Psychometric Validation of the Transthyretin Amyloidosis – Quality of Life (ATTR-QOL) Questionnaire

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INTRODUCTION / OBJECTIVE

- Transthyretin (ATTR) amyloidosis is a rare disease with 2 primary types, hereditary or variant (ATTRv) and wild-type (ATTRwt). Patients with ATTR amyloidosis may experience a varied and wide range of symptoms as a result of heterogenous clinical presentation
- This heterogeneity introduces challenges in the measurement of ATTR amyloidosis-related symptoms and impacts on health-related quality of life (HRQoL)
  - Clinicians, researchers, drug developers, and other stakeholders have relied on a patchwork of patient-reported outcome (PRO) measures developed in other conditions to measure these outcomes
- The Transthyretin Amyloidosis Quality of Life Questionnaire (ATTR-QOL) is a disease-specific PRO measure developed to capture the symptoms and impacts of ATTR amyloidosis across all types and symptomologies
  - Development of the ATTR-QOL followed best practices and included a literature review, concept elicitation interviews with patients and clinical experts, a series of Delphi expert panel reviews, translatability assessments, informal reviews by drug developers, and cognitive debriefing interviews with patients
- **Objective:** Confirm the scale structure, identify redundant items, develop a scoring algorithm, and evaluate the psychometric properties of the ATTR-QOL Impacts domain

METHODS

Study Design

- This study included adult patients with symptomatic ATTR amyloidosis in the United States recruited using convenience sampling and targeted outreach
- Participants completed the ATTR-QOLv1 at 2 timepoints, along with PRO surveys commonly used in ATTR amyloidosis to serve as criterion measures
  - These surveys included the SF-36v2 Health Survey (SF-36v2), Kansas City Cardiomyopathy Questionnaire – 12 Items (KCCQ-12), Norfolk Quality of Life Questionnaire – Diabetic Neuropathy (Norfolk QOL-DN), EuroQOL 5-Dimensions 5-Levels (EQ-5D-5L), and Patient Global Impressions of Severity (PGI-S) and Change (PGI-C)
- The ATTR-QOLv1 is a comprehensive PRO that includes:
  - A Symptoms domain comprised of 32 two-part items designed to assess the frequency and severity of cardiac, peripheral neuropathy, autonomic neuropathy (including gastrointestinal), and other symptoms attributed to ATTR amyloidosis
  - An Impacts domain comprised of 37 items designed to measure impacts of ATTR amyloidosis on HRQoL
  - One item regarding unintended weight loss/gain due to ATTR amyloidosis
  - Optional items on ATTR amyloidosis type and comorbid conditions
- Proposed Impacts domain scale scores ranging from 0 (No impact) to 100 (Greatest impact) were derived by averaging the item scores within a scale and transforming the mean to a 0 to 100 scale

Evaluation of Measurement Model

- Confirmatory factor analysis (CFA) was used to understand the scale structure of the ATTR-QOL Impacts domain and evaluate its correspondence with a conceptual model drafted during the development process
- Tests of differential item functioning (DIF), which evaluate whether items perform similarly in different clinical subgroups (e.g., ATTRwt versus ATTRv), were also considered
- Items showing evidence of redundance, poor fit, or DIF were considered for deletion
- Mokken scale analysis, multi-trait analysis, and examination of scale score distributions were used to confirm and further evaluate the measurement model

Psychometric Analyses

- A series of psychometric analyses were conducted to further confirm the model and to examine the reliability (internal consistency and test-retest), convergent/divergent validity, and known-groups validity of the ATTR-QOL Impacts domain scales
- Convergent validity was evaluated by examining Spearman correlations between ATTR-QOL Impacts domain scales and scales from other PRO criterion measures; correlations ≥ 0.30 indicate convergent validity; higher correlations with the hypothesized scales than with other scales indicate divergent validity
- For known-groups validity, subgroups were formed based on self-reported disease severity as measured by PGI-S, employment status, disease duration, and KCCQ Overall Summary categories
  - Group differences were tested using analysis of variance (ANOVA) for normally distributed scale scores, and Wilcoxon-Mann-Whitney and the Kruskal-Wallis tests for non-normally distributed scale scores
  - $p < 0.05$ was used to define statistically significant differences between groups

