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ORIGINAL RESEARCH

HEART FAILURE AND CARDIOMYOPATHIES

Age- and Sex-Related Differences in Patients With Wild-Type Transthyretin Amyloidosis

Insights From THAOS

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ABSTRACT

BACKGROUND Wild-type transthyretin amyloidosis (ATTRwt amyloidosis) is primarily diagnosed in elderly men but diagnoses in younger patients and women have recently increased.

OBJECTIVES The purpose of this study was to examine age- and sex-related differences in patients with ATTRwt amyloidosis enrolled in the THAOS (Transthyretin Amyloidosis Outcomes Survey).

METHODS THAOS was a global, longitudinal, observational survey of patients with transthyretin amyloidosis, including both hereditary and wild-type disease, and asymptomatic carriers of pathogenic transthyretin gene variants. Patient characteristics at enrollment were analyzed by age at enrollment and sex (data cutoff date: August 1, 2022).

RESULTS Of 1,251 patients with ATTRwt amyloidosis, 13.7%, 49.1%, 34.5%, and 2.8% were aged <70 years, 70 to 79 years, 80 to 89 years, and ≥90 years, respectively. The proportion of women increased with age, from 4.1% in patients aged <70 years to 14.3% in patients aged ≥90 years. In the respective age groups, median time from symptom onset to diagnosis overall (male, female) was 1.7 (1.3, 5.2), 2.0 (2.0, 2.2), 1.8 (1.9, 0.8), and 0.7 (0.6, 2.5) years. A Karnofsky Performance Status score ≤70 was observed in 17.1%, 30.1%, 46.1%, and 44.4% of patients aged <70 years, 70 to 79 years, 80 to 89 years, and ≥90 years, respectively.

CONCLUSIONS In this THAOS analysis of patients with ATTRwt amyloidosis, patients were diagnosed an average of 2 years after symptom onset, with the greatest diagnostic delay in women aged <70 years at 5 years. Patients were predominantly men, but the proportion of women increased with age. A substantial proportion of patients had significant functional impairment regardless of age. (Transthyretin Amyloidosis Outcome Survey [THAOS]; NCT00628745) (JACC Adv. 2024;3:101086) © 2024 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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ABBREVIATIONS AND ACRONYMS

ATTR amyloidosis = transthyretin amyloidosis

ATTRv amyloidosis = hereditary transthyretin amyloidosis

ATTRwt amyloidosis = wild-type transthyretin amyloidosis

BMI = body mass index

ECG = electrocardiogram

LV = left ventricular

NT-proBNP = N-terminal pro-B-type natriuretic peptide

TTR = transthyretin

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive disease characterized by the deposition of transthyretin (TTR) amyloid fibrils in the heart, peripheral nerves, and other tissue and organs.[1-3] There are 2 forms of ATTR amyloidosis: hereditary ATTR amyloidosis (ATTRv amyloidosis), in which a pathogenic *TTR* gene variant is present, and wild-type ATTR amyloidosis (ATTRwt amyloidosis), in which no *TTR* gene variant is identified.[2] ATTRwt amyloidosis is primarily characterized by cardiomyopathy,[4] although a mixed phenotype is increasingly described.[5,6] ATTRv amyloidosis has a more heterogeneous clinical presentation and can manifest as polyneuropathy, cardiomyopathy, or a mix of both.[5,7]

In recent years, there has been a substantial increase in the number of patients diagnosed with ATTR amyloidosis, mostly of the wild-type form, which is now assumed to be the most frequent form of cardiac amyloidosis.[8,9] Increased use of noninvasive diagnostic methods and greater clinical suspicion likely contribute to the growing number of diagnoses and the fact that patients with ATTRwt amyloidosis are increasingly diagnosed at an earlier stage of the disease.[10] In addition, the profile of patients diagnosed with ATTRwt amyloidosis is changing. For example, diagnoses of ATTRwt amyloidosis have increased in women and patients aged >80 years.[10,11] In addition, although the mean age at diagnosis has increased over time, diagnoses in younger patients have also been reported.[12] However, there is limited information about how the clinical manifestations of ATTRwt amyloidosis may differ according to age and sex. The objective of this analysis from the Transthyretin Amyloidosis Outcomes Survey (THAOS) was to compare baseline characteristics of patients with ATTRwt amyloidosis among 4 different age groups (<70 years, 70-79 years, 80-89 years, and ≥90 years) in the whole ATTRwt amyloidosis cohort and in male and female patients with ATTRwt amyloidosis.

METHODS

STUDY DESIGN AND POPULATION. THAOS was the largest global, longitudinal, observational study of patients with ATTR amyloidosis, including both ATTRv and ATTRwt amyloidosis, and asymptomatic carriers of pathogenic *TTR* gene variants, and was completed on June 16, 2023. The overall design and methodology of THAOS have been described in detail.[13] This analysis included all patients with ATTRwt amyloidosis enrolled in THAOS who had not received any disease-modifying treatment (data cut-off date: August 1, 2022).

