

Sex Differences in the Phenotype of Transthyretin Cardiac Amyloidosis Due to Val122Ile Mutation: Insights from Noninvasive Pressure–Volume Analysis

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ABSTRACT

Background: Transthyretin cardiac amyloidosis (ATTR-CA) is an under-recognized cause of heart failure with preserved ejection fraction. In the United States, the valine-to-isoleucine substitution (Val122Ile) is the most common inherited variant. Data on sex differences in presentation and outcomes of Val122Ile associated ATTR-CA are lacking.

Methods and Results: In a retrospective, single-center study of 73 patients diagnosed with Val122Ile associated ATTR-CA between 2001 and 2018, sex differences in clinical and echocardiographic data at the time of diagnosis were evaluated. Pressure–volume analysis using noninvasive single beat techniques was used to compare chamber performance. Compared with men ($n = 46$), women ($n = 27$) were significantly older at diagnosis, 76 years vs 69 years; $P < .001$. The end-systolic pressure–volume relationship, 5.1 mm Hg \cdot m²/mL vs 4.3 mm Hg \cdot m²/mL; $P = .27$, arterial elastance, 5.5 mm Hg \cdot m²/mL vs 5.7 mm Hg \cdot m²/mL; $P = .62$, and left ventricular capacitance were similar between sexes as was pressure–volume areas indexed to a left ventricular end-diastolic pressure of 30 mm Hg, a measure of overall pump function. The 3-year mortality rates were also similar, 34% vs 43%; $P = .64$.

Conclusions: Despite being significantly older at time of diagnosis with Val122Ile associated ATTR-CA, women have similar overall cardiac chamber function and rates of mortality to men, suggesting a less aggressive disease trajectory. These findings should be confirmed with longitudinal studies. (*J Cardiac Fail* 2021;27:67–74)

Key Words: Cardiac amyloidosis, sex differences, pressure–volume loops, echocardiography.

Across many cardiovascular conditions, including ischemic heart disease, heart failure, valvular disease, and hypertension, differences in presentation, progression, and outcomes between the sexes are well-recognized.^{1,2} These differences are driven by physiologic differences as well as various social, economic, and cultural factors.³ Within the heart failure population specifically, the incidence of disease is relatively similar between sexes. However, disease epidemiology is markedly different: women are more likely to develop heart failure with preserved ejection fraction as

compared with men, who have higher rates of heart failure with reduced ejection fraction.^{4–6} Further, in response to high afterload conditions such as aortic stenosis, women have less pathophysiologic hypertrophy and fibrosis, whereas men demonstrate an increased burden of concentric and eccentric hypertrophy.⁷ Understanding the influence of sex on cardiovascular disease is important because it can lead to insights to improve outcomes for both women and men.

Transthyretin cardiac amyloidosis (ATTR-CA) is increasingly recognized as the most common cause of restrictive cardiomyopathy in older adults and is characterized by the deposition of misfolded transthyretin (TTR) protein in the myocardium.^{8,9} Destabilization of the protein may either be due to age-related changes in wild-type disease or inherited mutations in the TTR gene. In the United States, the most common mutation observed is the valine-to-isoleucine substitution (Val122Ile).^{8,9} This mutation is primarily seen in individuals of Afro-Caribbean descent, and in the United States is estimated to be present in 3.4% of African Americans.^{10,11} ATTRwt cardiac amyloidosis is almost exclusively a disease of older men. ATTR-CA due to the Val122Ile variant, although inherited in an autosomal dominant fashion, also

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appears to disproportionately affect men, with women comprising 20%–30% of population-based studies.^{11,12} It is unclear to what extent these differences in prevalence reflect biases in diagnosis as opposed to sex-specific differences in disease expression or penetrance.

Although sex differences in the prevalence of Val122Ile associated ATTR-CA are well-established, little is known about whether the phenotype of the cardiomyopathy at presentation or long-term outcomes differ by sex. The purpose of this study was to investigate sex differences at diagnosis of Val122Ile associated ATTR-CA in clinical features and cardiac performance using noninvasive pressure–volume analysis, and to compare long-term outcomes. It was hypothesized that women would have less severe disease with more preserved cardiac function at the time of diagnosis.

