Amyloid cardiomyopathy in a large integrated health care system

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Background Light Chain (AL) and transthyretin (ATTR) amyloidosis are the most common forms of amyloid cardiomyopathy. Population based studies describing the epidemiology and clinical features of amyloid cardiomyopathy are often based in tertiary medical centers and thus may be limited by referral bias.

Methods and Results We performed a cohort study of 198 patients diagnosed and treated in the Kaiser Permanente Northern California health care system who had a confirmed diagnosis of cardiac amyloidosis between 2001 and 2016. Associations between demographic, clinical, laboratory and imaging data and patient outcomes were quantified using multivariable Cox proportional hazard models for both the AL and ATTR groups. The average length of follow up was 2.8 years (SD 2.9 years) and overall survival was 69.1 percent at one year and 35.4 percent at five years. In the AL group, lower left ventricular ejection fraction (HR 1.33 per 5-point decrease, $P < .001$), coronary artery disease (HR 3.56, $P < .001$), and diabetes mellitus (HR 3.19, $P < .001$) were associated with all-cause mortality. Increasing age at the time of diagnosis with associated with higher all-cause mortality in both the AL and ATTR groups. Higher levels of B-type natriuretic peptide were associated with all-cause mortality in both groups: Top quartile BNP HR 6.17, $P < .001$ for AL and HR 8.16, $P = .002$ for ATTR.

Conclusions This study describes a large cohort of patients with amyloid cardiomyopathy derived from a community based, integrated healthcare system and describes demographic, clinical, and laboratory characteristics associated with mortality and heart failure hospitalization. In this population, coronary artery disease, diabetes mellitus, and high BNP levels were strongly associated with mortality. (Am Heart J 2019;216:42-52.)

The term amyloidosis describes a group of disorders characterized by the extracellular deposition of misfolded protein fibrils. The most common forms of cardiac amyloidosis are AL, characterized by the deposition of immunoglobulin light chains secreted by clonal plasma cells, and ATTR, characterized by the deposition of transthyretin, a transport protein produced in the liver.[1] ATTR amyloidosis is further divided into wild-type (ATTRwt) and hereditary mutated (ATTRm) forms. Cardiac involvement and heart failure are common in all types of cardiac amyloidosis, though patients with AL amyloidosis have been reported to have a more rapid progression of disease and worse survival overall.[2]

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While amyloidosis is a rare disease, there has long been suspicion on the basis of pathologic[3] and clinical[4] evidence that it is underdiagnosed, especially in the ATTR form. Previous studies describing the epidemiology of amyloid cardiomyopathy are rare while studies describing its clinical features of have generally been based in tertiary medical centers and thus may be limited by referral bias.[5-9] The aims of this study are to characterize the incidence of the three major subtypes of Amyloid cardiomyopathy in a large, integrated health care system, to characterize the demographic, clinical, laboratory and imaging characteristics of patients with newly diagnosed amyloid cardiomyopathy, and to determine the impact of amyloid subtype, comorbid conditions and cardiac biomarkers on survival and heart failure hospitalization.

Methods

Source population

This is a cohort study of patients diagnosed and treated in the Kaiser Permanente Northern California (KPNC) health care system who had a confirmed diagnosis of cardiac amyloidosis between 2001 and 2016. KPNC is a large,

regional, and integrated health care network which provides care for patients residing in northern California. The source population consisted of 2.2 million adults older than age 18 in the year 2000, increasing steadily until reaching 3 million patients in 2016. The socio-demographic characteristics of the members are representative of the underlying population of Northern California.[10,11]

Patient selection

Patients were identified by searching the Kaiser Permanente Northern California electronic medical record for members having ICD-9 coded encounters for both amyloidosis and heart failure. Additional members were identified using a KPNC registry of patients with confirmed amyloidosis. In all cases, the diagnosis of cardiac amyloidosis was confirmed by physician chart review. For the purposes of the study, the diagnosis was considered confirmed if a treating cardiologist considered a patient to have amyloidosis along with biopsy, genetic testing, or supportive imaging and laboratory data. As patients and treating physicians may defer biopsy for various reasons including known extracardiac amyloidosis, lack of anticipated effect on management, poor prognosis, or patient refusal, endomyocardial biopsy data was not necessary to include a patient in the study if clinical, imaging and laboratory evidence favored amyloidosis. This was true for a minority of study subjects. Types of imaging reviewed included Cardiac Magnetic Resonance (CMR), Technetium Pyrophosphate (TPP) scans and Echocardiography.

Patient classification

Patients with confirmed amyloidosis were classified by amyloid subtype into three groups: AL, ATTR, and amyloid of unknown subtype (A-U). The ATTR groups was further divided into mutant (ATTRm), wild-type (ATTRwt) and unknown (ATTRu) subgroups for some of the descriptive results.

Patients with known multiple myeloma who subsequently developed heart failure and imaging evidence of cardiac amyloidosis were presumed to have AL amyloidosis unless otherwise noted. For patients with transthyretin amyloidosis, mutation status was determined using either genetic testing or mass spectroscopy. If the patient was determined to have transthyretin amyloidosis but not fully classified as wild type or mutant, the patient was classified as transthyretin amyloidosis of unknown type (ATTRu). If the presence of amyloid was known but not further specified on the biopsy report, or if the diagnosis was made based on imaging alone, patients were classified as amyloidosis of unknown subtype.

