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ORIGINAL RESEARCH

Latent Class Analysis to Classify Patients with Transthyretin Amyloidosis by Signs and Symptoms

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ABSTRACT

Introduction: The aim of this study was to develop an empirical approach to classifying patients with transthyretin amyloidosis (ATTR) based on clinical signs and symptoms.

Methods: Data from 971 symptomatic subjects enrolled in the Transthyretin Amyloidosis Outcomes Survey were analyzed using a latent class analysis approach. Differences in health status measures for the latent classes were examined.

Results: A four-class latent class solution was the best fit for the data. The latent classes were characterized by the predominant symptoms as severe neuropathy/severe autonomic, moderate to severe neuropathy/low to moderate autonomic involvement, severe cardiac, and moderate to severe neuropathy. Incorporating disease duration improved the model fit. It was found that measures of health status varied by latent class in interpretable patterns.

Conclusion: This latent class analysis approach offered promise in categorizing patients with ATTR across the spectrum of disease. The four-class latent class solution included disease duration and enabled better detection of heterogeneity within and across genotypes than previous approaches, which have tended to classify patients a priori into neuropathic, cardiac, and mixed groups. Although this study utilized a cross-sectional approach to disease duration, future work could include the application of longitudinal latent class analyses.

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INTRODUCTION

Transthyretin amyloidosis (ATTR) is a progressive, degenerative disease. In familial ATTR, a single gene mutation leads to instability and dissociation of the TTR tetramer, leading to amyloid formation. Wild-type TTR can de-stabilize with advancing age and also lead to amyloid formation.

Two common sites of amyloid deposition are peripheral nerves and the heart. Typical early neuropathic symptoms are paresthesias, sensory deficit, and distal neuropathic pain with a distal–proximal progression. Deposition in the myocardium leads to diastolic dysfunction, restrictive cardiomyopathy, arrhythmias, and heart failure. Autonomic neuropathy including erectile dysfunction, bladder paresis, postural hypotension, and gastrointestinal symptoms such as nausea, constipation, and diarrhea may also occur [1, 2].

The primarily neuropathic and cardiac phenotypes are known as transthyretin familial amyloid polyneuropathy (TTR-FAP) and transthyretin cardiomyopathy (TTR-CM), respectively. However, cardiac involvement is not uncommon in TTR-FAP, especially in later stages, and neuropathy can appear in patients with TTR-CM [3, 4]. Both groups can experience autonomic symptoms.

Attempts to classify patients based on genotype have limitations. There is significant overlap in presenting symptoms and various mutations have been classified on a "spectrum" ranging from predominantly neurologic to predominantly cardiac, with mixed presentations involving varying degrees of both neurologic and cardiac symptoms in between [4]. Even within the most common TTR mutation, V30M (valine is replaced by methionine at position 30), there is a tremendous heterogeneity of presentation [5, 6]. Classification by genotype has largely been focused on the distinction between the most common variant, V30M, and other mutations that are often lumped together into one non-V30M group, and the wild-type group. Another a priori approach to classification of patients with ATTR that has been widely used classifies them into neuropathic, cardiac, and mixed (with features of both neuropathy and cardiomyopathy) groups based on their phenotypic presentation, regardless of their genotype.

Until now, little empirical research has been undertaken to develop a classification scheme for the full spectrum of patients with ATTR. In this study, we grouped patients with symptomatic ATTR based on their clinical signs and symptoms using latent class analysis (LCA) [7, 8] and explored the relationships between latent class (LC) membership and clinical measures.

METHODS

Standard Protocol Approvals, Registrations, and Patient Consents

The Transthyretin Amyloidosis Outcomes Survey (THAOS; ClinicalTrials.gov number, NCT00628745) is a longitudinal, observational registry of symptomatic patients with ATTR (familial and wild type) and asymptomatic mutation carriers. One of its principal aims is to better understand and characterize the natural history of the disease by studying a large and heterogeneous patient population. The design and methodology of THAOS, including data collection and assessments, are

described elsewhere [9]. Approval from local Ethical Review Board/Institutional Review Board was obtained, all participants provided written informed consent, and use of THAOS data for this study was approved by the THAOS Scientific Board.

Patients

This analysis included symptomatic patients participating in THAOS as of June 2013. Patients who had liver or heart transplantation prior to enrollment were excluded.

Clinical Signs and Symptom Data

Signs and symptom data collected at THAOS enrollment were used. Individual signs and symptoms were dichotomously coded as "present" if assessed as possibly or definitely related to ATTR or "absent" if absent or deemed not related to ATTR. In total, 27 signs and symptoms reported for at least 5% of the patients were included in this study.

Other Measures

Demographic and clinical variables were examined. Of particular importance was ATTR disease duration, defined as the time since occurrence of the first ATTR symptom. Patients were categorized by disease duration <4 and ≥ 4 years, a cutoff value close to the median, therefore resulting in similar numbers of patients in each category.

