse left ventricular (LV) ejection function (50 (IQR 40, 55)% versus 60 (IQR 45, 60)%, respectively, p = 0.051), yet comparable LV diastolic function. By CMRI, left atrial area (31 (IQR 27, 36)cm² vs. 27 (IQR 23, 30)cm², respectively, p = 0.015) and LV mass index (109 (IQR 96, 130) grams/m² vs. 82 (IQR 72, 98) grams/m², respectively, p = 0.011) were increased in patients with ATTR-CA versus AL-CA. Nevertheless, during follow-up (median 20 (IQR 10, 38) months), patients with AL-CA were more frequently admitted with heart failure.
exacerbations (HR 2.87 (95% CI 1.42, 5.81), p = 0.003) and demonstrated increased mortality (HR 2.51 (95% CI 1.19, 5.28), p = 0.015).

Conclusion
Despite the various similarities of AL-CA and ATTR-CA, these diseases have distinct baseline cardiovascular profiles and different heart failure course, thus merit tailored-cardiac management.

Introduction
Cardiac amyloidosis (CA) is most commonly caused by the extracellular deposition of insoluble amyloid fibrils of either immunoglobulin light chain (AL) or amyloid transthyretin (ATTR) [1], and is considered to portend a poor prognosis [2]. This distinctive cardiomyopathy is most frequently categorized as heart failure with preserved ejection fraction (HFpEF), and patients with CA are oftentimes described with advanced heart failure (HF) and significant volume overload [3]. Electrical conduction abnormalities as well as atrial and ventricular arrhythmias are other common findings in both AL-CA and ATTR-CA.

The shared clinical and imaging characteristics of AL-CA and ATTR-CA, which most frequently present at advanced or end-stage amyloid heart disease, have often resulted in the combination of both diseases under one umbrella. However, important differences do exist, and most probably derive from their specific etiology and pathophysiology [4, 5]. Defining these differences may pave the way for an earlier, targeted diagnosis of AL or ATTR CA and improve our understanding of disease progression and management.

We sought to compare in a contemporary cohort of patients with AL-CA and ATTR-CA their clinical, laboratory and imaging characteristics, and to investigate patients’ long-term survival and HF-related complications.

Methods
The study population was comprised of consecutive AL-CA and ATTR-CA patients treated at a tertiary institution (Rabin Medical Center, Israel) between the years 2013–2020. For all patients, electronic medical records and echocardiographic and cardiac magnetic resonance (CMR) examinations were retrospectively reviewed.

The diagnosis criteria of ATTR-CA and AL-CA has been previously described [4]. Cardiac ATTR was defined as the combination of symptoms with an echocardiogram consistent with or suggestive of cardiac amyloidosis, grade 2 or 3 cardiac uptake on 99mTc-DPD scintigraphy in the absence of a monoclonal gammopathy [6]. In the presence of a monoclonal gammopathy, a cardiac biopsy positive for ATTR was warranted. Following a histological or non-invasive diagnosis of ATTR, all patients were referred to TTR genetic testing to differentiate between mutant ATTR and wild-type ATTR. The diagnosis and staging of AL amyloidosis were according to consensus criteria and required to prove the presence of amyloid deposition in tissue biopsy by Congo red staining [7, 8]. Further protein analysis confirming light chain deposits was made by immunohistochemistry [9]. Mass spectrometry proteomic analysis was undertaken in selected cases. The diagnosis of cardiac amyloid involvement in AL was based on either CMR imaging (with evidence of congo-red tissue staining elsewhere) or endomyocardial biopsy (EMB). Patients who were deferred by their treating physician from CMR or
EMB (high-risk patients) were provisionally diagnosed based on typical echocardiographic features (concentric LV thickening and diastolic dysfunction), as previously reported [10]. Patients were excluded if the diagnosis of CA did not meet the above criteria.

On echocardiography, the left atrial and ventricular diameters and left ventricular (LV) ejection fraction (LVEF) were measured according to accepted guidelines [11]. Relative wall thickness (RWT) was calculated as 2 times LV posterior wall (PW) diastolic thickness divided by LV diastolic diameter [11]. LV mass was calculated according to the Devereux formula [12]: 1.04 ((LV diastolic diameter + interventricular septal (IVS) diameter + LV PW diastolic thickness)² - (LV diastolic diameter)²) - 13.6. Right ventricular (RV) function was evaluated qualitatively by visual assessment [13]. The pulmonary artery systolic pressure was estimated from the peak velocity of the tricuspid regurgitation jet and estimated right atrial pressure based on inferior vena cava diameter and distensibility [13]. LV diastolic function was assessed by integrating mitral flow pattern, tissue Doppler imaging, indexed left atrial volume, and systolic pulmonary pressure [14]. Cut-off values for defining abnormalities in the reported echocardiographic variables were chosen according to published reference guidelines in the general population [11, 15–18].

