

Psychometric properties of MG-ADL items and MG-ADL score: An assessment of distributional characteristics, validity and factor structure in two large datasets

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ARTICLE INFO

Keywords:

Myasthenia gravis
Health-related quality of life
Psychometrics
Real-word study
Clinical trial

ABSTRACT

Background: The Myasthenia Gravis–Activities of Daily Living scale (MG-ADL) is an 8-item outcome measure to assess symptoms and functional limitations in myasthenia gravis (MG) patients. The MG-ADL score is an equally weighted level sum score that is used as primary outcome measures in clinical trials, in clinical practice, and as an end-point in health economic evaluation. This data analysis aims to obtain detailed knowledge of measurement properties of MG-ADL items and the MG-ADL score.

Methods: Cross-sectional data from a real-world prospective study (MRW) were combined with longitudinal data from the ADAPT trial. Outcome measures included were MG-ADL, Quantitative Myasthenia Gravis score (QMG), MG 15-item Quality of Life (MG-QOL15r) and EQ-5D-5L. Patients were categorized by their Myasthenia Gravis Foundation of America (MGFA) clinical classification. The following measurement properties were assessed: distributional characteristics, inter-item correlation, convergent, known groups and construct validity and internal factor structure.

Results: Correlations of items within MG-ADL dimensions were moderate, while MG-ADL correlations between comparable MG-QOL15r and QMG items were mixed. Known groups validity for the MG-ADL score was demonstrated for MGFA class. Mean MG-ADL item level scores by MGFA class demonstrated construct validity. PCA, including all four outcome measures, resulted in a nine factor solution.

Discussion: Psychometric properties of individual MG-ADL items were moderate to good. This study showed that the MG-ADL adequately captures the multidimensional heterogeneous nature of MG. This is, however, accompanied by mixed psychometric performance of the MG-ADL score, which may complicate health economic modelling.

Registration: MyRealWorld-MG was registered on November 25, 2019, with registration number NCT04176211. The ADAPT randomized clinical trial is registered at [ClinicalTrials.gov](https://clinicaltrials.gov) (NCT03669588).

1. Introduction

Myasthenia gravis (MG) is an autoimmune disease that impairs transmission at the neuromuscular junction and is characterized by extensive signs of muscle weakness. MG is a heterogeneous disorder whose clinical manifestation ranges from variable combinations of ocular, bulbar, limb and respiratory symptoms. This variability poses a

challenge when using assessment tools to quantify clinical dysfunction, symptoms or the impact on patients' lives. Two main clinical types of the disease are recognized: ocular and generalized MG [1].

Multiple measures have been developed for assessing outcomes in MG, focusing on clinical aspects such as symptoms and functioning, well-being, health-related quality of life (HRQoL), or a combination thereof [2–10]. Despite their abundant availability, only a limited

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<https://doi.org/10.1016/j.jns.2024.123135>

Received 28 February 2024; Received in revised form 13 June 2024; Accepted 10 July 2024

Available online 22 July 2024

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number of these assessment tools are routinely used in clinical practice [11] or research [12]. Among the recommended and most frequently used outcome measures are the Quantitative MG (QMG) score, MG Activities of Daily Living (MG-ADL), MG Composite (MGC) and MG Quality of Life 15-item Scale - Revised (MG-QOL15r) [11–13].

In recent years, the MG-ADL has increasingly been used in both clinical practice and clinical research [12,14,15]. Although initially used as a secondary endpoint in clinical trials, the MG-ADL has more recently evolved into a primary endpoint [14]. The instrument assesses the symptoms and functional status of MG using 8 items across 4 domains: talking, chewing, swallowing (bulbar domain); breathing (respiratory domain); impairment of ability to brush teeth or comb hair, impairment of ability to rise from a chair (limb weakness domain); and double vision, eyelid droop (ocular domain).

A recent review of a total of 48 clinical trials and observational studies found that the MG-ADL is a reliable and valid measure for use in clinical practice or as a study outcome [14]. The review included studies assessing psychometric properties such as test-retest reliability, responsiveness, convergent validity and concurrent validity. The performance of the MG-ADL as a primary or secondary endpoint in both clinical trials and observational studies was also reviewed, in terms of change in baseline MG-ADL score, responder threshold, minimal symptoms and duration of treatment effects. Most studies included in this review analyzed the MG-ADL (total) score in comparison with total scores of other MG outcome measures for validity testing, except for Luo et al. (2021), who also compared responses between similar items of MG-ADL and QMG [16].