Physical examination measures included change in supine-to-standing blood pressure (BP) and the presence of orthostatic hypotension (systolic BP decline >20 mmHg or diastolic BP decline >10 mmHg). The modified body mass index (mBMI), a marker of nutritional status (especially in patients with autonomic dysfunction) that adjusts for serum albumin concentration, was calculated by multiplying BMI (kg/m^2) by serum albumin concentration (g/L). The frequency of erectile dysfunction and depression was also examined.

The Karnofsky Performance Status is a clinician-rated assessment of functional impairment with scores ranging from 0 (dead) to 100 (normal functioning/no disease). The Karnofsky scores at enrollment were analyzed and patients were categorized as unable to care for self (scored 0–40), unable to work but able to self-care (scored 50–70), and able to accomplish normal activities and work (scored 80–100). Patients completed the European Quality of Life-5 dimension-3 level (EQ-5D-3L) instrument, a standardized measure of health consisting of five items to rate Mobility, Self-care, Ability to perform usual activities, Pain/discomfort, and Anxiety/depression on a 0 (not a problem) to 2 (unable to do/extreme problem) scale. Patients' responses were analyzed by item and used to calculate the EQ-5D-3L Index score. Patients' rating of their current health (using the sixth item, Health State, with 0 as the worst and 100 the best imaginable health state) was also analyzed.

Statistical Analysis

Latent class analysis [7, 8] is a statistical method used to find LCs (subgroups or natural taxa) using categorical data. Generally applied in social and behavioral science research, it is an extension of work pioneered in psychology that posits unobservable (latent) structures underlie observable or manifest psychological phenomena [10–12]. LCA classifies individuals into mutually exclusive LCs and assumes that all variables are independent within each LC; thus, the LC explains the associations among the observed variables (e.g., symptoms). Two

sets of parameters are estimated by LCA: class membership probabilities and item response probabilities within each LC. Each individual has a set of posterior probabilities, equal to the number of LCs in the model. Individuals are assigned to LC with the highest posterior probability.

As recommended, we fit an initial set of models, specifying two to six LCs, without any grouping variable or covariates [13]. The adjusted Bayesian information criteria (BIC) for the separate models were then compared (smaller is better). Measurement invariance across ATTR disease duration groups (<4 and ≥4 years) was tested by comparing a model in which there were free estimations of the model parameters with the same model including restrictions equating the class membership and item response probability parameters across groups.

Due to the large number of parameters estimated, each model selected the optimal set of 40 starting values to find the best parameter estimates and avoid suboptimal local maxima of the likelihood function [14].

The software used was the LCA procedure, developed for SAS® by the Methodology Center, Pennsylvania State University [13, 14].

General linear models (continuous data) and logistic regression (categorical data) were used to test the effect of LC, ATTR duration, and the interaction of the two on health status measures. A log-linear model was used to compare results for the non-ordinal groups based on a priori classification.

RESULTS

Patients

Of the 979 individuals who were symptomatic at enrollment, 971 had data on ATTR symptom duration and were included in this analysis. The mean age ± standard deviation (SD) was 53.5 ± 18.0 years. Males comprised 60% of the sample. The median ATTR duration was 3.33 years, with mean ± SD of 5.6 ± 6.7 years, and 57% had ATTR duration <4 years. Time since diagnosis was available for 608 patients with a mean ± SD of 1.8 ± 2.8 years.

Latent Class Analyses

Fit statistics were examined for two to six LC solutions by plotting the adjusted BIC as recommended by Nylund et al. [15]. The BIC improved (declined) from two to five class solutions. The four-class solution was chosen for better stability among the potential models. Analyses assessing the impact of ATTR duration as a grouping variable on the LCA indicated that it had a significant contribution ($\chi^2 = 338.7$; $df = 108$; $P < 0.0001$).

Each patient had a probability calculated for membership in each of the four LCs and was assigned to the LC with the highest probability. The individual posterior probabilities used to categorize patients into LCs were strong, with means within LC ranging from 0.91 to 0.98 (Table 1). The estimated item response probabilities for each LC grouped by ATTR duration are shown in Fig. 1 and in Table S1 in the electronic supplementary material (ESM).

LC1: Severe Neuropathy/Severe Autonomic

LC1 had high probabilities of neuropathic symptoms such as pain and tingling, autonomic symptoms (both upper and lower gastrointestinal, urinary, heart involvement, and weight loss), with markedly higher probabilities among patients with ATTR duration of ≥4 years (Fig. 1a). The probability of walking disability was high in both disease

Table 1 Class membership and mean assignment probabilities by LC and ATTR disease duration

	ATTR duration <4 years				ATTR duration ≥4 years			
LC:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**
Number of patients	87	86	120	256	59	114	119	130
Class membership probability	0.16	0.17	0.22	0.46	0.14	0.27	0.28	0.31
Mean assignment probability[a]	0.93	0.91	0.98	0.93	0.97	0.94	0.96	0.94

ATTR transthyretin amyloidosis, *LC* latent class, *LC1* severe neuropathy/severe autonomic, *LC2* moderate to severe neuropathy/low to moderate autonomic involvement, *LC3* severe cardiac, *LC4* moderate to severe neuropathy

[a] The mean assignment probability is the mean within LC and ATTR duration group of the probabilities used to assign individuals to LCs. Each individual had a probability of belonging to each of the four LCs. The largest of these four probabilities was used for assignment to the corresponding LC

duration groups. This class was best described as severe neuropathy/severe autonomic. The symptom pattern was the same in both disease duration groups, but with higher frequency in those with longer disease duration (Fig. 1a). The estimated class probabilities were 16% and 14% among those with ATTR duration of <4 and ≥4 years, respectively (Table 1).

