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Heart Failure Due to Age-Related Cardiac Amyloid Disease Associated With Wild-Type Transthyretin: A Prospective, Observational Cohort Study

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Abstract

Background—Heart failure due to wild-type transthyretin amyloidosis (ATTRwt) is an under-appreciated cause of morbidity and mortality in the aging population. The aims of this study were to examine features of disease and characterize outcomes in a large ATTRwt cohort.

Methods and Results—Over 20 years, 121 patients with ATTRwt were enrolled in a prospective observational study. Median age at enrollment was 75.6 years (range, 62.6–87.8); 97% of patients were Caucasian. The median survival, measured from biopsy diagnosis, was 46.69 months (95% CI, 41.95–56.77); 78% of deaths were due to cardiac causes. By Kaplan-Meier analysis, 5-year survival was 35.7% (95% CI, 25–46). Impaired functional capacity (mean VO_2 max of 13.5 mL/kg/min) and atrial fibrillation (67%) were common clinical features. Multivariate predictors of reduced survival were elevated serum brain natriuretic peptide (BNP, 482 ± 337 pg/mL) and uric acid (8.2 ± 2.6 mg/dL), decreased left ventricular ejection fraction (LVEF, 50% median ranging 10–70%), and increased relative wall thickness (RWT, 0.75 ± 0.19).

Conclusions—In this series of patients with biopsy-proven ATTRwt amyloidosis, poor functional capacity and atrial arrhythmias were common clinical features. Elevated BNP and uric acid, decreased LVEF, and increased RWT were associated with limited survival of only 35.7% at 5 years for the group as a whole. These data establish the natural history of ATTRwt, provide statistical basis for the design of future interventional clinical trials, and highlight the need for more sensitive diagnostic tests and disease-specific treatments for this disease.

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Keywords

amyloidosis; heart failure; wild-type transthyretin; prognosis; survival

Amyloidotic cardiomyopathy is due to infiltration of the myocardium with extracellularly-deposited amyloid fibrils. The amyloid consists of fibrils constructed from one of several circulating proteins, including transthyretin (TTR), an abundant plasma protein associated with inherited and acquired forms of cardiac amyloidosis. While it has long been recognized that the majority of >100 inherited TTR mutations¹ give rise to familial amyloidotic cardiomyopathy (FAC)², it has only been within the last 20 years that the amyloidogenic nature of wild-type TTR has become apparent³. In contrast to FAC, which stems from an aggregation-prone and amyloid-forming mutant TTR, wild-type TTR amyloidosis (ATTRwt) features destabilization and fibril formation of a 'normal' protein. Characterized by signs and symptoms of congestive heart failure in older men, wild-type TTR amyloid cardiomyopathy has been referred to as age-related, senile cardiac, or senile systemic amyloidosis, and most recently, ATTRwt amyloidosis to reflect the biochemical nature of amyloid deposits⁴.

ATTRwt amyloidosis is a disease of unknown etiology and prevalence; accurate population data are limited and prospective observations are few. It is generally believed that ATTRwt cardiac amyloid deposits cause cardiac dysfunction⁵ and lead to restrictive cardiomyopathy, arrhythmias, and conduction defects in patients over age 60⁶. Estimates of prevalence are based on data from several post-mortem studies indicating that at least 25% of individuals over age 80 have histologic evidence of amyloid deposits in the heart^{7,8}. It seems likely that ATTRwt cardiomyopathy is under-diagnosed⁹ as the clinical features mimic other cardiac pathologies that frequently co-exist in advanced age such as hypertensive or hypertrophic heart diseases.

Importantly, establishing a diagnosis can be challenging as there are no definitive biomarkers of disease and the clinical characteristics frequently overlap with other forms of amyloid disease featuring cardiac involvement¹⁰. The absence of disease-specific measures of progression and risk predictors for ATTRwt amyloidosis contributes to the limited data on natural history and survival. Moreover, treatment options are few and disease management is focused on control of heart failure symptoms. The recent emergence of novel therapeutics, such as tafamidis¹¹ and diflunisal¹² that act to prevent TTR amyloid formation by stabilizing the native protein, and other agents that inhibit TTR expression offer promise^{13,14}, but information detailing the natural history of ATTRwt amyloidosis is critical to understanding how effective these and other treatments may be.

The current study was undertaken to accurately characterize the clinical measures of disease in a large cohort of patients with biopsy-proven ATTRwt amyloidosis and to identify predictors of survival. The results document the natural history of ATTRwt amyloidosis in a large series, offering information that will aid early diagnosis, provide statistical power for future clinical trials, and accelerate development of effect drug treatment.

