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Sex-related differences in clinical presentation and all-cause mortality in patients with cardiac transthyretin amyloidosis and light chain amyloidosis

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ABSTRACT

We aimed to ascertain whether sex-related differences are relevant to clinical presentation, cardiac phenotype and all-cause mortality in different types of cardiac amyloidosis, a field still poorly investigated. Medical files from consecutive patients diagnosed with cardiac amyloidosis between 2000 and 2020, at Careggi University Hospital, were retrospectively evaluated.

Over this period, 259 patients (12% females) were diagnosed with wild type transthyretin amyloidosis (wtATTR), 52 (25% females) with hereditary transthyretin amyloidosis (hATTR) and 143 (47% females) with light chain amyloidosis (AL).

Women with wtATTR, compared to men, were significantly older at the time of diagnosis and showed higher National Amyloidosis Centre score, thicker normalized interventricular septum, higher diastolic dysfunction and worse right ventricular function. Females with hATTR and AL had lower normalized cardiac mass compared to men, otherwise, bio-humoral parameters, NYHA class, and ECG characteristics were similar. Comparing females and male with wtATTR, hATTR and AL, no differences in Kaplan-Meier curves for all-cause mortality were observed with regard to sex, p-value >0.05.

In conclusion, we did not observe major differences in clinical expression related to sex in different types of cardiac amyloidosis: specifically, all-cause mortality was not affected. Nevertheless, women with wtATTR had echocardiographic signs of more advanced disease and higher NAC score at diagnosis suggesting a possible later recognition of disease compared to men.

Sex-related differences in clinical presentation, phenotype and all-cause mortality across cardiovascular diseases including heart failure and cardiomyopathies are attracting increasing attention [1,2,3].

While men are more prone to heart failure with reduced ejection fraction, women predominate in heart failure with preserved ejection fraction, the development of which is favoured by traditional and sex-specific risk factors [3]. Across many cardiovascular conditions, differences in presentation, progression, and all-cause mortality between females and males are well-recognized [1,2].

A distinct cause of heart failure in older individuals is cardiac amyloidosis (CA), a heterogeneous condition that comprises distinct entities with diverse pathophysiology, with transthyretin amyloidosis

Abbreviations: AL, light chain amyloidosis; ATTR, transthyretin amyloidosis; BSA, body surface area; CA, cardiac amyloidosis; ECG, electrocardiogram; hATTR, hereditary transthyretin amyloidosis; HCM, hypertrophic cardiomyopathy; LV, left ventricle; MGUS, monoclonal gammopathy of undetermined significance; NAC, National Amyloidosis Centre; NtproBNP, N-terminal pro-b-type natriuretic peptide; NYHA, New York Heart Association Functional Classification; TAPSE, tricuspid annular plane systolic excursion; wtATTR, wild-type transthyretin amyloidosis.

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(ATTR) and light-chain amyloidosis (AL) representing the most common subtypes [4–6]. ATTR is characterized by the deposition of misfolded transthyretin protein in the myocardium' [7], following destabilization of the protein either due to age-related changes in wild-type ATTR (wtATTR) or inherited mutations in the transthyretin gene (hATTR). AL is caused by the deposition of insoluble amyloid fibrils derived from the misfolding of monoclonal immunoglobulin light chains. Recent studies have suggested possible differences in sex distribution among different types of amyloidosis [8,9,10] although the issue remains unresolved. In the present study, we, therefore, examined how women with different types of cardiac amyloidosis differ from men with respect to presenting characteristics and all-cause mortality in a large tertiary referral centre.

1. Methods

1.1. Study population

Since 2000, the cardiology, haematology, nephrology, neurology and genetic departments at Careggi University Hospital, Regional Referral Centre for Amyloidosis (Florence, Italy), have established a coordinated network for the diagnosis and treatment of systemic amyloidosis.

Patient selection and data were retrospectively retrieved from a centralized database providing standardized records of clinical, laboratory and instrumental data.

Patients included in this study must meet all the following inclusion criteria:

1) Males and females greater than or equal to 18 years of age
2) Evidence of CA
3) CA must be caused by wtATTR, hATTR or AL
4) Consecutive patients evaluated at Careggi University Hospital between January 2000 and December 2020
5) Complete clinical, bio-humoral and instrumental data availability in our centralized database.

Exclusion criteria:

1) Age < 18 years
2) Types of amyloidosis other than wtATTR, hATTR, AL

From January 2000 to December 2020, a total of 496 consecutive patients with amyloidosis were seen at Careggi University Hospital: 259 (52%) had wtATTR, 54 (12%) had hATTR and 183 (36%) had AL. All except one were Caucasians. After inclusion and exclusion criteria selection, n = 454 patients were considered eligible for this study (Fig. 1).