LC2: Moderate to Severe Neuropathy/Low to Moderate Autonomic Involvement

LC2 exhibited moderate to severe neuropathic symptoms, but no clear pattern of increase with longer ATTR duration (Fig. 1b). Numbness, temperature, tingling, muscle weakness, and walking disability were more probable with longer ATTR duration; vomiting, nausea, early satiety, and dizziness were more prevalent among those with shorter ATTR duration. This class included 17% and 27% of the patients with ATTR duration of <4 and ≥4 years, respectively (Table 1).

LC3: Severe Cardiac

LC3 was defined by high rates of heart failure and rhythm disturbance and appeared to be an almost purely cardiac symptom group, with high rates of heart failure and dyspnea in both ATTR duration groups (Fig. 1c). The almost overlapping curves in Fig. 1c indicated that ATTR duration had little effect. This class included 22% of the patients with ATTR duration <4 years and 28% of those with ≥4 years duration (Table 1).

LC4: Moderate to Severe Neuropathy

LC4 was the largest, comprising 46% of the patients with ATTR duration <4 years and 31% of those with ≥4 years duration (Table 1). This class was characterized by moderate to high probabilities of neuropathic symptoms and relatively low probabilities of the other symptoms (Fig. 1d).

Comparisons of Health Status Measures by LC and ATTR Duration

Table 2 compares patient characteristics and health status measures by LC and ATTR duration. Patients with ≥4 years of ATTR disease duration were older across the four LCs. Overall, patients in LC3 were the oldest, reflecting the tendency for the generally later onset of cardiac symptoms. ATTR duration was similar (ranging from 1.5 to 2.6 years) across the