All THAOS sites received ethical or Institutional Review Board approval before patient enrollment, and each patient provided written informed consent. The study followed the Good Pharmacoepidemiology Practice guidelines and the principles of the Declaration of Helsinki.

ASSESSMENTS. Assessments included those of general wellness (eg, modified body mass index [BMI] and Karnofsky Performance Status) and a range of cardiac parameters. Modified BMI was calculated by multiplying BMI by the serum albumin level to compensate for fluid accumulation. The Karnofsky Performance Status score is a measure of a patient's ability to perform normal daily life activities and their need for assistance; scores range from 10 (moribund; fatal processes progressing rapidly) to 100 (normal; no complaints). Cardiac parameters included NYHA functional class, presence of a pacemaker, electrocardiogram (ECG) and echocardiogram findings, and N-terminal pro-B-type natriuretic peptide (NT-proBNP) concentration. Carpal tunnel syndrome and other comorbidities were also assessed. Phenotype at enrollment is also reported based on previously published criteria.[14]

STATISTICAL ANALYSIS. Patients were grouped by age at enrollment into 1 of 4 groups: <70 years, 70 to 79 years, 80 to 89 years, and ≥90 years. Demographic and clinical characteristics at enrollment were compared between age groups in the overall ATTRwt amyloidosis cohort and among male and female patients only. Nominal *P* values were from the chi-square test for categorical variables, 1-way analysis of variance for means of continuous variables, and the Wilcoxon test for medians of continuous variables.

The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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TABLE 1 Demographic and General Clinical Characteristics According to Age at Enrollment and Sex

	Overall (N = 1,251)	Age <70 y (n = 171)	Age 70-79 y (n = 614)	Age 80-89 y (n = 431)	Age ≥90 y (n = 35)	*P* Value[a]
Sex						0.005
Male (n = 1,166)	1,166 (93.2)	164 (95.9)	582 (94.8)	390 (90.5)	30 (85.7)	-
Female (n = 85)	85 (6.8)	7 (4.1)	32 (5.2)	41 (9.5)	5 (14.3)	-
Age at enrollment (y)						
Overall (n = 1,251)	77.4 (68.5, 86.2)	66.3 (59.7, 69.5)	75.5 (71.4, 79.2)	83.7 (80.6, 87.7)	91.3 (90.2, 95.7)	-
Male (n = 1,166)	77.3 (68.5, 85.8)	66.3 (59.7, 69.5)	75.4 (71.4, 79.2)	83.7 (80.6, 87.6)	91.3 (90.3, 95.5)	-
Female (n = 85)	80.3 (70.6, 88.4)	68.2 (49.6, 69.4)	76.1 (71.8, 79.0)	83.9 (80.5, 88.3)	92.1 (90.1, 96.6)	-
Age at symptom onset (y)						
Overall (n = 1,150)	72.8 (60.0, 82.7)	61.5 (52.5, 67.5)	71.5 (61.5, 77.0)	79.5 (70.4, 84.8)	89.8 (84.0, 93.5)	-
Male (n = 1,070)	72.6 (60.0, 82.5)	61.5 (52.5, 68.0)	71.5 (61.5, 77.0)	79.5 (70.5, 84.5)	90.0 (84.0, 93.5)	-
Female (n = 80)	75.3 (59.3, 85.7)	61.5 (42.5, 65.5)	71.9 (59.3, 75.7)	80.8 (61.5, 85.9)	87.5 (80.0, 95.5)	-
Time from symptom onset to diagnosis (y)						
Overall (n = 1,081)	1.8 (0.0, 12.2)	1.7 (0.0, 11.8)	2.0 (0.0, 13.3)	1.8 (0.0, 12.2)	0.7 (0.0, 5.7)	0.167
Male (n = 1,007)	1.8 (0.0, 12.2)	1.3 (0.0, 12.0)	2.0 (0.0, 13.3)	1.9 (0.0, 11.8)	0.6 (0.0, 4.0)	0.072
Female (n = 74)	1.6 (0.0, 16.6)	5.2 (0.1, 11.4)	2.2 (0.0, 16.6)	0.8 (0.0, 16.8)	2.5 (0.4, 11.8)	0.397
Time from first definitely related symptom to enrollment (y)						
Overall (n = 1,150)	2.9 (0.3, 13.2)	2.3 (0.2, 12.4)	3.0 (0.4, 13.7)	3.1 (0.4, 13.2)	1.9 (0.3, 6.8)	0.134
Male (n = 1,070)	3.0 (0.3, 13.2)	2.2 (0.1, 12.6)	3.1 (0.3, 13.7)	3.2 (0.4, 12.7)	1.8 (0.2, 6.8)	0.041
Female (n = 80)	2.5 (0.6, 16.8)	5.9 (1.8, 11.5)	2.6 (0.6, 15.0)	1.9 (0.5, 19.6)	5.4 (0.8, 12.1)	0.328
Follow-up time (y)						
Overall (n = 1,251)	2.3 (0.4, 5.3)	3.1 (0.5, 6.7)	2.5 (0.5, 5.6)	2.0 (0.4, 4.0)	1.4 (0.0, 2.4)	<0.001
Male (n = 1,166)	2.3 (0.4, 5.3)	3.0 (0.5, 6.7)	2.5 (0.5, 5.6)	2.0 (0.4, 4.1)	1.6 (0.0, 2.6)	<0.001
Female (n = 85)	1.6 (0.1, 5.5)	4.4 (0.0, 7.4)	2.2 (0.5, 6.3)	1.3 (0.2, 3.2)	0.9 (0.0, 1.4)	0.016
Phenotype						
Overall (n = 1,142)						0.081
Predominantly cardiac	901 (78.9)	115 (75.7)	450 (79.5)	316 (80.6)	20 (62.5)	
Mixed	241 (21.1)	37 (24.3)	116 (20.5)	76 (19.4)	12 (37.5)	
Male (n = 1,062)						0.271
Predominantly cardiac	843 (79.4)	111 (76.6)	428 (79.9)	286 (80.8)	18 (66.7)	
Mixed	219 (20.6)	34 (23.4)	108 (20.1)	68 (19.2)	9 (33.3)	
Female (n = 80)						0.204
Predominantly cardiac	58 (72.5)	4 (57.1)	22 (73.3)	30 (78.9)	2 (40.0)	
Mixed	22 (27.5)	3 (42.9)	8 (26.7)	8 (21.1)	3 (60.0)	
mBMI						
Overall (n = 764)	1,065.2 (820.9, 1,322.7)	1,113.5 (836.0, 1,404.9)	1,091.0 (831.0, 1,340.3)	1,026.5 (815.0, 1,263.2)	892.8 (763.9, 1,221.9)	<0.001
Male (n = 705)	1,066.8 (820.9, 1,322.3)	1,120.3 (829.0, 1,418.5)	1,092.0 (831.0, 1,339.9)	1,017.3 (813.9, 1,256.7)	880.7 (769.8, 1,174.2)	<0.001
Female (n = 59)	1,046.6 (816.2, 1,360.3)	999.6 (947.6, 1,076.6)	1,046.6 (856.8, 1,373.7)	1,054.8 (816.2, 1,335.1)	952.0 (711.8, 1,300.0)	0.756