Diagnosis of ATTR was defined by histological documentation of Congo red staining and apple-green birefringence under cross-polarized light in at least one involved organ or biopsy demonstration of ATTR deposits, analyzed by immunochemistry or immune-electron-microscopy. After April 2016 diagnosis of ATTR-CA was largely performed according to the non-invasive diagnostic algorithm suggested by Gilmore et al. [11] The diagnosis of hATTR was confirmed by the presence of a pathogenic mutation in the transthyretin gene. Genetic counselling and genetic analysis were performed in all ATTR patients. The NAC (National Amyloidosis Centre) Staging system was used for patients stratifications in ATTR patients [12]. Among the wtATTR and hATTR patients, only 8 were on Tafamidis for mixed phenotype (neurological and cardiological) or as "expanded access".

AL was diagnosed in the presence of a plasma cell dyscrasia with clonal plasma cells in the bone marrow and/or monoclonal gammopathy detected by serum or urine immunofixation electrophoresis and concentration of serum free light chains. Confirmation by biopsy of abdominal fat pad or another involved organ with detection of AL amyloid by immunohistochemistry, optic/immunoelectron microscopy or proteomics was required. Patients with AL were managed and treated according to International recommendations [13]. The European modification of the Mayo Staging system was used to stratify patients [14].

1.2. Clinical data

Patient files were thoroughly reviewed for patient history including hypertension, onset of cardiological symptoms, disease duration, medical treatment, history of coronary artery disease or other relevant cardiac disorders. Hypertension was defined as systolic blood pressure exceeding 140 mmHg or diastolic blood pressure exceeding 90 mmHg at repeated visits or ongoing hypertensive treatment. Symptoms onset

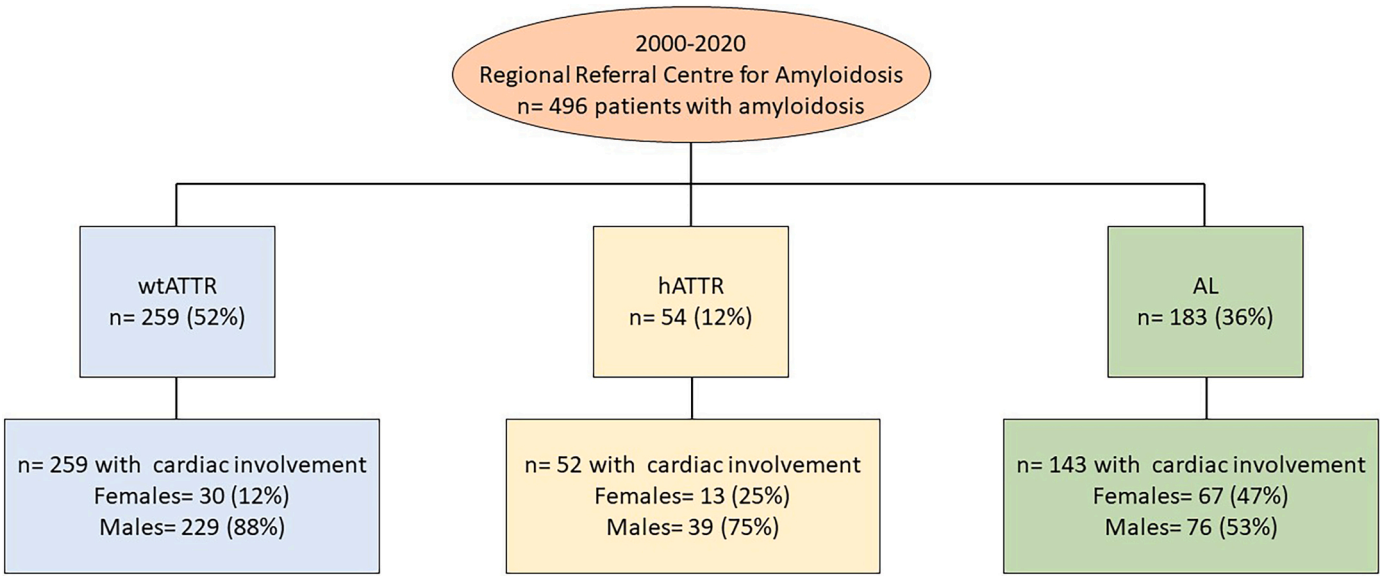

Fig. 1. Careggi University Hospital is the Tuscany Regional Referral Centre for Amyloidosis (Florence, Italy). From January 2000 to December 2020, 496 consecutive patients with a defined diagnosis of amyloidosis underwent a comprehensive evaluation at our institution: 259 (52%) had wtATTR, 54 (12%) had hATTR and 183 (36%) had AL. Cardiac involvement was diagnosed in 454 patients: 259 wtATTR (12% females), 52 hATTR (25% females) and 143 AL (47% females).
Abbreviations: AL: light chain amyloidosis, hATTR: hereditary transthyretin amyloidosis, wtATTR: wild-type transthyretin amyloidosis.

were defined as patient-reported heart failure symptoms or other cardiological amyloidosis-related symptoms leading to health care contact.