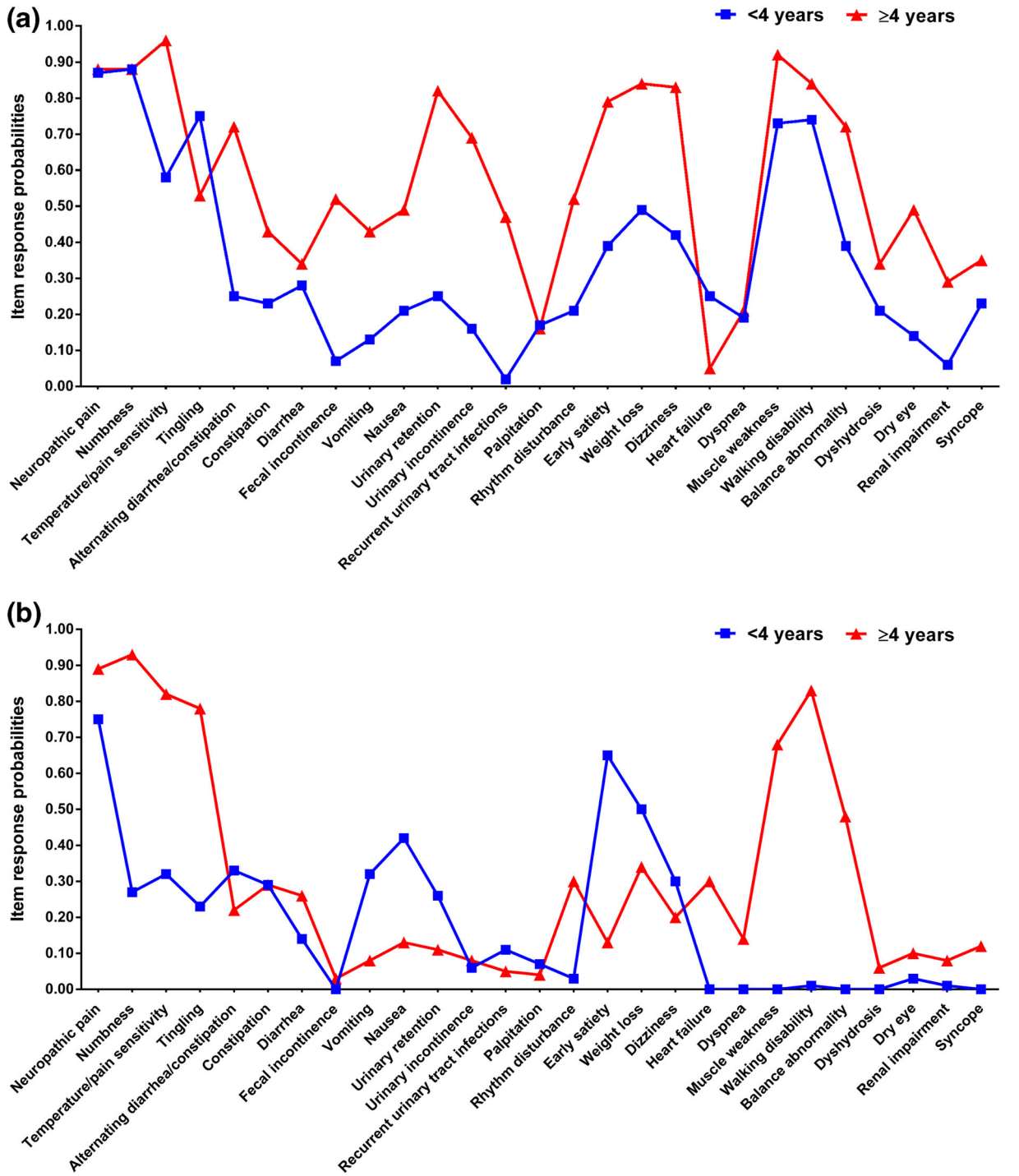

Fig. 1 Item response probabilities by LC and disease duration (<4 and ≥4 years): **a** LC1, **b** LC2, **c** LC3, **d** LC4. *LC* latent class, *LC1* severe neuropathy/severe autonomic, *LC2* moderate to severe neuropathy/low to moderate autonomic involvement, *LC3* severe cardiac, *LC4* moderate to severe neuropathy