Patient data

Sociodemographic and medication data were obtained from KPNC research databases, along with appropriate ICD9/ICD10 diagnoses codes for comorbid conditions such as hypertension (HTN) and coronary artery disease (CAD). Laboratory values were measured according to standard clinical laboratory practice. Laboratory data from within 30 days of diagnosis was extracted from the electronic medical record. The relevant biomarker data were divided into quartiles for analysis. B-type natriuretic peptide, cardiac troponin I, and uric levels are frequently obtained on amyloid cases at KPNC whereas cardiac troponin T and N-terminal pro B-type natriuretic peptide levels (NT-proBNP) are not typically obtained.

Transthoracic echocardiographic data was obtained using review of the electronic medical record. Echocardiography was performed using standard commercial equipment and echocardiographic parameters were measured according to American Society of Echocardiography guidelines, including left ventricular ejection fraction (LVEF) and assessment for left atrial enlargement (LAE). For measurement of left ventricular wall thickness, the posterior wall thickness (LVPWT) was used when available. When measurements were not available in the echocardiographic report, the presence and degree of left ventricular hypertrophy (LVH) was qualitatively described. Echocardiograms were reviewed for alternative causes of left ventricular hypertrophy as part of the manual confirmation of cardiac amyloidosis. When the echocardiogram report included mention of likely amyloid cardiomyopathy, this was noted. CMR was performed using 1.5 T MR scanners and the presence of amyloidosis was determined using the presence of diffuse subendocardial or transmural late gadolinium enhancement coupled with abnormal myocardial and blood-pool gadolinium kinetics.

Electrocardiograms were reviewed for evidence of low voltage or left ventricular hypertrophy. Low voltage was defined as total QRS amplitude <0.5 mV in each of the standard limb leads. Presence of ECG left ventricular hypertrophy was determined by applying Cornell or Sokolow-Lyon criteria. Endomyocardial biopsy histology was reviewed either by a pathologist at the local medical center, or in most cases, sent to either the Mayo Clinic or Stanford Medical Center pathology department for review.

The date of onset of heart failure was obtained using the electronic medical record. The date was taken as the first patient encounter that describes typical clinical features of heart failure, including dyspnea, edema, fatigue, chest pain, or dizziness in the appropriate context. The date of onset of amyloidosis was determined using the first clinical documentation that acknowledged the presence of definite cardiac amyloidosis, whether invoking biopsy or imaging data. Mortality was assessed using the electronic medical record and the California Death Registry. Repeat hospitalization dates were obtained from the medical record and manually reviewed to confirm a separate hospitalization if it occurred within 30 days of the initial diagnosis date. For patients receiving heart transplantation, date of heart transplantation was recorded.

Statistical analysis

For most descriptive statistics, patients were divided into three groups: AL, ATTR, and A-U. Baseline demographic, clinical and imaging characteristics were compared across groups. Treatments, including pharmacologic therapy at the time of diagnosis and chemotherapy in the case of AL amyloidosis, were recorded. Categorical variables were compared between groups using χ^2 or Fisher's exact tests. Continuous variables were compared using Student's *t* tests, ANOVA, or Wilcoxon rank-sum tests. For all patients, the presence or absence of left ventricular hypertrophy (LVH) on echocardiogram was compared to LVH by electrocardiographic criteria.

To explore factors that could be associated with mortality and heart failure hospitalization, we conducted multivariable analysis of a set of variables that were selected for their potential clinical significance. The primary outcome variable was all-cause mortality and the secondary outcome was hospitalization for heart failure (HF) after the initial diagnosis of cardiac amyloidosis. These analyses were done separately for the AL and ATTR subgroups.

The associations between outcomes and patients' sociodemographic and clinical characteristics were examined using multivariable Cox proportional hazard models. Covariates with strong biologic plausibility or a potentially significant association with the dependent variable on bivariate analysis (defined as a $P \leq .1$) were included in the initial model, which was then refined using stepwise selection. Base models were developed using a set of variables that included age, race, coronary artery disease (CAD), diabetes mellitus (DM), serum creatinine, specific categories of medications, and left ventricular ejection fraction (LVEF). Medications included in the base model were beta blockers, diuretics, angiotensin converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), aldosterone antagonists, digoxin, antiarrhythmic medications, and oral anticoagulants. To investigate the relationship of cardiac biomarkers with mortality as well as with hospitalization, the selected biomarkers (uric acid [UA], cardiac troponin I [cTnI], and B-type natriuretic peptide [BNP]) were added to the base models, categorized by quartile.

For the mortality outcome, follow-up time started on the date of amyloid diagnosis and continued to the date of censoring for death, date of disenrollment from the KPNC, or the end of the study follow-up period (10/31/2017). For the HF hospitalization outcome, follow up started from the date of amyloid diagnosis and continued to the date of HF hospitalization, death, date of disenrollment from KPNC, or the end of study follow-up.

The Kaplan Meier method was used to plot the survival curves for overall mortality and hospitalization. For multivariable analysis, levels of cardiac biomarkers (cTnI, BNP, UA) were divided into quartiles, with the lowest quartile being the reference category. Hazard ratios (HR) and 95% confidence intervals (CI) were calculated. An alpha level of 0.05 was used as the threshold for statistical significance. All analyses were conducted using SAS statistical software, version 9.3 (Cary, N.C.). Approval for the study and waiver of informed consent was obtained from the Institutional Review Board of Kaiser Permanente Northern California. No extramural funding was used to support this work. The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the manuscript, and its final contents.