1.3. Electrocardiography and echocardiography

We reviewed electrocardiograms at the time of diagnosis for the presence of arrhythmias, conduction abnormalities, low QRS voltage, and pseudo-infarction pattern.

Echocardiographic data were derived from routine initial evaluations. Two-dimensional, Doppler techniques and M-mode measures were performed. Standard measurements of cardiac size and function were obtained according to the recommendations of the American Society of Echocardiography [15]. Left ventricular (LV) mass was calculated according to Deveraux et al. [16]. Chamber volumes and cardiac mass were normalized to body surface area (BSA) [17,18].

1.4. All-cause mortality

All-cause mortality was assessed by clinical files or telephone interviews and was censored in December 2020.

1.5. Ethical committee

All patients at diagnosis or during the first contact to our center signed an informed consent for research purposes. Patient still in active follow up were asked to sign a further informed consent. This was waived for the patients lost to follow up. A specific approval for this research registry were obtained by the local ethical committee (code 15291).

1.6. Statistical analysis

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 test for continuous variables and for categorical variables using chi-square test or Fisher's exact test, as appropriate.

All-cause mortality was estimated by the Kaplan-Meier method, and comparisons were performed using the log-rank test. All tests were 2 tailed with a critical p-value <0.05.

Cox multivariable regression analysis (variable selection method with backward stepwise elimination) was performed including all candidate variables ($P < 0.10$ at univariate analysis). A 2-sided P value less than 0.05 was considered statistically significant.

All statistical analyses were performed using SPSS statistics 21.0 for Windows.

2. Results

2.1. Wild-type transthyretin amyloidosis

Over the study period, 259 consecutive patients were diagnosed with cardiac wtATTR (12% females), Fig. 1, Table 1. Women were significantly older at the time of diagnosis compared to men (82 ± 5 vs 79 ± 7 years; p = 0.003). Estimated glomerular filtration rate and troponin did not differ significantly between sexes, whereas women showed higher n-terminal pro-b-type natriuretic peptide (NTproBNP) values at diagnosis compared to men (4212 [2744–7025] vs 3046 [1179–5790] pg/ml; p = 0.03). Women had higher NAC score at referral for investigation, as approximately 75% were classified as NAC II or III, while more than 80% of men were classified as NAC I or II.

New York Heart Association functional classification (NYHA) was similar between sexes with most patients included within NYHA class II or III. Overall, 12 (40%) women and 80 (35%) men showed atrial fibrillation or flutter at first evaluation. Other electrocardiographic characteristics did not differ between sexes. Both women and men presented relative wall thickness consistent with severe concentric ventricular hypertrophy with women showing thicker normalized interventricular septum, smaller normalized LV end-diastolic volume

Table 1
wild-type transthyretin amyloidosis patients grouped according to sex: demographic, clinical, electrocardiographic and echocardiographic characteristics at diagnosis.