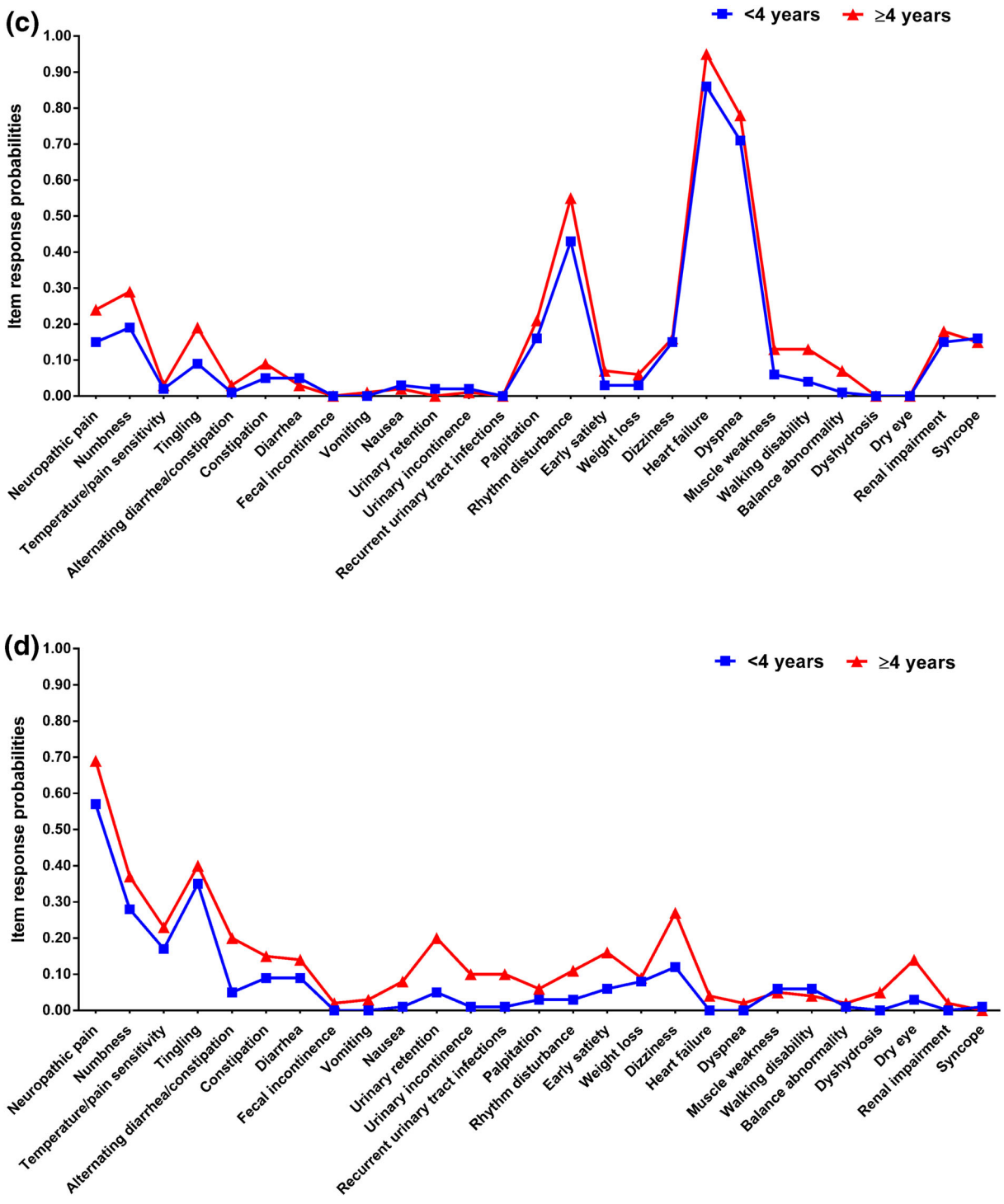

Fig. 1 continued

Table 2 Patient characteristics and demographics at enrollment

	ATTR duration <4 years				ATTR duration ≥4 years				*P* values[a]		
LC:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**LC**	**A-Du**	**LC/A**
Number of patients	87	86	120	256	59	114	119	130			
Age, years	52.0 (15.9)	35.4 (9.6)	69.6 (12.2)	42.2 (14.0)	53.0 (13.5)	62.6 (13.8)	72.3 (8.6)	48.7 (15.3)	0.0001	0.0001	0.0001
Male, *n* (%)	58 (66.7)	47 (54.7)	99 (82.5)	122 (47.7)	34 (57.6)	78 (68.4)	100 (84.0)	43 (33.1)	<0.0001	0.6246	0.0096
ATTR duration, years	2.58 (0.91)	2.00 (1.14)	1.74 (1.19)	1.54 (1.07)	11.14 (6.00)	10.18 (7.37)	12.64 (9.23)	8.37 (6.91)	0.0001	0.0001	0.0001
Time since diagnosis, years	*N* = 67	*N* = 63	*N* = 74	*N* = 133	*N* = 44	*N* = 72	*N* = 77	*N* = 78	0.0001	0.0001	0.0001
	1.22 (2.09)	1.09 (1.27)	0.89 (1.37)	1.14 (2.72)	5.45 (4.99)	2.63 (2.64)	1.00 (1.72)	2.85 (2.15)			
Modified BMI, kg/m^2 g/L	*N* = 51	*N* = 80	*N* = 65	*N* = 190	*N* = 42	*N* = 63	*N* = 63	*N* = 86	0.0001	0.0001	0.0102
	931.2 (242.9)	1047.3 (216.9)	1093.5 (185.2)	1171.1 (247.9)	768.2 (215.6)	887.5 (260.5)	1099.3 (216.2)	1109.6 (258.4)			
Arterial BP change, mmHg[b]	*N* = 64	*N* = 81	*N* = 39	*N* = 209	*N* = 46	*N* = 72	*N* = 26	*N* = 103	0.0001	0.0001	0.0200
	−4.1 (10.3)	1.3 (11.0)	−0.3 (4.9)	3.7 (7.8)	−8.1 (14.0)	−6.9 (11.2)	−2.0 (5.2)	1.2 (8.3)			
Orthostatic hypotension, *n* (%)[c]	*N* = 64	*N* = 82	*N* = 39	*N* = 209	*N* = 46	*N* = 72	*N* = 26	*N* = 103	<0.0001	0.9604	0.3951
	10 (15.6)	8 (9.8)	0 (0.0)	10 (4.8)	17 (37.0)	24 (33.3)	2 (7.7)	7 (6.8)			
Erectile dysfunction, *n* (%)[d]	21 (36.2)	22 (46.8)	9 (9.1)	30 (24.6)	18 (52.9)	28 (35.9)	9 (9.0)	9 (20.9)	<0.0001	0.9885	0.2529
Depression, *n* (%)	15 (17.2)	1 (1.2)	3 (2.5)	10 (3.9)	9 (15.3)	9 (7.9)	7 (5.9)	3 (2.3)	<0.0001	0.1477	0.1340
Karnofsky score	*N* = 74	*N* = 83	*N* = 97	*N* = 242	*N* = 54	*N* = 91	*N* = 97	*N* = 119	0.0001	0.0001	0.0001
	73.1 (16.5)	88.2 (6.7)	78.5 (13.2)	92.4 (7.7)	58.9 (14.9)	64.4 (16.9)	73.8 (16.2)	88.0 (10.1)			
Karnofsky category, *n* (%)									<0.0001	<0.0001	<0.0001
Unable to self-care	5 (6.8)	0 (0.0)	3 (3.1)	0 (0.0)	9 (16.7)	14 (15.4)	7 (7.2)	1 (0.8)			
Unable to work	29 (39.2)	3 (3.6)	30 (30.9)	6 (2.5)	35 (64.8)	51 (56.0)	31 (32.0)	9 (7.6)			
Normal	40 (54.1)	80 (96.4)	64 (66.0)	236 (97.5)	10 (18.5)	26 (28.6)	59 (60.8)	109 (91.6)			

ATTR transthyretin amyloidosis, *A-Du* ATTR disease duration group, *BMI* body mass index, *BP* blood pressure, *EQ-5D-3L* European Quality of Life-5 dimensions-3 levels instrument, *LC* latent class, *LC1* severe neuropathy/severe autonomic, *LC2* moderate to severe neuropathy/low to moderate autonomic involvement, *LC3* severe cardiac, *LC4* moderate to severe neuropathy, *LC/A* the interaction of LC and A-Du

Values are mean (standard deviation) or *n* (%); *N* number of patients with available data in each LC; *n* number of patients with specific characteristic

[a] *P* values are for the main effects of LC, A-Du, and LC/A

[b] BP change from supine to standing

[c] Defined as systolic BP decline from supine to standing >20 mmHg or diastolic BP decline >10 mmHg

[d] Percentage among male patients

four LCs if it was <4 years, compared with a range of 8.4–12.6 years in those with ≥4 years duration. A similar pattern was observed for time since diagnosis.