Results

Study population

A total of 500 patients were identified using ICD-9 codes for amyloidosis and heart failure or included in a local amyloidosis registry. After chart review, 198 patients were confirmed to have amyloid cardiomyopathy and comprised the study cohort. Of these patients, 63 were alive at the end of follow up, 127 died and 8 left KPNC. The total source population consisted of 2.2 million patients in 2000, rising to 3 million in 2016. The yearly incidence of confirmed amyloidosis rose during the study period, from 0.44 cases per million prior to 2006 to 3.76 cases per million between 2006 and 2010 and 10.9 cases per million from 2011 to 2016. Of the 198 patients, 15 (5.4%) were found to have amyloidosis prior to a diagnosis of heart failure while 183 (94.6%) presented with heart failure symptoms prior to a diagnosis of amyloidosis.

Patient characteristics

The demographic and clinical characteristics of the study cohort are described in Table I. The largest amyloid group was AL amyloidosis (N = 101, 51%). The different subtypes of amyloidosis varied widely in age at time of diagnosis, with AL amyloid patients being significantly younger. A large majority of patients with ATTR amyloidosis were male. As expected, the different subtypes of amyloidosis varied significantly with respect to race and 48 percent of patients with AATTR were of African descent. The average follow-up time was 2.8 years (SD 2.9 years) for the entire cohort.

Among comorbid conditions, significant differences were seen in the prevalence of hypertension and atrial fibrillation across the groups, with ATTR patients being significantly more likely to carry these diagnoses. Of the 29 patients with ATTR and a confirmed genetic mutation, 23 were found to have the valine-122-isoleucine mutation (V122I) and there was 1 patient with each of the following mutations: ASP18, ILE84, Leu58his, Ser77Try, and V50 m. One patient had missing mutation data. Of the 101 patients with AL amyloidosis, 34 (34%) also carried a diagnosis of multiple myeloma.

The different patient cohorts had significantly different baseline levels of serum UA, BNP, hemoglobin, bilirubin, and

Table I. Cohort characteristics

	Total cohort N = 198	AL N = 101	ATTR N = 67	A-U N = 30	P*
Demographic variables					
Age, years, mean (SD)	70.9 (12.1)	64.6 (11.1)	75 (9.4)	82.9 (7.1)	<.001
Female sex	65 (33%)	44 (44%)	15 (22%)	6 (20%)	.004
Race					
Hispanic	12 (6%)	6 (6%)	4 (6%)	2 (7%)	<.001
African-American	56 (28%)	16 (16%)	32 (48%)	8 (27%)	
Asian/Pacific Islander	16 (8%)	12 (12%)	1 (1%)	3 (10%)	
Native American / multiracial/unknown	14 (7%)	9 (9%)	1 (1%)	4 (13%)	
White	100 (51%)	58 (58%)	29 (43%)	13 (43%)	
Body Mass Index					
< 25 kg/m^2	104 (53%)	48 (48%)	41 (61%)	15 (50%)	.37
26–30 kg/m^2	71 (36%)	38 (38%)	20 (30%)	13 (43%)	
≥31 kg/m^2	23 (12%)	15 (15%)	6 (9%)	2 (7%)	
Smoking	86 (43%)	43 (43%)	27 (40%)	16 (53%)	.47
Hyperlipidemia	122 (62%)	59 (59%)	46 (69%)	17 (57%)	.34
Diabetes mellitus	34 (17%)	16(16%)	12 (18%)	6 (20%)	.85
Coronary Artery Disease	89 (45%)	39 (39%)	32 (48%)	18 (60%)	.10
Hypertension	122 (62%)	53 (53%)	49 (73%)	20 (67%)	.022
Carpal tunnel syndrome	33 (17%)	14 (14%)	15 (22%)	4 (13%)	.31
Chronic Kidney disease	103 (52%)	55 (55%)	32 (48%)	16 (53%)	.68
Atrial fibrillation or flutter	72 (36%)	23 (23%)	32 (48%)	17 (57%)	<.001
Pacemaker Status	9 (5%)	3 (3%)	5 (7%)	1 (3%)	.41
Defibrillator Status	5 (3%)	3 (3%)	1 (1%)	1 (3%)	.85
Laboratory Values (mean, SD)					
Serum Creatinine (mg/dL) N = 197	1.42 (0.98)	1.40 (1.2)	1.38 (0.7)	1.58 (0.8)	.63
Serum Troponin I (ng/mL) N = 161	0.34 (0.86)	0.48 (1.12)	0.17 (0.25)	0.18 (0.14)	.08
Serum Uric Acid (mg/dL) N = 90	8.4 (3.3)	8.0 (3.3)	8.5 (2.3)	12.7 (5)	.009
Serum BNP (pg/mL) N = 183 Median (IQR)	606 (799)	651 (965)	508 (462)	662 (1159)	.030**
Serum Na (mEq/L) N = 194	139 (3.6)	137.5 (3.4)	139 (3.4)	137 (4.4)	.18
Hemoglobin (g/dL) N = 196	12.5 (1.7)	12.2 (1.7)	13.1 (1.7)	12.4 (1.9)	.004
Total Bilirubin (mg/dL) N = 175	1.1 (0.8)	0.9 (0.7)	1.4 (0.9)	1.2 (0.9)	.006
ALT (U/L) N = 191	33 (41)	37 (54)	30 (21.2)	26.7 (9.9)	.35
AST (U/L) N = 178	35 (29)	38 (38)	33 (16.5)	35 (17.4)	.60
Serum albumin (g/dL) N = 159	3.5 (0.6)	3.4 (0.6)	3.8 (0.5)	3.4 (0.6)	.001
Echocardiographic variables					
LVEF (n = 197), mean (SD)	54 (14)	58 (11.3)	48.6 (14.4)	54.2 (16.2)	<.001
<35%	22 (11%)	6 (6%)	12 (18%)	4 (13%)	.003
35–54%	58 (29%)	23 (23%)	27 (41%)	8 (27%)	
> = 55%	117 (59%)	72 (72%)	27 (41%)	18 (60%)	
LVPWT (n = 188)	1.6 (0.4)	1.4 (0.3)	1.7 (0.4)	1.7 (0.4)	<.001
Presence of LVH	189 (95%)	94 (93%)	65 (98%)	30 (100%)	.85
Presence of LAE	168 (85%)	78 (77%)	60 (92%)	30 (10%)	.002