Methods

Study Design, Variables, and Definitions

Patients who presented to the Center for Advanced Cardiac Care at Columbia University Irving Medical Center between 2001 and 2018 with clinically significant CA owing to Val122Ile mutations were included in this analysis. The diagnosis of ATTRh cardiac amyloidosis was made by at least one of the following in the presence of the Val122Ile mutation: (1) endomyocardial biopsy-proven congophilic deposits with confirmation of TTR as the precursor protein, (2) histologic documentation of congophilic deposition in at least 1 noncardiac organ and echocardiographic evidence of infiltrative cardiomyopathy without another cause of left ventricular hypertrophy, (3) positive technetium-99m pyrophosphate cardiac scintigraphy defined by grade 2 or 3 myocardial uptake or a heart to contralateral ratio of greater than 1.5 without evidence of a monoclonal protein in serum or urine, and (4) cardiac magnetic resonance or echocardiographic imaging consistent with ATTR-CA without another cause of increased wall thickness.¹³ Evidence for TTR as the precursor protein causing amyloid was confirmed by either immune histochemistry or mass spectroscopy.^{14,15} This study was approved by the Institutional Review Board at Columbia University.

Electrocardiographic and Echocardiographic Parameters

We reviewed electrocardiograms at the time of diagnosis for the presence of arrhythmias, conduction abnormalities, low QRS voltage, and pseudo-infarct (anterior or lateral) patterns. Standard measurements of cardiac size and function, and classification of left ventricular geometry per the American Society of Echocardiography guidelines, were obtained by Doppler transthoracic echocardiography at the time of diagnosis.¹⁶ Left ventricular volume and mass measurements were calculated using a formula described by Devereux et al.¹⁷ The left ventricular end-diastolic volume (LVEDV) and end-systolic volume (LVESV) were extrapolated from linear end-diastolic and end-systolic chamber dimensions, respectively, using formulas from de Simone et al.¹⁸ Stroke volume was calculated as the

difference between LVEDV and LVESV. Transmitral Doppler recordings in the apical 4-chamber view were used to calculate the mitral peak velocity of early filling (E). Early diastolic mitral annular velocity (e') was determined from tissue Doppler imaging in the apical 4-chamber view. The myocardial contraction fraction (the ratio of stroke volume to myocardial volume) was measured from linear dimensions in the parasternal long axis view as described elsewhere.¹⁹

Noninvasive Pressure–Volume Loop Analysis

In a subset of 56 patients with complete echocardiographic data available at the time of diagnosis, chamber performance was assessed using noninvasive, single-beat techniques to estimate pressure–volume indices.²⁰ Patients that were not included in this analysis had echocardiograms performed outside of this institution by local providers, which were not available for review. Pressure–volume loops were constructed from 3 points on the pressure–volume plane, estimated from the brachial systolic blood pressure and diastolic blood pressure, LVEDV, LVESV, and Doppler-based estimates of the left ventricular end-diastolic pressure. To account for the scaling relationship between cardiac chamber and body size, chamber volumes were indexed to body surface area (BSA).^{21,22} This was done by dividing both the LVEDV and LVESV by BSA. The end-systolic pressure was estimated as $0.9 \times$ systolic blood pressure. The left ventricular end-diastolic pressure was estimated by $11.96 + 0.596 \times (E/e')$.²³ Cardiac chamber contractility, represented by the end-systolic pressure–volume relationship in this case, was estimated by the ratio of end-systolic pressure to end-systolic volume in which V_0 was assumed to be 0 mL.²⁴ The end-diastolic pressure–volume relationship was characterized using a noninvasive single beat estimation described by Klotz et al,²³ and was used to estimate the end-diastolic volume at a pressure of 30 mm Hg, an index of ventricular capacitance. Arterial elastance, a measure of the hydraulic load of the arterial system imposed on the ventricle, was measured by dividing the end-systolic pressure by the stroke volume. The ratio of arterial elastance to cardiac chamber contractility, a measure of ventricular–vascular coupling, was also calculated.^{24,25} Finally, to quantify and compare overall pump function between women and men, the areas between their respective end-diastolic pressure–volume relationship and end-systolic pressure–volume relationship curves as a function of the EDP were calculated. This area, termed the isovolumic pressure–volume area, indexes left ventricular performance by integrating both diastolic and systolic function, independent of afterload.²⁶ A schematic demonstrating how the PV loops were constructed is provided in Supplemental Fig. 1.

Outcomes

The outcome of interest was all-cause mortality. This outcome was ascertained through review of the electronic medical record. For patients diagnosed after May 1, 2016, outcomes were censored at May 1, 2019. For all other patients, outcomes were censored at 3 years after the date of diagnosis.