Gender differences across the disease duration categories varied by LC, except for LC3, which had similar proportions (83% and 84%) of male patients. The rate of erectile dysfunction (symptom of autonomic dysfunction) was higher for the LC1 and LC2 groups than the other two, and was lowest in the LC3 group (9% in both disease duration groups; Table 2).

Mean changes in BP (from supine to standing) showed the highest declines for patients in LC1 across both disease duration categories. The presence of orthostatic hypotension for those with disease duration <4 years was highest in LC1 (15.6%). For those with disease duration ≥4 years in LC1, the prevalence was 37.0%. The difference in prevalence between disease durations was even greater for LC2: 9.8% for <4 years and 33.3% for ≥4 years. Differences for LC3 and LC4 were more modest, but for both groups those with longer duration had higher rates (Table 2).

In LC1 and LC2, mBMI was lower for patients with disease duration ≥4 years, while LC3 and LC4 showed relatively little difference between disease duration categories (Table 2).

Karnofsky scores for patients with longer disease duration were lower than those with shorter disease duration for each LC (Table 2). The proportions of patients who were categorized (based on the Karnofsky score) as having normal functions tended to be lower in LC1 and LC2 patients with longer disease duration, while the percentages of patients who were unable to work were greater with longer disease duration. Few differences in the Karnofsky categories were seen between patients with <4 and ≥4 years of disease duration in the LC3 and LC4 groups.

The EQ-5D-3L Index and Health Status scores in LC1 and LC2 were lower for patients with disease duration ≥4 years, while for LC3 and LC4 the differences were more modest (Table 3). Generally, the responses to the EQ-5D-3L individual items for Mobility, Performance of usual activities, and Self-care indicated greater impairment across all LCs with longer disease duration (Table 3). With longer disease duration, LC1 and LC2 had more patients reporting problems than LC3 and LC4. Responses to the Pain/discomfort item were similar. However, extreme pain or discomfort was reported by similar proportions of patients in LC1, LC3, and LC4 in both disease duration categories, while in LC2 the proportions were 3.8% and 13.3% in the <4 and ≥4 years disease duration categories, respectively. In both disease duration groups, the highest proportion of patients reporting no anxiety/depression was in LC3 (approximately 70%), while patients in LC1 had the highest proportion reporting anxiety/depression. Medical history data also showed that the prevalence of depression was higher in patients in LC1 with <4 years ATTR disease duration (17.2%) and those with longer ATTR disease duration (15.3%), compared with other LC groups (≤7.9%) regardless of disease duration (Table 2).

Most of the differences in the health status measures of interest were statistically significant among the LC groups, as well as between the two disease duration categories. The interactions between LC membership and ATTR disease duration were significant for most of the comparisons, indicating that the effects of disease duration varied by LC group. However, the interactions for erectile

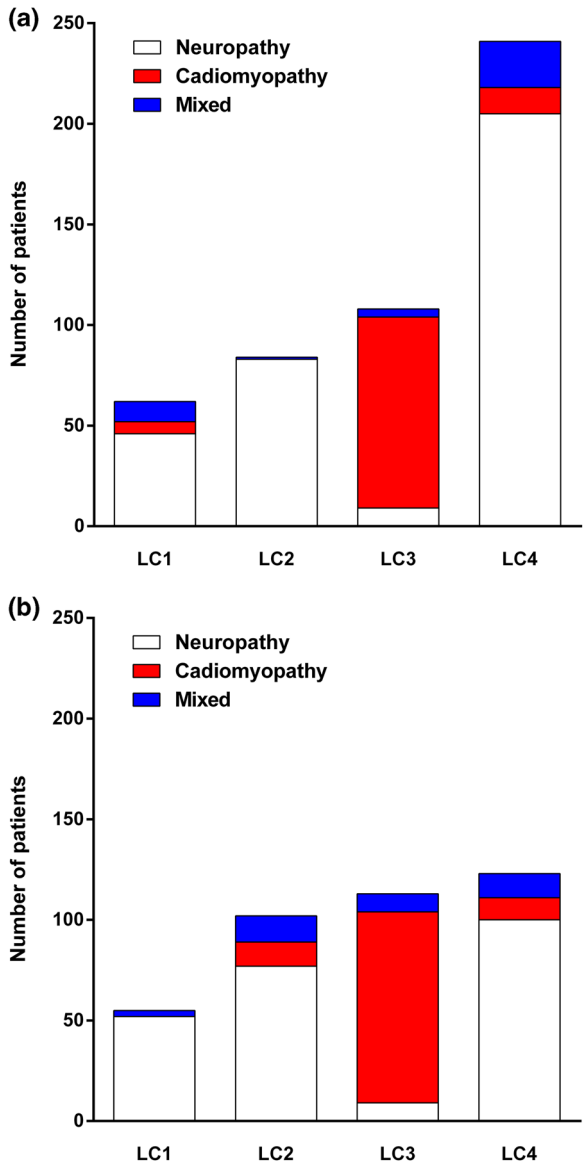

Fig. 2 Comparison between the LC analysis classification and the a priori patient classification: **a** disease duration <4 years, **b** disease duration ≥4 years. *P* values for the main effects of LC, the A-Du, and the interaction of LC and A-Du were <0.0001, 0.3522, and 0.0438, respectively. *ATTR* transthyretin amyloidosis, *A-Du* ATTR disease duration group, *LC* latent class, *LC1* severe neuropathy/severe autonomic, *LC2* moderate to severe neuropathy/low to moderate autonomic involvement, *LC3* severe cardiac, *LC4* moderate to severe neuropathy