Wild-type transthyretin amyloidosis, total patients n = 259			
	Females	Males	p-value
	n = 30 (12%)	n = 229 (88%)	
BSA (m^2)	1.7 ± 0.1	1.9 ± 0.2	<0.0001
Delay from symptom onset to diagnosis (months)	5 (2–13)	4 (1–11)	0.27
Age at diagnosis (years)	82 ± 5	79 ± 7	0.003
Perugini score (n,%), (bone tracer scintigraphy available for 254 patients)			0.52
Perugini 0	0	0	
Perugini 1	4 (13%)	18 (8%)	
Perugini 2	8 (27%)	76 (34%)	
Perugini 3	18 (60%)	130 (58%)	
Previous carpal tunnel surgery (n, %)	18 (60%)	142 (62%)	0.71
Hypertension (n,%)	22 (73%)	146 (64%)	0.32
CAD (n,%)	3 (10%)	46 (20%)	0.22
Blood systolic pressure at first visit (mmHg)	130 (120–145)	125 (110–135)	0.27
Atrial fibrillation (n,%)	12 (40%)	80 (35%)	0.56
1st degree AV block (n,%)	6 (20%)	46 (20%)	0.96
RBBB (n,%)	1 (3%)	43 (18%)	0.12
LBBB (n,%)	4 (13%)	20 (9%)	0.36
Low voltages (n,%)	7 (23%)	64 (28%)	0.67
Pseudo-infarction (n,%)	8 (27%)	48 (21%)	0.46
PM/ICD (n,%)	1 (3%)	24 (10%)	0.22
NYHA class (n,%)			0.37
NYHA I	2 (7%)	43 (19%)	
NYHA II	18 (60%)	122 (53%)	
NYHA III	10 (33%)	62 (27%)	
NYHA IV	0	2 (1%)	
eGFR (ml/min/1.73m^2)	58 ± 33	59 ± 19	0.97
NTproBNP (pg/ml)	4212 (2744–7025)	3046 (1179–5790)	0.03
Troponin I (ng/ml)	0.08 (0.05–0.21)	0.07 (0.04–0.13)	0.37
NAC score (n, %)			0.004
I	8 (26%)	105 (46%)	
II	11 (37%)	94 (41%)	
III	11 (37%)	30 (13%)	
IVS (mm)	16 ± 2	17 ± 2	0.052
Normalized IVS (mm/ m^2)	10 ± 1	9 ± 1	0.009
PW (mm)	15 ± 2	15 ± 2	0.84
LVDD (mm)	43 (38–45)	46 (41–50)	0.003
Normalized LVDD (mm/m^2)	25 (21–27)	24 (21–26)	0.21
LVEDV (ml)	65 (60–73)	94 (78–111)	<0.0001
Normalized LVEDV (ml/m^2)	40 (35–46)	50 (42–59)	<0.0001
Normalized LV mass (g/m^2)	169 (141–206)	177 (148–209)	0.60
EF (%)	55 ± 9	52 ± 10	0.44
Stroke Volume (ml)	36 (33–45)	49 (41–60)	<0.0001
LA volume (ml)	91 ± 33	92 ± 31	0.90
E/e'	25 (19–28)	16 (13–20)	0.03
TAPSE (mm)	15 ± 4	17 ± 4	0.04

Abbreviations: AV = atrioventricular, BSA = body surface area, CAD = coronary artery disease, E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity, eGFR = estimated Glomerular Filtration Rate, EF = ejection fraction, ICD = implantable cardioverter defibrillator, IVS = inter ventricular septum, LA = left atrium, LBBB = left bundle branch block, LV = left ventricle, LVEDD = left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, NAC = National Amyloidosis Centre, NYHA = New York Heart Association, NTproBNP = N-terminal pro b-type Natriuretic Peptide, PM = pacemaker, PW = posterior wall, RBBB = right bundle branch block, TAPSE = tricuspid annular plane systolic excursion.

and smaller LV stroke volume compared to men (Table 1). Moreover, women showed higher E/e' (p = 0.03) indicating higher LV filling pressures and worse right ventricular function measured by tricuspid annular plane systolic excursion (TAPSE) (p = 0.04).

Carpal tunnel involvement was observed in 18 (60%) females and 142 (62%) males with no significant difference between sexes.

At a median follow-up of 20 (10−33) months from initial diagnosis, there was no difference in mortality between women and men (log-rank p = 0.14, Supplementary Fig. S1, Panel A).

2.2. Hereditary transthyretin amyloidosis

Main demographic and clinical characteristics at diagnosis for the 52 (25% females) hATTR patients with CA are presented in Table 2. Eleven (21%) hATTR patients had a mixed phenotype (cardiac and neurologic). Neurological involvement was observed in 4 (30%) females and 7 (17%) males (Table 1). Age at diagnosis and incidence of neurological involvement were not meaningfully different between sexes. Females with hATTR had lower normalized cardiac mass (160 [140–171] vs 209 [154–230] g/m^2; p = 0.014). Otherwise, bio-humoral parameters, NYHA class, NAC score and ECG characteristics were similar (Table 2).

At a mean follow-up of 37 ± 23 months from the initial diagnosis, there was no difference in mortality between women and men (log-rank p = 0.78, Supplementary Fig. S1, Panel B).

2.3. Light-chain amyloidosis

Main demographic and clinical characteristics at diagnosis for the 143 patients (47% females) with AL and cardiac involvement are presented in Table 3. Age at diagnosis was similar between women and men (67 ± 9 years vs 69 ± 10 years respectively; p = 0.42). There were no differences in underlying hematological disease (monoclonal gammopathy of undetermined significance MGUS, smouldering myeloma and multiple myeloma) between sexes.

