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### Permalink

<https://escholarship.org/uc/item/1606332c>

### Journal

Cardiology and Therapy, 13(1)

### ISSN

2193-8261

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### Publication Date

2024-03-01


### DOI

10.1007/s40119-023-00344-3

Peer reviewed



# Clinical and Genotype Characteristics and Symptom Migration in Patients With Mixed Phenotype Transthyretin Amyloidosis from the Transthyretin Amyloidosis Outcomes Survey

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Received: September 10, 2023 / Accepted: November 21, 2023 / Published online: December 20, 2023  
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## ABSTRACT

**Introduction:** Transthyretin amyloidosis (ATTR amyloidosis) is primarily associated with a cardiac or neurologic phenotype, but a mixed phenotype is increasingly described.

**Prior presentation** These data were presented in part at the XVIII International Symposium on Amyloidosis, Heidelberg, Germany, September 4–8, 2022.

The members of the THAOS investigators are mentioned in the Acknowledgements section.

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**Methods:** This study describes the mixed phenotype cohort in the Transthyretin Amyloidosis Outcomes Survey (THAOS). THAOS is an ongoing, longitudinal, observational survey of patients with ATTR amyloidosis, including both hereditary (ATTRv) and wild-type disease, and asymptomatic carriers of pathogenic transthyretin variants. Baseline characteristics of patients with a mixed phenotype (at enrollment or reclassified during follow-up) are described (data cutoff: January 4, 2022).

**Results:** Approximately one-third of symptomatic patients ( $n = 1185/3542$ ; 33.5%) were

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classified at enrollment or follow-up as mixed phenotype (median age, 66.5 years). Of those, 344 (29.0%) were reclassified to mixed phenotype within a median 1–2 years of follow-up. Most patients with mixed phenotype had ATTRv amyloidosis (75.7%). The most frequent genotypes were V30M (38.9%) and wild type (24.3%).

**Conclusions:** These THAOS data represent the largest analysis of a real-world mixed phenotype ATTR amyloidosis population to date and suggest that a mixed phenotype may be more prevalent than previously thought. Patients may also migrate from a primarily neurologic or cardiologic presentation to a mixed phenotype over time. These data reinforce the need for multidisciplinary evaluation at initial assessment and follow-up of all patients with ATTR amyloidosis.

**Trial Registration:** ClinicalTrials.gov: NCT00628745.

**Keywords:** Amyloidosis; Cardiomyopathy; Mixed phenotype; Polyneuropathy; Transthyretin; THAOS

## Key Summary Points

### *Why carry out this study?*

Transthyretin amyloidosis (ATTR amyloidosis) is primarily associated with a predominantly cardiac or neurologic phenotype, but a mixed phenotype is increasingly described.

This study utilized data from the Transthyretin Amyloidosis Outcomes Survey (THAOS) to describe characteristics of patients with ATTR amyloidosis and a mixed phenotype.

### *What was learned from this study?*

Approximately one-third of symptomatic patients from THAOS had a mixed phenotype, suggesting that it may be more prevalent than previously thought.

Patients may migrate from a primarily neurologic or cardiologic presentation to a mixed phenotype over time.

These data reinforce the need for multidisciplinary evaluation at initial assessment and follow-up of all patients with ATTR amyloidosis.

## INTRODUCTION

Transthyretin amyloidosis (ATTR amyloidosis) is a progressive, multisystemic disease with hereditary (variant; ATTRv amyloidosis) and acquired (wild-type; ATTRwt amyloidosis) etiologies [1]. ATTR amyloidosis results from the deposition of transthyretin (TTR) amyloid fibrils in organs and tissues throughout the body, leading to cardiac and peripheral nervous system dysfunction [2]. ATTRv amyloidosis is characterized by variants in the *TTR* gene that lead to increased tetramer instability, monomer dissociation, and aggregation, whereas ATTRwt amyloidosis is characterized by instability of the native TTR tetramer, resulting in age-related

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monomer release, misfolding, and fibrillogenesis [1]. Although ATTR amyloidosis is a heterogeneous disease, its phenotypic presentation is classified as predominantly neurologic, predominantly cardiac, or mixed [1]. The perceived clinical phenotype is a function of both the anatomic sites of fibril deposition, which may depend on the specific *TTR* variant, and, perhaps more importantly, the ability of healthcare professionals to ascertain the impact of the fibrillar deposits on specific organ function [2, 3]. More than 130 pathogenic variants have been reported to be associated with ATTRv amyloidosis [4]. One of the most frequently reported variants worldwide, V30M (p.V50M), is primarily associated with neurologic or mixed phenotypes [5]. Conversely, ATTRwt amyloidosis is primarily associated with a cardiac phenotype but can also present with a mixed phenotype [5, 6]. Although consensus guidelines on the management of patients with ATTR amyloidosis recommend both comprehensive neurologic and cardiologic assessment at initial evaluation [3, 7], this is typically not done in clinical practice; rather, the focus of the assessment largely depends on provider expertise (i.e., cardiologist or neurologist). The resulting referral bias may lead to an underreporting of the prevalence of mixed phenotype in the ATTR amyloidosis population [5]. Furthermore, a patient may present with a predominantly neurologic or cardiac phenotype at initial assessment, but as the disease progresses, clinical presentation may evolve to a mixed phenotype.

The Transthyretin Amyloidosis Outcomes Survey (THAOS) is the largest ongoing, longitudinal, observational study of patients with ATTR amyloidosis, including both ATTRv and ATTRwt amyloidosis, as well as asymptomatic carriers of pathogenic *TTR* variants (NCT00628745) [8]. Owing to its large patient population, THAOS has provided valuable insights into ATTR amyloidosis and has highlighted the genotypic, phenotypic, and geographic heterogeneity of the disease [5, 9–13]. The objective of this analysis was to examine baseline demographic and clinical characteristics of a large sample of patients with mixed-phenotype ATTR amyloidosis in THAOS,

including comparison of those classified as mixed phenotype at enrollment vs those who migrated from a predominantly cardiac or neurologic phenotype at enrollment to a mixed phenotype during follow-up. This is the first report to date registering the disease evolution and migration from one phenotype to another in an ATTR amyloidosis patient population.

## METHODS

The study design and eligibility criteria for THAOS have been described [8]. All study sites received ethical or institutional review board approval prior to patient enrollment, and each patient provided written informed consent. The study followed the Good Pharmacoevidence Practice guidelines and the principles of the Declaration of Helsinki. The study was approved at the primary site in this analysis by Comité de Ética de la Investigación de las Illes Balears (CEIM-IB).

### Patient Populations and Classifications

The full analysis set (FAS) included all untreated symptomatic patients enrolled in THAOS as of the data cutoff date who met inclusion/exclusion criteria with signed informed consent, and who were classified as having a mixed phenotype at enrollment or who were classified as either predominantly cardiac or predominantly neurologic at enrollment and were reclassified as having a mixed phenotype at any subsequent follow-up visit. Patients were either never treated with tafamidis, or if they were started on tafamidis treatment post-enrollment, then only data from the time of enrollment until the day prior to the first date of tafamidis treatment were included in this analysis. Symptomatic patients included patients with at least one symptom reported as definitely ATTR-related at enrollment regardless of whether or not all symptoms were assessed. Symptom onset was defined as the date of first occurrence of symptom(s) that were reported as definitely ATTR-related. Symptom relatedness was determined by the investigator.

Patients were analyzed according to genotype group; the ATTRwt amyloidosis group included all patients classified as wild type at enrollment in THAOS, and the ATTRv amyloidosis group included all patients with a documented *TTR* variant. Patients with ATTRv amyloidosis were further subdivided into V30M (patients with either V30M, V30M + G6S [p.G26S], or V30M + E7V [p.E27V]) and non-V30M (all other patients with ATTRv amyloidosis) groups.