dysfunction, presence of orthostatic hypotension, depression from medical history, and the EQ-5D-3L Self-care and Anxiety/depression items were not significant. Orthostatic hypotension was significantly different across LC groups, but not by disease duration category.

Comparison to a Priori Patient Classification

Within LC1, 74.2% of patients with <4 years ATTR disease duration would have been classified into the neuropathic group based on their phenotypic presentation, followed by 16.1% as mixed, while 9.7% would have been in the cardiac group (Fig. 2). This pattern was even stronger in the category with disease duration ≥4 years, where 94.55% would have been classified into the a priori neuropathy group compared with 5.45% for the mixed group, respectively.

Nearly all (98.8%) patients in LC2 with disease duration <4 years would have been classified as being neuropathic. However, with longer disease duration, there was greater variability: 75.5% would have been classified into neuropathy, 12.8% mixed, and 11.8% cardiac groups (Fig. 2a).

Patients in LC3 would have been largely classified as having cardiomyopathy using the a priori approach, regardless of disease duration. However, among those with disease duration ≥4 years, 8.0% would have been classified as mixed, compared with 3.7% for patients with disease duration <4 years (Fig. 2b).

Patients in LC4 would have been primarily classified a priori as having neuropathy in both disease duration categories (85.1% and 81.3% for <4 and ≥4 years duration, respectively) (Fig. 2). Patients would have been classified as mixed in 9.5% and 9.8% and as having cardiomyopathy in 5.4% and 8.9% for the <4 and ≥4 years duration groups, respectively.

Table 3 Patient responses to the EQ-5D-3L instrument at enrollment

	ATTR duration <4 years				ATTR duration ≥4 years				*P* values[a]		
LC:	**1**	**2**	**3**	**4**	**1**	**2**	**3**	**4**	**LC**	**A-Du**	**LC/A**
Number of patients	59	80	71	205[b]	52	60	78	97			
EQ-5D-3L index score, mean (SD)	0.63 (0.23)	0.79 (0.14)	0.84 (0.14)	0.84 (0.15)	0.42 (0.27)	0.61 (0.23)	0.78 (0.17)	0.81 (0.17)	0.0001	0.0001	0.0001
Mobility, *n* (%)									<0.0001	<0.0001	<0.0001
No problems walking	16 (27.1)	62 (77.5)	41 (57.8)	176 (85.4)	4 (7.7)	8 (13.3)	29 (37.2)	74 (76.3)			
Some problems walking	40 (67.8)	18 (22.5)	30 (42.3)	30 (14.6)	36 (69.2)	48 (80.0)	49 (62.8)	23 (23.7)			
Confined to bed	3 (5.1)	0 (0.0)	0 (0.0)	0 (0.0)	12 (23.1)	4 (6.7)	0 (0.0)	0 (0.0)			
Usual activity, *n* (%)									<0.0001	<0.0001	0.0011
No problems	19 (32.2)	55 (68.8)	39 (54.9)	179 (86.9)	4 (7.7)	14 (23.3)	31 (39.7)	71 (73.2)			
Some problems	37 (62.7)	24 (30.0)	31 (43.7)	27 (13.1)	25 (48.1)	36 (60.0)	44 (56.4)	22 (22.7)			
Unable to perform	3 (5.1)	1 (1.3)	1 (1.4)	0 (0.0)	23 (44.2)	10 (16.7)	3 (3.9)	4 (4.1)			
Self-care, *n* (%)									<0.0001	<0.0001	0.1244
No problems	41 (69.5)	72 (90.0)	66 (93.0)	201 (97.6)	11 (21.2)	30 (50.0)	66 (84.6)	87 (89.7)			
Some problems washing or dressing	16 (27.1)	8 (10.0)	5 (7.0)	5 (2.4)	22 (42.3)	23 (38.3)	11 (14.1)	9 (9.3)			
Unable to wash or dress oneself	2 (3.4)	0 (0.0)	0 (0.0)	0 (0.0)	19 (36.5)	7 (11.7)	1 (1.3)	1 (1.0)			
Pain/discomfort, *n* (%)									<0.0001	<0.0001	0.0288
No	9 (15.3)	25 (31.3)	49 (69.0)	105 (51.2)	4 (7.7)	6 (10.0)	30 (38.5)	44 (45.4)			
Moderate	40 (67.8)	52 (65.0)	19 (26.8)	96 (46.8)	38 (73.1)	46 (76.7)	46 (59.0)	52 (53.6)			
Extreme	10 (17.0)	3 (3.8)	3 (4.2)	4 (2.0)	10 (19.2)	8 (13.3)	2 (2.6)	1 (1.0)			
Anxiety/depression, *n* (%)									<0.0001	0.4807	0.8275
Not anxious or depressed	18 (30.5)	36 (45.0)	50 (70.4)	102 (49.5)	16 (30.8)	28 (46.7)	53 (68.0)	51 (52.6)			
Moderately anxious or depressed	32 (54.2)	40 (50.0)	21 (29.6)	88 (42.7)	22 (42.3)	27 (45.0)	20 (25.6)	36 (37.1)			
Extremely anxious or depressed	9 (15.3)	4 (5.0)	0 (0.0)	16 (7.8)	14 (26.9)	5 (8.3)	5 (6.4)	10 (10.3)			
Health state score, mean (SD)	$N = 57$	$N = 80$	$N = 71$	$N = 201$	$N = 52$	$N = 57$	$N = 77$	$N = 95$	0.0001	0.0001	0.0002
	61.3 (18.3)	72.5 (17.5)	68.3 (21.0)	78.0 (17.1)	42.9 (21.5)	53.1 (23.6)	62.4 (21.0)	73.4 (17.4)			