There were no clear differences between sexes in bio-humoral parameters, NYHA class, Mayo revised score and ECG characteristics. However, women demonstrated significantly lower median values for normalized LV end-diastolic volume, stroke volume and mean normalized LV mass (Table 3).

At a median follow-up of 12 (4–33) months from the initial diagnosis, there was no difference in all-cause mortality between women and men (log-rank; p = 0.58, Supplementary Fig. S1, Panel C).

2.4. Survival analysis

Cox multivariable regression analysis was used to assess factors associated with all-cause mortality.

In all the three study groups, sex was excluded from the analysis (method selection backward deletion) confirming the findings highlighted at univariable study.

Results are summarized in the e-component table. Briefly, in patients with wtATTR, age at diagnosis, NYHA class, NAC score and EF were independently associated with all-cause mortality. Whereas in patients with both hATTR and AL, NYHA class was independently associated with all-cause mortality (e-component).

3. Discussion

The main findings of the present study are the following: 1) the percentage of women diagnosed with CA varied according to the different types amyloidosis; 2)women with wtATTR were older at diagnosis and showed more advanced disease than men, with higher NTproBNP, NAC score, LV filling pressures, greater concentric hypertrophy and worse right ventricular systolic function; 3) women with hATTR and AL did not present relevant clinical differences compared to men at baseline, despite lower normalized LV end-diastolic volume and

Table 2
hereditary transthyretin amyloidosis patients with cardiac involvement grouped according to sex: demographic, clinical, electrocardiographic and echocardiographic characteristics at diagnosis.

Hereditary transthyretin amyloidosis, total patients with cardiac involvement n = 52			
	Females N = 13 (25%)	Males N = 39 (75%)	p-value
BSA (m^2)	1.7 (1.6–1.9)	1.9 (1.8–2.0)	0.02
Delay from symptom onset to diagnosis (months)	5 (2–13)	7 (3–20)	0.28
Age at diagnosis (years)	72 ± 16	73 ± 7	0.67
Neuropathy	4 (30%)	7 (17%)	0.32
Perugini score (n, %) (bone tracer scintigraphy available for 42 patients)			0.81
Perugini 0	0	1 (3%)	
Perugini 1	1 (9%)	2 (6%)	
Perugini 2	3 (27%)	12 (39%)	
Perugini 3	7 (64%)	16 (52%)	
Hypertension (n,%)	6 (46%)	22 (56%)	0.54
CAD (n,%)	1 (7%)	5 (12%)	0.52
Blood systolic pressure at first visit (mmHg)	115 (110–140)	120 (110–136)	0.48
Atrial fibrillation (n,%)	2 (15%)	8 (20%)	0.29
1st degree AV block (n,%)	4 (30%)	6 (15%)	0.37
RBBB (n,%)	0	4 (10%)	0.34
LBBB (n,%)	2 (15%)	3 (7%)	0.59
Low voltages (n,%)	5 (38%)	11 (27%)	0.64
Pseudo-infarction (n,%)	2 (15%)	8 (20%)	0.62
PM/ICD before or at the time of diagnosis (n,%)	1 (15%)	5 (13%)	0.69
NYHA class (n,%)			0.18
NYHA I	2 (15%)	3 (8%)	
NYHA II	5 (39%)	27 (68%)	
NYHA III	6 (46%)	8 (21%)	
NYHA IV	0	1 (3%)	
eGFR (ml/min/1.73m^2)	66 ± 27	66 ± 21	0.95
NTproBNP (pg/ml)	2333 (1421–4463)	3252 (2255–5652)	0.43
Troponin I (ng/ml)	0.06 (0.03–0.15)	0.09 (0.05–0.23)	0.22
NAC score (n, %)			0.71
I	4 (31%)	17 (44%)	
II	7 (54%)	15 (39%)	
III	2 (15%)	7 (17%)	
IVS (mm)	15 ± 2	18 ± 3	0.015
Normalized IVS (mm/ m^2)	9 (8–10)	10 (9–11)	0.17
PW (mm)	15 ± 2	17 ± 3	0.08
LVDD (mm)	44 ± 3	46 ± 6	0.19
Normalized LVDD (mm/m^2)	25 ± 2	25 ± 6	0.99
LVEDV (ml)	72 ± 18	95 ± 25	0.006
Normalized LVEDV (ml/m^2)	44 (35–47)	50 (43–56)	0.015
Normalized LV mass (g/m^2)	160 (140–171)	209 (154–230)	0.014
EF (%)	54 ± 11	48 ± 12	0.12
Stroke volume (ml)	39 ± 12	45 ± 17	0.21
LA area (cm^2)	26 ± 6	29 ± 7	0.38
E/e'	21 ± 6	19 ± 6	0.22
TAPSE (mm)	17 ± 5	16 ± 4	0.41
Genetic mutations			N/A
Ile68Leu, n (%)	7 (53%)	24 (61%)	
Val122Ile, n (%)	3 (23%)	11 (28%)	
Gly57Arg, n (%)	0	2 (5%)	
Val30Met, n (%)	1 (8%)	1 (3%)	
Glu55Lys, n (%)	1 (8%)	0	
Gly47Glu, n (%)	1 (8%)	0	
Phe64Leu, n (%)	0	1 (3%)	