This study set out to investigate the internal structure of the MG-ADL by analyzing both the MG-ADL score and the item scores in comparison with other outcome measures, both MG-specific instruments and generic instruments of health, in relation to disease severity, and to an overall rating of an individual's current health state. Our aim was to assess the psychometrics properties of the MG-ADL items and the MG-ADL score, taking the heterogeneous nature of MG into account.

2. Methods

2.1. Datasets

2.1.1. MyRealWorld-MG

The MRW-MG study is a prospective, observational, real-world evidence study using a digital data collection platform, conducted among adult MG patients in 6 countries (US, UK, Canada, Italy, Germany, Spain). A smartphone application, developed by Vitaccess Limited, enabled participants to self-report monthly data about their experience of living with MG over a period of approximately 2 years. A diverse cohort of MG patients of all severity levels was recruited through clinical centres and patient advocacy groups. Inclusion criteria were being over 18 years old and having an MG diagnosis. The period of recruitment for the current analysis was from December 12, 2019, to April 1, 2020. Patients transcribed their MGFA status from their medical file. The current analyses is performed on data entered at baseline only, defined as the time point of downloading the smartphone application and logging the first measurements in the app. More information on the rationale, methods and study design of MRW-MG has been published elsewhere [17].

2.1.2. ADAPT

The purpose of the phase 3 ADAPT trial was to investigate the efficacy, safety, tolerability, impact on normal daily activities and HRQoL of efgartigimod add-on therapy versus conventional therapy in patients with generalized MG. ADAPT trial inclusion criteria were ≥ 18 years of age with generalized MG, an MG-ADL score of ≥ 5 ($>50\%$ non-ocular symptoms), and being on a stable dose of at least one treatment for generalized MG prior to randomization. MG patients from 15 countries in North America, Europe, and Japan were included in ADAPT. More

information on ADAPT is available elsewhere [18]. All available longitudinal data were included in the current study.

Additional information on data collection and data handling is available elsewhere [17,18].

2.2. Study variables and outcome measures

Both datasets included basic demographic data, acetylcholine receptor (AChR) status, MGFA classification, MG-ADL, MG-QOL15r and EQ-5D-5L, among other variables and instruments. The MGFA classification divides MG into 5 main classes, with class I describing ocular problems only, and with the further classes including bulbar problems, respiratory problems and limb and axial weakness of increasing severity. ADAPT additionally included QMG and body mass index (BMI) that were used in the current study.

2.2.1. Myasthenia Gravis Activities of Daily Living (MG-ADL)

The MG-ADL is a patient-reported measure, usually administered by a physician or trained clinic personnel. Note that while in ADAPT physicians scored the MG-ADL, in MRW-MG the MG-ADL was self-reported by patients. There is no specified recall period. The MG-ADL comprises 8 items in a set order (talking, chewing, swallowing, breathing, ability to brush teeth or comb hair, ability to rise from a chair, double vision and eyelid droop), and for each item there are four response options scored from 0 to 3 (none, mild, moderate, severe, using specific level descriptors for every level for every item). The MG-ADL score is the equally weighted level sum score of all the item scores, ranging from 0 to 24 [4,19].

2.2.2. Quantitative Myasthenia Gravis score (QMG)

The QMG is a physician-assessed 13-item instrument of functional MG disease severity, consisting of three domains, including ocular symptoms (2 items), facial/oropharyngeal symptoms (5 items, including the 2 ocular items), and non-facial symptoms (8 items) [3,11]. Each item is given a score of 0 to 3, resulting in an equally weighted level sum score of 0–39.

2.2.3. Myasthenia Gravis Quality of Life 15-item revised scale (MG-QOL15r)

The MG-QOL15r is a 15-item MG-specific HRQoL questionnaire, which assesses the impact of MG on the following domains: emotions, physical health, self-care, social life, and impact on role [6,7]. Each item contains three response options, scored from 0 to 2, and allow for the calculation of an equally weighted level sum score, ranging from 0 to 30. HRQoL is assessed over the past few weeks.