ATTR transthyretin amyloidosis, *A-Du* ATTR disease duration group, *EQ-5D-3L* European Quality of Life-5 dimensions-3 levels instrument, *LC* latent class, *LC1* severe neuropathy/severe autonomic, *LC2* moderate to severe neuropathy/low to moderate autonomic involvement, *LC3* severe cardiac, *LC4* moderate to severe neuropathy, *LC/A* the interaction of LC and A-Du, *SD* standard deviation

Values are mean (standard deviation) or *n* (%); *N* number of patients with available data in each LC; *n* number of patients with specific characteristic

[a] *P* values are for the main effects of LC, A-Du, and LC/A

[b] For patients in LC4 and with <4 years disease duration, 206 had answered the questions in the sections of Mobility, Usual activity, Self-care, and Anxiety/depression, 205 patients had answered the questions in the Pain/discomfort section, and the EQ-5D-3L index score was available for 205 patients

LC Groups by Mutation Type and Country

There were >40 mutations represented in this analysis (Table S2 in the ESM), plus the non-mutant wild type, representing 15 countries (Table S3 in the ESM). The most common mutation in the world, the V30M mutation, was predominant in the LC groups involving neuropathy (i.e., LC1, LC2, and LC4), regardless of disease duration, although it was found in all four LCs. For LC3 (Severe cardiac), the primary mutation was V122I followed by the non-mutant wild type. Most non-V30M mutations occurred with low frequency (<10 patients per mutation), making it difficult to discern a distribution pattern, though most of these mutations were dispersed across the LC groups.

DISCUSSION

This study is the first attempt to empirically categorize a broad spectrum of patients with ATTR based on signs and symptoms using LCA. After testing various models, we found a four-class LC solution best suited the data. These classes were characterized by the predominant symptoms to be severe neuropathy/severe autonomic (LC1), moderate to severe neuropathy/low to moderate autonomic involvement (LC2), severe cardiac (LC3), and moderate to severe neuropathy (LC4). These groups reflected the variability in the clinical presentation of ATTR. The measures of health status varied by LC in interpretable patterns, supporting the LCA approach.

Disease duration affected the clinical presentation for the majority of patients with ATTR studied, with either a greater number of symptoms emerging as the disease progressed or an apparent increase in the frequency of the earlier symptoms over time. The exception was LC3, in which clinical presentation varied little between the disease duration groups.

This analysis included many different mutations to arrive at patient groups that would encompass the entire range of ATTR. In this study, the most common mutation in the world, the V30M mutation, was found in all four LCs, mirroring the variability in symptom presentation in that single mutation [5, 6]. Future LCA work could be done to further explore this variability as well as the impact of the age of disease onset.

This four-class LC solution offers promise in categorizing patients with ATTR across the spectrum of disease; it also offers a refinement of the a priori approach classifying patients with ATTR based on phenotype: neuropathy, cardiac, or mixed. Although there was overlap between these two classification approaches, a particular strength of the LCA solution was that it allowed for finer distinctions between patients with neuropathy and those with mixed presentation. An additional strength was that it incorporated disease duration, which is an important factor in understanding ATTR.

The LCA approach may be useful for studying ATTR disease progression over time and in examining the clinical outcome of this disease. Although this study was limited in its cross-sectional approach to disease duration, future work could include the application of longitudinal LCA to look at shifts between the LCs over time to confirm and extend the results reported here.

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Compliance with ethics guidelines. The study protocol of the Transthyretin Amyloidosis Outcomes Survey (THAOS) was approved by local Ethical Review Board/ Institutional Review Board and conducted in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1964, as revised in 2013. All participants of THAOS provided written informed consent, and use of THAOS data for this study was approved by the THAOS Scientific Board.

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