Continued on the next page

RESULTS

DEMOGRAPHIC AND GENERAL CLINICAL CHARACTERISTICS. A total of 1,251 patients with ATTRwt amyloidosis from 53 centers in 15 countries were included in the analysis; 171 (13.7%) were aged <70 years, 614 (49.1%) were aged 70 to 79 years, 431 (34.5%) were aged 80 to 89 years, and 35 (2.8%) were aged ≥90 years. Overall, the majority of patients were men (93.2%) (Table 1). The proportion of women increased with age from 4.1% in patients <70 years old to 14.3% in patients ≥90 years old. Median time from symptom onset to diagnosis was 1.8 years overall and did not differ between age groups (Table 1, Central Illustration). Median time from symptom onset to diagnosis was numerically highest in women aged <70 years at 5.2 years. Similarly, median time from first definitely related symptom to enrollment in THAOS did not differ between age groups and was numerically highest in women aged <70 years at 5.9 years (Table 1).

A majority of patients had a predominantly cardiac phenotype (78.9%) with the rest having a mixed phenotype (21.1%) (Table 1). Phenotype distribution did not differ between age groups or between men and women.

TABLE 1 Continued

	Overall (N = 1,251)	Age <70 y (n = 171)	Age 70-79 y (n = 614)	Age 80-89 y (n = 431)	Age ≥90 y (n = 35)	*P* Value[a]
Karnofsky Performance Status						
Overall (n = 515)						<0.001
80-100	338 (65.6)	58 (82.9)	174 (69.9)	96 (53.9)	10 (55.6)	
50-70	167 (32.4)	9 (12.9)	73 (29.3)	77 (43.3)	8 (44.4)	
10-40	10 (1.9)	3 (4.3)	2 (0.8)	5 (2.8)	0 (0.0)	
Male (n = 468)						0.008
80-100	311 (66.5)	53 (81.5)	162 (69.8)	87 (55.4)	9 (64.3)	
50-70	148 (31.6)	9 (13.8)	68 (29.3)	66 (42.0)	5 (35.7)	
10-40	9 (1.9)	3 (4.6)	2 (0.9)	4 (2.5)	0 (0.0)	
Female (n = 47)						0.080
80-100	27 (57.4)	5 (100.0)	12 (70.6)	9 (42.9)	1 (25.0)	
50-70	19 (40.4)	0 (0.0)	5 (29.4)	11 (52.4)	3 (75.0)	
10-40	1 (2.1)	0 (0.0)	0 (0.0)	1 (4.8)	0 (0.0)	
Bilateral carpal tunnel syndrome						