Values are mean ± standard deviation or n (%).
* *P* values are from χ^2 or Fisher's exact tests for categorical variables and ANOVA for continuous variables.
** *P* value is from Kruskal-Wallis Test.

serum albumin. BNP and UA were highest in the A-U group while hemoglobin was higher in the AATTR subgroup, likely due to a lower proportion of women in that group.

Medications

As shown in Table II, a total of 85% of patients were receiving diuretic therapy, 51% were on a beta blocker, 46% were receiving an ACEi or ARB, 35% an anticoagulant, and 27% an aldosterone antagonist. Smaller numbers of patients were receiving calcium channel blockers (12%) antiarrhythmic agents (11%) or digoxin (8%). ATTR patients were more likely than AL patients to be receiving an ACEi or ARB and oral anticoagulants. For AL amyloidosis patients, the chemotherapy agents used matched standard therapy at the time of diagnosis and treatment. A total of 66 patients with AL amyloidosis were treated with bortezomib-based regimens which have been associated with improved outcomes.[12-14] During this period at KPNC, ATTR patients were not treated with experimental agents such as diflunisal or tafamidis.

Table II. Cardiovascular medication use in the cohort, n (%)

Medication	Total Cohort N = 198	AL N = 101	ATTR N = 67	A-U N = 30	*P**
Diuretic	168 (85%)	83 (82%)	62 (93%)	23 (77%)	.07
Beta-blocker	101 (51%)	44 (44%)	37 (55%)	20 (67%)	.06
Calcium channel blocker	21 (11%)	9 (9%)	10 (15%)	2 (7%)	.35
ACE inhibitor or angiotensin receptor blocker	91 (46%)	39 (39%)	39 (58%)	13 (43%)	.042
Aldosterone antagonist	54 (27%)	25 (25%)	21 (31%)	8 (27%)	.64
Digoxin	16 (8%)	8 (8%)	4 (6%)	4 (13%)	.47
Antiarrhythmic agent	24 (12%)	10 (10%)	13 (19%)	1 (3%)	.05
Oral anticoagulant	69 (35%)	27 (27%)	28 (42%)	14 (47%)	.045

* *P* values are from χ^2 tests.

Table III. Biopsy data according to amyloid type*

	Performed	Performed AL	Performed ATTR	Positive (Yield %)	Positive (Yield %) AL	Positive (Yield %) AATTR
Cardiac	84	37	43	83 (99)	35 (95)	43 (100)
Fat Pad	56	36	17	30 (54)	21 (58)	7 (41)
Rectal	2	2	0	2 (100)	2 (100)	-
Bladder	2	0	2	2 (100)	-	2 (100)
Gastrointestinal	9	9	0	7 (78)	7 (78)	-
Liver	6	6	0	6 (100)	6 (100)	-
Salivary gland	2	2	0	1 (50)	1 (50)	-
Renal	9	9	0	9 (100)	9 (100)	-
Skin	2	2	0	2 (100)	9 (100)	-
Prostate	1	1	0	1 (100)	9 (100)	-
Tongue	2	3	0	2 (100)	3 (100)	-

* Note: The A-U subgroup is not included in this analysis.

Diagnostic data

Biopsy data is displayed in Table III. A total of 84 cardiac biopsies were performed of which 83 were positive. Notably, of the 56 fat pad biopsies performed, only 30 were positive in patients ultimately deemed to have confirmed amyloidosis, yielding a sensitivity of 54 percent in this cohort. Other extracardiac biopsies performed included gastrointestinal, liver, renal, tongue, rectal, salivary gland, prostate, skin, and bladder biopsies. In addition, 18 subjects had bone marrow biopsies positive for amyloid deposits. CMR was performed in 29 patients as part of the initial evaluation for cardiac amyloidosis and was abnormal in all cases. There were seven patients in whom CMR was considered the confirmatory test such that the treating team opted not to pursue a tissue diagnosis. Among these seven patients, one had a biopsy outside of the Kaiser system, one had genetic testing considered diagnostic of ATTR, one was considered to have AL based on elevated light chains and a known plasma cell dyscrasia, and four for whom a tissue diagnosis was deferred due to limited goals of care. One patient had a TPP scan as part of the diagnostic work up.

Of the patients for whom no biopsy data was available within the internal health care system, 16 had AL amyloid, seven ATTRm, one ATTRwt, five ATTRu, and 25 amyloidosis of unknown subtype. All patients with ATTRm who were not biopsied were confirmed to have undergone genetic testing. In the A-U group, most patients were diagnosed using imaging data alone, but five patients had biopsy data that confirmed amyloidosis but did not specify subtype.

Mortality results

The results of the cox proportional hazards model for mortality are shown in Table IV. In the AL group, CAD, diabetes, increasing age, and lower ejection fraction were associated with higher mortality whereas treatment with diuretics, digoxin, oral anticoagulants, and bortezomib were associated with lower mortality. In the ATTR group, only increasing age and African-American race were associated with higher mortality. There was no association between beta blocker use and mortality in either the AL group or ATTR group.