Methods

Study Population

Informed consent for data and sample collection was obtained from all patients under a repository protocol approved by the Boston University Medical Campus Institutional Review Board. A series of 156 patients evaluated at the Boston University Amyloidosis Center between June 1994 and January 2014 were suspected of having ATTRwt amyloidosis based upon age and absence of a plasma cell dyscrasia or mutant TTR allele, the latter determined by genomic DNA sequencing or mass spectrometry. In this same time period, 2885 patients with other types of systemic amyloidosis were evaluated at our tertiary referral center. In the group of 156, 153 were confirmed to have amyloid by Congo red staining of a tissue biopsy. Of these, TTR was identified as the deposited amyloid protein by immunohistochemistry, immunogold electron microscopy, or mass spectrometry in 121 cases (Figure 1). Available clinical data included medical history, physical examination, and laboratory studies of organ function. Standard of care included annual evaluation; information on death was obtained from medical records or publicly available databases.

Cardiac function was assessed by echocardiography and cardiopulmonary exercise testing. Electrocardiogram (ECG), brain natriuretic peptide (BNP), and troponin I (Tn-I) levels were also determined. Cardiac involvement was defined by interventricular septum thickness (IVST) > 12 mm in the absence of other causes of cardiomyopathy and BNP > 100 pg/mL. Severity of heart failure symptoms was assessed using the New York Heart Association (NYHA) functional classification system. Renal involvement was diagnosed when 24-hour urinary protein excretion was > 1.0 g or renal insufficiency was present; renal insufficiency was defined as the progressive decline of glomerular filtration rate not attributed to cardiac dysfunction, diabetes, or hypertension. Neurologic involvement was determined by the presence of peripheral neuropathy on neurologic exam or autonomic neuropathy assessed by orthostasis. Orthostasis was defined as a drop in systolic blood pressure of ≥ 20 mm Hg after a positional change from supine to standing in patients without significant dehydration. Gastrointestinal tract involvement was demonstrated by Congo red positive biopsy. Patients were followed annually; cardiac function and laboratory data were reassessed at follow-up visits.

Serologic Testing

Blood samples were obtained at initial and follow-up visits to our clinic and stored at -80 °C. Serum concentrations of total protein, albumin, creatinine, uric acid, calcium, BNP, Tn-I, and C-reactive protein (CRP) were measured as part of routine laboratory testing. Corrected calcium values were calculated using published clinical practice guidelines¹⁵.

Cardiopulmonary Exercise Testing

Cardiopulmonary exercise testing was performed on a standard exercise treadmill using the Medgraphics CPX Ultima. Expired gas analysis was performed with the highest values obtained during the final 30 seconds used as peak scores. Peak oxygen consumption (VO₂ max), ventilatory equivalent for carbon dioxide (VE/VCO₂ slope), tidal volume (VT),

exercise duration, breathing reserve (VE/MVV), and respiratory exchange ratio (RER) were calculated using standard methods¹⁶.

Echocardiography

Two-dimensional, color flow, and spectral Doppler echocardiographic imaging was performed from standard parasternal, apical, and subcostal views using Philips Sonos, Philips iE 33, or General Electric Vivid 7 systems. Image loops and still frames were recorded onto videotape (pre-2005) or stored digitally (post-2005) and analyzed using standard video-playback (pre-2005), Philips Xcelera or GE EchoPAC. Echocardiograms were interpreted in a blinded manner to patient diagnosis. Left ventricular (LV), right ventricular (RV), and left atrial (LA) volumes, as well as measurements of systolic and diastolic chamber dimensions, and wall thickness (WT) were obtained from 2-D imaging according to the recommendations of the American Society of Echocardiography¹⁷. Left ventricular ejection fraction was determined by two independent observations including both the clinical echocardiographic report (qualitative assessment) and, to demonstrate reproducibility, a secondary analysis using the modified Simpson's biplane technique (n=110) from the two- and four-chamber orientations. Stages of diastolic dysfunction were defined according to recommendations of the European and American Societies for Echocardiography¹⁸. LVWT was derived from an average of the interventricular septum and posterior wall thickness. LV mass and mid-wall fractional shortening, a cardiac function variable that accounts for wall thickness and chamber volume, were determined as previously described^{19–21}. Relative wall thickness (RWT) was calculated as: $(IVST + PWT) / LVEDD$. Transmitral Doppler LV filling recordings were performed from the apical 4-chamber view and analyzed for diastolic filling indexes, including peak E- and A-wave velocities and their ratio, and E-wave deceleration time. Similarly, tissue Doppler imaging was used to determine the myocardial velocity of the mitral annulus and derivation of e-prime (E'). A lower early diastolic mitral annular motion (E') velocity (< 10 cm/s) by tissue Doppler imaging suggested impaired diastolic function. A higher E/E' index indicated greater LV end-diastolic pressure. Longitudinal systolic strain, measured by a speckle tracking technique using GE EchoPAC, was determined from 3 apical views (apical 4-chamber, apical long-axis, and apical 2-chamber) to afford analysis of the entire LV segmented into the standard American Heart Association 16 segment model. Strain results were expressed per segment, per level (base, mid, apical), and global average longitudinal strain. Ratios of average strain in all apical to all basal segments, as well as apical to basal + mid segments (relative apical strain), were determined.