Overall (n = 1,251)	218 (17.4)	35 (20.5)	110 (17.9)	67 (15.5)	6 (17.1)	0.507
Male (n = 1,166)	198 (17.0)	32 (19.5)	103 (17.7)	58 (14.9)	5 (16.7)	0.508
Female (n = 85)	20 (23.5)	3 (42.9)	7 (21.9)	9 (22.0)	1 (20.0)	0.647
Kidney involvement						
Overall (n = 1,251)	12 (1.0)	2 (1.2)	6 (1.0)	4 (0.9)	0	0.890
Male (n = 1,166)	10 (0.9)	2 (1.2)	4 (0.7)	4 (1.0)	0	0.799
Female (n = 85)	2 (2.4)	0	2 (6.3)	0	0	0.403
Vitreal involvement						
Overall (n = 1,251)	16 (1.3)	2 (1.2)	6 (1.0)	8 (1.9)	0	0.640
Male (n = 1,166)	16 (1.4)	2 (1.2)	6 (1.0)	8 (2.1)	0	0.597
Female (n = 85)	0	0	0	0	0	-
Diabetes mellitus						
Overall (n = 1,251)	164 (13.1)	22 (12.9)	68 (11.1)	66 (15.3)	8 (22.9)	0.071
Male (n = 1,166)	148 (12.7)	21 (12.8)	62 (10.7)	59 (15.1)	6 (20.0)	0.107
Female (n = 85)	16 (18.8)	1 (14.3)	6 (18.8)	7 (17.1)	2 (40.0)	0.601
Inflammatory arthritis						
Overall (n = 1,251)	60 (4.8)	6 (3.5)	33 (5.4)	18 (4.2)	3 (8.6)	0.420
Male (n = 1,166)	56 (4.8)	4 (2.4)	33 (5.7)	17 (4.4)	2 (6.7)	0.277
Female (n = 85)	4 (4.7)	2 (28.6)	0	1 (2.4)	1 (20.0)	0.009
Osteoarthritis						
Overall (n = 1,251)	179 (14.3)	22 (12.9)	88 (14.3)	62 (14.4)	7 (20.0)	0.717
Male (n = 1,166)	170 (14.6)	21 (12.8)	85 (14.6)	58 (14.9)	6 (20.0)	0.732
Female (n = 85)	9 (10.6)	1 (14.3)	3 (9.4)	4 (9.8)	1 (20.0)	0.618

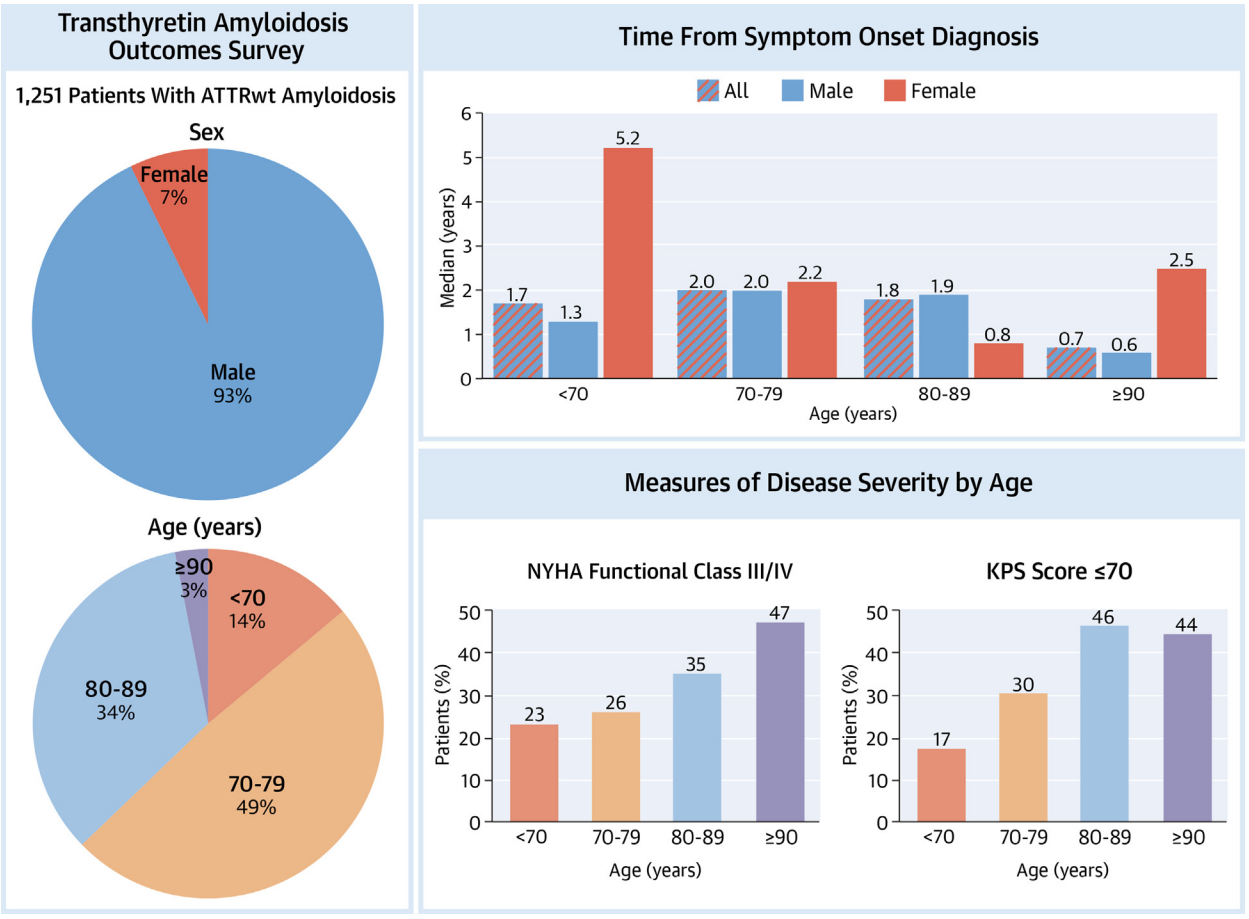
Values are n (%) or median (10th, 90th percentile). Available n (male, female) for variables with missing data in the respective age groups: age at symptom onset: 156 (149, 7), 571 (541, 30), 391 (353, 38), and 32 (27, 5); time from symptom onset to diagnosis: 145 (138, 7), 541 (513, 28), 367 (332, 35), and 28 (24, 4); mBMI: 101 (97, 4), 387 (364, 23), 250 (221, 29), 26 (23, 3); phenotype: 152 (145, 7), 566 (536, 30), 392 (354, 38), 32 (27, 5); Karnofsky Performance Status score: 70 (65, 5), 249 (232, 17), 178 (157, 21), 18 (14, 4). [a]*P* values are nominal and not indicative of statistical significance.