Phenotypes were defined as follows. The predominantly cardiac phenotype included patients with abnormal electrocardiogram (ECG) due to rhythm disturbance, heart failure (HF), or dyspnea, and no more than mild neurologic or gastrointestinal (GI) symptoms (excluding erectile dysfunction, constipation, and carpal tunnel). Cardiac symptoms did not need to be ongoing at a given visit to be included for phenotyping; however, symptoms needed to be definitely related to ATTR amyloidosis. The predominantly neurologic phenotype included patients with neurologic or GI symptoms of any severity and who did not have abnormal ECG due to rhythm disturbance, HF, or dyspnea. Neurologic and GI symptoms had to be ongoing and definitely related to ATTR amyloidosis. A modified polyneuropathy disability (mPND) score  $\geq$  I was included as a neurologic symptom wherever applicable. The mixed phenotype included patients with abnormal ECG due to rhythm disturbance, HF, or dyspnea and neurologic or GI symptoms of any severity but did not satisfy the criteria for predominantly cardiac or predominantly neurologic. Symptomatic patients with unknown phenotype included all other symptomatic patients who did not meet any of the above criteria for any of the predominantly cardiac, predominantly neurologic, or mixed phenotypes. All patients with ATTRwt amyloidosis at enrollment were classified as predominantly cardiac unless they had any neurologic symptoms that were definitely related to ATTR amyloidosis, in which case they were classified as having a mixed phenotype.

Under the assumption that phenotype-related symptoms do not truly disappear but are only masked or temporarily resolved,

phenotype classifications were carried forward to future visits even if there were no available symptom data at the subsequent visit. Patients classified as predominantly cardiac or predominantly neurologic at a given visit continued to be classified as such at subsequent visits unless the patient developed additional symptoms warranting a reclassification to mixed phenotype. The mixed phenotype is considered a persistent state, so once a patient was classified as having a mixed phenotype at a given visit, that patient remained in the mixed category at all subsequent visits.

Patients were further divided according to the following categories: the mixed phenotype throughout set included all patients in the FAS who were classified as having a mixed phenotype at enrollment; the predominantly cardiac to mixed phenotype set included all patients in the FAS classified as predominantly cardiac at enrollment and were reclassified as having a mixed phenotype at any subsequent follow-up visit; and the predominantly neurologic to mixed phenotype set included all patients in the FAS classified as predominantly neurologic at enrollment and were reclassified as having a mixed phenotype at any subsequent follow-up visit. The phenotype reclassification visit was defined as the first visit during which a patient was reclassified as having a mixed phenotype from either predominantly cardiac or predominantly neurologic. New symptom categories were those reported at the time of phenotype reclassification that were not reported at enrollment.

## Assessments

Demographic and clinical characteristics of untreated patients in THAOS with mixed-phenotype ATTR amyloidosis at enrollment or reclassified as mixed phenotype during follow-up were assessed descriptively (data cutoff date: January 4, 2022). Symptoms at baseline were categorized as autonomic neuropathy, cardiac disorder, GI manifestations, motor neuropathy, and sensory neuropathy. Autonomic neuropathy included dizziness, palpitations, dry eye, constipation, diarrhea, diarrhea/constipation,

early satiety, fecal incontinence, nausea, vomiting, recurrent urinary tract infections, urinary incontinence, urinary retention, dyshidrosis, and erectile dysfunction. Cardiac disorder included coronary artery disease, dyspnea, HF, myocardial infarction, rhythm disturbance, syncope, arterial hypertension, cardiomyopathy, and other cardiovascular disease. GI manifestations included constipation, diarrhea, diarrhea/constipation, early satiety, fecal incontinence, nausea, unintentional weight loss, and vomiting. Motor neuropathy included muscle weakness and walking disability. Sensory neuropathy included balance abnormality, neuropathic arthropathy, neuropathic pain/paresthesia, numbness, temperature or pain insensitivity, and tingling. Symptom categories were not mutually exclusive.

Patients' ability to perform normal daily life activities and their need for assistance was assessed using the Karnofsky Performance Status Scale score, ranging from 10 (moribund; fatal processes progressing rapidly) to 100 (normal; no complaints). Neurologic impairment was measured in symptomatic patients using the derived Neuropathy Impairment Score in the Lower Limbs (NIS-LL; ranges from 0 to 88) [14]. Higher scores indicate greater impairment, and the NIS-LL scale includes reflex, motor, and sensory subscales. mPND scores were analyzed in symptomatic patients with a predominantly neurologic or mixed phenotype. The mPND score is a measure of walking disability and ranges from 0 to IV, where 0 indicates no sensory disturbance in the feet and ability to walk without difficulty; I indicates sensory disturbance in the feet but preserved walking capacity; II indicates some difficulties walking but able to walk without aid; IIIa indicates one stick or crutch required for walking; IIIb indicates two sticks or crutches required for walking; and IV indicates patients confined to a wheelchair or bed. Health-related quality of life (HRQoL) was assessed using the European Quality of Life five-dimension three-level scale (EQ-5D-3L) and the Norfolk Quality of Life–Diabetic Neuropathy questionnaire. The EQ-5D-3L is a measure of self-reported health status. The first part assesses health on five dimensions (mobility, self-care, usual activities,

pain/discomfort, and anxiety/depression), each with three levels: no problems, some problems, and extreme problems/unable to perform. Health state profiles are assigned a summary index score ranging from 0 (death) to 1 (perfect health). The second part is a visual analog scale in which patients rate perceived health from 0 (worst) to 100 (best). The 35-item Norfolk Quality of Life (QoL)–Diabetic Neuropathy (DN) questionnaire assesses diabetic neuropathy across five domains: physical functioning/large fiber neuropathy, activities of daily living, symptoms, small fiber neuropathy, and autonomic neuropathy. Scores range from –4 to 136, with higher scores indicating worse HRQoL.

Measures of cardiac involvement in symptomatic patients were left ventricular septal wall thickness (LVSWT) and left ventricular ejection fraction (LVEF). New York Heart Association (NYHA) functional class was analyzed in patients with HF.

### Statistical Analysis

This descriptive analysis examined baseline characteristics of patients with a mixed phenotype and compared patients with a mixed phenotype classified at enrollment vs those reclassified as having a mixed phenotype during the study. Continuous data are presented as median (10th, 90th percentile), and categorical data are presented as count (percentage).

## RESULTS

### Patient Demographics and Genotype

At the time of the analysis, 3542/5286 untreated patients enrolled in THAOS were symptomatic. Approximately one-third of symptomatic patients ( $n = 1185$ , 33.5%) were classified as having a mixed phenotype (68.9% male, 73.0% White); 897 (75.7%) had ATTRv amyloidosis and 288 (24.3%) had ATTRwt amyloidosis. Median age at enrollment was 66.5 years and median symptom duration was 5.2 years (Table 1). Most patients 841/1185 (71.0%) were

**Table 1** Demographic and clinical characteristics of patients with mixed phenotype ATTR amyloidosis enrolled in THAOS according to genotype

	<b>Overall (N = 1185)</b>	<b>ATTRwt amyloidosis (n = 288)</b>	<b>V30M ATTRv amyloidosis (n = 461)</b>	<b>Non-V30M ATTRv amyloidosis (n = 436)</b>
Male, n (%)	817 (68.9)	265 (92.0)	274 (59.4)	278 (63.8)
Age at enrollment (years), median (10th, 90th percentile)	66.5 (41.7, 80.7)	77.5 (68.0, 87.1)	58.3 (35.2, 75.7)	62.9 (46.9, 77.2)
Race, n	895	259	256	380
White, n (%)	653 (73.0)	233 (90.0)	190 (74.2)	230 (60.5)
Black, n (%)	94 (10.5)	8 (3.1)	18 (7.0)	68 (17.9)
Asian, n (%)	95 (10.6)	12 (4.6)	39 (15.2)	44 (11.6)
Other, n (%)	53 (5.9)	6 (2.3)	9 (3.5)	38 (10.0)
Symptom duration (years), median (10th, 90th percentile)	5.2 (1.0, 16.8)	4.2 (0.7, 18.0)	6.4 (1.7, 16.8)	4.8 (0.9, 15.1)
mBMI, n	759	170	324	265
Median (10th, 90th percentile)	983.3 (717.9, 1265.6)	1045.0 (822.2, 1323.3)	953.8 (667.7, 1248.0)	963.6 (705.9, 1257.8)
Karnofsky Performance Status score, n	927	194	385	348
10–30, n (%)	6 (0.6)	1 (0.5)	1 (0.3)	4 (1.1)
40–60, n (%)	209 (22.5)	26 (13.4)	106 (27.5)	77 (22.1)
70–90, n (%)	676 (72.9)	162 (83.5)	269 (69.9)	245 (70.4)
100, n (%)	36 (3.9)	5 (2.6)	9 (2.3)	22 (6.3)