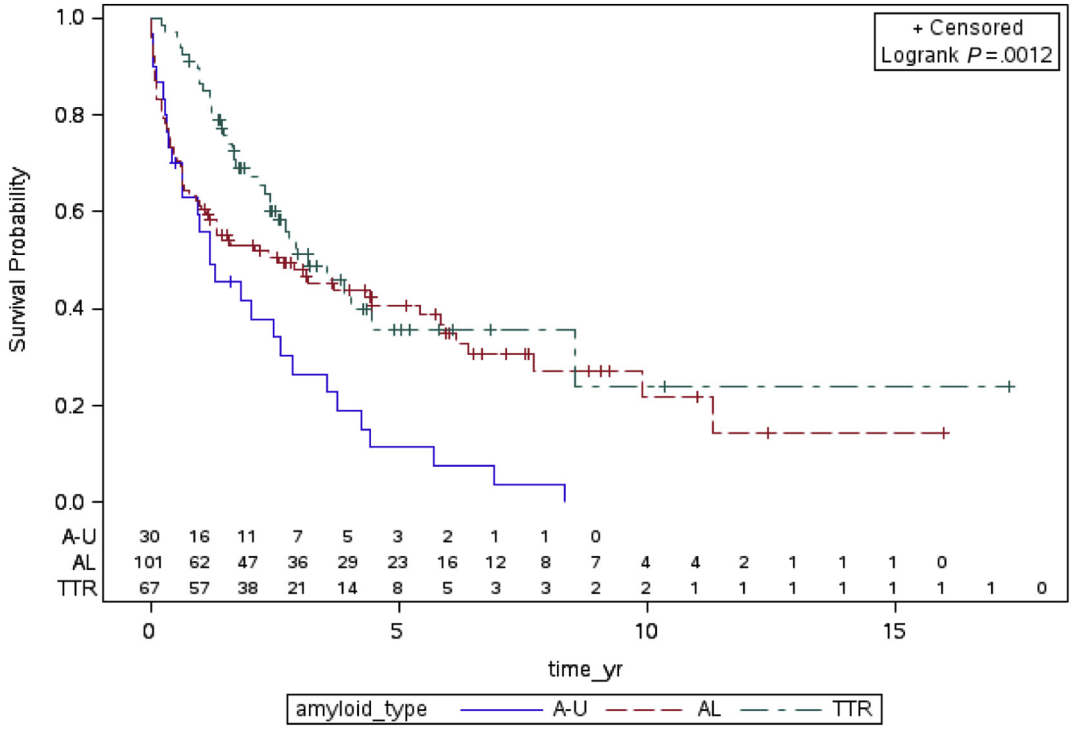
Unadjusted survival curves are shown in Figure 1. AL patients' survival was 61.4 percent at 1 year and 40.6 percent at 5 years. In ATTR patients, one-year survival was 86.5 percent and five-year survival was 35.8 percent. In the A-U group, one and five-year survival was 56.0 and 11.4 percent, respectively. This finding was not unexpected given the older mean age at the time of diagnosis

Table IV. Clinical predictors of all-cause mortality

Predictor variable	AL group		ATTR group	
	HR (95% CI)	*P*	HR (95% CI)	*P*
LVEF (per 5 point ↓)	1.33 (1.16–1.52)	<.0001	-*	-
Diuretic	0.29 (0.15–0.56)	.0002	-	-
Digoxin	0.35 (0.12–1.0)	.05	-	-
Oral anticoagulant	0.38 (0.19–0.76)	.007	-	-
Bortezomib	0.14 (0.08–0.25)	<.0001	-	-
CAD	3.56 (2.04–6.27)	<.0001	-	-
DM	3.19 (1.53–6.64)	.002	-	-
Age (per 5 y↑)	1.23 (1.10–1.49)	.0016	1.71 (1.35–2.16)	<.001
African American (vs white)	-	-	2.31 (1.14–4.71)	.021

* Dashes indicate that variable was not in the final model due to lack of statistical significance.

Figure 1



Unadjusted survival by amyloid subtype.

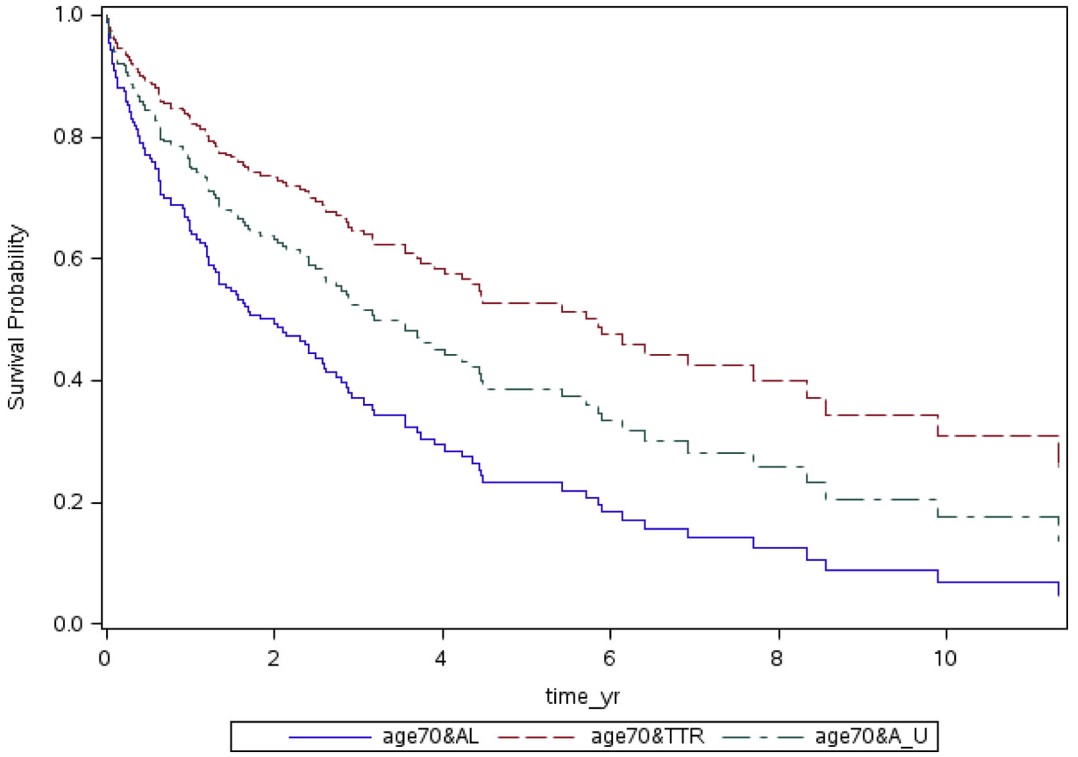
in the A-U group. In Figure 2, age-adjusted survival curves are shown for patients diagnosed at age 70, demonstrating worse survival in the AL group after accounting for differences in age at the time of diagnosis.