Abbreviations: AV = atrioventricular, BSA = body surface area, CAD = coronary artery disease, E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity, eGFR = estimated Glomerular Filtration Rate, EF = ejection fraction, ICD = implantable cardioverter defibrillator, IVS = inter ventricular septum, LA = left atrium, LBBB = left bundle branch block, LV = left ventricle, LVEDD = left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, NAC = National Amyloidosis Centre, NYHA = New York Heart Association, NTproBNP = N-terminal pro b-type Natriuretic Peptide, PM = pacemaker, PW = posterior wall, RBBB = right bundle branch block, TAPSE = tricuspid annular plane systolic excursion.

Table 3
Light chain amyloidosis patients with cardiac involvement grouped according to sex: demographic, clinical, electrocardiographic and echocardiographic characteristics at diagnosis.

Light chain amyloidosis, total patients with cardiac involvement n = 143			
	Females	Males	p-value
	n = 67 (47%)	n = 76 (53%)	
BSA (m^2)	1.6 (1.5–1.7)	1.8 (1.7–1.9)	<0.0001
Delay from symptom onset to diagnosis (months)	4 (2–9)	5 (2–10)	0.42
Age at diagnosis (years)	67 ± 9	69 ± 10	0.42
MGUS (n,%)	24 (36%)	27 (35%)	0.84
SM (n,%)	34 (51%)	41 (54%)	
MM (n,%)	9 (13%)	8 (11%)	
Hypertension (n,%)	13 (20%)	30 (40%)	0.19
CAD (n,%)	8 (11%)	12 (16%)	0.81
Blood systolic pressure at first visit (mmHg)	115 (100–129)	112 (102–126)	0.83
Atrial fibrillation (n,%)	10 (15%)	17 (22%)	0.42
1st degree AV block (n,%)	22 (33%)	26 (34%)	0.94
RBBB (n,%)	4 (5%)	13 (16%)	0.16
LBBB (n,%)	6 (8%)	5 (6%)	0.72
Low voltages (n,%)	41 (61%)	46 (61%)	0.98
Pseudo-infarction (n,%)	32 (48%)	39 (51%)	0.74
PM/ICD (n,%)	1 (1%)	0	0.46
NYHA class (n,%)			0.18
NYHA I	7 (10%)	2 (2%)	
NYHA II	29 (43%)	36 (47%)	
NYHA III	20 (30%)	29 (38%)	
NYHA IV	11 (16%)	9 (12%)	
Renal involvement (n,%)	29 (43%)	27 (35%)	0.34
eGFR (ml/min/1.73m^2)	68 ± 33	66 ± 25	0.67
Proteinuria (n,%)	24 (35%)	29 (38%)	0.77
NTproBNP (pg/ml)	6285 (2739–16,113)	4526 (2213–9213)	0.08
Troponin I (ng/ml)	0.12 (0.06–0.28)	0.08 (0.04–0.18)	0.07
K (mg/mL)	13 (6–64)	16 (9–49)	0.22
λ (mg/mL)	146 (61–412)	147 (42–519)	0.92
dFLC (mg/mL)	241 (118–693)	292 (93–933)	0.80
BJ (n,%)	50 (75%)	59 (77%)	0.82
Revised MAYO staging (n,%)			0.54
I	3 (4%)	6 (8%)	
II	6 (9%)	11 (15%)	
IIIa	31 (47%)	29 (38%)	
IIIb	27 (40%)	30 (39%)	
IVS (mm)	14 (12–16)	16 (14–17)	0.004
Normalized IVS (mm/m^2)	8 ± 2	8 ± 1	0.71
PW (mm)	14 (12–15)	14 (13–16)	**0.04**
LVDD (mm)	42 ± 5	46 ± 5	0.001
Normalized LVDD (mm/m^2)	26 ± 3	25 ± 3	0.56
LVEDV (ml)	63 (55–75)	86 (71–103)	<0.0001
Normalized LVEDV (ml/m^2)	39 (34–47)	47 (39–56)	0.006
Normalized LV mass (gr/m^2)	147 ± 39	171 ± 51	0.037
EF (%)	60 (50–64)	58 (51–62)	0.64
Stroke volume (ml)	38 (31–46)	49 (41–57)	<0.0001
LA area (cm^2)	22 (21–27)	24 (29–17)	0.78
E/e'	17 (12–23)	15 (11–21)	0.49
TAPSE (mm)	17 (14–20)	19 (16–21)	0.15