A sub-group of the cohort underwent CMR with a 1.5 Tesla scanner. The following standardized protocol was applied: contiguous cine short axis views covering the whole LV; 3 cine long axis views of the LV (two- three and four-chamber) planned on the short-axis orientation; for delayed enhancement contiguous short axis views covering the whole LV and 3 long axis views of the LV (two- three and four-chamber) were acquired. LV end-diastolic wall thickness of the septum and lateral wall were measured in a basal short-axis view. For volume measurements, endocardial borders were traced manually at end diastole and end systole. LV end-diastolic volume (LVEDV) and LV end-systolic volume (LVESV) were assessed and indexed to body mass index. LVEF was calculated by using Simpson’s rule.

The primary endpoint of this study was overall survival, and the secondary endpoint was survival free of the occurrence of malignant ventricular arrhythmias (defined as sustained ventricular tachycardia or ventricular fibrillation) or high degree atrioventricular block. Other clinical endpoints were HF-related admissions or arrhythmias-related admissions. Only unplanned admissions post-diagnosis were reported. Chronic kidney disease was defined by estimated glomerular filtration rate (eGFR)<60 ml/min as calculated by the CKD-EPI formula. Mortality during follow-up was determined for all patients through the Israeli National Population Registry. The study protocol was approved by the Rabin Medical Center Institutional Review Board.

The statistical analysis was carried out using SAS Statistical Software, Version 9.4 (SAS Institute Inc., Cary, NC). Continuous variables were presented by median and interquartile 25th, 75th range. Categorical variables were presented by (N, %). T-Test was used to compare the values of continuous variables, displaying normal distribution between study groups and the Wilcoxon test was used for non-Gaussian distributions. Chi-square was used to compare the values of categorical variables, displaying normal distribution and the Fisher’s exact test was used for non-Gaussian distributions. Overall survival was defined as the time from diagnosis to death from any cause. For time to death and for the combined endpoint of malignant ventricular arrhythmias/high degree atrioventricular block or death, the survival curve during study follow-up was assessed by Kaplan-Meier survival analysis, with the log-rank test. The Cox proportional hazards model was used to calculate hazard ratios (HR) and for multivariable analysis.

For analysis of survival endpoints which did not include death (time to subsequent HF exacerbations or arrhythmias-related admissions) death with no admission was considered as
a competing risk. The Anderson Gill method, in the Cox model, was used to analyze repeated admissions.

Two-sided p values less than 0.05 were considered statistically significant.

**Results**

**Baseline clinical parameters**

The study cohort included 67 patients with a diagnosis of CA of whom 31 (46%) and 36 (54%) patients were diagnosed with AL and ATTR CA, respectively. Seven patients with ATTR were diagnosed with mutant ATTR. Patients’ baseline characteristics and amyloid type-specific parameters are presented in Table 1 and S1 and S2 Tables. Patients with ATTR-CA were significantly older than patients with AL-CA (median age at the diagnosis of ATTR was 80 (IQR 70, 85) years vs. 65 (IQR 60, 71) years in AL, p<0.001) with male predominance (78% vs. 52% p = 0.038). Moreover, patients with ATTR versus AL-CA more frequently presented with cardiovascular co-morbidities including diabetes mellitus (19% vs. 3%, respectively, p = 0.060), coronary artery disease (39% vs. 10%, respectively, p = 0.010) and acute myocardial infarction (19% vs. 0%, respectively, p = 0.011). The rate of chronic kidney disease was similar between groups (36% of study patients, p = 0.615). The prevalence of prior carpal tunnel syndrome was higher in patients with ATTR-CA versus AL-CA (56% vs. 29%, respectively, p = 0.027). Laboratory tests including baseline levels of NT-proBNP and troponin were comparable between patients with AL-CA and ATTR-CA. Ten patients diagnosed with AL-CA (32%) were treated with anti-CD38 monoclonal antibodies as 2nd or 3rd line treatment.

**Baseline echocardiographic evaluation**

Patients’ baseline echocardiographic findings are presented in Table 2. The median time from the reported echocardiography evaluation to the diagnosis of CA was -5 (IQR -40, +30) days, regardless of amyloid type. Patients with ATTR-CA versus AL-CA had a trend towards worse LV systolic function as demonstrated by reduced LVEF (50 (IQR 40, 55)% vs. 60 (IQR 45, 60%), respectively, p = 0.051), yet comparable LV diastolic function. Patients with ATTR-CA vs. AL-CA presented with thicker septal (1.6 (IQR 1.5, 1.9) cm vs. 1.40 (IQR 1.3, 1.6) cm, respectively, p = 0.004) and posterior (1.5 (IQR 1.3, 1.8) cm vs. 1.30 (IQR 1.2, 1.5) cm, respectively, p = 0.017) LV walls. Moreover, LV mass was significantly increased in patients with ATTR versus AL-CA even after adjusting to body surface area (148 (IQR 129, 198) grams/m$^2$ vs. 113 (IQR 97, 138) grams/m$^2$, respectively, p = 0.027). Notably, rates of arterial hypertension and clinically significant aortic stenosis were similar between groups. Similar quantitative results were observed in a subgroup analysis that included only AL-CA vs. ATTR-CA male patients (septal thickness 1.5 (IQR 1.3, 1.7) cm vs. 1.6 (IQR 1.5, 1.9) cm, respectively, p = 0.012 and LV mass index (115 (IQR 96, 146) grams/m$^2$ vs. 160 (IQR 138, 203) grams/m$^2$, respectively, p = 0.016).