For MG-ADL, QMG and MG-QOL15r scores, higher scores indicate more reported symptoms or more severe disease.

2.2.4. EQ-5D-5L

The EQ-5D-5L is a validated generic instrument to measure health status and its impact on HRQoL, consisting of a descriptive system and a visual analogue scale (EQ-VAS) [20,21]. The descriptive system defines health in terms of five single-item dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression, with five severity levels for each dimension. The EQ-VAS measures the self-rated health on a scale with a grade ranging from 0 (the worst health you can imagine) to 100 (the best health you can imagine). EQ-5D-5L asks respondents to score their health on the day of completion. The responses on the descriptive system can be converted into a utility value ranging from health states considered to be worse than dead (<0), to 1 for full health, anchoring dead at 0. Multiple country-specific value sets are available that allow for the conversion of the EQ-5D-5L responses into utility scores [22]. The United States (US) value set was used in the current study [23].

Only data of patients who fully completed the MG-ADL, QMG (ADAPT data only), MG-QOL15r and EQ-5D-5L were included for

analysis.

2.3. Statistical analysis

For the main analyses, we pooled the MRW-MG and ADAPT data, resulting in a total of 3471 observations (Table 1). QMG and BMI data were available for ADAPT only. MG-ADL, QMG, MG-QOL15r and EQ-5D-5L outcomes were compared at the level of items and (total) scores. For EQ-5D-5L, utilities were also analyzed.

The MG-ADL profile consists of the sequence of the eight responses to the items in the same (fixed) order as they appear in the questionnaire (see above). The total number of MG-ADL profiles and the number of profiles per MG-ADL score were calculated, as well as the proportion of patients having each profile. There are 65,536 profiles theoretically possible.

The ceiling and floor of all instruments were analyzed at the item level. The average ceiling and floor by instrument was calculated by taking the mean ceiling and floor percentages across all items for that instrument. Informativity was analyzed using the Shannon H' index (absolute informativity, variable range) [24] and the Shannon J' Evenness index (relative informativity by adjusting for the number of response items, range 0–1) [25]. Shannon's H' combines the absolute amount of information expressed by the item with the extent to which the responses are distributed evenly across the response categories, while Shannon's J' solely reflects the latter component of evenness. The Shannon indices are purely descriptive measures of the informativity of an instrument and have no relation to the content or meaning of what the instrument aims to measure. The minimum value for both H' and J' is 0, while the maximum value for H' is the base-2 log of the number of levels, which is 1.58 for 3-level instruments and 2.00 for 4-level instruments, while for J' the maximum value is standardized at 1.0. We also assessed distributional characteristics between similar item pairs of MG-ADL and QMG, and of MG-ADL and MG-QOL15r. For this item-level analyses, we included item pairs of selected items from the instruments

assessing similar symptoms or aspects of health or HRQoL.

To assess the inter-relational structure between MG-ADL items, we calculated Spearman rank correlation coefficients between all 8 items [26]. We expected strong correlations between items within the same MG-ADL domains. A correlation of <0.3 was interpreted as weak; 0.3–0.49 as moderate; 0.5–0.59 as strong; and ≥ 0.6 as very strong [27].

Convergent validity between similar items of different instruments was assessed with the Spearman rank correlation coefficients, and between total scores with Pearson's correlation coefficients. We expected strong correlations between similar items of different instruments, strong to very strong correlations between MG-ADL and QMG and MG-QOL15r scores, and moderate correlations between MG-ADL and EQ VAS scores and EQ-5D-5L utilities.

We assessed known groups validity using the total scores as dependent variables for MGFA classification, gender, AChR status and BMI, using analysis of variance and the F statistic (level of significance: $p < 0.05$), which is commonly used to assess the discriminatory power of outcome measures [28,29]. MGFA is by definition related to the severity of the MG-ADL, so we expected a strong effect (high F statistic) with regard to known groups validity. For gender there is evidence that lower scores are observed for females on the MG-ADL, QMG and MG-QOL15r [30,31]. We hypothesized MG-ADL to be at least sensitive with regard to the two limb weakness items for age, and to breathing and ability to rise from chair for BMI. For MGFA we also tested for significant differences between consecutive classes.