*ATTR amyloidosis* transthyretin amyloidosis, *ATTRv amyloidosis* hereditary transthyretin amyloidosis, *ATTRwt amyloidosis* wild-type transthyretin amyloidosis, *mBMI* modified body mass index, *THAOS* Transthyretin Amyloidosis Outcomes Survey

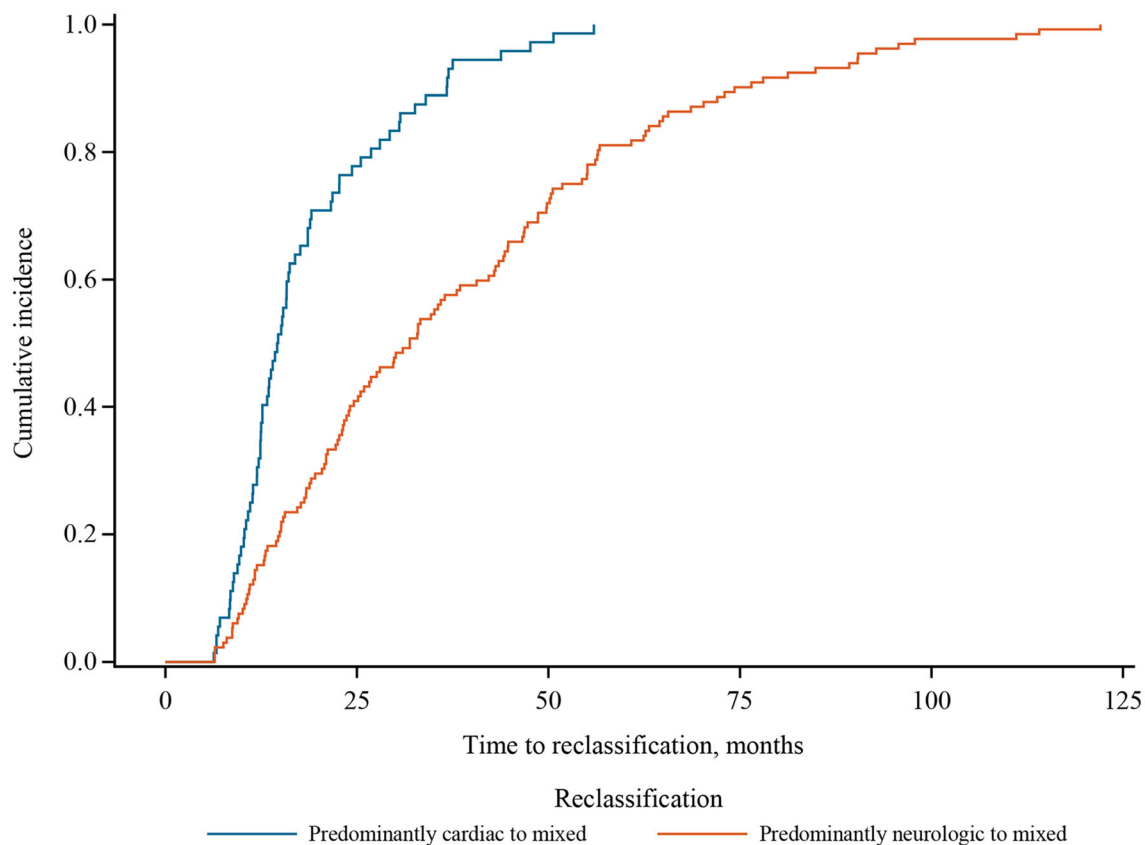
classified as having a mixed phenotype at enrollment and 344/1185 (29.0%) were reclassified as having a mixed phenotype during the study.

In patients who were classified as having a mixed phenotype at enrollment ( $n = 841$ ; 72.2% male, 72.5% White), 605 (71.9%) had ATTRv amyloidosis and 236 (28.1%) had ATTRwt amyloidosis. Median age at enrollment was 68.5 years and median symptom duration at enrollment was 5.7 years. A higher proportion of patients with ATTRwt amyloidosis vs ATTRv amyloidosis were male (91.5% vs 64.6%)

and White (91.5% vs 63.7%). Patients with ATTRwt amyloidosis vs ATTRv amyloidosis were also older (median age at enrollment, 77.5 vs 63.5 years) and had a higher modified body mass index (median, 1042.9 vs 936.2).

In 344 patients reclassified as having a mixed phenotype during the study, 238 (69.2%) were reclassified from a predominantly neurologic phenotype and 106 (30.8%) were reclassified from a predominantly cardiac phenotype.

All 238 patients initially enrolled with a predominantly neurologic phenotype (54.2% male, 76.3% White) had ATTRv amyloidosis.



**Fig. 1** Cumulative incidence of time to reclassification to mixed phenotype according to initial phenotype

Median age at enrollment was 55.0 years and median symptom duration at enrollment was 4.4 years. Median time from enrollment to phenotype reclassification was 32.2 months (Fig. 1).

Among 106 patients initially enrolled with a predominantly cardiac phenotype (76.4% male, 71.9% White), 54 (50.9%) had ATTRv amyloidosis and 52 (49.1%) had ATTRwt amyloidosis. Median age at enrollment was 70.6 years and median symptom duration was 3.8 years. Median time from enrollment to phenotype reclassification was 14.8 months.

In the overall mixed phenotype population, the most frequent genotype was V30M ( $\pm$  G6S or E7V) (38.9%) followed by wild type (24.3%) (Table 2). The most common non-V30M variants (36.8% of the overall genotypes represented) were V122I (p.V142I) (7.4%) and E89Q (p.E109Q) (6.8%).

### Symptom Categories at Enrollment

In the overall mixed phenotype population, cardiac disorder and sensory neuropathy were the most common symptom categories, followed by autonomic neuropathy, GI symptoms, and motor neuropathy (Fig. 2). Neuropathy and GI symptoms were more common in ATTRv amyloidosis than ATTRwt amyloidosis and more common in V30M ATTRv amyloidosis than non-V30M ATTRv amyloidosis.