ATTRwt amyloidosis = wild-type transthyretin amyloidosis; mBMI = modified body mass index.

Modified BMI and Karnofsky Performance Status score differed by age. Median modified BMI decreased with age from 1,113.5 in patients aged <70 years to 892.8 in patients aged ≥90 years (Table 1). The same pattern was observed in men, but there was no clear age-related pattern in women. The proportion with a Karnofsky Performance Status score ≤70, indicating the patient is unable to work and requires assistance for self-care, generally increased with age from 17.1% in patients aged <70 years to 44.4% in patients aged ≥90 (Table 1, Central Illustration).

The incidence of comorbidities was generally similar across age groups (Table 1). The incidence of bilateral carpal tunnel syndrome was 17.4% and was numerically higher in women than men in all age groups. Median time from bilateral carpal tunnel syndrome onset to cardiomyopathy onset was 8.9 years in all patients, 8.4 years in men, and 9.2 years in women.

CENTRAL ILLUSTRATION Age and Sex Differences in Patients With ATTRwt Amyloidosis



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A total of 1,251 patients with ATTRwt amyloidosis from the Transthyretin Amyloidosis Outcomes Survey were included in this analysis; most were aged 70 to 79 or 80 to 89 years and male. Median time from symptom onset to diagnosis was ~2 years overall and was numerically highest in women aged <70 years. The proportion of patients with NYHA functional class III/IV heart failure and Karnofsky Performance Status (KPS) scores ≤70 generally increased with age, indicating greater disease severity. ATTRwt amyloidosis = wild-type transthyretin amyloidosis.

CARDIAC PARAMETERS. ECG abnormalities were observed in most patients, but the proportion of patients with ECG abnormalities increased with age in the overall population (Table 2). Mean NT-proBNP concentration generally increased with age, as did the proportion with NYHA functional class III/IV heart failure, reflecting more advanced disease in older patients (Table 2, Figure 1, Central Illustration). The same pattern in NT-proBNP concentration and NYHA functional class was observed among men, but no clear age-related pattern was observed among women.

Left ventricular (LV) wall thickness and other structural and functional cardiac measures did not differ between age groups (Table 2). Men versus women had numerically higher diastolic interventricular septum wall thickness and LV mean wall thickness, but these measures were numerically higher in women when indexed by height. Diastolic interventricular septum wall thickness and LV mean

TABLE 2 Cardiac Characteristics of Patients With ATTRwt Amyloidosis According to Age at Diagnosis and Sex