Statistical Analysis

The cutoff date for data analyses was March 2014. Data characteristics were summarized by median and range (min, max) for non-normal distributed continuous variables, mean and standard deviation (SD) for normally distributed continuous variables, and frequency and percentage for categorical variables. Some measures at baseline were summarized over unequal sample sizes due to the limited number in the cohort. We report the characteristics regardless of sample sizes to provide clinical information for future studies. The Cox proportional hazard regression model was used to analyze the data over a 5-year follow-up period for variables with at least 80 observations. Univariate analysis was initially

performed to identify factors associated with survival from demographic, clinical, laboratory, electrocardiographic, and Doppler echocardiographic variables. Multivariate analysis was used to further quantify the survival risks adjusting for age at biopsy. Overall survival was measured from biopsy diagnosis to death. A survival curve was estimated using the Kaplan-Meier method. Receiver operator characteristic (ROC) curves were calculated and area under the curve (AUC) was used to assess the ability of each predictor to identify patients who died within 24 months of diagnosis. All analyses were conducted in SAS 9.3 (SAS Institute, Inc, Cary, NC); a p-value < 0.05 was used to determine statistical significance.

Results

ATTRwt Cohort Characteristics

Demographic and baseline clinical characteristics of the ATTRwt cohort are presented in Table 1. In this series, 98% of patients were male and 97% were Caucasian; 3 men and 1 woman self-identified as Black. By comparison, in 2885 patients evaluated at our tertiary referral center during the same time period with other types of systemic amyloidosis, 60% were male and 89% were Caucasian; differences between the two populations were statistically significant ($p < 0.0001$ for gender and $p = 0.0003$ for race). Median ages at onset of symptoms and diagnosis of ATTRwt amyloidosis were 73.5 (range, 58.8–86.6) and 75.1 years (range, 59.0–87.5), respectively. The median time from onset of symptoms to diagnosis was 0.8 years (range, 0.0–9.5). Cardiac biopsies, performed on 82% of the cohort, were all Congo red positive. Other biopsies (n), some from the same patient, that showed histologic evidence of amyloid included bone marrow (11), gastrointestinal (8), bladder (4), lung (3), and flexor tenosynovium (4). Fat pad aspirates were positive for amyloid in less than one-third (28%) of the group. A monoclonal gammopathy was detected in 10% of patients by the finding of clonal plasma cells in the bone marrow and/or amyloidogenic light chain in the serum or urine; however, amyloid deposits were uniformly negative for immunoglobulin light chains. While there were 4 patients of African descent in our ATTRwt cohort, TTR genotyping was negative for V122I or any other pathologic TTR mutation. Interestingly, the non-pathologic TTR-G6S was found in 7%, slightly lower than the reported frequency²².

Almost all (98%) patients had evidence of cardiac amyloid disease as demonstrated by biopsy, abnormal echocardiography, electrocardiography, and/or cardiac biomarker measurements. Autonomic neurologic involvement manifest as orthostasis occurred in 12% of the cohort. Two patients had gastrointestinal tract involvement with no clinical signs of cardiac amyloidosis. Common clinical features included dyspnea on exertion (86%) and peripheral edema (64%). Carpal tunnel syndrome was identified in 46% of patients. Malignancies were present in one-third (34%) of the group with prostate cancer the most common type (n = 25). Other morbidities included coronary artery disease (33/106), gout (17/106), and diabetes mellitus type II (16/106). A majority (90%) of patients were being treated with diuretics at time of baseline evaluation.

Sixty-eight of 121 (56%) patients had died by the study end date (March 2014). The median age at death was 77.9 years (range, 64.0–89.6); 55 (45%) deaths occurred within 5 years of

ATTRwt diagnosis. Of 46 patients whose cause of death was known, 31 (67%) expired from heart failure, 5 (11%) had a sudden death, and 10 (22%) died of malnutrition, pneumonia, or renal failure.