RESULTS

- The analytic sample included 233 participants. Key demographic and clinical characteristics are included in **Table 1**
- CFA was applied to assess the prespecified 3-factor model for the ATTR-QOL Impacts domain scales
  - Results supported the formation of 4 Impacts domain scales: Daily Activities, Social/Role Functioning, Emotional Wellbeing, and Physical Functioning (**Figure 1**)
  - The revised model had satisfactory fit for both the initial and follow-up surveys, and was confirmed with a secondary dataset
- ATTR-QOL Impacts items were evaluated based on the model factor loadings and DIF
  - Twelve items were selected for deletion due to cross-loading (loading on multiple factors) or DIF
  - Three items that were flagged for cross-loading and/or DIF were retained as they measured concepts highly important to patients during qualitative interviews. These 3 items do not contribute to scale scores
- See **Table 2** for results of the Mokken scale analysis, multi-trait analysis, examination of scale score distributions, and the psychometric analyses

The ATTR-QOL is a disease-specific PRO measure developed to capture the symptoms and impacts of ATTR amyloidosis across all types and symptomologies.

Findings from this study support the use of the 4 ATTR-QOL Impacts domain scales in all patients with ATTR amyloidosis; similar efforts are underway for the ATTR-QOL Symptoms domain scales.

Table 1: Sample Characteristics: Socio-demographics and Clinical Characteristics (N=233)

	Median (IQR) [Range]
Age, years	59 (19) [25-94]
Age at Symptom Onset, years	54 (20) [22-90]
Time since Diagnosis, years	4 (3) [0-32]
	N (%)
Sex – Male	181 (77.7%)
Race[1]	
White	208 (89.3%)
Black or African	23 (9.9%)
Other	3 (1.3%)
Ethnicity – Hispanic or Latino	46 (19.7%)
Education – At least some college	220 (94.4%)
ATTR Amyloidosis Type	
Hereditary, also known as variant (ATTRv)	132 (56.7%)
Wild-type (ATTRwt)	101 (43.3%)
Affected Organs/Systems[2]	
Heart	182 (78.1%)
Nervous system	124 (53.2%)
Gastrointestinal system	79 (33.9%)
Kidney	44 (18.9%)
Other	15 (6.4%)

Abbreviations: IQR, interquartile range.
[1]Multiple responses allowed. Responses endorsed by <5% of sample are categorized as 'Other' and include Asian and American Indian or Alaska Native.
[2]Multiple responses allowed.

Figure 1: ATTR-QOL Impacts Domain Scales

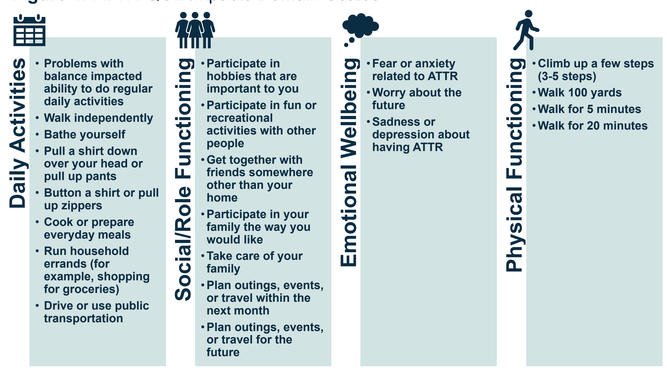

Table 2: Measurement Model and Psychometric Analyses for ATTR-QOL Impacts Domain Scales