Table 1. Baseline Characteristics of Patients With Val122Ile associated ATTR-CA, by Sex

	Women (n = 27)	Men (n = 46)	P value
Clinical characteristics			
Age at registry entry, years	76.4 ± 5.6	68.9 ± 7.77	<.0001
Ethnicity			
Black	26 (96.3)	44 (95.6)	.89
Other	1 (3.7)	2 (4.4)	
Systolic blood pressure, mm Hg	115.6 ± 14.7	111.3 ± 18.1	.13
Diastolic blood pressure, mm Hg	71.1 ± 10.6	70.1 ± 0.1	.77
Mean arterial blood pressure	85.1 ± 10.8	83.0 ± 10.7	.33
Pulse pressure, mm Hg	44.4 ± 11.2	41.2 ± 14.6	.29
Albumin, g/dL	3.9 ± 0.3	4.0 ± 0.4	.38
BMI, kg/m ²	27.2 ± 6.2	26.2 ± 4.0	.36
Modified BMI	1067 ± 248	1058 ± 209	.97
BSA, m ²	1.78 ± 0.22	1.99 ± 0.22	<.0001
eGFR, mL/min/1.73 m ²	43.4 ± 12.6	46.9 ± 15.9	.37
NYHA functional class			
I	0 (0)	3 (6.5)	.20
II	9 (33.3)	14 (30.4)	
III	18 (66.7)	25 (54.4)	
IV	0 (0)	4 (8.7)	
Year of diagnosis			
2001–2006	0 (0)	3 (6.5)	.0211
2007–2012	6 (22.2)	22 (47.8)	
2013–2018	21 (77.8)	21 (45.6)	
Means of diagnosis			
EMB	12 (44.4)	32 (69.6)	.055
Extracardiac biopsy	0 (0)	2 (4.4)	
^{99m} Tc-PYP	13 (48.2)	9 (19.6)	
Imaging (MRI or TTE)	2 (7.4)	3 (6.5)	
History of carpal tunnel	13 (48.2)	29 (63.0)	.021
History of lumbar spinal stenosis	6 (22.2)	9 (19.5)	.79
Medications			
Daily furosemide dose, mg*	40 [40–80]	80 [40–100]	.022
ACEi/ARB	14 (51.9)	21 (45.7)	.81
Beta-blocker	10 (37.0)	24 (51.2)	.23
Biomarkers†			
BNP, pg/mL	740 [428–1092]	816 [500–1652]	.60
NT-proBNP, pg/mL	3819 [2227–9406]	2098 [1331–3446]	.059
Troponin T, ng/mL	0.06 [0.04–0.10]	0.05 [0.01–0.11]	.45
Troponin I, ng/mL	0.1 [0.05–0.17]	0.2 [0.10–0.35]	.059

Values are mean ± standard deviation, number (%), or median [interquartile range]. ATTR-CA, transthyretin cardiac amyloidosis; ^{99m}Tc-PYP, technetium-99m pyrophosphate cardiac scintigraphy; ACEi, angiotensin converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BNP, brain natriuretic peptide; BSA, body surface area; eGFR, estimated glomerular filtration rate; EMB, endomyocardial biopsy; NT-proBNP, N-terminal pro-hormone brain natriuretic peptide; NYHA, New York Heart Association; Val122Ile, valine-to-isoleucine substitution.

*Includes furosemide and equivalent diuretic dosages.

†For each biomarker, the number of patients with data available to calculate statistics are as follows: BNP = 41 patients, NT-proBNP = 45 patients, Troponin T = 38 patients, Troponin I = 54 patients.

Statistical Methods

Baseline characteristics, including clinical, electrocardiographic, and 2-dimensional echocardiographic data were compared between women and men. Variables were reported as means with standard deviations or medians with interquartile ranges if continuous and numbers with percentages if categorical. Differences between groups were tested for statistical significance using Wilcoxon rank-sum tests for continuous variables and for categorical variables, χ^2 tests or Fisher's exact tests for expected values of less than 10. Cochran-Armitage trend testing was used to evaluate trends in diagnosis patterns over the study period.

Survival curves for the primary end point of survival within 3 years after diagnosis were estimated by the Kaplan–Meier method. Mortality estimates with 95% confidence intervals

were derived from the life table. Difference in survival between groups was analyzed using log-rank testing.

All tests were 2 tailed with a critical *P* value of .05. All statistical analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC).