Construct validity was assessed by calculating mean level scores at the item level for all MG-ADL items, by MGFA class and by MG-ADL score. We also calculated the relative contribution of the MG-ADL domains by MGFA and MG-ADL score. We expected mean level scores to increase by MGFA class of increasing disease severity.

We performed principal components analysis (PCA) including all items from all available instruments (ADAPT data only as MRW-MG data did not include the QMG score) to identify “latent constructs” in the data and to verify whether similar items across all instruments were grouped

Table 1
Patient characteristics of the two study samples.

	Sample Size	MRW-MG		ADAPT		TOTAL	
		N	%	N	%	N	%
Patients		508		163		671	
Observations baseline		508		163		671	
Observations follow-up		0		2800		2800	
Observations total		508		2963		3471	
Sociodemographics		N	%	N	%	N	%
	18–29	68	14%	20	12%	88	13%
	30–39	103	21%	34	21%	137	21%
	40–49	110	22%	45	28%	155	24%
	50–59	114	23%	25	15%	139	21%
	60–69	79	16%	23	14%	102	15%
Age	70+	22	4%	16	10%	38	6%
	F	344	70%	117	72%	461	70%
Gender	M	150	30%	46	28%	196	30%
Disease specific variables		N	%	N	%	N	%
	NEGATIVE	135	37%	37	23%	172	32%
AChR	POSITIVE	232	63%	126	77%	358	68%
	Class I	73	15%	0	0%	73	11%
	Class II	132	28%	64	39%	196	31%
	Class III	189	40%	94	58%	283	44%
MGFA classification	Class IV	75	16%	5	3%	80	13%
	Underweight (< 18.5)	NA	NA	4	2%	4	2%
	Healthy (18.5–25)	NA	NA	56	34%	56	34%
	Overweight (25–30)	NA	NA	43	26%	43	26%
	Low risk (30–35)	NA	NA	35	21%	35	21%
	Moderate risk (35–40)	NA	NA	14	9%	14	9%
BMI	High risk (> 40)	NA	NA	11	7%	11	7%

AChR Acetylcholine Receptor, MGFA Myasthenia Gravis Foundation of America, BMI body mass index, NA not available.

together in domains that can be traced back to the structure of the instruments and are related to clinical dysfunction or symptoms typically affected in MG. A Promax oblique rotation was used, which assumes that components are correlated. A second PCA analysis was performed on the 8 MG-ADL items alone.

2.4. Ethical considerations

For MRW-MG, ethics approval was granted by Veritas Institutional Review Board (Quebec, Canada) for Canadian participants and by Salus IRB (Austin TX, USA) for residents of all other countries. For ADAPT, independent ethics committees and international review boards provided written approval for the study protocol and amendments. All respondents provided written informed consent before starting the study, and both studies were conducted according to principles of the Declaration of Helsinki.

3. Results

3.1. Demographic and clinical characteristics of the participants

A total of 508 MRW-MG respondents with full data on MG-ADL, QMG, MG-QOL15r and EQ-5D-5L were included, while data from the ADAPT trial were included from 163 respondents on all 5 outcome measures (Table 1), leading to a total of 671 included patients. Taking the longitudinal data from ADAPT into account, the total number of observations was 3471.

Age and gender strata between the two study samples were comparable. The mean (SD) age for the pooled dataset was 47 (15), with 70% being female. There were lower patient numbers observed for MGFA IV and V classes, while for ADAPT there were no patients in MGFA class I due to exclusion criteria. For MRW, data from 5 patients who reported MGFA V were excluded as this classification was thought to be improbable, taking into account that patients self-reported their responses. Mean (SD) baseline total scores were 6.5 (3.8) for MG-ADL, 15.9 (4.8) for QMG (ADAPT data only) and 12.6 (7.2) for MG-QOL15r. Mean (SD) EQ VAS was 61.6 (21.0), and EQ-5D-5L utility value was 0.69 (0.24).