**Baseline cardiac magnetic resonance imaging**

Twenty-two (71%) AL-CA patients and 24 (67%) ATTR-CA patients completed CMR examination as part of their baseline evaluation (Table 2). LV and RV systolic function as demonstrated by CMR were comparable in AL-CA and ATTR-CA patients. However, LA area (31 (IQR 27, 36) cm$^2$ vs. 27 (IQR 23, 30) cm$^2$, respectively, p = 0.015), LV septal thickness (1.9 (IQR 1.5, 2.1) cm vs. 1.6 (IQR 1.3, 1.8) cm, respectively, p = 0.040) and LV mass index (109 (IQR 96, 130) grams/m$^2$ vs. 82 (IQR 72, 98) grams/m$^2$, respectively, p = 0.011) were significantly increased in patients with ATTR-CA versus AL-CA. The majority of CA patients
Table 1. Baseline characteristics of patients with cardiac amyloidosis stratified by the misfolded amyloid protein.

|                                    | AL (n = 31) | ATTR (n = 36) | p-value |
|------------------------------------|------------|---------------|---------|
| Age at amyloidosis diagnosis (years) | 65 (60, 71) | 80 (70, 85)   | <0.001  |
| Sex, male (%)                      | 16 (52)    | 28 (78)       | 0.038   |
| Body mass index (Kg/m²)            | 28 (25, 35) | 25 (23, 29)   | 0.141   |
| Diabetes mellitus (%)              | 1 (3)      | 7 (19)        | 0.060   |
| Hypothyroidism (%)                 | 2 (6)      | 3 (8)         | 1.000   |
| Hypertension (%)                   | 10 (32)    | 17 (47)       | 0.318   |
| Dyslipidemia (%)                   | 9 (29)     | 15 (42)       | 0.314   |
| Family history of ischemic heart disease (%) | 6 (19) | 2 (6) | 0.132 |
| Coronary artery disease (%)        | 3 (10)     | 14 (39)       | 0.010   |
| Myocardial infarction (%)          | 0 (0)      | 7 (19)        | 0.011   |
| Atrial fibrillation (%)            | 7 (23)     | 16 (44)       | 0.075   |
| Moderate-severe aortic stenosis (%)| 0 (0)      | 1 (3)         | 1.000   |
| Carpal tunnel syndrome (%)         | 9 (29)     | 20 (56)       | 0.027   |
| Past smoker (%)                    | 3 (10)     | 9 (25)        | 0.117   |
| Alcohol consumption (%)            | 0 (0)      | 0 (0)         |         |
| NYHA FC (%)                        |            |               | 0.130   |
| 1                                  | 8 (26)     | 11 (31)       |         |
| 2                                  | 9 (29)     | 18 (50)       |         |
| 3                                  | 13 (42)    | 7 (19)        |         |
| 4                                  | 1 (3)      | 0 (0)         |         |
| **Laboratory parameters**          |            |               |         |
| Hemoglobin (g/dL)                  | 13 (12, 14)| 13 (12, 14)   | 0.642   |
| Creatinine (mg/dL)                 | 1.1 (0.77, 1.3)| 1.0 (0.86, 1.5)| 0.984 |
| Estimated GFR by CKD-EPI(\(^\text{\textsuperscript{1}}\)) (ml/min/1.73m²) | 70 (53, 83) | 68 (46, 83) | 0.615 |
| Sodium (mEq/L)                     | 139 (138, 142)| 139 (136, 141)| 0.582 |
| Potassium (mEq/L)                  | 4.3 (3.9, 4.7)| 4.5 (4.3, 4.8)| 0.091 |
| Albumin (g/dL)                     | 3.9 (3.5, 4.3)| 3.9 (3.8, 4.2)| 0.690 |
| AST (U/L)                          | 27 (20, 35) | 26 (21, 34)   | 0.711   |
| γGT (U/L)                          | 52 (26, 102)| 46 (28, 104)  | 0.740   |
| NT-proBNP (pg/ml)^\(^\text{\textsuperscript{2}}\) | 3370 (1661, 13924) | 3467 (1202, 6192) | 0.598 |
| Troponin T (ng/L)^\(^\text{\textsuperscript{2,3}}\) | 84 (52, 134) | 62 (49, 99)  | 0.290   |
| ECG Holter monitoring performed at diagnosis | 14 (45) | 24 (67) | 0.084 |
| **Medications (%)**                |            |               |         |
| Mineralocorticoid-receptor antagonists | 11 (35) | 19 (53) | 0.141 |
| Furosemide                         | 26 (84)    | 30 (83)       | 0.745   |
| Beta-blockers                      | 9 (29)     | 15 (42)       | 0.442   |
| Digoxin                            | 1 (3)      | 2 (6)         | 1.000   |
| Renin-angiotensin-aldosterone system inhibitors | 11 (35) | 9 (25) | 0.421 |
| Anti-arrhythmic drugs              | 2 (6)      | 4 (11)        | 0.681   |
| Oral anti-coagulation therapy      | 2 (6)      | 20 (55)       | <0.001  |