Results

Over the study period, 73 patients (27 women and 46 men) presented with Val122Ile associated ATTR-CA. Baseline characteristics are summarized in Table 1. More than 90% (*n* = 68) of patients were diagnosed by biopsy or technetium-99m pyrophosphate cardiac scintigraphy. Overall, diagnosis of Val122Ile-associated ATTR-CA increased over time, with approximately 60% (*n* = 42) of the study

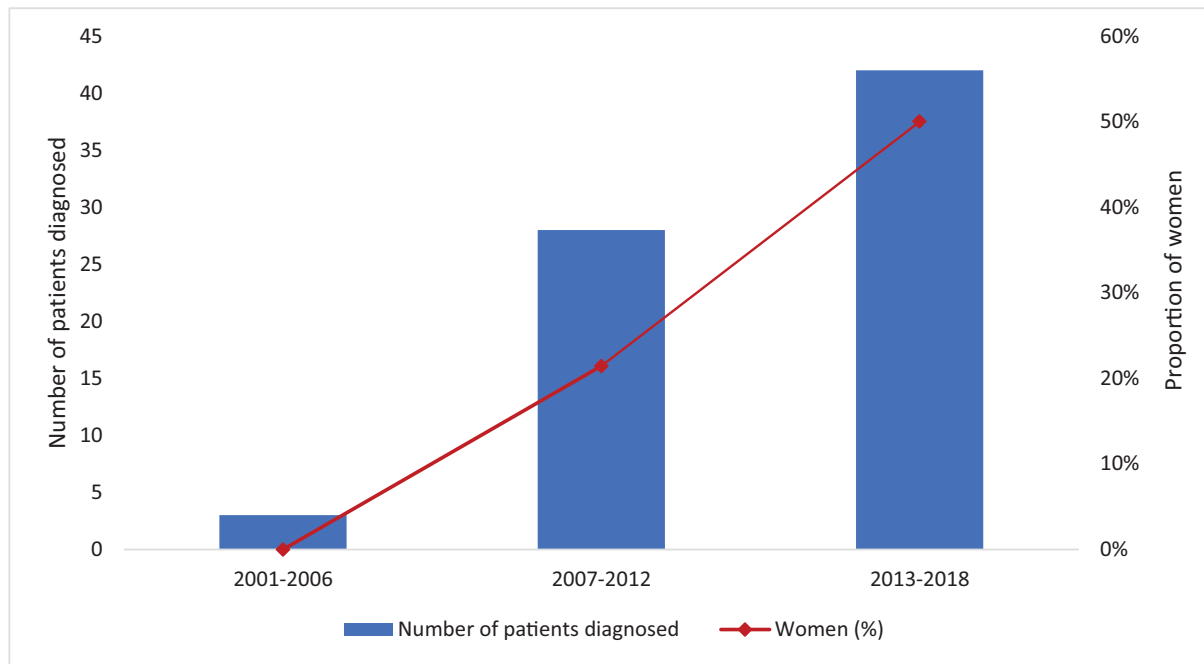


Fig. 1. Trends in diagnosis of Val122Ile associated ATTR-CA from 2001 to 2018.

cohort diagnosed in the last 6 years of the 18-year study period. The proportion of women diagnosed also increased considerably over the study period, from 0% throughout the first third of the study period to 50% from 2013 to 2018 ($P = .021$; Fig. 1).

Almost all patients self-identified as Black. Women were significantly older at the time of diagnosis compared with men, 76 years vs 69 years, $P < .0001$. New York Heart Association Functional Classification scores were similar between sexes with approximately two-thirds of patients presenting with New York Heart Association functional class III or IV symptoms. Body mass index, modified body mass index (calculated as the product of body mass index and serum albumin concentration), estimated glomerular filtration rate, and biomarkers, including serum brain natriuretic peptide and troponin, did not differ significantly between sexes. The BSA of men were significantly larger than that of women, 1.78 m^2 vs 1.99 m^2 , $P < .0001$. Regarding extracardiac manifestations of ATTR-CA, women had significantly lower rates of carpal tunnel, 48% vs 63%, $P = .021$.

A review of electrocardiographic data, including conduction abnormalities and the presence of low voltages, did not yield significant differences between sexes (Table 2). Overall, 20%, $n = 15$, of the study population was in atrial fibrillation or flutter at the time of initial electrocardiograph.

Both women and men had relative wall thicknesses consistent with severe concentric ventricular hypertrophy (Table 2). Left ventricular ejection fraction was significantly higher in women, 49.5% vs 43.2%; $P = .046$, driven more by smaller LVEDV volumes, 82.9 mL vs 93.8 mL; $P = .11$, than by differences in stroke volume, 40.8 mL vs 38.9 mL, $P = .86$ (Table 2). Myocardial contraction fraction did not differ significantly between groups, 15.5% vs 13.8%, $P = .40$.

Fifty-six patients—77% of the study cohort—had complete echocardiographic data from the time of diagnosis available for review. Twenty-two women and 34 men were included. Baseline characteristics for this subgroup are provided in Supplemental Table 1 and did not differ significantly from characteristics of the overall study cohort.