3.2. MG-ADL profiles

Among 3471 MG-ADL measurements, 1471 different MG-ADL item score profiles were observed (of the 65,536 profiles theoretically possible). The most frequently occurring profiles were 00000000 ($N = 178$, which is no symptoms across all eight domains), 00010000 ($N = 50$, patients only suffering from shortness of breath with exertion), 11112222 ($N = 32$, patients with occasional bulbar problems, shortness of breath with exertion, moderate problems with limb weakness, daily problems with vision), 00000001 ($N = 27$, patients with occasionally occurring eyelid droop), 10100000 ($N = 24$, patients with intermittent slurring and rare episode of choking).

There were many different MG-ADL profiles observed that had the same MG-ADL score, ranging from 1 (by definition for MG-ADL score = 0), to 194 different profiles for MG-ADL score = 7, with an average of 67 profiles across all observed MG-ADL scores.

3.3. Distributional characteristics

A considerable average ceiling (representing the least severe score) across items was observed for all four instruments: 42% (MG-ADL), 35% (MG-QOL15r), 33% (QMG, ADAPT data only) and 43% (EQ-5D-5L). The floor was below 5% for MG-ADL (2.6%), QMG (4.6%) and EQ-5D-5L (0.3%), but considerably higher for MG-QOL15r (17%). Absolute informativity H' indices across items were 1.54 (MG-ADL), 1.40 (MG-QOL15r), 1.47 (QMG, ADAPT data only) and 1.70 (EQ-5D-5L), while relative informativity J' indices were 0.77 (MG-ADL), 0.89 (MG-

QOL15r), 0.74 (QMG, ADAPT data only) and 0.73 (EQ-5D-5L).

For the item pairs of the MG-ADL and the MG-QOL15r, the MG-QOL15r had generally lower ceilings whereas the MG-ADL had lower floors (Table 2). Absolute informativity was higher for MG-ADL (Appendix Table 1), while relative informativity was higher for MG-QOL15r for all items pairs except one.

For the item pairs of the MG-ADL and the QMG differences in ceiling varied considerably and were mixed, with lower ceilings observed for QMG for 11 items pairs, and lower ceilings for MG-ADL for 9 items pairs (Table 2). More lower floors were generally observed for the MG-ADL item pairs. Relative informativity was higher for QMG for 11 items pairs (Appendix Table 2), while J' was higher for MG-ADL for the remaining 9 item pairs.

3.4. Inter-item correlation

Spearman correlations between MG-ADL items belonging to the same domain were all moderate: bulbar (range 0.36 to 0.43); limb weakness (0.40); and ocular domain (0.36) (Table 3). For the remaining item pairs belonging to different domains, 19 pairs were weakly correlated, while 4 were moderately correlated.

3.5. Convergent validity

For similar items between the MG-ADL and MG-QOL15r, Spearman correlations were moderate for 11 item pairs (range 0.34 to 0.48); strong for 2 item pairs (range 0.54 to 0.59) and very strong for 3 item pairs (range 0.64 to 0.69) (Table 2).

When comparing similar items between MG-ADL and QMG, Spearman correlations were low for 10 out of 20 item pairs (range 0.11–0.28); moderate for 8 item pairs (range 0.30–0.46), and strong to very strong for 2 item pairs (0.59 and 0.72, respectively) (Table 2).

Convergent validity of MG-ADL score with QMG (ADAPT only) and MG-QOL15r scores were very strong (0.66; 0.64 respectively), while correlations of MG-ADL with EQ VAS and EQ-5D-5L utility were moderate (−0.49) and strong (−0.52).

3.6. Known groups validity

Known groups validity of MG-ADL scores showed a significant association of higher MG-ADL scores with increasing MGFA classes and with AChR positive status (Table 4). For the QMG and MG-QOL15r scores and utilities, significant results were observed only by MGFA class. Significant differences were found between all consecutive MGFA classes for all 4 total scores.

3.7. Construct validity

Fig. 1 (left panel) shows average level scores for all MG-ADL items according to MGFA classes. As expected, overall symptoms across all 8 items increase with increasing MGFA class. Problems in the bulbar domain remain lowest at MGFA Class IV, while ocular problems are more prominent in MGFA classes I (by definition) and II. Fig. 1 (right panel) shows the relative contribution to the MG-ADL score by MG-ADL domain for each MGFA class. While the contribution of the ocular domain decreases with increasing MGFA class, the contribution of the bulbar and limb weakness domains increases overall.