In the subset of patients who were classified as having a mixed phenotype at enrollment, cardiac disorder (92.4%) was the most common symptom category at enrollment, followed by sensory neuropathy (71.6%), autonomic neuropathy (62.9%), GI symptoms (48.5%), and motor neuropathy (43.5%). A greater proportion of patients with ATTRv amyloidosis vs ATTRwt amyloidosis had cardiac disorder (100.0% vs 72.9%), sensory neuropathy (84.3%



**Table 2** Genotype distribution of patients with mixed phenotype ATTR amyloidosis enrolled in THAOS

Genotype, <i>n</i> (%)	Overall ( <i>N</i> = 1185)
V30M (p.V50M) + G6S (p.G26S)/ V30M (p.V50M) + V30M (p.V50M)/E7V (p.E27V)	461 (38.9)
Wild type	288 (24.3)
V122I (p.V142I)	88 (7.4)
E89Q (p.E109Q)	81 (6.8)
T60A (p.T80A) + T60A (p.T80A)/ G6S (p.G26S)	39 (3.3)
S50R (p.S70R)	27 (2.3)
I68L (p.I88L)	22 (1.9)
D38A (p.D58A)	17 (1.4)
E89K (p.E109K)	12 (1.0)
I107V (p.I127V)	11 (0.9)
S77Y (p.S97Y)	11 (0.9)
S77F (p.S97F)	10 (0.8)
F64L (p.F84L)	9 (0.8)
H88R (p.H108R)	7 (0.6)
A97S (p.A117S)	6 (0.5)
G47A (p.G67A)	6 (0.5)
F33L (p.F53L)	6 (0.5)
T59K (p.T79K)	6 (0.5)
delV122 (p.delV142)	5 (0.4)
V20I (p.V40I)	4 (0.3)
E54Q (p.E74Q)	3 (0.3)
L58H (p.L78H)	3 (0.3)
S52P (p.S72P)	3 (0.3)
V122A (p.V142A)	3 (0.3)
A120S (p.A140S)	2 (0.2)
A19D (p.A39D)	2 (0.2)
R34S (p.R54S)	2 (0.2)
D38V (p.D58V)	2 (0.2)
E54L (p.E74L)	2 (0.2)

**Table 2** continued

Genotype, <i>n</i> (%)	Overall ( <i>N</i> = 1185)
E62K (p.E82K)	2 (0.2)
G47E (p.G67E)	2 (0.2)
K70N (p.K90N)	2 (0.2)
S50I (p.S70I)	2 (0.2)
T49A (p.T69A)	2 (0.2)
Y116S (p.Y136S)	2 (0.2)
V28M (p.V48M)	2 (0.2)
M13dup (p.M33dup)	2 (0.2)
A19D (p.A39D)/G6S (p.G26S)	1 (0.1)
A45D (p.A65D)	1 (0.1)
A45S (p.A65S)	1 (0.1)
A45T (p.A65T)	1 (0.1)
D18N (p.D38N)	1 (0.1)
C10R (p.C30R)	1 (0.1)
E42G (p.E62G)	1 (0.1)
E54G (p.E74G)	1 (0.1)
E54K (p.E74K)	1 (0.1)
E61G (p.E81G)	1 (0.1)
E61K (p.E81K)	1 (0.1)
E92K (p.E112K)	1 (0.1)
G47V (p.G67V)	1 (0.1)
G6S (p.G26S)	1 (0.1)
G6S (p.G26S)/T49I (p.T69I)	1 (0.1)
I107M (p.I127M)	1 (0.1)
I107F (p.I127F)	1 (0.1)
I73V (p.I93V)	1 (0.1)
I84N (p.I104N)	1 (0.1)
I84S (p.I104S)	1 (0.1)
I84T (p.I104T)	1 (0.1)
L111M (p.L131M)	1 (0.1)
L12P (p.L32P)	1 (0.1)
K35N (p.K55N)	1 (0.1)

**Table 2** continued

Genotype, <i>n</i> (%)	Overall ( <i>N</i> = 1185)
P24S (p.P44S)	1 (0.1)
S23N (p.S43N)	1 (0.1)
T40N (p.T60N)	1 (0.1)
T59R (p.T79R)	1 (0.1)
T75I (p.T95I)	1 (0.1)
T80I	1 (0.1)
V71A (p.V91A)	1 (0.1)

*ATTR amyloidosis* transthyretin amyloidosis, *THAOS* Transthyretin Amyloidosis Outcomes Survey

vs 39.0%), autonomic neuropathy (76.9% vs 27.1%), motor neuropathy (55.7% vs 12.3%), and GI symptoms (64.1% vs 8.5%). A greater proportion of patients with V30M ATTRv amyloidosis vs non-V30M ATTRv amyloidosis had sensory neuropathy (95.1% vs 74.5%), autonomic neuropathy (87.1% vs 67.6%), motor neuropathy (67.2% vs 45.3%), and GI symptoms (74.2% vs 55.0%).

In patients who were reclassified from a predominantly neurologic to mixed phenotype, sensory neuropathy (85.7%) was the most common symptom, followed by autonomic neuropathy (66.0%), GI symptoms (60.1%), motor neuropathy (49.6%), and cardiac disorder (10.1%). In patients with V30M ATTRv amyloidosis vs non-V30M ATTRv amyloidosis, sensory neuropathy (92.1% vs 71.2%), autonomic neuropathy (74.5% vs 46.6%), motor neuropathy (57.0% vs 32.9%), and GI symptoms (70.3% vs 37.0%) were more common.

In patients who were reclassified from a predominantly cardiac to mixed phenotype, cardiac disorder (94.3%) was the most common symptom category, followed by autonomic neuropathy (37.7%), sensory neuropathy (34.0%), GI symptoms (16.0%), and motor neuropathy (6.6%). Cardiac disorder (100.0% vs 88.5%), autonomic neuropathy (53.7% vs 21.2%), sensory neuropathy (51.9% vs 15.4%), motor neuropathy (11.1% vs 1.9%), and GI

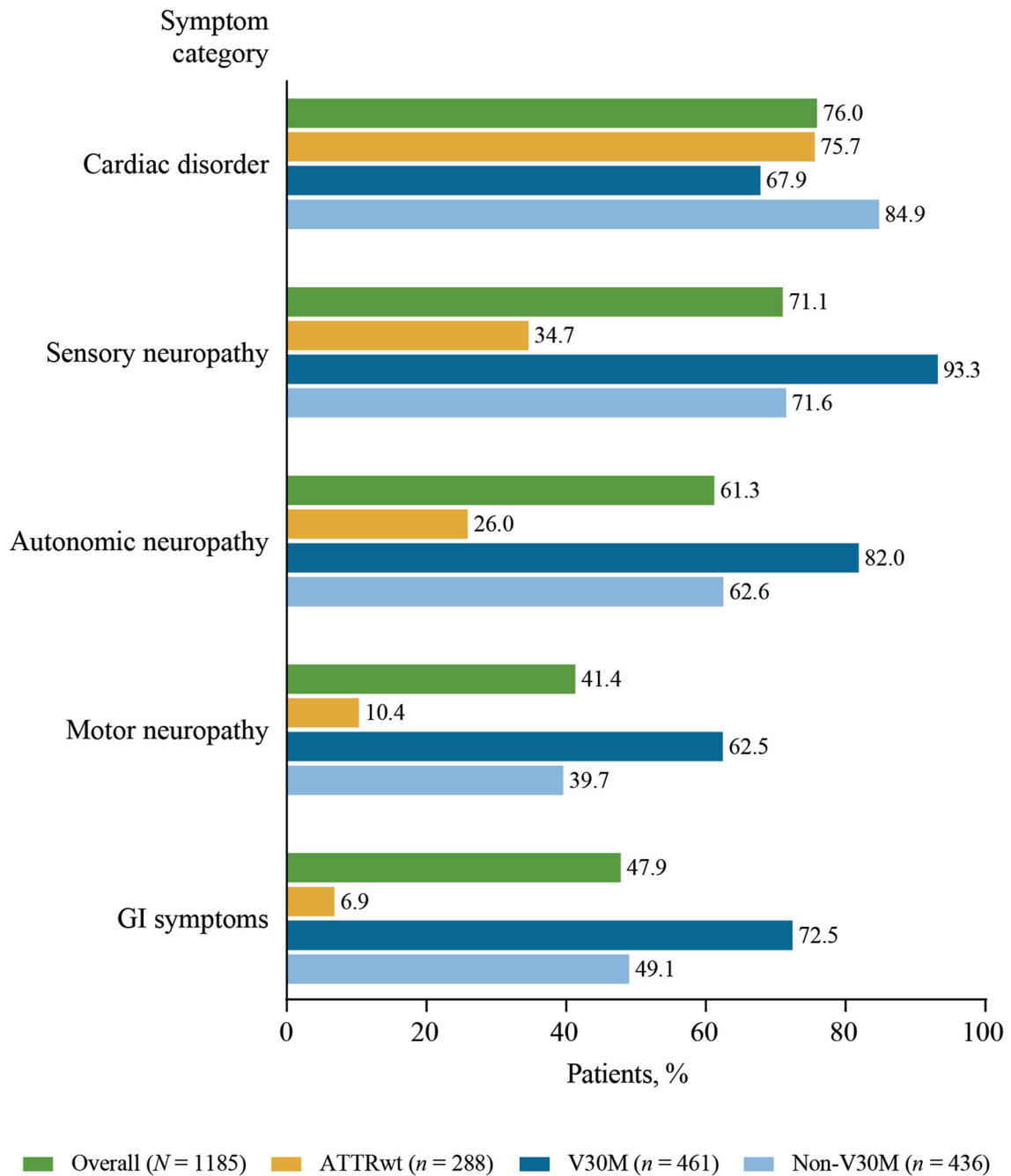
symptoms (31.5% vs 0%) were more common in ATTRv amyloidosis vs ATTRwt amyloidosis. Sensory neuropathy (55.6% vs 51.1%), autonomic neuropathy (55.6% vs 53.3%), and GI symptoms (55.6% vs 26.7%) were more common in V30M ATTRv amyloidosis vs non-V30M ATTRv amyloidosis.