Clinical and Laboratory Features of ATTRwt Cardiomyopathy

Baseline serologic testing results (Table 2) were within normal ranges for total protein, albumin, corrected calcium, and sedimentation rate. High sensitivity CRP concentrations, available on 36 patients (data not shown), were within normal limits. Mean levels of serum creatinine and uric acid were elevated at 1.40 ± 0.59 and 8.2 ± 2.6 mg/dL, respectively. The presence of gout did not appear to be a confounding variable as mean serum uric acid level in the 17 patients with co-morbidity was lower (7.6 ± 2.8 mg/dL). Serum BNP and Tn-I were substantially increased. The mean value of BNP was 482 ± 337 pg/mL ($n = 100$); all but one patient (99%) had concentrations > 100 pg/mL. Troponin I levels ranged from 0.020–1.198 ng/mL with a median of 0.126 ng/mL ($n = 80$) and the majority (66%) had concentrations > 0.100 ng/mL.

In this series, 85% had heart failure symptoms with NYHA Functional Class $> I$ (Table 2). Abnormal electrocardiography occurred in 98% of patients. Findings included low voltage (an average of < 5 mV in the limb leads) in 33% and atrial fibrillation in 67%. Pacemakers and/or defibrillators had been implanted in 40% of the group. All patients had abnormal echocardiograms with identifiable structural and/or functional abnormalities. Diastolic function parameters were abnormal in all tested patients with 34% classified as grade II and 66% as grade III. The median measurements of LV end-diastolic and end-systolic diameters were within normal limits; mean values ($\pm$ SD) were $44 (\pm 6)$ and $34 (\pm 6)$, respectively. For LVEF, values ranged from 10 to 70% in 120 patients. The median IVST in 111 patients was 16 mm, ranging from 9 to 25 mm. LV mass indexed with body surface area (BSA) ranged from 58–308 g/m² in men ($n = 96$) and 116–173 g/m² in women ($n = 3$).

Cardiopulmonary testing was performed (Table 2) on 34 patients; 10 patients were in severe heart failure and unable to exercise. Mean maximal oxygen consumption, VO_2 max, was 13.5 ± 4.9 mL/kg/min; this was substantially below the normal value of 25 mL/kg/min reported for 75 year old men²³ and symptomatic of severe circulatory limitation. Duration of exercise averaged approximately 7 minutes. VE/VCO_2 slope, an index of ventilatory efficiency and predictor of mortality in heart failure, exceeded the upper normal limit by over 35%.

Baseline echocardiographic results (Table 3) showed increased LV wall thickness and LV mass, as well as significant LA dilation and increased RV free wall thickness. RWT ($n = 110$) was 0.75 ± 0.19 , indicative of significant concentric remodeling characterized by a small LV chamber and thickened walls. Longitudinal systolic strain was reduced, as compared to established normal values, in all myocardial segments with an increase in the apical:basal strain ratio. Estimated pulmonary artery systolic pressures were increased (41.5 ± 10.5 mmHg). For longitudinal strain, measurements more positive than -14% were considered abnormal. Doppler E/A and E/E' suggested advanced diastolic dysfunction with increased LA pressures. The right ventricle had a normal diameter (38.7 ± 5.0 mm),

increased wall thickness (9.9 ± 2.0 mm), and borderline systolic function with tricuspid annular plane systolic excursion (TAPSE) of 15.9 ± 3.3 mm (data not shown).

Survival

The median survival, measured from time of biopsy diagnosis, was 46.69 months (95% CI, 41.95–56.77). Kaplan-Meier analysis of survival predicted 64% would die within 5 years of diagnosis (Figure 2). Heart failure was the principal reported cause of death. Two patients with gastrointestinal amyloid and no cardiac involvement survived 6.8 and 3.6 years from the time of diagnosis, with causes of death uncertain and due to malnutrition, respectively.

Mortality Indicators

Univariate and multivariate analyses for correlations to survival were performed on clinical, laboratory, echocardiographic, and metabolic testing results where values were available on at least 80 patients (Table 4). A total of 14 parameters were significantly associated with shorter survival in the univariate analysis. By multivariate analysis on variables with 95 observations, 4 significant prognostic determinants were identified. Increased levels of serum uric acid (HR, 1.28; 95% CI, 1.10–1.51; $p = 0.003$), BNP (HR, 1.002; 95% CI, 1.0015–1.0030; $p < 0.0001$), and RWT (HR, 34.0; 95% CI, 6.41–180.51; $p < 0.0001$) were related to shorter survival, while a decrease in LVEF (HR, 0.94; 95% CI, 0.93–0.97; $p = 0.0001$) was associated with a worsening prognosis. In the secondary analysis of global systolic function using the Simpson's biplane technique, biplane LVEF was similarly correlated to survival (HR, 0.96; 95% CI, 0.94–0.98; $p = 0.0007$) demonstrating reproducibility of the LVEF assessment.