Data are presented as medians (25\textsuperscript{th}, 75\textsuperscript{th} quartiles) or as percentages, as appropriate.

**Abbreviations:** AL, immunoglobulin light-chain; AST, aspartate aminotransferase; ATTR, amyloid-transthyretin; CA, cardiac amyloidosis; GFR, glomerular filtration rate; γGT, gamma-glutamyltransferase; NYHA FC, New-York Heart Association functional class; NT-proBNP, N-terminal-pro hormone brain natriuretic peptide.

\(^{1}\)CKD-EPI; Chronic Kidney Disease Epidemiology Collaboration

\(^{2}\)NT-proBNP levels at baseline were available in 22 (71\%) and 26 (72\%) of AL and ATTR-CA patients, respectively.

\(^{3}\)Troponin T normal laboratory range <13ng/L.

[https://doi.org/10.1371/journal.pone.0255487.t001](https://doi.org/10.1371/journal.pone.0255487.t001)
Table 2. Echocardiographic and cardiac magnetic resonance imaging findings among patients with CA stratified by amyloid subtype.

| Echocardiography studies                              | AL (n = 31) | TTR (n = 36) | p-value |
|-------------------------------------------------------|-------------|--------------|---------|
| LVEF (median)                                         | 60 (45, 60) | 50 (40, 55)  | 0.051   |
| RV dysfunction (%)                                    | 11 (35)     | 15 (42)      | 0.606   |
| Posterior wall (cm)                                   | 1.30 (1.20, 1.50) | 1.50 (1.30, 1.80) | 0.017   |
| Intraventricular septum (cm)                          | 1.40 (1.30, 1.60) | 1.60 (1.45, 1.90) | 0.004   |
| Wall thickness ≥1.4cm (%)                             | 20 (65)     | 31 (86)      | 0.048   |
| LVESD (cm)                                            | 4.1 (3.9, 4.5) | 4.3 (3.8, 4.6) | 0.645   |
| RVSD (cm)                                             | 2.8 (2.5, 3.3) | 3.1 (2.6, 3.5) | 0.092   |
| Relative wall thickness                               | 0.65 (0.57, 0.81) | 0.74 (0.60, 0.92) | 0.111   |
| LA area (cm²)                                         | 24 (20, 26)  | 27 (24, 31)  | 0.005   |
| LA diameter (cm)                                      | 4.3 (3.7, 4.6) | 4.4 (4.0, 4.7) | 0.202   |
| LV mass (grams)                                      | 212 (168, 280) | 253 (220, 330) | 0.042   |
| LV mass index (grams/m²)                              | 113 (97, 138) | 148 (129, 198) | 0.027   |
| TAPSE (mm)                                            | 15 (11, 18)  | 14 (12, 17)  | 0.928   |
| Diastolic grade 2, 3 (%)                              | 26 (84)     | 20 (56)      | 0.306   |
| E/A                                                   | 2.1 (1.6, 3.0) | 2.8 (1.6, 3.3) | 0.521   |
| Deceleration time (msec)                              | 144 (117, 193) | 134 (118, 148) | 0.476   |
| e' lateral                                            | 4.0 (4.0, 5.0) | 5.0 (3.9, 6.0) | 0.522   |
| E/e'                                                  | 20 (17, 26)  | 17 (14, 20)  | 0.103   |
| SPAP (mmHg)                                           | 41 (31, 51)  | 42 (35, 55)  | 0.768   |
| CMR studies                                           | n = 22      | n = 24       |         |
| LA area (cm²)                                         | 27 (23, 30)  | 31 (27, 36)  | 0.015   |
| LVEF (median), %                                      | 54 (51, 67)  | 52 (39, 62)  | 0.206   |
| Stroke index (ml/m²)                                  | 29 (26, 40)  | 36 (30, 44)  | 0.118   |
| LVEDVi (ml/m²)                                        | 63 (53, 76)  | 81 (59, 94)  | 0.038   |
| LVESVi (ml/m²)                                        | 26 (20, 33)  | 43 (22, 60)  | 0.167   |
| Cardiac output (L/min)                                | 4.4 (4.1, 5.4) | 5.6 (4.8, 6.8) | 0.065   |
| Septal thickness (cm)                                 | 1.6 (1.3, 1.8) | 1.9 (1.5, 2.1) | 0.040   |
| LV mass (grams)                                       | 150 (120, 180) | 211 (149, 264) | 0.022   |
| LV mass index (grams/m²)                              | 82 (72, 98)  | 109 (96, 130) | 0.011   |
| RVEF (median), %                                      | 43 (40, 51)  | 45 (35, 62)  | 0.709   |