	Overall (N = 1,251)	Age <70 y (n = 171)	Age 70-79 y (n = 614)	Age 80-89 y (n = 431)	Age ≥90 y (n = 35)	*P* Value[a]
Abnormal ECG						
Overall (n = 1,074)	1,003/1,074 (93.4)	136/154 (88.3)	491/527 (93.2)	350/367 (95.4)	26/26 (100.0)	0.014
Male (n = 999)	936/999 (93.7)	130/147 (88.4)	466/499 (93.4)	318/331 (96.1)	22/22 (100.0)	0.009
Female (n = 75)	67/75 (89.3)	6/7 (85.7)	25/28 (89.3)	32/36 (88.9)	4/4 (100.0)	0.901
Complete AV block or pacemaker						
Overall (n = 953)	405/953 (42.5)	52/133 (39.1)	201/473 (42.5)	143/322 (44.4)	9/25 (36.0)	0.672
Male (n = 889)	386/889 (43.4)	50/127 (39.4)	195/448 (43.5)	133/293 (45.4)	8/21 (38.1)	0.669
Female (n = 64)	19/64 (29.7)	2/6 (33.3)	6/25 (24.0)	10/29 (34.5)	1/4 (25.0)	0.853
LAHB						
Overall (n = 669)	160/669 (23.9)	21/97 (21.6)	75/344 (21.8)	57/210 (27.1)	7/18 (38.9)	0.209
Male (n = 626)	143/626 (22.8)	18/92 (19.6)	70/326 (21.5)	50/193 (25.9)	5/15 (33.3)	0.412
Female (n = 43)	17/43 (39.5)	3/5 (60.0)	5/18 (27.8)	7/17 (41.2)	2/3 (66.7)	0.414
LPHB						
Overall (n = 669)	13/669 (1.9)	3/97 (3.1)	8/344 (2.3)	2/210 (1.0)	0/18 (0.0)	0.515
Male (n = 626)	13/626 (2.1)	3/92 (3.3)	8/326 (2.5)	2/193 (1.0)	0/15 (0.0)	0.554
Female (n = 43)	0/43 (0.0)	0/5 (0.0)	0/18 (0.0)	0/17 (0.0)	0/3 (0.0)	-
LBBB						
Overall (n = 670)	93/670 (13.9)	8/97 (8.2)	45/344 (13.1)	35/211 (16.6)	5/18 (27.8)	0.073
Male (n = 627)	85/627 (13.6)	8/92 (8.7)	41/326 (12.6)	32/194 (16.5)	4/15 (26.7)	0.124
Female (n = 43)	8/43 (18.6)	0/5 (0.0)	4/18 (22.2)	3/17 (17.6)	1/3 (33.3)	0.757
RBBB						
Overall (n = 673)	172/673 (25.6)	22/97 (22.7)	95/345 (27.5)	52/213 (24.4)	3/18 (16.7)	0.567
Male (n = 630)	158/630 (25.1)	20/92 (21.7)	88/327 (26.9)	48/196 (24.5)	2/15 (13.3)	0.519
Female (n = 43)	14/43 (32.6)	2/5 (40.0)	7/18 (38.9)	4/17 (23.5)	1/3 (33.3)	0.780
Pacemaker						
Overall (n = 1,251)	177 (14.1)	17 (9.9)	73 (11.9)	84 (19.5)	3 (8.6)	0.001
Male (n = 1,166)	170 (14.6)	17 (10.4)	71 (12.2)	79 (20.3)	3 (10.0)	0.001
Female (n = 85)	7 (8.2)	0 (0.0)	2 (6.3)	5 (12.2)	0 (0.0)	0.820
NT-proBNP (pg/mL)						
Overall (n = 805)	4,429.6 ± 7,543.2	3,716.1 ± 9,433.0	3,621.0 ± 4,946.5	5,778.5 ± 9,110.9	6,891.6 ± 12,772.8	<0.001
Male (n = 752)	4,303.8 ± 7,373.0	3,630.3 ± 9,519.7	3,428.4 ± 4,350.9	5,729.9 ± 9,078.2	7,467.5 ± 13,418.9	<0.001
Female (n = 53)	6,213.4 ± 9,549.2	5,216.2 ± 8,350.8	6,694.9 ± 10,345.3	6,349.7 ± 9,700.7	1,997.0 ± 1,405.7	0.919
Diastolic interventricular septum wall thickness (mm)						
Overall (n = 919)	17.4 ± 3.6	17.1 ± 3.7	17.5 ± 3.7	17.3 ± 3.5	17.2 ± 3.4	0.650
Male (n = 865)	17.4 ± 3.6	17.3 ± 3.6	17.6 ± 3.7	17.3 ± 3.5	16.1 ± 2.4	0.348
Female (n = 54)	16.9 ± 3.9	14.2 ± 4.5	16.8 ± 3.6	17.0 ± 3.3	21.7 ± 3.5	0.019
Diastolic interventricular septum wall thickness (mm)/height (m)						
Overall (n = 905)	10.1 ± 2.3	9.9 ± 2.6	10.1 ± 2.2	10.1 ± 2.4	10.4 ± 2.5	0.698
Male (n = 851)	10.0 ± 2.3	10.0 ± 2.6	10.0 ± 2.2	10.1 ± 2.5	9.5 ± 1.5	0.713
Female (n = 54)	10.6 ± 2.5	8.6 ± 2.7	10.5 ± 2.4	10.6 ± 2.1	14.1 ± 2.2	0.004
LV mean wall thickness (mm)						
Overall (n = 936)	16.4 ± 3.1	16.4 ± 3.2	16.5 ± 3.1	16.2 ± 2.9	16.2 ± 3.2	0.618
Male (n = 881)	16.4 ± 3.0	16.5 ± 3.1	16.6 ± 3.1	16.2 ± 2.9	15.2 ± 2.4	0.180
Female (n = 55)	15.8 ± 3.2	14.4 ± 4.1	15.4 ± 3.2	15.9 ± 2.5	20.5 ± 2.1	0.013
LV mean wall thickness (mm)/height (m)						
Overall (n = 922)	9.5 ± 2.0	9.4 ± 2.4	9.5 ± 1.9	9.5 ± 2.1	9.8 ± 2.3	0.906
Male (n = 867)	9.5 ± 2.0	9.5 ± 2.3	9.5 ± 1.8	9.5 ± 2.1	8.9 ± 1.5	0.725
Female (n = 55)	9.9 ± 2.2	8.7 ± 2.5	9.6 ± 2.2	9.9 ± 1.7	13.3 ± 1.4	0.003