The value of single or multiple variables in predicting 2-year survival was assessed by ROC analysis (Figure 3). Using a nonparametric approach, AUC values were compared to each other individually and to the combination value (BNP + RWT + uric acid, UA + LVEF). Individually, the AUC values indicated that sensitivity was comparable for RWT (AUC, 0.67), uric acid (AUC, 0.67) and LVEF (AUC, 0.70), and least for BNP (AUC, 0.57). However, an inclusive model which utilized all 4 factors gave the greatest power, AUC of 0.78 (95% CI, 0.68–0.88).

Follow-up Data

Laboratory and echocardiographic testing results at 1-year and 2-year evaluations were available on 34 and 24 patients, respectively. The only parameter that changed significantly over the follow-up interval was creatinine, which increased from 1.27 mg/dL at baseline to 1.63 mg/dL ($p = 0.046$) at 2-year evaluation. Increasing BNP and decreasing LVEF values were noted in patients over time, but these changes did not reach significance likely due to the limited group sizes. Worsening functional status and increasing impairment were indicated by an increasing number of patients who were unable to perform cardiopulmonary exercise testing. In patients who underwent testing, mean peak VO_2 decreased from 16.0 to 15.7 mL/kg/min at baseline and 1-year follow-up ($n = 7$), respectively, and from 17.3 to 16.7 mL/kg/min at initial and 2-year evaluations ($n=8$).

Discussion

This report provides detailed clinical and laboratory data on 121 patients with histological and biochemical confirmation of ATTRwt amyloidosis. Categorical and continuous data on more than 75 variables were examined to identify potential diagnostic markers and to ascertain risk factors associated with survival. Major findings in this ATTRwt cohort study included: 1) confirmation that patients are overwhelmingly male and Caucasian compared to a tertiary referral population of patients with amyloidosis, where most patients have AL amyloidosis and 60% are men, 89% Caucasian; 2) identification of cardiac disease as the predominating clinical presentation, as all patients had elevated cardiac biomarkers and/or identifiable abnormalities on echocardiography including markedly increased concentric wall thickening, severe diastolic dysfunction with normal global systolic function, reduced longitudinal systolic strain, and markedly reduced functional capacity; 3) the association of serum uric acid, BNP, LV ejection fraction, and relative wall thickness with survival in multivariate analysis; and 4) the reduced life expectancy compared to other series^{6,24} and to control populations of elderly males derived from the US Social Security Actuarial Life Table²⁵.

Men with ATTRwt amyloidosis represented 8.0% of all males, 11.3% of males age 60 or older, and 14.7% of males age 60 or older with cardiac amyloidosis seen at our center during the study period. Notably, these data demonstrate a sizeable percentage of ATTRwt in our referral population and suggest that this cardiac amyloid disease may be an underdiagnosed cause of heart failure and death in the general aged population. In fact, patients with ATTRwt amyloidosis most frequently presented with heart failure with preserved ejection fraction (HFpEF) and grade III diastolic dysfunction, features shown to increase in prevalence with advancing age in the general population²⁶. Clinical characteristics did not distinguish ATTRwt from other types of amyloidosis with cardiac involvement. Presentation commonly featured dyspnea on exertion (86%), peripheral edema (64%), and atrial fibrillation (67%) with onset of symptoms ranging from 59 to 87.5 years of age. It is interestingly to note that the prevalence of atrial fibrillation in ATTRwt was higher than the age-adjusted frequency reported in the general population²⁷; this finding contrasts with other types of amyloidosis where occurrence of atrial fibrillation is nearly equal²⁸ and underscores the significance of heart failure in this population. Thus, it appears that factors other than age and cardiomyopathy contribute to the increased prevalence of atrial fibrillation in our cohort; the biochemical nature of the amyloid fibril, location of the deposits, and interactions with the extracellular matrix may be key elements in the process.

Serologic measures of cardiac disease, used for prognostication in AL amyloidosis²⁹, were assessed and correlated with severity of disease at presentation or survival (Table 2). Median (range) concentrations for BNP and Tn-I were 411 (52–1756) pg/mL and 0.126 (0.020–1.198) ng/mL, respectively. The majority (66%) of our ATTRwt series had elevated levels of both BNP and Tn-I; 33% had one marker above normal and only 1 patient had normal levels of both BNP and Tn-I. Elevated levels of serum uric acid and BNP correlated with shorter survival (Table 4). While an elevated level may be related to the use of diuretics, the significance of uric acid as a prognostic indicator in ATTRwt is supported by several recent studies suggesting that the metabolite is an indicator of congestive heart failure in cardiac

amyloidosis and not simply a sign of renal dysfunction^{30,31}. Elevated serum uric acid is also associated with hypertension; however, we found that mean values were above normal in both patients with and without a history of hypertension and there was no significant difference between the groups (8.6 vs. 8.0 mg/dL, $p = 0.11$). Interestingly, BNP, but not Tn-I, was found to correlate significantly with survival; however, in ROC analyses of the 4 significant prognostic determinants, BNP had the lowest sensitivity (AUC, 0.57) in predicting 2-year survival when assessed individually.