Data are presented as medians (25th, 75th quartiles) or as percentages, as appropriate.

Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid-transferrin; CA, cardiac amyloidosis; LA, left atria; LV, left ventricular; LVEDD, left ventricular end diastolic diameter; LVESD, left ventricular end systolic diameter; LVEDVi, left ventricular end diastolic volume index; LVESVi, left ventricular end systolic volume index; LVEF, left ventricular ejection fraction; RV, right ventricular; RVEF, right ventricular ejection fraction; RWT, relative wall thickness; SPAP, systolic pulmonary artery pressure; TAPSE, tricuspid annular plane systolic excursion.

https://doi.org/10.1371/journal.pone.0255487.t002

(n = 38) demonstrated subendocardial late gadolinium enhancement pattern, while 8 patients (5 AL-CA and 3 ATTR-CA) demonstrated a transmural late gadolinium enhancement pattern.

Survival and cardiac-related admissions

Over study observational follow-up (median 20 (IQR 10, 38) months), all-cause mortality in patients with AL-CA versus ATTR-CA was significantly higher (HR 2.51 (95%CI 1.19, 5.28), p = 0.015) (Fig 1). When analyzed for ATTR sub-populations, survival was similar between mutant ATTR-CA versus wild-type ATTR-CA (Log-rank p = 0.560), yet higher when compared with AL-CA (AL vs. mutant ATTR-CA, Log-rank p = 0.044; AL vs. wild-type, Log-rank...
The cause of death was cardiac in 23% (n = 7) vs. 11% (n = 4) in patients with AL-CA versus ATTR-CA, respectively. Similar quantitative results were observed in a subgroup analysis that included only AL-CA patients with <20% plasma cells at bone marrow biopsy (HR 2.50 (95%CI 1.03, 6.04), p = 0.042). AL-CA versus ATTR-CA was found as an independent predictor for mortality on a multivariable analysis adjusted to age, sex and renal function.

Table 3. Multivariate analysis of predictors for death in patients with CA.

| Parameter                          | HR (95% CI) | p-value |
|------------------------------------|-------------|---------|
| AL-CA versus ATTR-CA               | 2.93 (1.1, 7.6) | 0.027   |
| Age at diagnosis                   | 1.01 (0.97, 1.06) | 0.549   |
| Female sex                         | 1.20 (0.55, 2.6) | 0.642   |
| Estimated GFR by CKD-EPI*          | 0.99 (0.98, 1.01) | 0.606   |

**Abbreviations:** AL, immunoglobulin light-chain; ATTR, amyloid-transthyretin; CA, cardiac amyloidosis; CI, confidence interval; GFR, glomerular filtration rate; HR, hazard ratio.

*CKD-EPI: Chronic Kidney Disease Epidemiology Collaboration.

https://doi.org/10.1371/journal.pone.0255487.t003
function (HR 2.93 (95% CI 1.1, 7.6), p = 0.027), Table 3). The composite endpoint of malignant ventricular arrhythmias/high degree atroventricular block or death was higher in patients with AL-CA versus ATTR-CA at 1-year follow-up (HR 4.45 (95% CI 1.45, 13.6), p = 0.009), yet comparable at 3-year (Log-rank p = 0.208) (S2 Fig).

We also used the Anderson-Gil Model to investigate the recurrence of HF-related admissions controlling for death as a competing risk. During follow-up, patients with AL-CA versus ATTR-CA were more frequently admitted with HF exacerbations (HR 2.87 (95% CI 1.42, 5.81), p = 0.003). No differences were noted in the frequency of arrhythmias-related admissions (p = 0.890).

**Discussion**

This study which included a contemporary cohort of patients with cardiac amyloid involvement highlights the distinct clinical and prognostic cardiac profiles of patients with AL-CA versus ATTR-CA. We found that although patients with AL-CA were younger, with fewer cardiovascular comorbidities and more benign echocardiographic phenotype, they had increased rates of HF exacerbations and all-cause mortality compared to patients with ATTR-CA.