For these patients, left ventricular mechanical properties indexed to BSA were estimated using noninvasive pressure–volume loop analysis. These parameters are summarized in Table 3 and graphically represented in Fig. 2A. Parameters without adjustment for BSA are included in the Supplemental File. Chamber contractility, reflected by cardiac chamber contractility, $5.12 \text{ mm Hg} \cdot \text{m}^2/\text{mL}$ vs $4.34 \text{ mm Hg} \cdot \text{m}^2/\text{mL}$, $P = .27$, and afterload conditions, reflected by the arterial elastance, $5.52 \text{ mm Hg} \cdot \text{m}^2/\text{mL}$ vs $5.69 \text{ mm Hg} \cdot \text{m}^2/\text{mL}$, $P = .62$, were not significantly different between sexes. Chamber capacitance, reflected in predicted end-diastolic volume at a left end-diastolic pressure of 30 mm Hg, was also similar between the sexes, $53.1 \text{ mL}/\text{m}^2$ vs $48.8 \text{ mL}/\text{m}^2$, $P = .93$.

Isovolumic pressure–volume area indexed to BSA as a function of EDP is shown in Fig. 2B. Overall, pressure–volume areas at a left ventricular end-diastolic pressure of 30 mm Hg, were not significantly different in women compared with men, $4,711$ vs $4,223 \text{ mm Hg} \cdot \text{mL}/\text{m}^2$ for women and men, respectively, $P = .20$, indicating that, after integration of both systolic and diastolic function, overall pump function was comparable (Table 3).

At a median follow-up of 1.8 years from the initial diagnosis, there was no difference in mortality between women and men using Kaplan-Meier estimates, 34%, 95% confidence interval 13%–70% vs 43%, 95% confidence interval 28%–63%, respectively, log-rank $P = .64$.

Table 2. Electrocardiographic and Echocardiographic Parameters of Patients With Val122Ile associated ATTR-CA, by Sex

	Women (n = 27)	Men (n = 46)	p value
Electrocardiogram			
Atrial fibrillation/flutter	7 (28.0)	8 (18.1)	.34
Conduction abnormalities*	11 (40.7)	24 (52.2)	.35
Low voltage	10 (37.0)	21 (45.6)	.47
tQRS/LVPW [†]	58.8 (21.5)	61.5 (29.9)	.92
Echocardiogram			
IVS, mm	1.7 ± 0.4	1.7 ± .4	.34
LVPW, mm	1.7 ± 0.3	1.7 ± 0.4	.85
LVEDD, cm	4.2 ± 0.7	4.5 ± 0.7	.11
LVEDS, cm	3.3 ± 0.7	3.7 ± 0.7	.028
LVEDV, mL	82.9 ± 26.6	93.8 ± 29.9	.11
LVEDVI, mL/m ²	47.3 ± 16.7	47.3 ± 14.1	.56
LVESV, mL	41.8 ± 16.8	51.8 ± 19.8	.028
LVESVI, mL/m ²	23.4 ± 10.1	28.2 ± 9.2	.050
SV, mL	40.8 ± 16.2	38.9 ± 13.8	.86
SVI, mL/m ²	23.5 ± 10.2	20.1 ± 8.1	.32
E, cm/s	73.3 ± 16.9	71.9 ± 21.4	.99
e', cm/s	4.9 ± 1.5	4.6 ± 1.7	.16
E/e'	16.5 ± 7.2	17.2 ± 6.7	.47
LV mass, g	307.0 ± 116.2	345.2 ± 134.2	.23
LV mass index, g/m ²	175.2 ± 75.7	172.9 ± 59.3	.76
Relative wall thickness	0.8 ± 0.2	0.8 ± 0.2	.51
LVEF, %	49.5 ± 12.0	43.2 ± 10.8	.046
Myocardial contraction fraction %	15.5 ± 8.3	13.8 ± 7.2	.40

Values are number (%) or mean ± standard deviation. IVS, interventricular septum; LVEDD, left ventricular end-diastolic diameter; LVEDV, left ventricular end-diastolic volume; LVEDVI, left ventricular end-diastolic volume indexed; LVESD, left ventricular end-systolic diameter; LVEF, left ventricular ejection fraction; LVESV, left ventricular end-systolic volume; LVESVI, left ventricular end-systolic volume indexed; LVPW, left ventricular posterior wall; SD, standard deviation; SV, stroke volume; SVI, stroke volume indexed; tQRS, total QRS

*Conduction abnormalities are intraventricular conduction abnormalities, including bundle branch blocks and fascicular blocks, and atrioventricular blocks.

[†]tQRS/LVPW: summation of the height of all QRS complexes divided by left ventricular wall thickness.