Identifiable abnormalities on echocardiography included markedly increased concentric wall thickening (as determined by relative wall thickness), severe diastolic dysfunction with preserved global systolic function, and reduced longitudinal systolic strain. Left ventricular (LV) hypertrophy is a cardinal manifestation of preclinical cardiovascular disease that strongly predicts cardiovascular events in hypertensive patients, as well as in general population^{32,33}. Concentric LV geometry, defined by alterations in LV RWT and LV mass, has important pathophysiologic and prognostic implications^{34,35}. In patients 70 years of age or older, concentric remodeling is associated with adverse prognosis and higher mortality when compared to eccentric remodeling or normal geometry³⁶. It has been reported that the reproducibility of relative wall thickness values was higher than that of LV mass³⁷. In cardiac amyloidosis, the cause of “hypertrophy” in the setting of infiltrative heart disease is extensive extracellular matrix expansion caused by amyloid deposition and a likely toxic effect on cardiomyocytes and their architecture as has been demonstrated in AL amyloidosis³⁸. While the cytotoxicity of amyloid deposits in ATTRwt cardiac amyloidosis is yet to be demonstrated, the severe extent of concentric geometric remodeling may cause or be associated with diastolic dysfunction, as well as systolic impairment. This translates to a higher risk of cardiovascular events or death and thus, a worse prognosis, in patients with cardiac amyloidosis and concentric remodeling (RWT > 0.42). Indeed, RWT, mid-wall fractional shortening, ejection fraction, and TDI E' (indices of LV geometry, systolic and diastolic function, respectively) were all univariate predictors of survival (Table 4).

Several previous studies reporting clinical and echocardiographic features in ATTRwt amyloidosis from our center and others have been limited to small series descriptions^{6,28}. Recently, a report described 99 patients in the United Kingdom and concluded that troponin T, the presence of a pacemaker, and NYHA class IV symptoms were indicators of a worse outcome in ATTRwt²⁴. While the cohorts studied by Pinney *et al.*²⁴ and presented in this report are similar, some provocative differences will require further analysis and follow-up to determine their significance. In our study, we found a greater predominance of male patients (98 vs. 89%); a higher incidence of dyspnea on exertion (86 vs. 54%), atrial fibrillation (67 vs. 10%), and peripheral edema (64 vs. 8%); and more frequent NYHA class > 1 (85 vs. 57%), pacemaker usage (40 vs. 13%), and troponin elevation (66 vs. 52%). In addition, median survival measured from onset of symptoms to death was shorter in our cohort (4.6 vs. 6.1 years). These variations may reflect advanced disease features observed at initial evaluation in our series vs. early stage ATTRwt characteristics at presentation as described by Pinney *et al.*²⁴. Alternatively, the dissimilarities may represent a variety of statistical biases or true differences in the study populations at the two sites.

In summary, this report details the findings from a prospective, observational study of 121 patients with histological, biochemical, and clinical proof of ATTRwt amyloidosis. Patients with ATTRwt were predominantly men who presented with dominant cardiac involvement as evidenced by an abnormal echocardiogram, ECG, and/or cardiac biomarker measurements. Heart failure and atrial fibrillation were common, as was markedly impaired functional capacity. The median age at diagnosis was 75.1 years. Median survival measured from diagnosis was < 4 years and 5-year survival was 35.7% by Kaplan-Meier analysis. Multivariate analysis identified uric acid, BNP, LVEF, and RWT as predictors of shorter survival. While BNP and Tn-I are prognosis predictors in both AL and ATTRwt, functional indices (LVEF, strain) have a different trend and significance. Only mid-wall fractional shortening showed a similar diagnostic/prognostic value in AL and ATTRwt amyloidosis. Importantly, this cohort represented > 10% of all male patients referred over age 60 and approximately 15% of male patients over age 60 that had any cardiac amyloid involvement. In this study of a large ATTRwt cohort presenting echocardiographic, functional capacity and laboratory data, we conclude that reduced survival and exercise capacity (VO₂) are new and important findings, and note that patients with ATTRwt amyloidosis can manifest much more advanced disease than previously appreciated.