Several studies have sought to investigate the association between the different CA subtypes and amyloid cardiac involvement. Rapezzi et al. have observed increased LV wall thickness and LV mass among men in a cohort of patients with ATTR-CA (mainly mutant) versus AL-CA, as assessed by echocardiography [19]. In a CMR-based study, Martinez-Naharro et al. have demonstrated higher LV and RV mass index as well as an increase in myocardial extracellular volume in patients with ATTR-CA compared to patients with AL-CA [20]. Our observations are in line with these findings and further characterize each CA sub-population from a clinical cardiac perspective. Patients with ATTR-CA versus AL-CA were older, had increased rates of diabetes mellitus, coronary artery disease and myocardial infarction as well as impaired LV systolic function by echocardiography. Moreover, the composite endpoint of malignant arrhythmias and death at 1-year was higher in patients with AL-CA versus ATTR-CA. At longer follow-up, the relative rate of malignant arrhythmias increased in ATTR-CA versus AL-CA patients with no significant differences between study groups, most probably due to survival bias. In summary, patients with ATTR-CA revealed a “sicker” baseline cardiovascular profile at the time of CA diagnosis. Nevertheless, as shown, patients with ATTR-CA (either wild-type or mutant) had better overall and HF-related prognosis compared to patients with AL-CA, findings which persisted even after the exclusion of patients with increased percentage of bone marrow plasma cells, an adverse prognostic factor in AL-CA [21].

To note, we observed similar levels of NT-proBNP between patients with AL-CA and ATTR-CA. However, considering the older age, increased LV mass and worse LV systolic function of ATTR-CA patients, it is plausible to infer that patients with AL-CA had relatively higher NT-proBNP levels, again signifying for worse HF status [22].

Both AL-CA and ATTR-CA are associated with myocardial extracellular fibril deposition, which ultimately results in myocardial restriction and diastolic dysfunction [5]. Nevertheless, over 2 decades ago, Dubrey et al. have postulated for a unique toxic component of AL-CA in addition to its recognized infiltrative pathophysiology [23], a hypothesis that was later confirmed in an isolated mouse heart model [24]. Moreover, recently, a proteomics analysis by Kourelis et al. characterized ATTR by a higher abundance of complement and contractile proteins and AL by a higher abundance of keratins, suggesting different mechanisms of tissue damage [25]. Importantly, other than the toxicity of the immunoglobulin light chains, the systemic, particularly renal, involvement in AL-CA adversely contributes to patients’ morbidity and mortality [26]. We believe that our contemporary observations, documented in an era of
advanced AL-CA suppressive-therapies, support those prior reports by demonstrating an inverse association between the better cardiovascular phenotype of AL-CA patients and their worse HF status and overall survival. Moreover, our findings highlight the discrepancy between the well-documented prognostic imaging parameters in non-amyloid cardiomyopathy and the distinct pathophysiology of AL cardiomyopathy.

**Limitations**

This study has several limitations. First, our study is limited by its relatively small sample size and single-center nature possibly limiting generalizability. Moreover, the rate of patients with mutant ATTR versus wild-type ATTR in this cohort was low, and thus our observations may not accurately reflect the echocardiographic findings in this sub-population. Second, although global longitudinal strain analysis is an important element in the echocardiographic evaluation of cardiac amyloid involvement, these data were missing in the majority of our study patients, and thus not presented. This is because global longitudinal strain analysis was not routinely used at our institution during most of the study long-term observation period.

In conclusion, despite the shared similarities of AL-CA and ATTR-CA, these diseases have distinct baseline cardiovascular profiles and different HF clinical course. We believe our findings will help promote a differential diagnostic work-up, which is amyloid-subtype directed. The pathophysiology and management of light-chain cardiac toxicity merit further study in order to improve HF-related prognosis of AL-CA patients.

**Supporting information**

**S1 Fig.** Kaplan-Meier curve of all-cause survival of patients with CA stratified by the pathogenetic amyloid subtype: (A) mutant ATTR-CA versus wild-type ATTR-CA and (B) mutant and wild-type ATTR-CA versus AL-CA. Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid-transthyretin, CA, cardiac amyloidosis.

(DOCX)

**S2 Fig.** Kaplan-Meier curve of the combined endpoint of survival free of malignant arrhythmias of patients with CA stratified by the pathogenetic amyloid subtype at 1-year (A) and 3-year (B) follow-up. Abbreviations: AL, immunoglobulin light-chain; ATTR, amyloid-transthyretin, CA, cardiac amyloidosis.