### Cardiac, Neurologic, and HRQoL Measures

HF was present in 60.7% of the overall mixed phenotype population (Fig. 3A). The incidence of HF was highest in ATTRwt amyloidosis (82.6%) (Fig. 3B) and lowest in V30M ATTRv amyloidosis (31.2%) (Fig. 3C). Most patients with HF were classified as NYHA class II or III at enrollment (78.5%; Fig. 3A). The proportion of patients classified as NYHA class I was higher in patients with V30M ATTRv amyloidosis (26.4%) (Fig. 3C) than in patients with ATTRwt amyloidosis (8.0%) (Fig. 3B) and non-V30M ATTRv amyloidosis (10.1%) (Fig. 3D), whereas the proportion of patients in NYHA class III status was lower, respectively (18.8% vs 33.6% and 32.3%).

In patients classified as having a mixed phenotype at enrollment, HF was present in 70.2% of patients, and most (81.3%) were classified as NYHA class II or III at enrollment. In patients reclassified from a predominantly neurologic to mixed phenotype, HF was present in 16.4% of patients, and 51.3% had missing NYHA classification at enrollment. In patients reclassified from having a predominantly cardiac to mixed phenotype, HF was present in 84.9% of patients, and most (81.1%) were classified as NYHA class II or III at enrollment.

Differences between genotype subgroups were also observed for other clinical characteristics in the overall mixed phenotype population. Median LVSWT was lower and median LVEF higher in V30M ATTRv amyloidosis vs ATTRwt amyloidosis and non-V30M ATTRv amyloidosis (Fig. 4A and B). Median derived NIS-LL total score was higher in V30M ATTRv amyloidosis vs ATTRwt amyloidosis and non-V30M ATTRv amyloidosis (Fig. 4C). In addition, a higher proportion of patients with V30M ATTRv amyloidosis had mPND scores of II or

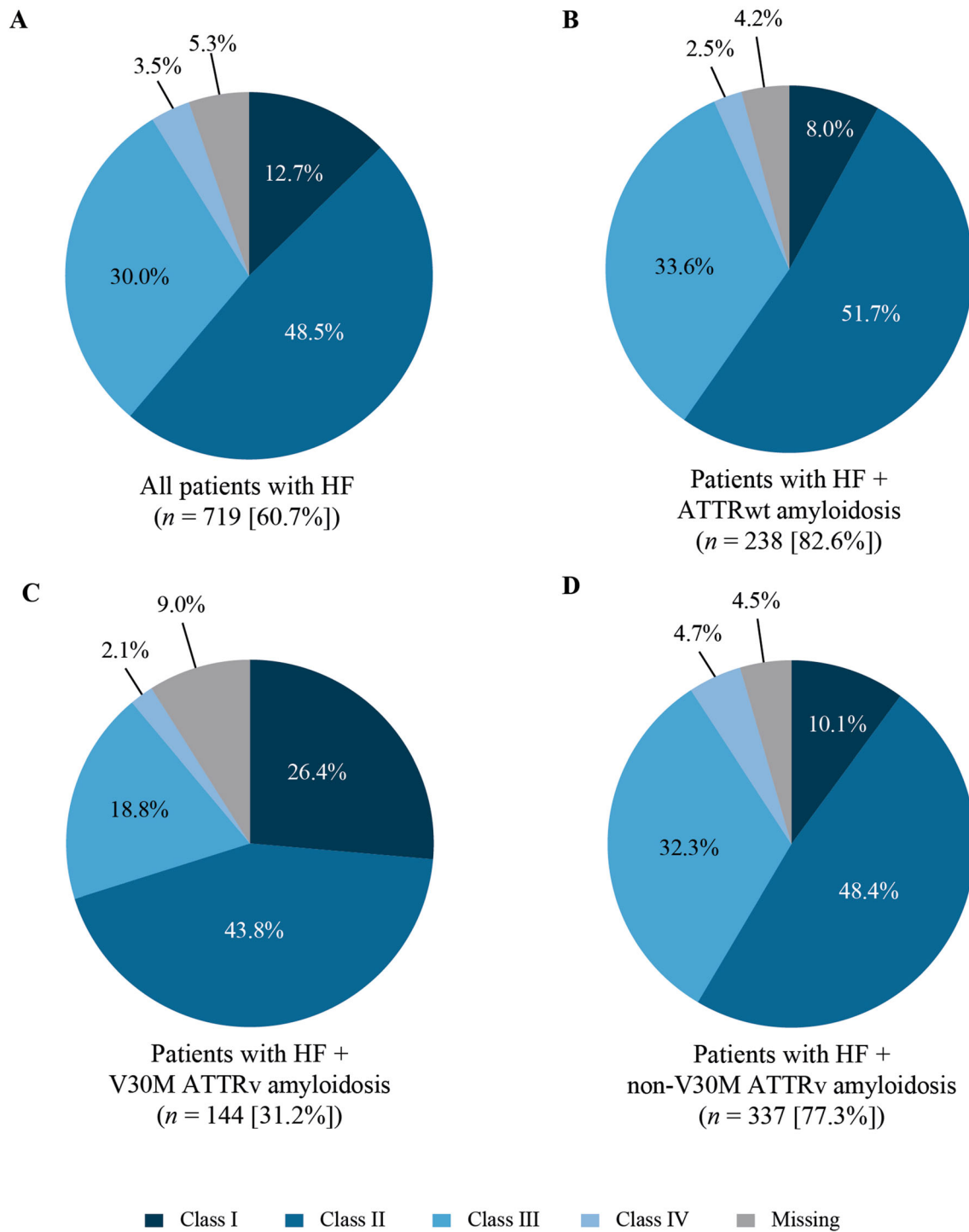


**Fig. 2** Summary of symptom categories reported at enrollment in patients with mixed phenotype ATTR amyloidosis overall and by genotype category. *ATTR*

*amyloidosis* transthyretin amyloidosis, *ATTRwt* wild-type transthyretin amyloidosis, *GI* gastrointestinal