Continued on the next page

TABLE 2 Continued

	Overall (N = 1,251)	Age <70 y (n = 171)	Age 70-79 y (n = 614)	Age 80-89 y (n = 431)	Age ≥90 y (n = 35)	*P* Value[a]
LVEF (%)						
Overall (n = 927)	48.4 ± 12.5	49.3 ± 13.7	48.6 ± 12.2	47.5 ± 12.4	51.4 ± 14.1	0.309
Male (n = 874)	48.2 ± 12.4	49.2 ± 13.4	48.4 ± 12.1	47.1 ± 12.2	50.4 ± 14.2	0.309
Female (n = 53)	52.2 ± 14.3	53.0 ± 19.3	50.7 ± 13.7	53.1 ± 13.9	55.3 ± 15.3	0.919

Values are n/N (%), n (%), or mean ± SD. Available n (male, female) for variables with missing data in the respective age groups: NT-proBNP: 111 (105, 6), 407 (383, 24), 268 (247, 21), 19 (17, 2); diastolic interventricular septum wall thickness: 136 (129, 7), 455 (433, 22), 308 (287, 21), and 20 (16, 4); diastolic interventricular septum wall thickness/height: 134 (127, 7), 448 (426, 22), 303 (282, 21), 20 (16, 4); LV wall thickness: 144 (137, 7), 458 (435, 23), 314 (293, 21), and 20 (16, 4); LV mean wall thickness/height: 142 (135, 7), 451 (428, 23), 309 (288, 21), and 20 (16, 4); LVEF: 144 (137, 7), 453 (430, 23), 310 (291, 19), and 20 (16,4). [a]*P* values are nominal and not indicative of statistical significance.

ATTRwt amyloidosis = wild-type transthyretin amyloidosis; AV = atrioventricular; ECG = electrocardiogram; LAHB = left anterior hemiblock; LBBB = left bundle branch block; LPHB = left posterior hemiblock; LV = left ventricular; LVEF = left ventricular ejection fraction; NT-proBNP = N-terminal pro-B-type natriuretic peptide; RBBB = right bundle branch block.

wall thickness increased with age in women but stayed relatively stable across age groups in men. Mean LV ejection fraction was numerically higher in women than men in all age groups, but there was no clear age-related pattern.

DISCUSSION

ATTRwt amyloidosis is a condition that is primarily diagnosed in elderly men, although recent reports have revealed an increase in diagnoses in women and younger patients. This analysis from the THAOS database examined age- and sex-related differences in baseline characteristics in more than 1,200 patients with ATTRwt amyloidosis.

In this analysis, 13.7% of patients with ATTRwt amyloidosis were aged <70 years at enrollment. Although this cohort tended to present with less severe disease than older patients, a considerable proportion exhibited significant functional impairment and advanced cardiac disease. Specifically, 17.1% of patients with ATTRwt amyloidosis aged <70 years had a Karnofsky score at or below 70, indicating that they were unable to work and required varying levels

FIGURE 1 NYHA Functional Class

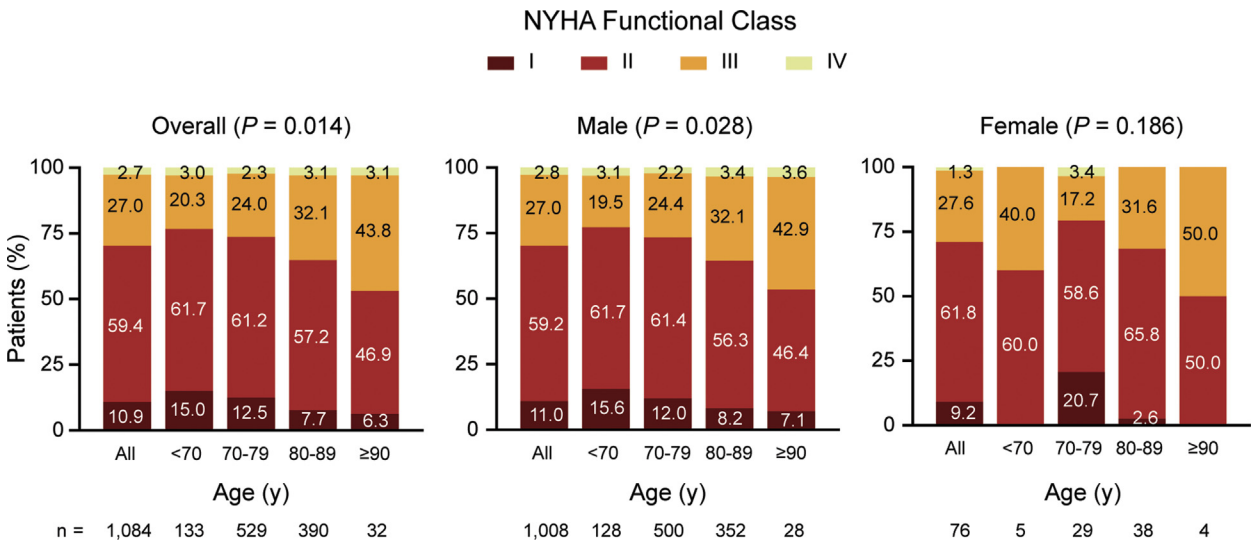

Figure shows NYHA functional class collected at enrollment in the Transthyretin Amyloidosis Outcomes Survey in patients with wild-type transthyretin amyloidosis according to age at enrollment and sex. *P* values correspond to differences between age groups. The proportion of patients with NYHA functional class III/IV heart failure increased with age overall and among men, but no clear age-related pattern was observed among women.