Of the total cohort, 19 patients received heart transplants during the study period (8 AL, 7 ATTRm, 4 ATTRw). Of these patients, 17 were still alive at the end of the study. One patient (ATTRm) died 9 years post-transplant and one (AL) died 6 years post-transplant.

Mortality and biomarkers

To investigate the relationships between cardiac biomarkers and mortality, the selected biomarkers (UA, cTnI, and BNP) were added to the model, categorized by quartile. For each type of amyloid, multivariable analysis was then performed using forward stepwise selection. The results of the Cox proportional hazard model for the relationship between all-cause mortality and cardiac

Figure 2



Age adjusted survival probabilities by amyloid subtype for patient 70 years old.

Table V. B-type natriuretic peptide levels and all-cause mortality

	AL Group*		ATTR Group**	
BNP (pg/mL)	HR (95% CI)	*P*	HR (95% CI)	*P*
Bottom quartile (reference)	1.0	-	1.0	-
2nd quartile	2.57 (0.93–7.09)	.07	2.95 (0.89–9.73)	.08
3rd quartile	3.46 (1.45–8.23)	.005	4.67 (1.55–14.09)	.006
Top quartile	6.17 (2.61–14.62)	<.0001	8.16 (2.13–31.37)	.002
Missing	2.44 (0.74–8.07)	.15	1.54 (0.14–16.98)	.72

*Model adjusted for age, diuretics, digoxin, oral anticoagulant, bortezomib, CAD, DM, and LVEF.
**Model adjusted for age and African American race.

biomarkers is described in Table V. Only BNP levels were significantly associated with mortality. The effect of the level of BNP by quartile is shown, with the lowest quartile being the reference value. There was an incremental increase in the hazard for death with each increasing quartile of BNP level. Of note, patients with missing BNP did not have significantly higher mortality than the patients with the lowest quartile of BNP. Uric acid quartiles and troponin I quartiles were tested in the models but not retained due to lack of association with the outcome after multivariable adjustment. (See Table VI.)

Hospitalization after diagnosis of cardiac amyloidosis

The base model variables and biomarker variables were also tested for associations with HF hospitalization. In the AL group, CAD and diabetes mellitus were associated with an increased risk of heart failure hospitalization whereas bortezomib therapy was associated with lower risk. In the AATTR group, higher levels of creatinine and the use of ACE inhibitors or angiotensin receptor blockers was associated with an increased risk of heart failure hospitalization.

Table VI. Predictors of heart failure hospitalization outcome after multivariable adjustment*

Predictor variable	AL Group		ATTR Group	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Bortezomib	0.25 (0.12–0.53)	<.001	-	-
CAD	2.84 (1.36–5.93)	.006	-	-
DM	2.83 (1.29–6.22)	.009	-	-
Creatinine (per 1 point ↑)	-	-	2.86 (1.86–4.40)	<.001
ACE inhibitor or angiotensin receptor blocker	-	-	4.05 (1.40–11.71)	.001

* Dashes indicate that variable was not in the final model due to lack of statistical significance.

Echocardiographic and ECG data

In most cases (86%), the echocardiogram was obtained before the diagnosis of cardiac amyloidosis was made. An additional 5% of cases had their echocardiogram performed within 30 days after the diagnosis. The mean left ventricular ejection fraction (LVEF) at diagnosis was 54 percent and the average left ventricular posterior wall thickness was 1.6 cm. ATTR patients had a lower mean ejection fraction (48.6 vs 58.0), were more likely to have a LVEF <35% (18% vs 6%), had a greater mean posterior wall thickness (1.7 vs 1.4 cm), and were more likely to have left atrial enlargement (92% vs 77%).

Most patients had LVH demonstrated on echocardiogram without LVH on ECG (N = 180). 17 patients had LVH on both ECG and echocardiogram. One patient had LVH on neither ECG nor echocardiogram. Of the total cohort, 101 patients (51%) had low voltage on ECG. Low voltage on ECG was more common among AL patients (56%) than non-AL patients (45%).