Abbreviations: AV = atrioventricular, BJ = Bence Jones protein, BSA = body surface area, CAD = coronary artery disease, dFLC = difference in involved and uninvolved free light chains, E/e' = ratio between early mitral inflow velocity and mitral annular early diastolic velocity, eGFR = estimated Glomerular Filtration Rate, EF = ejection fraction, ICD = implantable cardioverter defibrillator, IVS = inter ventricular septum, LA = left atrium, LBBB = left bundle branch block, LV = left ventricle, LVEDD = left ventricular end diastolic diameter, LVEDV = left ventricular end diastolic volume, MGUS = Monoclonal Gammopathy of Undetermined Significance, MM = multiple myeloma, NYHA = New York Heart Association, NTproBNP = N-terminal pro b-type Natriuretic Peptide, PM = pacemaker, PW = posterior wall, RBBB = right bundle branch block, SM = smouldering myeloma, TAPSE = tricuspid annular plane systolic excursion.

mass; 4) for each subtype of cardiac amyloidosis, all-cause mortality was similar in both sexes (Supplementary Fig. S1).

Women are represented with different prevalence in the wtATTR, hATTR and AL groups, respectively representing the 12%, 25% and 47% of our study population ($p < 0.0001$). This is expected, and in agreement with existing reports [19]. Indeed, wtATTR is an acquired condition know to affects male in large predominance, possibly due to the effect of sex hormones in determining the likelihood of amyloid accumulation. The same trend is present, but less evident, in hATTR, in which genetic predisposition is likely strong enough to partially overcome sex-related predisposition. In AL amyloidosis, due to a lack of preferential propensity between sexes in the underlying hematological conditions, no gender bias is observed in disease expression and prevalence.

WtATTR was mainly diagnosed in males, with a male-female ratio of 7:1 (Fig. 1). Women were diagnosed at an older age and developed symptoms later than men. These findings are in agreement with previous studies [20,21,22,23], and suggest more advanced expression of disease in women at the time of diagnosis. Notably, while normal reference values in females show smaller wall thickness and LV mass than males [24], our wtATTR patients showed higher normalized interventricular septum thickness in women with no difference in normalized LV mass, suggesting greater degree of myocardial infiltration at the time of diagnosis. Nevertheless, mortality was similar between sexes (Supplementary Fig. S1, Panel A) in accordance with a large-scale study of patients in the United Kingdom with ATTR cardiomyopathy, which found no association between sex and all-cause mortality [25].

The reason for sex-related differences in ATTR at referral for investigation is still poorly understood but may involve a combination of sex-specific biological factors and delayed clinical recognition in female patients. Sex hormones may play a role in the prevalence and earlier onset of wtATTR in men [9]. Transthyretin production by the liver of castrated mice increases four-fold in response to exogenous 5α-dihydrotestosterone, which is more effective than estradiol in raising transthyretin expression. In men, the age-related testosterone reduction is a slowly progressive phenomenon, while in women there is a steep decrease in testosterone levels during reproductive age, followed by ovarian estradiol withdrawal after menopause [26]. Therefore, these hormonal changes may concur for lower levels of transthyretin compared to males. In a different pathophysiological model, Alzheimer's disease, estrogens are associated with reduced cerebral amyloid deposition and oxygen-related cell damage [27,28,29]. The issue, however, is far from solved, and other studies show discrepant results. Tanskanen et al. reported that the severity of wtATTR was significantly associated with male sex [30]. Similarly, Siepen et al., Gonzalez-Lopez et al., and Yamamoto et al. reported reduced disease severity in females compared to males [23,31,32].

A different, non mutually exclusive interpretation of our results suggests the role of non-biological factors such as gender disparities in accessing health care systems and comparative delays in women seeking out health care resources. Such biases are well-documented in ischemic heart disease and heart failure, but have not been elucidated in amyloidosis [33,3]. The later age at referral for investigation and echocardiographic signs of more advanced disease and higher NAC-scores at diagnosis suggest that clinicians have to be more aware of CA in women to avoid delay in patient referral. Due to the overt male prevalence in wtATTR, physicians may not raise a suspicion of ATTR until the phenotype is more evident (and therefore severe) compared to men. Furthermore, starting from lower LV wall thickness values, myocardial infiltration may be recognized only when marked. In other words, the disease is diagnosed later, rather then less, in women.