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Clinical Perspectives

Wild-type transthyretin amyloidosis (ATTRwt, previously known as senile cardiac amyloidosis) is an under-recognized cause of heart failure in the elderly and is likely more common than currently appreciated. While recent studies have reproducibly suggested that up to 25% of hearts over the age of 80-85 years have demonstrable transthyretin (TTR) amyloid deposits, only 15-20% of patients with heart failure and preserved ejection fraction owing to ATTRwt amyloidosis are recognized antemortem. Previously untreatable, medical therapies for ATTRwt amyloidosis are in advanced stages of clinical testing and appear imminently available. In an effort to better characterize the functional impairment and survival limitation of this population, we present rigorously phenotyped data from the largest cohort of ATTRwt patients yet reported (n=121) referred to our institution over a 20-year observational period. The cohort was elderly (median age at enrollment of 75.6 years), 97% Caucasian, and 98% male. From biopsy diagnosis, median survival was 46.69 months and 5-year survival was predicted to be only 35.7% – far worse than previously appreciated. Functional capacity as determined by cardiopulmonary exercise testing was markedly impaired with a VO_2 max of 13.5 mL/kg/min. Predictors of mortality included increased serum B-type natriuretic peptide, relative wall thickness, and uric acid as well as decreased left ventricular ejection fraction. These data underscore the marked impairment conferred by ATTRwt amyloidosis and will inform interpretation of disease course modification by future studies of novel therapeutics.

Figure 1.
ATTRwt cohort testing schema.

Figure 2.

Kaplan-Meier analysis of the probability of survival over time for patients with ATTRwt. The median survival, measured from time of biopsy diagnosis, was 46.69 months (95% CI, 41.95–56.77) and 5-year survival was 35.7% (95% CI, 25–46).

Figure 3. Receiver-operating characteristic (ROC) curves assessing the value of BNP, RWT, uric acid (UA), and LVEF as predictors of 2-year survival in patients with ATTRwt.

Table 1

Demographics and baseline clinical features of ATTRwt cohort.

Characteristic	N	(%)	Median (Min, Max)
Gender, M	118/121	(98)	
Race, Caucasian	117/121	(97)	
Age, years	121/121		
- clinical presentation			73.5 (58.8 – 86.6)
- histopathological diagnosis			75.1 (59.0 – 87.5)
- baseline evaluation			75.6 (62.6 – 87.8)
Presentation to diagnosis, years	121/121		0.8 (0.0 – 9.5)
Body mass index	102/121		27.5 (16.7 – 39.2)
Amyloid deposits in fat aspirate	32/115	(28)	
MGUS*	12/120	(10)	
TTR-G6S	9/121	(7)	
Cardiac involvement at presentation	119/121	(98)	
Neurologic involvement			
- autonomic	14/119	(12)	
- peripheral	3/120	(3)	
Renal involvement	0/119	(0)	
Gastrointestinal involvement	2/121	(2)	
Dyspnea on exertion	103/120	(86)	
Peripheral edema	78/121	(64)	
History of hypertension	30/119	(25)	
Elevated jugular venous pressure	38/121	(31)	
Carpal tunnel syndrome	56/121	(46)	
Comorbidities			
- malignancies	40/118	(34)	
- coronary artery disease	33/106	(31)	
- gout	17/106	(16)	
- diabetes mellitus, type II	16/106	(15)	
Medications – diuretics	94/105	(90)	

Characteristic	N	(%)	Median (Min, Max)
Mortality	68/121		
- age at death, years			77.9 (64.0 – 89.6)
- presentation to death, years			4.6 (0.3 – 12.7)
- diagnosis to death, years			3.1 (0.1 – 8.9)

* MGUS, monoclonal gammopathy of undetermined significance

Table 2

Baseline laboratory data, cardiac findings, and functional status in patients with ATTRwt.

Serological Marker	N	Mean $\pm$ SD	Normal*
Total protein, g/dL	118	7.1 $\pm$ 0.6	6.0 – 8.2
Albumin, g/dL	120	4.1 $\pm$ 0.4	3.5 – 4.8
Creatinine, mg/dL	121	1.40 $\pm$ 0.59	0.80 – 1.30
Uric acid, mg/dL	119	8.2 $\pm$ 2.6	3.4 – 7.0
Corrected calcium, mg/dL	116	9.5 $\pm$ 2.1	8.5 – 10.5
BNP, pg/mL	100	482 $\pm$ 337	0 – 72

Median (Range)			
Sedimentation rate, mm/h	118	14 (1 – 88)	0 – 15 (M)
BNP, pg/mL	100	411 (52 – 1756)	0 – 72
Tn-I, ng/mL	80	0.126 (0.020 – 1.198)	0 – 0.049

Cardiac Findings	N	(%)
NYHA functional class > I	102/120	(85)
ECG	119/121	(98)
- Low voltage	29/89	(33)
- Atrial fibrillation	70/104	(67)
Pacemakers, defibrillators	36/89	(40)
Diastolic dysfunction degree		
- I	0/76	(0)
- II	26/76	(34)
- III	50/76	(66)