Table 3. Noninvasive Pressure–Volume Loop Indices Indexed to Body Surface Area in Patients With Val122Ile associated ATTR-CA, by Sex

	Women (n = 22)	Men (n = 34)	P value
<i>P</i> _{es} , mm Hg	103.5 ± 14.0	99.2 ± 16.4	.14
Estimated LVEDP, mm Hg	21.6 ± 4.26	22.2 ± 4.00	.36
Res, mm Hg*m ² /mL	5.12 ± 2.74	4.34 ± 1.91	.27
Ea, mm Hg*m ² /mL	5.52 ± 2.62	5.69 ± 2.64	.62
Ea/Res	1.23 ± 0.65	1.46 ± 0.66	.22
V30, mL/m ²	53.1 ± 22.0	48.8 ± 15.8	.93
PVAiso30, mm Hg*mL	4711	4223	.20
		[3622–6461]	3173–5025]

Values are mean ± standard deviation or median [interquartile range]. Ea, arterial elastance; *P*_{es}, end-systolic pressure; PVAiso30, pressure–volume areas at a left ventricular end-diastolic pressure of 30 mm Hg; Res, cardiac chamber contractility; V30, end-diastolic volume at a pressure of 30 mm Hg. Other abbreviations as in Table 1.

Discussion

This retrospective cohort study of 73 patients with Val122Ile-associated ATTR-CA examined differences in the clinical presentation and echocardiographic measures of cardiac performance at diagnosis between sexes. We found that the number of patients diagnosed with ATTR-CA and specifically the proportion of women diagnosed, increased over the past 2 decades, an encouraging sign of both increasing awareness of the disease among clinicians and advances in noninvasive diagnostic testing. Women presented at an older age than men. Based on noninvasive pressure–volume assessments, women and men demonstrated similar cardiac structural changes and similar overall cardiac pump function, suggesting a more indolent disease process in women. Mortality was similar between the sexes.

Despite marked sex differences in disease prevalence both in ATTRwt-CA and, to a lesser extent, in ATTRv-CA, few previous studies have investigated sex differences in the clinical presentation of ATTR-CA. In this study, women were significantly older than men at the time of diagnosis. Nonbiological factors likely play a role, including known sex disparities in access to health care resources, a lack of clinical suspicion among physicians for the diagnosis of CA in women, and comparative delays in women seeking out health care resources. These mechanisms are well-documented in the literature on sex disparities in ischemic heart disease and heart failure, but to this point have not been studied in CA.^{3,4,27} The older age of women at the time of diagnosis may also reflect a relative delay in the development of clinical symptoms. This finding is supported by the fact that many markers of heart failure severity and overall morbidity were similar between sexes at the time of diagnosis despite the difference in age, including New York Heart Association functional class, myocardial contraction fraction, and pressure–volume areas at a left ventricular end-diastolic pressure of 30 mm Hg. Longitudinal observations of women and men with hereditary TTR amyloidosis are needed to investigate this hypothesis. Sex-specific differences in time to disease onset are well-documented in other forms of ATTR amyloidosis, especially Val30Met familial amyloid polyneuropathy, where several studies have demonstrated that women are significantly older at the time of diagnosis.^{28,29} This finding has not been studied to the same extent in Val122Ile associated ATTR-CA, which may in part be due to the male predominance of the disease. In population-based studies of Val122Ile associated ATTR-CA, age at diagnosis ranges from 69 to 77 years, which is consistent with a median age of 73 years (IQR 68–77) at the time of diagnosis in this study.^{11,12}

Additionally, women in this study cohort trended toward higher N-terminal pro-hormone brain natriuretic peptide (NT-proBNP) levels at the time of diagnosis compared with men, although the difference did not meet a level of statistical significance. NT-proBNP is commonly used for staging and risk stratification in ATTR-CA. In this study, NT-proBNP levels were available for 45 of 73 patients in this