(DOCX)

**S1 Table. Baseline characteristics of patients with AL cardiac amyloidosis.** Data are presented as medians (25th, 75th quartiles) or as percentages, as appropriate. ^ Kumar S, Dispenzieri A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. Journal of clinical oncology 2012;30(9):989–95. Nine (29%) patients had missing NT-proBNP levels at baseline, thus precluding the calculation of cardiac prognostic stage. # Palladini G, Hegenbart U, Milani P, Kimmich C, Foli A, Ho AD, et al. A staging system for renal outcome and early markers of renal response to chemotherapy in AL amyloidosis. Blood. 2014;124(15):2325–32. Eight (26%) patients had missing urine-24 hour protein assessment at baseline, thus precluding the calculation of renal stage. Abbreviations: AL, immunoglobulin light-chain.

(DOCX)

**S2 Table. Baseline characteristics of patients with ATTR cardiac amyloidosis.** Data are presented as percentages, as appropriate. Abbreviations: ATTR, transthyretin amyloidosis.

(DOCX)
Acknowledgments
We thank Ms. Tzippy Shochat for performing the statistical analysis.

Author Contributions

Conceptualization: Osnat Itzhaki Ben Zadok.

Methodology: Osnat Itzhaki Ben Zadok, Mordehay Vaturi, Iuliana Vaxman.

Writing – original draft: Osnat Itzhaki Ben Zadok.

Writing – review & editing: Osnat Itzhaki Ben Zadok, Mordehay Vaturi, Iuliana Vaxman, Zaza Iakobishvili, Noa Rhurman-Shahar, Ran Kornowski, Ashraf Hamdan.

References

1. Dasari S, Theis JD, Vrana JA, Rech KL, Dao LN, Howard MT, et al. Amyloid Typing by Mass Spectrometry in Clinical Practice: a Comprehensive Review of 16,175 Samples. Mayo Clinic proceedings. 2020; 95(9):1852–64. https://doi.org/10.1016/j.mayocp.2020.06.029 PMID: 32861330

2. Gertz MA, Dispenziere A. Systemic Amyloidosis Recognition, Prognosis, and Therapy: A Systematic Review. Jama. 2020; 324(1):79–89. https://doi.org/10.1001/jama.2020.5493 PMID: 32633805

3. Kittleson MM, Maurer MS, Ambarekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, et al. Cardiac Amyloidosis: Evolving Diagnosis and Management: A Scientific Statement From the American Heart Association. Circulation. 2020;Circ0000000000000792. https://doi.org/10.1161/CIR.0000000000000792 PMID: 32476490

4. Itzhaki Ben Zadok O, Eisen A, Shapiro Y, Monakier D, Iakobishvili Z, Schwarzenberger S, et al. Natural History and Disease Progression of Early Cardiac Amyloidosis Evaluated by Echocardiography. The American journal of cardiology. 2020. https://doi.org/10.1016/j.amjcard.2020.07.050 PMID: 32811652

5. Falk RH, Alexander KM, Liao R, Durbala S. AL (Light-Chain) Cardiac Amyloidosis: A Review of Diagnosis and Therapy. Journal of the American College of Cardiology. 2016; 68(12):1323–41. https://doi.org/10.1016/j.jacc.2016.06.053 PMID: 27634125

6. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenziere A, et al. Nonbiopsy Diagnosis of Cardiac Transthyretin Amyloidosis. Circulation. 2016; 133(24):2404–12. https://doi.org/10.1161/CIRCULATIONAHA.116.021612 PMID: 27143678

7. Rajkumar SV, Dimopoulos MA, Palumbo A, Blade J, Merlini G, Mateos MV, et al. International Myeloma Working Group updated criteria for the diagnosis of multiple myeloma. The Lancet Oncology. 2014; 15(12):e538–48. https://doi.org/10.1016/S1470-2045(14)70442-5 PMID: 25439696

8. Kumar S, Dispenzier A, Lacy MQ, Hayman SR, Buadi FK, Colby C, et al. Revised prognostic staging system for light chain amyloidosis incorporating cardiac biomarkers and serum free light chain measurements. Journal of clinical oncology: official journal of the American Society of Clinical Oncology. 2012; 30(9):988–95. https://doi.org/10.1200/JCO.2011.38.5724 PMID: 22331953

9. Merlini G, Dispenzieri A, Sanchorawala V, Schonland SO, Palladini G, Hawkins PN, et al. Systemic immunoglobulin light chain amyloidosis. Nature reviews Disease primers. 2018; 4(1):38. https://doi.org/10.1038/s41572-018-0034-3 PMID: 30361521

10. Durbala S, Cuddy S, Falk RH. How to Image Cardiac Amyloidosis: A Practical Approach. JACC Cardiovascular imaging. 2019. https://doi.org/10.1016/j.jcmg.2019.07.015 PMID: 31607664

11. Lang RM, Badano LP, Mor-Avi V, Afifi J, Armstrong A, Ernande L, et al. Recommendations for cardiac chamber quantification by echocardiography in adults: an update from the American Society of Echocardiography and the European Association of Cardiovascular Imaging. Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography. 2015; 28(1):1–39.e14