Echocardiography	N	Median (Range)	Normal*
LV end-diastolic diameter, mm	120	45 (28 – 57)	< 57
LV end-systolic diameter, mm	119	34 (21 – 50)	21 – 40
LV ejection fraction (LVEF), %	120	50 (10 – 70)	50
Interventricular septum thickness (IVST), mm	111	16 (9 – 25)	< 11
LV mass/BSA (LVMI), g/m ²	96	150 (58 – 308)	<131 (M)
	3	144 (116 – 173)	< 100 (F)

Cardiopulmonary	N	Mean $\pm$ SD	Normal*
VO ₂ max, mL/kg/min	34	13.5 $\pm$ 4.9	25 – 28 (M)
Exercise duration, min	34	6.8 $\pm$ 3.1	
Peak respiratory exchange ratio (RER)	31	1.15 $\pm$ 0.11	

Cardiopulmonary	N	Mean $\pm$ SD	Normal*
VE/VCO ₂	33	41 $\pm$ 11	< 30
Ventilatory reserve, VE/MVV, %	33	44 $\pm$ 14	> 20

* Age-adjusted established normal values

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Table 3

Baseline echocardiography measures of morphology, diastolic function, and longitudinal strain.

Parameter	N	Mean $\pm$ SD	Normal*
LVEF, %	110	48.1 $\pm$ 10.5	50
IVST, mm	110	16.3 $\pm$ 3.0	< 11
Posterior wall thickness, mm	110	16.0 $\pm$ 2.8	
LVMI, g/m ²	80	156.5 $\pm$ 42.0	< 131 (M)
LA indexed volume	80	45.4 $\pm$ 19.3	
RV free wall thickness, mm	72	9.9 $\pm$ 2.0	
Relative wall thickness, RWT	110	0.75 $\pm$ 0.19	0.22 – 0.42
Pulmonary artery systolic pressure, mmHg	92	41.5 $\pm$ 10.5	
Endocardial fractional shortening, %	96	24.1 $\pm$ 7.9	
Mid-wall fractional shortening	110	8.0 $\pm$ 3.2	
Longitudinal strain 2-chamber, %	62	–9.8 $\pm$ 3.5	
Longitudinal strain 4-chamber, %	62	–9.0 $\pm$ 3.8	
Longitudinal strain apical long, %	61	–9.1 $\pm$ 3.0	
Global longitudinal strain average, %	61	–9.3 $\pm$ 3.0	< –15
Longitudinal strain basal segments, %	62	–5.4 $\pm$ 2.9	< –13
Longitudinal strain medial segments, %	62	–8.5 $\pm$ 2.8	
Longitudinal strain apical segments, %	62	–13.6 $\pm$ 4.3	
Apical/Basal strain ratio	62	–2.7 $\pm$ 2.6	< 1.7
Relative apical longitudinal strain	62	1.1 $\pm$ 0.4	< 1
E/A	73	2.7 $\pm$ 1.3	
E/E' septal	89	24.3 $\pm$ 12.3	
E/E' lateral	86	16.9 $\pm$ 7.0	
E/E' (lateral + septal average)	86	20.5 $\pm$ 8.6	< 8

* Age-adjusted established normal values

Table 4

Univariate and multivariate analyses of factors associated with shorter survival from time of biopsy diagnosis.

Variable	N	Univariate*			Multivariate**		
		Hazard Ratio	95% CI	P-value	Hazard Ratio	95% CI	P-value
Total protein	118	1.003	0.34 – 0.97	0.04			
Albumin	120	0.23	0.10 – 0.55	0.001			
Serum creatinine	121	5.52	3.28 – 9.31	< 0.0001			
Serum uric acid	119	1.28	1.16 – 1.43	< 0.0001	1.28	1.10 – 1.51	0.003
BNP	100	1.002	1.0015 – 1.003	< 0.0001	1.002	1.0015 – 1.0030	< 0.0001
Sedimentation rate	118	1.02	1.005 – 1.04	0.048			
LVEF	120	0.96	0.95 – 0.98	0.0002	0.94	0.93 – 0.97	0.0001
IVST	121	1.11	1.03 – 1.21	0.01			
Posterior wall thickness	110	1.13	1.03 – 1.25	0.02			
Relative wall thickness, RWT	110	5.85	1.61 – 21.43	0.008	34.0	6.41 – 180.51	< 0.0001
Endocardial fractional shortening	96	0.95	0.92 – 0.99	0.01			
Mid-wall fractional shortening	110	0.85	0.76 – 0.95	0.005			
E/E' septal	89	0.75	0.58 – 0.98	0.03			
E/E' lateral	86	0.77	0.63 – 0.95	0.02			

* Univariate analysis was used to identify individual factors that were significantly associated with death (type I error of 0.05).

** Multivariate analysis was performed on data from 95 patients to examine the simultaneous impact of significant risk factors from the univariate analysis. Only those factors significantly associated with death are presented.