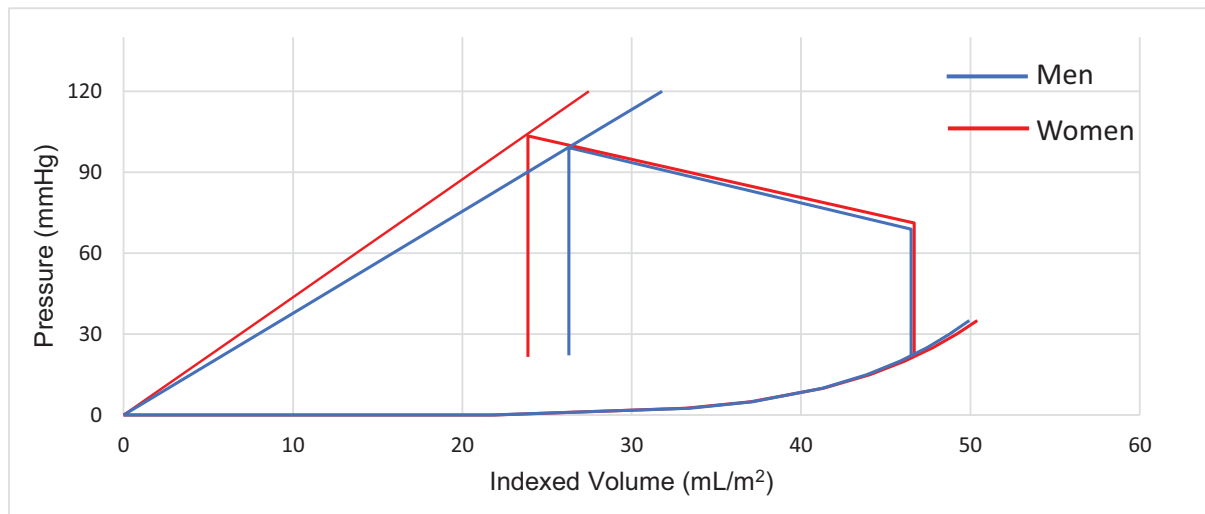


Fig. 2. (A). Noninvasive pressure–volume loops in Val122Ile associated ATTR-CA by sex, indexed to body surface area.

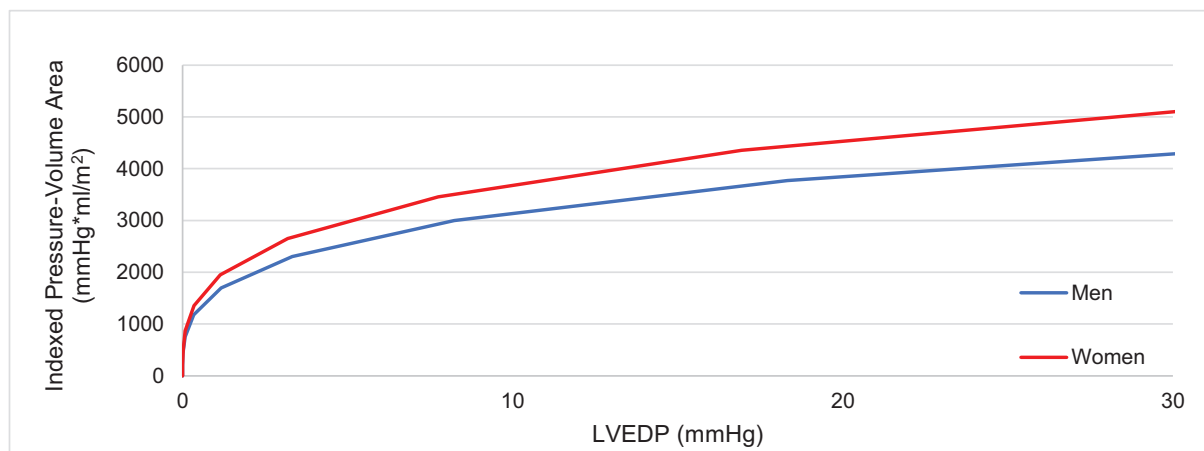


Fig. 2. (B). Isovolumic pressure–volume area in Val122Ile associated ATTR-CA by sex, indexed to body surface area.

study (62%), which in part is due to the fact that the study period spans 2001–2018, and routine measurement of NT-proBNP is a relatively recent practice. This factor limits interpretation of the difference in NT-proBNP levels by sex.

This study was the first, to our knowledge, to use the technique of pressure–volume analysis to compare overall cardiac chamber performance between women and men with Val122Ile associated ATTR-CA. When volumes were indexed to BSA to account for known differences in chamber sizes between sexes,^{21,22} women and men with Val122Ile-associated ATTR-CA had structurally similar hearts at the time of diagnosis, in terms of both systolic and diastolic function, and similar overall cardiac chamber function.

These observations are important for several reasons. They reinforce that a diagnosis of ATTR-CA should be considered in all older patients with concentric hypertrophy and diastolic dysfunction, including women for whom clinical

suspicion for CA may initially be lower. These findings also demonstrate that pressure–volume analysis is a useful technique to understand cardiac pathophysiology in ATTR-CA using parameters derived from peripheral blood pressure readings and transthoracic echocardiography.