12. Devereux RB, Reichek N. Echocardiographic determination of left ventricular mass in man. Anatomic validation of the method. Circulation. 1977; 55(4):613–8. https://doi.org/10.1161/01.cir.55.4.613 PMID: 138494

13. Rudski LG, Lai WW, Afifi J, Hua L, Handschumacher MD, Chandrasekaran K, et al. Guidelines for the echocardiographic assessment of the right heart in adults: a report from the American Society of Echocardiography endorsed by the European Association of Echocardiography, a registered branch of
14. Silbiger JJ. Pathophysiology and Echocardiographic Diagnosis of Left Ventricular Diastolic Dysfunction. Journal of the American Society of Echocardiography: official publication of the American Society of Echocardiography. 2019; 32(2):216–32.e2. https://doi.org/10.1016/j.echo.2018.11.011 PMID: 30717860

15. Nagueh SF, Smiseth OA, Appleton CP, Byrd BF 3rd, Dokainish H, Edvardsen T, et al. 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. European heart journal cardiovascular Imaging. 2016; 17(12):1321–60. https://doi.org/10.1093/ehjci/jew082 PMID: 27422899

16. Boldrini M, Cappelli F, Chacko L, Restrepo-Cordoba MA, Lopez-Sainz A, Giannoni A, et al. Multiparametric Echocardiography Scores for the Diagnosis of Cardiac Amyloidosis. JACC Cardiovascular Imaging. 2019.

17. Kou S, Caballero L, Dulgheru R, Voilliot D, De Sousa C, Kacharava G, et al. Echocardiographic reference ranges for normal cardiac chamber size: results from the NORRE Study. European heart journal cardiovascular Imaging. 2014; 15(6):680–90.

18. Caballero L, Kou S, Dulgheru R, Gonjilashvili N, Anagnostopoulos GD, Barone D, et al. Echocardiographic reference ranges for normal cardiac Doppler data: results from the NORRE Study. European heart journal cardiovascular Imaging. 2015; 16(9):1031–41. https://doi.org/10.1093/ehjci/jev083 PMID: 25896355

19. Rapezzi C, Merlino G, Quarta CC, Vaira L, Longhi S, Leone O, et al. Systemic cardiac amyloidoses: disease profiles and clinical courses of the 3 main types. Circulation. 2009; 120(13):1203–12. https://doi.org/10.1161/CIRCULATIONAHA.108.843334 PMID: 19752327

20. Martinez-Naharro A, Treibel TA, Abdel-Gadir A, Bulluck H, Zumbo G, Knight DS, et al. Magnetic Resonance in Transthyretin Cardiac Amyloidosis. Journal of the American College of Cardiology. 2017; 70(4):466–77. https://doi.org/10.1016/j.jacc.2017.05.053 PMID: 28728692

21. Muchtar E, Gertz MA, Kourelis TV, Sidana S, Go RS, Lacy MQ, et al. Bone marrow plasma cells 20% or greater discriminate presentation, response, and survival in AL amyloidosis. Leukemia. 2020; 34(4):1135–43. https://doi.org/10.1038/s41375-019-0655-x PMID: 31758090

22. Perfetto F, Bergesio F, Grifoni E, Fabbri A, Ciuti G, Frusconi S, et al. Different NT-proBNP circulating levels for different types of cardiac amyloidosis. J Cardiovasc Med (Hagerstown). 2016; 17(11):810–7. https://doi.org/10.2459/JCM.0000000000000349 PMID: 26765991

23. Dubrey S, Mendes L, Skinner M, Falk RH. Resolution of heart failure in patients with AL amyloidosis. Annals of internal medicine. 1996; 125(6):481–4. https://doi.org/10.7326/0003-4819-125-6-199609150-00009 PMID: 8779461

24. Liao R, Jain M, Teller P, Conners LH, Ngoy S, Skinner M, et al. Infusion of Light Chains From Patients With Cardiac Amyloidosis Causes Diastolic Dysfunction in Isolated Mouse Hearts. Circulation. 2001; 104(14):1594–7. PMID: 11581134

25. Kourelis TV, Dasari SS, Dispenziere A, Malesszewski JJ, Redfield MM, Fayyaz AU, et al. A Proteomic Atlas of Cardiac Amyloid Plaques. JACC: CardioOn cology. 2020; 2(4):632–43. https://doi.org/10.1016/j.jaccacco.2020.08.013 PMID: 33511353

26. Gertz MA, Comenzo R, Falk RH, Fermund JP, Hazenberg BP, Hawkins PN, et al. Definition of organ involvement and treatment response in immunoglobulin light chain amyloidosis (AL): a consensus opinion from the 10th International Symposium on Amyloid and Amyloidosis, Tours, France, 18–22 April 2004. American journal of hematology. 2005; 79(4):319–28. https://doi.org/10.1002/ajh.20381 PMID: 16044444