However, milder or atypical disease progression in females also plays a role in postponing diagnosis [22,34,35]. The initial process of amyloid deposition is generally subtle and patients are generally referred to our centre for completing the diagnostic process when wall thickness is thicker than 12 mm. Garcia-Pavia et al. set a cut-off of ≥12 mm of wall thickness as an index of suspicion for amyloidosis [36]. However,

according to the recommendation of the American Society of Echocardiography, normal reference values for interventricular septum in women range from 6 to 9 mm [37]. In our opinion a lower threshold than 12 mm might be proposed in women to avoid late diagnoses, particularly in the presence of other ECG and echocardiographic red flags (i.e. low voltages, atrial fibrillation, diastolic disfunction, apical sparing).

The fact that such unfavorable profile in women with wtATTR did not result in impaired survival or symptomatic status, compared to men, may be due to the small sample of women enrolled. At multivariable Cox regression analysis, sex did not emerge as an independent predictor of survival (while age at diagnosis, NYHA class, NAC score and LV EF did). However, again the small sample size of females in the cohort limits the interpretability of this analysis.

In hATTR, there is a wide genotype and clinical variability in different countries and in different regions of the same county [19,38] and our data should be interpreted in the context of the Tuscany region scenario, characterized by the predominance of Ile68Leu and Val122Ile.

Ile68Leu is a mutation almost exclusively reported in Italy and appears to be endemic in central-northern Italy [39], particularly in the Apennines of Tuscany and Romagna. Whereas Val122Ile is considered the most common worldwide pathogenic variant with an allele frequency of 3.5% in the United States African American population [40], and supposed extremely rare in Caucasian patients. Notably, Mazzarotto et al. demonstrated that Tuscan Val122Ile patients are of ancestral European origin, excluding a mixed African ancestry, implying that the same variant originated in Africans and Europeans independently [41].

These 2 main representative mutations in Tuscany (Ile68Leu and Val122Ile) are considered as late-onset variants, with an exclusively cardiac phenotype in most patients and a neurologic involvement only in a minority of cases [39]. Both mutations show similar phenotypes and their clinical manifestations have been considered very similar to wtATTR manifestations [39].

Despite the intrinsic difficulties and limitations in comparing patients with different ATTR mutations, we tried to provide an overview of sex-related clinical presentation in a population characterized by late phenotypic onset and prevalently isolated cardiac expression.

In our hATTR cohort, patients were more frequently males (75% males vs 25% females, Fig. 1) and younger at diagnosis than those with wtATTR. hATTR is an autosomal dominant disease [42], and should therefore affect men and women equally. However, a male predominance of amyloid heart disease has been shown in late-onset ATTR Val30Met patients in Japan [43] and Sweden [44], as well as in other hATTR mutations [45,46].

In our study, males presented higher normalized mass that may suggest greater myocardial involvement. This behaviour might be influenced by fibril composition. In a Swedish cohort with late-onset Val30Met amyloidosis, women with type A fibrils (a mixture of truncated and full-length ATTR fibrils) had lesser concentric remodeling compared with men, while no difference between sexes was reported in patients with type B fibrils (full length) [47].

Physiological differences in LV mass and LV end-diastolic volumes, related to hormonal production, body size and physical activity, may also play a role [48]. Notably, many markers of heart failure severity and overall morbidity were similar between sexes at the time of diagnosis, including NYHA class, ejection fraction and NAC score and all-cause mortality was similar (Supplementary Fig. S1, Panel B).

In conclusion, we did not observe major differences in clinical expression and all-cause mortality related to sex in different types of CA. However, in wtATTR a sex imbalance in the number of diagnosis was present, women were older than men and showed subtly but significant echocardiographic signs of more advanced disease and higher NAC-scores at diagnosis. Such discrepancy likely reflects true biological diversity as well as social aspects such as differential access to care. Similar to other cardiovascular conditions, clinicians have to be more aware of ATTR in women to avoid overlooking diagnosis. Notably, an earlier and correct diagnosis enables physicians to optimize pharmacotherapy and avoid contraindicated drugs [49]. As several disease-modifying drugs for ATTR-CA will be available in the near future, early diagnosis is essential for timely intervention.

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ijcard.2021.12.048.

Declaration of Competing Interest

None declared.

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