Discussion

This study describes a large cohort of patients with amyloid cardiomyopathy derived from a community based, integrated healthcare system. In this population, the annual incidence of confirmed amyloidosis rose during the study period, reaching 10.9 cases per million from 2011 to 2016, though underdiagnosis is still likely present.[15] This is similar to a population based study of the incidence of AL amyloidosis in Olmstead county, MN, which reported an incidence of 5.1–12.8 cases per million person-years.[5]

We describe demographic, clinical, and laboratory characteristics for different subtypes of cardiac amyloidosis and quantify the associations between clinical predictor variables and both all-cause mortality and heart failure hospitalization. The clinical features of the disease and the rates of adverse outcomes differ according to amyloid subtype, consistent with prior studies.[2] For example, there was more pronounced left ventricular hypertrophy and a greater frequency of atrial arrhythmias in ATTR amyloidosis, as well as a more indolent clinical course in the AATTR group.

Previously reported clinical predictors of disease have included levels of NT-ProBNP,[16,17] Cardiac troponin T,[17,18] and Uric Acid,[19] as well as the glomerular filtration rate (GFR).[20,21] Staging systems have been proposed for both AL and ATTR amyloidosis. In the case of AL amyloidosis, the most commonly used staging system includes cTnT, and N-Terminal pro B type brain natriuretic peptide (NT-ProBNP).[17] For AATTR disease, a recently proposed staging system incorporates NT-ProBNP and GFR.[21] Novel markers of disease including serum transthyretin levels have been proposed.[22] Cardiac biomarkers have been demonstrated to predict disease course independently of amyloid subtype.[23] While the most commonly used staging systems for cardiac amyloidosis use N-Terminal BNP and Troponin T, troponin I was a component of the original Mayo staging system[17] and is routinely used in clinical practice. BNP has also been shown to predict cardiac disease in patients with AL amyloidosis and may be preferred as a biomarker in patients with renal involvement.[24,25] In the present study, demographic and clinical predictors of mortality were age, presence of CAD, DM, African American race, and LVEF.

Table IV describes variables which are associated with all-cause mortality in the AL and ATTR cohorts. It is not surprising that therapy with bortezomib improves outcomes in the AL group, though we do not know in the current study if bortezomib treatment was offered to AL patients regardless of their cardiovascular condition. The presence of traditional cardiovascular risk factors such as coronary artery disease and diabetes has not been previously reported as a significant modifier of mortality in patients with cardiac amyloidosis. In the present study, advancing age was not unexpectedly a risk factor for mortality in both the AL and ATTR groups. A history of CAD and diabetes mellitus were associated with higher mortality in the AL but not the AATTR group, whereas treatment with diuretics, digoxin, and anticoagulants was associated with lower mortality rates. These finding suggest that there are important interactions between traditional cardiovascular risk factors and treatments with the myofibrillar effects of AL amyloidosis. As patients get older the burden of cardiovascular disease increases, in

part due to increased cumulative exposure to risk factors. These risk factors may interact with cardiac amyloidosis synergistically to increase morbidity and mortality.[26,27] In the ATTR group, the only independent association with mortality (other than age) was African-American race, who are the most common group in the United States affected by ATTRm.[28] The reasons for this association are not clear, as risk factors such as hypertension which are more predominant in the African-American population were included in the model construction. Previous studies have highlighted the disparity in heart failure and amyloid outcomes for African-American patients.[29]

The heart failure hospitalization (HFH) models also produced different results for the AL versus ATTR group. For the AL group, bortezomib treatment was associated with less risk of HFH whereas CAD and diabetes mellitus were associated with an increased risk. These findings are not surprising and are consistent with what was observed for the mortality outcome. For the ATTR group, an association between worsening renal function and HFH was observed and is not surprising as volume overload is more likely to contribute to HF in the setting of renal failure. The association between the use of ACE inhibitors or ARBs and HFH is not intuitive as these drugs are proven to improve HF outcomes in patients with heart failure and reduced ejection fraction. While there are no published trials investigating the use of these drugs in patients with cardiac amyloidosis, hypotension following administration of these agents has been described. Several mechanisms for this phenomenon have been hypothesized. First, use of these agents may expose an underlying subclinical autonomic neuropathy, and it has been suggested that tolerability of ACEi/ARB in setting of ATTR is dependent on the presence or absence of a concomitant neuropathy. Second, augmentation of cardiac output in response to vasodilation may be limited in the setting of restrictive disease. Finally, it is possible that sicker patients with worse HF are being given these medications and that the association between the medications and HFH is confounded by disease severity. As all subtypes of ATTR were pooled into one group for the purpose of this analysis, it is not possible to draw conclusions about which, if any, of these mechanisms may have driven the increase in HFH in these patients.

Left ventricular hypertrophy is a common finding in amyloid cardiomyopathy and has long been part of the imaging diagnostic criteria. Low voltage on ECG has been associated with cardiac amyloidosis, though it is recognized that this finding is not sensitive. The absence of ECG criteria for left ventricular hypertrophy in the presence of echocardiographic evidence of LVH has been described as a sensitive marker of amyloid cardiomyopathy, while other schemes such as voltage to mass ratio have been used.[30] In our patients, the majority of patients had imaging evidence of LVH combined with the absence of LVH on ECG.

The different forms of amyloid cardiomyopathy represent different diseases with varying epidemiology, pathophysiology, clinical course, and treatment. Due to the relatively high barrier to positive identification of cardiac amyloidosis using a biopsy, it has been recognized that cardiac amyloidosis is frequently underdiagnosed. Historically, AL amyloidosis was considered the most common type, accounting for up to 70 percent of cases, but recent advances in noninvasive imaging have the potential to increase the number of diagnoses of transthyretin amyloidosis.[4] In this investigation, the use of nuclear medicine imaging for detection of cardiac amyloidosis was low. In 2017, the year after the end of this study cohort, Kaiser Permanente Northern California implemented a consistent process for ordering, obtaining and interpreting technetium pyrophosphate images for this diagnosis. The relative ease of a non-invasive diagnosis and the promise of new therapies for ATTR amyloidosis in the horizon will likely lead to an increase in detection of this condition.