Analysis	Results for ATTR-QOL Impacts Domain Scales
Mokken scale analysis	• Acceptable scalability for all ATTR-QOL Impacts domain items (all coefficients >0.45)
Multi-trait analysis	• Evidence of item convergent validity (all item-scale correlations ≥ 0.65) • Evidence of item discriminant validity in all but one item—"Participate in hobbies that are important to you" correlated slightly more with the Daily Activities scale than with the assigned Social/Role Functioning scale at follow-up timepoint (difference in correlation r < 0.05)
Floor and ceiling effects	• Slight floor effect observed for Physical Functioning scale; best possible score (no impact) observed in 17.6% of participants
Internal consistency reliability	• Evidence of internal consistency reliability (Cronbach's α ≥ 0.85 for all scales)
Test-retest reliability	• Evidence of test-retest reliability (all intraclass correlation coefficients [ICCs] ≥ 0.80)
Convergent and divergent validity	• Evidence of convergent and divergent validity for all scales (see **Table 3**)
Known-groups or discriminant validity	• Evidence of known-groups validity was found for all scales, with statistically significant differences across subgroups and higher (greater impact) scores among participants with worse symptom severity, cardiac functioning, or unemployment due to ATTR amyloidosis • Scale scores did not discriminate between participants based on duration of disease

Table 3: Correlations between ATTR-QOL Impacts Domain Scale Scores and Related PRO Scores at Initial Survey (N=233)

PRO Scales	ATTR-QOL Impacts Domain Scale			
	Daily Functioning	Social/Role Functioning	Emotional Wellbeing	Physical Functioning
Norfolk QOL-DN Small Fiber Neuropathy	**0.78**	0.63	0.54	0.55
Norfolk QOL-DN Activities of Daily Living	**0.85**	0.74	0.56	0.66
KCCQ-12 Social Limitations[1]	-0.74	**-0.82**	-0.59	-0.68
SF-36v2 – Social Function	-0.66	**-0.73**	-0.65	-0.58
SF-36v2 – Role Emotional	-0.64	**-0.70**	-0.67	-0.59
SF-36v2 – Mental Health	-0.52	-0.49	**-0.68**	-0.33
SF-36v2 – MCS	-0.58	-0.59	**-0.73**	-0.41
KCCQ-12 Physical Limitations[1]	-0.76	-0.76	-0.57	**-0.74**
SF-36v2 – Physical Function	-0.73	-0.84	-0.53	**-0.88**
SF-36v2 – PCS	-0.46	-0.66	-0.31	**-0.68**

Abbreviations ATTR-QOL, Transthyretin Amyloidosis Quality of Life Questionnaire; KCCQ-12, Kansas City Cardiomyopathy Questionnaire – 12 item; MCS, mental component summary; Norfolk QOL-DN, Norfolk Quality of Life – Diabetic Neuropathy; PCS, physical component summary; PRO, patient-reported outcome; SF-36v2, SF-36v2® Health Survey
Note Highlighted cells represent variables that were hypothesized to be more highly correlated as evidence for convergent validity. Due to the directionality of the scales, correlations between ATTR-QOL Impact Scale scores with Norfolk QOL-DN scales are expected to be positive and correlations between all other scales are expected to be negative.
[1]The KCCQ-12 was only administered to patients who indicated they had a diagnosis of heart failure (N=148)

SUMMARY / CONCLUSION

- Findings from this study support the use of the 4 ATTR-QOL Impacts domain scales in all patients with ATTR amyloidosis
- Twelve items were removed from the Impacts domain based on the study results; the updated survey is called the ATTR-QOLv2
  - Daily Activities, Social/Role Functioning, Emotional Wellbeing, and Physical Functioning scale scores can be calculated from both ATTR-QOL versions
- Limitations of the study included lack of clinical information and potential for selection bias—only patients active in the recruitment channels encountered study advertisements
- The ATTR-QOL is currently being evaluated in clinical and trial settings to understand relationship with key clinical markers, explore responsiveness, and establish meaningful within-patient change thresholds

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