Finally, the findings of this study may have important implications for the role of sex in the pathogenesis of Val122Ile associated ATTR-CA and disease trajectory. Overall pump function at the time of diagnosis, indexed by the pressure–volume areas at a left ventricular end-diastolic pressure of 30 mm Hg, was similar between women and men, as were mortality rates from that point forward. This finding is consistent with a large-scale study of patients in the UK with ATTR-CA, which found no association between sex and survival.¹² In contextualizing these findings, it is notable that at the time of diagnosis, women were on average more than 5 years older than men in this study. In contrast

with the previously held conception of ATTR-CA as a slowly progressive condition, several recent studies suggest a more aggressive clinical trajectory, characterized by severe refractory heart failure, considerable morbidity and hospitalizations, and a median survival ranging from 20 to 30 month from the time of diagnosis.^{11,12,30} Using serial pressure–volume loop analyses over 2 years from the time of diagnosis, Bhuiyan et al²⁰ demonstrated the physiologic basis for this decline: worsening over a relatively short time course of both ventricular diastolic and systolic function, ultimately resulting in progressive ventricular pump dysfunction. Given the rapidity of progressive cardiac dysfunction in hereditary ATTR-CA, the observation in this study cohort that, at the time of presentation, women are older but have similar cardiac function as do men, indicates that women may have a less aggressive disease phenotype. Women had a similar left ventricular wall thickness as men. Physiologically, women have lower normal values, so this finding may indicate that, at the time of diagnosis the degree of myocardial infiltration was relatively higher in women. However, relative wall thickness did not differ by sex. Further interpretation of these findings is limited by the fact that cardiac amyloid deposition was not directly measured in this study by, for example, quantification of extracellular volume on cardiovascular magnetic resonance imaging. However, even if women had a relatively higher degree of myocardial infiltration, perhaps owing to longer exposure to disease, it did not seem to be driving poorer cardiac chamber performance.

Sex hormones may be important modulators of the degree of amyloid deposition and disease phenotype. In a study of patients with both hereditary and wild-type ATTR-CA, Rapezzi et al³¹ found that women, compared with men, had lower levels of myocardial involvement on echocardiographic review. Those women with higher degrees of myocardial involvement were more likely to be post menopausal, implicating female sex hormones as a potential protective factor.³¹ Additionally, Gonçalves et al³² showed using mouse models that, although both estrogen and androgen upregulate liver production of TTR, androgens are a relatively stronger inducer. Longitudinal study of the progression of ATTR-CA in women and men is needed to understand the relationship between age, sex, and disease progression.

Limitations

This study has several limitations. First, the study sample size was small and represents the experience of a single clinical center. Second, linear ventricular dimensions measured using 2-dimensional transthoracic echocardiography were used to estimate ventricular volumes. Although 3-dimensional cardiac imaging modalities provide more accurate estimates, logistical and technical challenges make these studies more difficult to obtain. Data on biomarkers at the time of diagnosis, including troponin and pro-BNP, which are important prognostic markers in ATTR-CA, were not consistently available. Not all patients in the study cohort had echocardiograms available for review. The

baseline characteristics of the patients with available imaging did not differ significantly from the characteristics of the study cohort. Nevertheless, the missingness of the dataset may introduce biases for which we cannot adjust for. Additionally, comparisons were made between men and women, not between sex- and age-matched controls. Because under normal conditions men have larger hearts than women, even after accounting for body size, it could be that men with ATTR-CA actually exhibit a greater degree of ventricular size decrease than women. This factor would render our conclusion of a more indolent form of disease in women conservative. Finally, estimates of cardiac performance were derived from noninvasively measured pressure–volume loop relationships using single-beat techniques. Although direct catheter-based measurements of end-diastolic pressure–volume relationship and end-systolic pressure–volume relationship are the gold standard for this analysis, their necessarily invasive nature makes it difficult to gather data on large patient cohorts and restricts use to a small number of technically capable centers. Despite these limitations, this study is the first to describe and compare clinical and ventricular properties of women and men with Val122Ile associated ATTR-CA.

Conclusions

This retrospective pressure-volume–based analysis demonstrates that despite being significantly older at time of diagnosis of Val122Ile associated ATTR-CA, women have similar overall cardiac pump function and 3-year mortality rates compared with men. Given the rapidity of progressive cardiac dysfunction in hereditary ATTR-CA, these findings suggest that sex is an important modifier of illness trajectory.

Disclosures

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All authors made substantial contributions to all of the following: (1) the conception and design of the study, or acquisition of data, or analysis and interpretation of data, (2) drafting the article or revising it critically for important intellectual content, (3) final approval of the version to be submitted.

All authors have approved the final article.

Supplementary materials

Supplementary material associated with this article can be found in the online version at doi:[10.1016/j.cardfail.2020.08.007](https://doi.org/10.1016/j.cardfail.2020.08.007).

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