of assistance with everyday activities or frequent medical care. Furthermore, 23.3% of patients had NYHA functional class III or IV heart failure at enrollment, suggesting that ATTRwt amyloidosis is often diagnosed late in the disease course in this age group. The proportion of patients with ECG abnormalities also increased with age, but this is not unexpected given the age of these patients and could be related to conditions other than ATTRwt amyloidosis.

Median time from symptom onset to diagnosis was ~2 years in this group of patients. One factor that may contribute to the delay in diagnosis is that many patients in THAOS were diagnosed using biopsy, before the advent of scintigraphy, and biopsy has been linked with delayed diagnosis of ATTR amyloidosis. One of the most striking findings was that the median time from symptom onset to diagnosis was longest among women aged <70 years at 5 years. This may be a consequence of the historical association of ATTRwt amyloidosis with elderly men, resulting in lower clinical suspicion and delayed diagnosis in women aged <70 years, and highlights an important area of improvement in patient screening. Delayed diagnosis in patients with ATTRwt amyloidosis has been previously reported,[15] and the current study suggests that women aged <70 years may be the most impacted.

Recent reports indicate that women may make up a greater proportion of ATTRwt amyloidosis patients than previously thought, with some studies reporting rates as high as 20%.[4,16] Although men accounted for over 90% of patients in the current analysis, consistent with a prior THAOS analysis of patients with ATTRwt amyloidosis,[17] the proportion of women increased with age. The prior THAOS analysis and other studies have suggested that women with ATTRwt amyloidosis have a later age at onset and milder cardiac phenotype than men.[4,17,18] In line with these prior findings, women in this cohort were, on average, older at symptom onset and at enrollment. Diastolic interventricular septum and LV mean wall thickness were numerically lower in women than men, although women had slightly higher measures when indexed by height. It has been suggested that a uniform LV wall thickness threshold to screen for transthyretin amyloid cardiomyopathy in men and women could lead to underdiagnosis in women[19] and that an indexed threshold should be used instead.[20] Our finding of greater wall thickness in women when indexed by height supports this position. We also observed that diastolic interventricular septum thickness and LV mean wall thickness increased with age in women but not in men, and women aged ≥90 years had numerically higher measures than men in the same age group. Despite this, mean NT-proBNP concentration was lower and LV ejection fraction higher in women than men aged ≥90 years, indicating less severe heart failure.

STUDY LIMITATIONS. Our study has several limitations. The number of women in this analysis was small, with only 7 patients in the youngest cohort and 5 in the oldest, thereby limiting our ability to draw robust conclusions from these data. Findings should be confirmed in larger samples. Prognostic data were not available for this analysis, so we were not able to assess whether cardiac manifestations were associated with worse outcomes. The THAOS registry includes detailed data on cardiac manifestations, but fewer details were available for neuropathy and musculoskeletal symptoms in ATTRwt amyloidosis. This may be the result of underreporting due to inconsistent assessment across centers and the fact that these patients were seen or referred primarily by cardiologists who did not perform neurologic assessments. Additionally, given the small sample sizes for some of the cohorts, we were not able to examine how patient characteristics based on age and sex may have changed over the life of THAOS; future studies should look at temporal trends in these age- and sex-based findings. Lastly, some patients were missing cardiac and other baseline clinical data.

CONCLUSIONS

In this THAOS analysis, patients aged <70 years with ATTRwt amyloidosis had less severe disease than older patients. Nevertheless, a substantial proportion displayed functional impairment and advanced heart failure. Importantly, women aged <70 years had the greatest diagnostic delay of all the cohorts at 5 years, which may be the result of low clinical suspicion in this patient population. The proportion of women with ATTRwt amyloidosis increased with age. Overall, this analysis provides important information about the clinical manifestations of ATTRwt amyloidosis across different age groups and in men and women.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Patients aged <70 years with ATTRwt amyloidosis present with less severe disease than older patients, but a substantial proportion still exhibit significant impairment. Women aged <70 years with ATTRwt amyloidosis experience the greatest delay in diagnosis.

TRANSLATIONAL OUTLOOK: Increased clinical suspicion may be warranted in patients aged <70 years, especially female patients, so that they may benefit from early treatment before further disease progression.

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KEY WORDS age, amyloid, cardiomyopathy, sex differences

APPENDIX For a list of the additional THAOS investigators, please see the online version of this paper.