In the present study, patients with ATTR were older, more likely to have chronic medical conditions, more likely to have atrial fibrillation, and had increased LV wall thickness in comparison to patients with AL amyloidosis. Patients with ATTR had a more indolent clinical course than patients with AL amyloid, with an average survival of 87 percent at one-year vs 61 percent one-year survival for patients with AL amyloidosis. In general, these finding are consistent with prior studies.[2] The rapid clinical progression observed in AL amyloidosis despite less pronounced LVH is thought to be due to the myotoxicity of the deposited immunoglobulin light chain fibrils.[31] A majority of patients and all confirmed ATTRwt patients, were male. Prior studies demonstrate a male majority in all subtypes, with a much more pronounced male predominance in ATTR amyloidosis.[2,32,33] ATTRwt in particular afflicts older men for reasons that have not been elucidated and prior studies show a male predominance in excess of 95 percent.[32,33] The gender distribution of patients with ATTRwt in our study follows published data about the male predominance of transthyretin amyloidosis. Notably, one study screening patients with heart failure with preserved ejection fraction and an LV thickness greater than 1.2 cm found 13 percent of patients had ATTR amyloid, without gender differences, suggesting that ATTR amyloidosis may be especially underdiagnosed in women.[4] The male predominance of ATTRm is slightly less pronounced. In one study, 82 percent of patients with the V122I mutation were men and, in another study, including patients with European forms of AATTRm, 80 percent of patients with ATTRm were men. In our study, including a cohort of ATTRm patients with the V122I mutation, the male predominance of ATTRm was less pronounced (55 percent male) than in prior studies. As our cohort is community based with no opportunity for referral bias, this gender distribution may be closer to the true gender distribution of ATTRm.

We also report a group of patients who were determined to have amyloidosis but complete tissue characterization was not performed. While this raises the possibility of overdiagnosis, we chose to prioritize sensitivity in patient inclusion and describe this cohort of patients as a separate group for several reasons. First, amyloidosis is a disease of older adults and disease specific therapies in the case of AL amyloidosis may either carry significant morbidity or in the case of ATTR amyloidosis are for the most part experimental. Thus, historically, establishing a diagnosis with full characterization of amyloid subtype may not have been necessary to direct care. Second, as new therapies for amyloid cardiomyopathy emerge, it is important to characterize the patients who may become candidates for such therapy. Up to 13 percent of patients with heart failure and preserved ejection fraction screened in one study were found to have evidence of ATTR amyloidosis.[4] This group of patients was older and had higher BNP and UA levels on presentation than other subtypes. Presumably, this group includes patients who had advanced disease on presentation and thus their disease was not further characterized.

As studies of amyloidosis are frequently constrained to tertiary care referral centers, they may be limited by referral bias and the true characteristics of the disease in the population may not be fully recognized. Our group of ATTRu patients have similar echocardiographic characteristics and similar comorbidities to the ATTR group. As may be expected, these patients were older and had significantly worse survival than the other groups. Their echocardiographic parameters were more like patients with transthyretin amyloidosis while their laboratory markers suggested more advanced heart disease than the other subgroups of amyloidosis.

Strengths

The present study presents a large cohort of patients diagnosed with Amyloid Cardiomyopathy derived from a community based clinical practice representative of a large region of the United States. The diversity of race and ethnicity similarly mirror the population of the region. The multivariable Cox proportional hazard models used to explore associations between patient characteristics and outcomes were able to include and control for several covariates with results suggesting that traditional cardiovascular risk factors such as diabetes and coronary artery disease adversely outcome in cardiac amyloidosis.

Limitations

This study has several limitations. Not all patients had a tissue diagnosis (some diagnosed by CMR), allowing for a small degree of misclassification, though this should bias the analysis results towards the null whereas the results show significant differences between the AL and ATTR groups. For the group of patients with AL amyloidosis, our data does not include some predictors of disease outcome such as the difference between serum level of affected and unaffected serum light chains (FLC-Diff) and the use of stem cell transplantation. The study sample size did not provide enough power to divide the ATTR group into subtypes in the models.

For the investigation of the relationship of cardiac biomarkers with mortality, a significant proportion (108/198 or 55% of patients) did not have a serum UA level checked during the period of the study. This may have affected the results, as UA may have been checked in a biased manner related to subtypes of patients.

The incidence of confirmed amyloidosis increased over time. This likely reflects both increasing awareness and increasing use of the electronic medical record. As the use of the EMR increased over time, for earliest eras, there is inclusion bias of the healthier subgroup of patients who survived long enough to have been captured in the medical record.

We describe medication use at time of diagnosis. A small percentage of patients were being treated with medications that are thought to potentially be harmful in the setting of amyloidosis, such as calcium channel blockers or digoxin. We did not track changes in cardiac medications over time.

Conclusions

This study describes a cohort of patients with amyloid cardiomyopathy derived from a community based, integrated healthcare system and describes demographic, clinical, and laboratory factors associated with mortality and heart failure hospitalization. High BNP levels were strongly associated with mortality and with heart failure hospitalization. The results from this community-based cohort indicate that there may be a strong association between traditional cardiovascular risk factors (coronary artery disease, diabetes) and survival in cardiac amyloidosis.

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