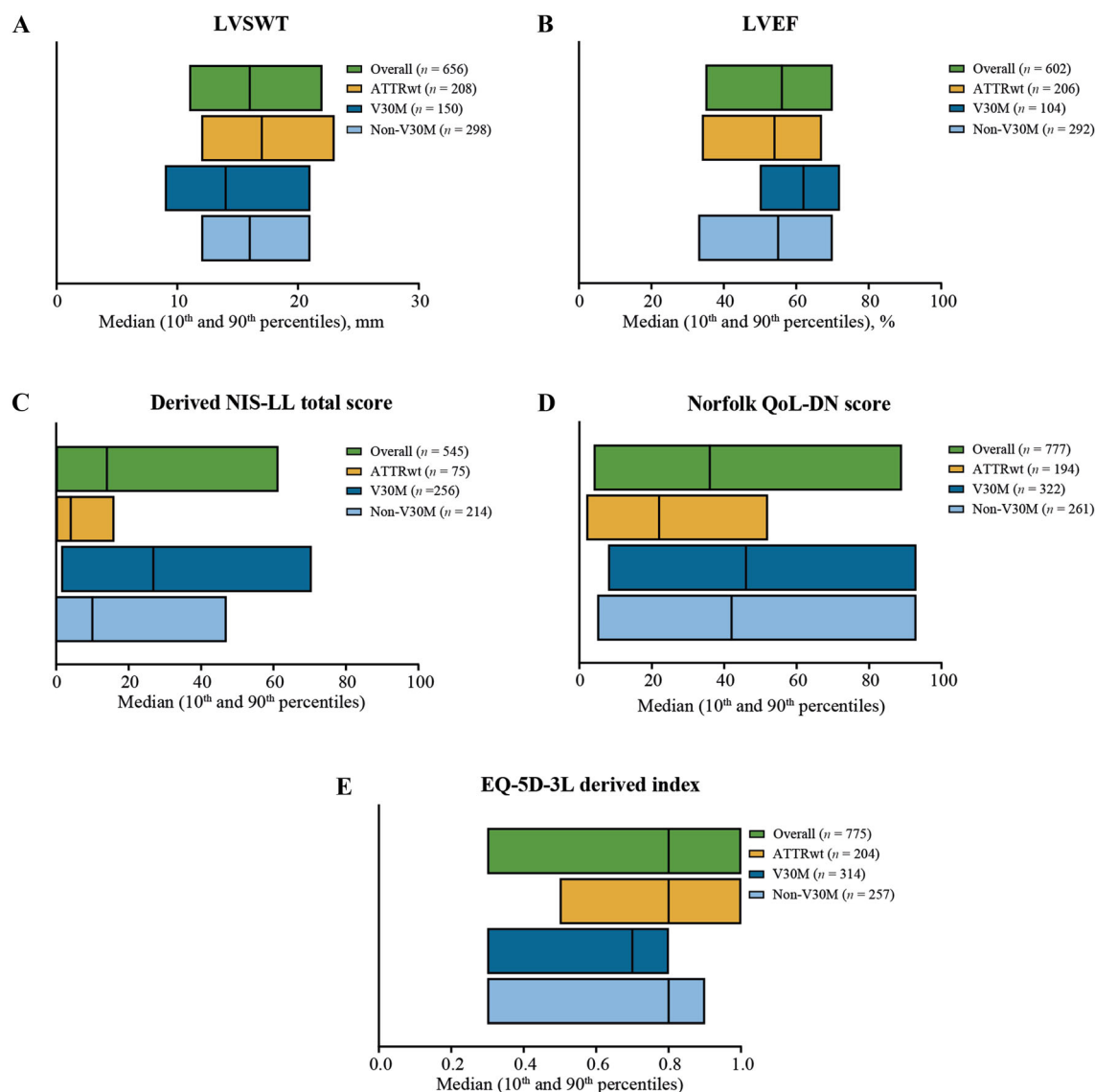
higher than patients with *ATTRwt* amyloidosis or non-V30M *ATTRv* amyloidosis (Fig. 5). HRQoL impairment was worse in *ATTRv* amyloidosis (both V30M and non-V30M genotypes)

vs *ATTRwt* amyloidosis, as indicated by higher median Norfolk QoL-DN total scores (Fig. 4D). Median EQ-5D-3L derived index was similar between genotype subgroups (Fig. 4E).



**Fig. 3** Distribution of NYHA functional class at enrollment in patients with mixed phenotype **A** ATTR amyloidosis, **B** ATTRwt amyloidosis, **C** V30M ATTRv amyloidosis, and **D** non-V30M ATTRv amyloidosis. NYHA class is reported only in mixed phenotype patients

with HF ( $n = 719/1185$ ). *ATTR amyloidosis* transthyretin amyloidosis, *ATTRv amyloidosis* hereditary transthyretin amyloidosis, *ATTRwt amyloidosis* wild-type transthyretin amyloidosis, *HF* heart failure, *NYHA* New York Heart Association



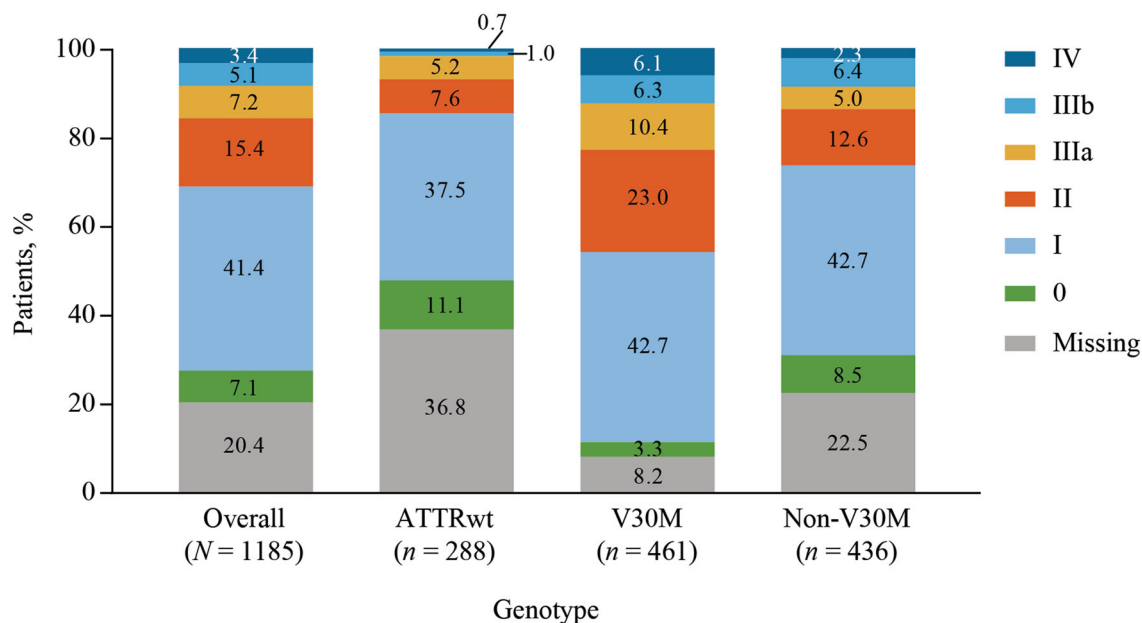
**Fig. 4** Other clinical and HRQoL characteristics in patients with mixed phenotype ATTR amyloidosis overall and by genotype. Cardiac measures, **A** LVSWT and **B** LVEF; neuropathy measure, **C** derived NIS-LL total score; and HRQoL measures, **D** EQ-5D-3L derived index and **E** Norfolk QoL-DN scores are shown. Lines within boxes denote medians; outer limits of boxes denote 10th

and 90th percentiles. *ATTR amyloidosis* transthyretin amyloidosis, *ATTRwt amyloidosis* wild-type transthyretin amyloidosis, *DN* diabetic neuropathy, *EQ-5D-3L* EQ-5D three-level version, *HRQoL* health-related quality of life, *LVEF* left ventricular ejection fraction, *LVSWT* left ventricular septal wall thickness, *NIS-LL* Neuropathy Impairment Score in the Lower Limbs

In the subset of patients classified as having a mixed phenotype at enrollment, median derived NIS-LL total score was higher in patients with V30M ATTRv amyloidosis (40.8) compared with patients with non-V30M ATTRv

amyloidosis (14.0) and patients with ATTRwt amyloidosis (4.0).

In patients reclassified from a predominantly neurologic to a mixed phenotype, cardiac involvement (median LVSWT and LVEF, respectively) was similar between V30M



**Fig. 5** Distribution of mPND scores in patients with mixed phenotype ATTR amyloidosis overall and by genotype. Denominators are the number of patients with

non-missing data. *ATTR amyloidosis* transthyretin amyloidosis, *ATTRwt amyloidosis* wild-type transthyretin amyloidosis, *mPND* modified polyneuropathy disability

(13.0 mm and 63.0%) and non-V30M (15.0 mm and 62.5%) ATTRv amyloidosis. Median derived NIS-LL total score was higher in V30M ATTRv amyloidosis (15.0) vs non-V30M ATTRv amyloidosis (6.0). HRQoL impairment was similar in V30M vs non-V30M ATTRv amyloidosis as indicated by median Norfolk QoL-DN total scores (35.0 vs 26.0) and the median EQ-5D-3L index (0.8 vs 0.8).

In patients reclassified from having a predominantly cardiac to mixed phenotype, median LVEF was higher in patients with V30M ATTRv amyloidosis (61.0%) vs patients with ATTRwt amyloidosis (52.5%) and patients with non-V30M ATTRv amyloidosis (55.5%), whereas median LSVWT was not different between genotype subgroups (16.0, 17.0, and 16.0 mm, respectively). Median derived NIS-LL total score was higher in non-V30M ATTRv amyloidosis (4.0) vs V30M ATTRv amyloidosis (0.0) and ATTRwt amyloidosis (2.0). HRQoL impairment was worse in V30M ATTRv amyloidosis vs non-V30M ATTRv amyloidosis and ATTRwt amyloidosis as indicated by higher

median Norfolk QoL-DN total scores (52.0 vs 17.0 and 15.5).

## DISCUSSION

Data from this THAOS analysis represent the largest analysis of a mixed phenotype ATTR amyloidosis population recorded to date, with approximately one-third of untreated symptomatic patients in THAOS classified as mixed phenotype. Furthermore, approximately one third of the overall population of patients with a mixed phenotype were initially classified at enrollment as having a predominantly neurologic or predominantly cardiac phenotype and were reclassified as having a mixed phenotype within a median 1 to 2 years of follow-up. To the best of our knowledge, this is the first report to document a migration from one phenotype to another over time.

The clinical presentation of ATTR amyloidosis has historically been characterized by three phenotypes: predominantly neurologic, predominantly cardiac, or mixed (both

neurologic and cardiologic abnormalities present) [1]. However, classification into these phenotype subgroups is subject to referral bias depending on the availability or absence of a multidisciplinary team and the type of clinical evaluation performed on the patient. As the evidence for the multisystemic nature of the disease grows, a more holistic approach is recommended [15], which could lead to patients who were initially classified as having a singular phenotype being reclassified as having a mixed phenotype. For example, in one study, 20 of 29 (69%) patients with I68L (p.I88L) ATTRv amyloidosis, traditionally considered a primarily cardiac phenotype, were reclassified as having a mixed phenotype after a complete evaluation [16]. Similar findings have been described with the more frequent V122I genotype, historically known as a mainly cardiac phenotype, where reports have highlighted the occurrence of neurologic involvement when specifically explored [17, 18].

In addition to referral bias, the primary symptom may overshadow and exclude other multisystemic clinical presentations, hindering an understanding of the genotype–phenotype relationship and clinical management. For example, at the onset of disease, orthopedic symptoms may occur in conjunction with the cardiac phenotype, GI symptoms may occur with the neurologic phenotype [19], and other organs and systems, such as the eye, central nervous system or renal system, may be involved in both phenotypes [20, 21]. Furthermore, some rare ATTR variants, such as A18G or L12P, may present with oculoleptomeningeal amyloidosis, a well characterized clinical grouping of central nervous system symptoms (e.g., seizures, stroke-like episodes) and vitreous TTR deposits [22]. Hence, these patients may be classified within any of the three phenotypes depending on the severity of the primary clinical presentation of ATTR amyloidosis. This evidence suggests that patients with a mixed phenotype may represent a heterogeneous patient population, and characterization of patients with a mixed phenotype using real-world experience is critical to establishing appropriate clinical management.

Differences were also observed in the clinical presentation of the mixed phenotype-genotype subgroups analyzed. In comparison with patients with ATTRwt amyloidosis, patients with ATTRv amyloidosis more commonly presented with neurologic and GI symptoms and had worse neuropathic impairment and lower HRQoL. In patients with ATTRv amyloidosis, those with the V30M variant more frequently reported neurologic and GI symptoms and had worse neuropathic progression than those patients with non-V30M variants. Despite worse neuropathic progression, measures of HF and left ventricular structure and function were less severe in patients with V30M ATTRv amyloidosis vs patients with non-V30M ATTRv amyloidosis or ATTRwt amyloidosis. However, most patients with HF, regardless of phenotype, were classified as NYHA class II or III at the time of enrollment. Lastly, the observation that nearly a quarter of the mixed phenotype patients in this analysis had ATTRwt amyloidosis is not surprising as, although it is typically associated with a cardiac phenotype, neurologic involvement other than carpal tunnel syndrome in ATTRwt amyloidosis has been described and ranges from 24% to as high as 70% [23–25].

The factors underlying why patients with the same *TTR* variant could present with different phenotypes are not completely known. One possible explanation is that single amino-acid alterations may change tissue tropism by altering the molecular structure of the TTR protein [26]. Tissue pH, the presence of proteolytic activity, or certain protein interactions may also influence the protein deposition [26–28]. It has also been shown that structural differences in amyloid fibrils have been related to different phenotypes in V30M ATTRv amyloidosis [29–31].

Strengths of this analysis include that THAOS is the largest registry of patients with ATTR amyloidosis, and this analysis represents the largest cohort of ATTR amyloidosis patients with a mixed phenotype analyzed to date. Furthermore, to the best of our knowledge this is the first report to examine ATTR amyloidosis progression from a single phenotype to a mixed phenotype. The study also has several limitations. First, as ATTR amyloidosis is a rare

disease, the number of patients in the phenotype subgroups analyzed was relatively small. Second, referral bias could have been present in the registry depending on whether the included cases were mainly being followed by a neurologist, a cardiologist, or a multidisciplinary unit. Thirdly, the higher rate of reclassification to a mixed phenotype in patients with a neurologic vs cardiologic phenotype at enrollment could be biased by the more symptomatic nature of early neurologic disease. Extra-cardiac manifestations in patients with a predominantly cardiologic phenotype are likely evident at a more advanced stage of disease and require evaluation by a clinician familiar with these symptoms. Fourthly, neurologic impairment is also a common feature of aging, and we cannot exclude the possibility that some patients reclassified from a cardiologic to mixed phenotype may have had some neurologic symptoms caused by aging. To reduce the risk of misclassification, all symptoms contributing to the phenotype must have been definitely related to ATTR amyloidosis. Lastly, there was a substantial amount of missing data, which is not unexpected in a registry analysis, but the classification of the mixed phenotype was based on an algorithm that used available data from the database.

## CONCLUSION

These THAOS data represent the largest analysis of a real-world mixed phenotype ATTR amyloidosis population to date and suggest that a mixed phenotype may be more prevalent in ATTR amyloidosis than previously thought. Mixed phenotype ATTR amyloidosis represents a heterogeneous group of patients with different clinical presentations. A key finding was that patients may migrate from a predominantly neurologic or cardiologic presentation to a mixed phenotype over time, and this can have important clinical implications for patient management. Overall, these data reinforce the need for multidisciplinary evaluation of all patients with ATTR amyloidosis at initial evaluation and follow-up.

## ACKNOWLEDGEMENTS

We thank all THAOS patients and investigators for their important contributions to this study.

Additional THAOS investigators contributing to this analysis: Violaine Plante-Bordeneuve, CHU Henri Mondor, Créteil, France; Isabel Conceicao, Hospital Santa Maria, Lisboa, Portugal; Eun-Seok Jeon, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea; Mathew Maurer, Columbia University Medical Center, New York, NY, USA; Jose Gonzalez Costello, Hospital Universitari de Bellvitge, Barcelona, Spain; Olivier Lairez, CHU de Toulouse, Hopital Rangueil, Toulouse, France; Mitsuharu Ueda, Kumamoto University, Kumamoto, Japan; Arnt Kristen, Medical University of Heidelberg, Heidelberg, Germany; Yoshiki Sekijima, Shinshu University School of Medicine, Matsumoto, Japan; Brian Drachman, University of Pennsylvania, Perelman Center for Advanced Medicine, Philadelphia, PA, USA; David Slosky, Vanderbilt University School of Medicine, Nashville, TN, USA; Anna Hüsing-Kabar, Universitätsklinikum Muenster, Transplant Hepatology, Muenster, Germany; Maria Alejandra Gonzalez Duarte Briseno, Instituto Nacional de Ciencia Medicas y Nutricion Salvador Zubiran, Distrito Federal, Mexico; Miriam Freimer, The Ohio University College of Medicine, Columbus, OH, USA; Marco Luigetti, Fondazione Policlinico Gemelli, Universita Cattolica del Sacro Cuore, Roma, Italy; Daniel Lenihan, Washington University School of Medicine, St. Louis, MO, USA; Michael Polydefkis, Johns Hopkins Hospital, Baltimore, MD, United States; Mazen Hanna, Cleveland Clinic Foundation, Cleveland OH, USA; Hans Nienhuis, University Medical Center Groningen, Groningen, Netherlands; Stephen Gottlieb, University of Maryland, Baltimore, MD, USA; Jose Nativi Nicolau, The University of Utah Health Sciences Center, Salt Lake City, UT, USA; Jocelyn Inamo, Chu De Fort De France, Fort de France, France; Michele Emdin, Fondazione Toscana Gabriele Monasterio Per La Ricerca Medica E Di Sanita Pubblica, Pisa, Italy; Olga Azevedo, Centro Hospitalar Do Alto Ave, Epe, Guimaraes, Portugal; Robert Brunkhorst,



University Hospital of RWTH Aachen, Aachen, Germany; Edward Miller, Smilow Cancer Hospital, New Haven, CT, USA; Alberta Warner, VA Greater Los Angeles Healthcare System, Los Angeles, CA, USA; Fabio Adrian Barroso, FLENI, Ciudad Autonoma de Buenos aires, Argentina; Rayomand Press, Karolinska University Hospital, Huddinge, Stockholm, Sweden; Scott Hummel, University of Michigan, Ann Arbor, MI, USA; Francisco Munoz Beamud, Hospital Juan Ramon Jimenez, Huelva, Spain; Anna Mazzeo, AOU Policlinico G. Martino, Messina, Italy; Luca Gentile, AOU Policlinico G. Martino, Messina, Italy; Soon Chai Low, University Malaya Medical Centre, Kuala Lumpur, Malaysia; Sorina Badelita, Institutul De Cardiologie, Bucuresti, Romania; Dianna Quan, UC Denver, Aurora, CO, USA; James Tauras, Montefiore Medical Center, Jack D. Weiler Hospital, Bronx, NY, USA; Sasa Zivkovic, University of Pittsburgh Medical Center, Pittsburgh, PA, USA; Johan Van Cleemput, Afdeling Klinische Cardiologie, O&N I, Leuven, Belgium; Henning Moelgaard, Aarhus University Hospital, Skejby, Aarhus, Denmark; Josep Maria Campistol Plana, Institut Clinic de Nefrologia i Urologia, ICNU, Hospital Clinic i Provincial de Barcelona, Barcelona, Spain; Roberto Fernández Torrón, Hospital Universitario Donostia, Gipuzkoa, San Sebastian, Spain; Nitasha Sarswat, University of Chicago Medical Center, Chicago, IL, USA; Srinivas Murali, Wexford Health and Wellness Pavillion, Pittsburgh, PA, USA; Christopher Mueller, Medical College of Wisconsin, Milwaukee, WI, USA; Nowell Fine, University of Alberta Foothills Medical Centre, Calgary, Canada; Felix Darstein, Johann-Gutenberg-Universität, Mainz, Germany; David Adams, CHU de Bicetre, Cedex, France; Amir Dori, Sheba Medical Center, Ramat Gan, Israel; Laura Obici, Centro per lo Studio e la Cura delle Amiloidosi Sistemiche, Pavia, Italy; Calogero Lino Ciriaco, Azienda Ospedaliero-Universitaria di Careggi, Firenze, Italy; Sonoko Misawa, Chiba University Hospital, Chiba-shi, Japan; Sanjiv Shah, Northwestern University, Chicago, IL, USA; Carsten Tschoepe, Charite Campus Rudolf-Virchow-Klinikum, Berlin, Germany; Lucia Galan Davila, Hospital Clinico San Carlos, Madrid, Spain; Jeeyoung Oh, Konkuk University Medical Center, Seoul,

Republic of Korea; Yesim Parman, Istanbul University, Istanbul Faculty of Medicine, Department of Neurology, Istanbul, Turkey; Tessa Marburger, Oregon Health and Science University, Portland, OR, USA; Jeffrey Ralph, University of California, Department of Neurology, San Francisco, CA, USA.

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**Medical Writing, Editorial, or Other Assistance** Editorial support was provided by Emily Balevich, PhD, of Engage Scientific Solutions and was funded by Pfizer.

**Author Contributions.** Juan González-Moreno, Angela Dispenzieri, Martha Grogan, Teresa Coelho, Ivailo Tournev, Márcia Waddington-Cruz, Jonas Wixner, Igor Diemberger, Pablo Garcia-Pavia, Doug Chapman, Pritam Gupta, Oliver Glass and Leslie Amass each contributed to the design and conduct of this analysis; interpretation of the data; and the preparation, review, and approval of the manuscript.

**Funding.** The THAOS registry, this analysis, and the journal's Rapid Service Fee were sponsored by Pfizer.

**Data Availability.** Upon request, and subject to review, Pfizer will provide the data that support the findings of this study. Subject to certain criteria, conditions and exceptions, Pfizer may also provide access to the related individual de-identified participant data. See <https://www.pfizer.com/science/clinical-trials/trial-data-and-results> for more information.

**Conflict of Interest.** Juan González-Moreno reports speaker fees from Akcea, Alnylam,

and Pfizer. Angela Dispenziera reports research grants from Alnylam, Celgene, Janssen, Millenium, and Pfizer; funding for meeting expenses (travel) from Pfizer; and advisory board fees from Akcea and Intellia. Martha Grogan reports grants and advisory board/consultancy fees paid to her institution from Alnylam, Eidos, Pfizer, and Prothena. Teresa Coelho served as a medical advisor for Pfizer, without honoraria; and reports funding for meeting expenses (travel, accommodation, registration) from Pfizer. Ivailo Tournev reports research funding, honoraria for presentations, and advisory board fees from Alnylam, Pfizer, and Pharma Pro. Márcia Waddington-Cruz reports research funding, consulting fees, and travel support for advisory boards and meetings from FoldRx Pharmaceuticals and Pfizer. Jonas Wixner reports consulting fees and travel support for lectures and advisory boards from Alnylam and Pfizer; and consulting fees from Akcea. Igor Diemberger reports research funding and speaker fees from Daiichi Sankyo and Pfizer (outside scope of present research). Pablo Garcia-Pavia reports speaker fees from Akcea, Alnylam, Eidos, and Pfizer; consulting fees from Alnylam, Akcea, AstraZeneca, Eidos, Neurimmune, and Pfizer; and research/educational support to his institution from Alnylam, Eidos, and Pfizer. Doug Chapman, Pritam Gupta, Oliver Glass, and Leslie Amass are full-time employees of Pfizer and hold stock and/or stock options.

**Ethical Approval.** 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. The study was approved at the primary site in this analysis by Comité de Etica de la Investigación de las Illes Balears (CEIM-IB).

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