3.8. Principal components analysis

The PCA analysis on all 41 items across the 4 outcome measures resulted in a 9-factor solution (Table 5, we only showed item loadings ≥ 0.3). Components emerging from the analysis were congruent to the domains from the different instruments and were, in order of eigenvalue magnitude: daily activities, limb weakness, bulbar problems, emotions, functioning and pain, self-care/vital capacity, hand grip, ptosis and eye

Table 2
Distributional and convergent validity comparison of the MG-ADL with the MG-QOL15r (N = 3.471) and QMG (ADAPT dataset, N = 2.963).

Dimension	MG-ADL (4 levels)			MG-QOL15r (3 levels)					Correlation
	Item	Ceiling	Floor	Item	Ceiling	Floor	Δ Ceiling	Δ Floor	
Bulbar/oropharyngeal	Talking	49.8%	0.9%	Eating	40.3%	8.0%	9.5%	-7.1%	0.46
				Speaking	46.7%	7.5%	3.1%	-6.6%	0.68
	Chewing	45.4%	0.1%	Eating	40.3%	8.0%	5.1%	-7.8%	0.69
				Speaking	46.7%	7.5%	-1.3%	-7.4%	0.46
	Swallowing	49.8%	0.1%	Eating	40.3%	8.0%	9.5%	-7.8%	0.48
				Speaking	46.7%	7.5%	3.0%	-7.4%	0.37
	Brush teeth or comb hair	39.9%	0.8%	Meeting needs of family	24.5%	25.4%	15.4%	-24.5%	0.35
				Performing work	20.9%	27.7%	19.0%	-26.9%	0.34
				Independence	36.6%	18.4%	3.3%	-17.6%	0.34
				Meeting needs of family	30.6%	18.2%	7.2%	-17.6%	0.44
Performing work				20.9%	27.7%	16.9%	-27.1%	0.40	
Independence				36.6%	18.4%	1.2%	-17.8%	0.43	
Limb weakness	Rise from chair	37.8%	0.6%	Walking	35.6%	12.9%	2.2%	-12.4%	0.59
				Getting around	38.1%	15.8%	-0.3%	-15.2%	0.54
Ocular	Double vision	45.6%	6.9%	Eye problems	30.9%	18.0%	14.8%	-11.1%	0.64
				Eyelid droop	37.7%	11.0%	6.8%	-7.0%	0.44

Dimension	MG-ADL (4 levels)			QMG (4 levels)					Correlation
	Item	Ceiling	Floor	Item	Ceiling	Floor	Δ Ceiling	Δ Floor	
Bulbar/oropharyngeal	Talking	48.6%	0.8%	Facial muscles	33.2%	2.4%	15.4%	-1.6%	0.27
				Swallowing	73.2%	0.1%	-24.5%	0.7%	0.31
				Speech	64.4%	3.9%	-15.8%	-3.1%	0.46
	Chewing	43.8%	0.0%	Facial muscles	33.2%	2.4%	10.6%	-2.4%	0.22
				Swallowing	73.2%	0.1%	-29.4%	-0.1%	0.34
				Speech	64.4%	3.9%	-20.6%	-3.9%	0.27
	Swallowing	49.0%	0.0%	Facial muscles	33.2%	2.4%	15.8%	-2.4%	0.11
				Swallowing	73.2%	0.1%	-24.2%	-0.1%	0.46
				Speech	64.4%	3.9%	-15.4%	-3.9%	0.21
	Respiratory	Breathing	27.6%	0.0%	Vital capacity	62.0%	3.6%	-34.4%	-3.6%
Right arm outstretched					18.2%	3.0%	20.1%	-2.1%	0.36
Limb weakness	Brush teeth or comb hair	38.3%	0.9%	Left arm outstretched	17.8%	2.5%	20.5%	-1.6%	0.35
				Right hand grip	13.8%	0.6%	24.4%	0.2%	0.27
				Left hand grip	25.7%	0.4%	12.6%	0.4%	0.28
	Rise from chair	36.6%	0.5%	Right leg outstretched	11.7%	1.5%	24.8%	-0.9%	0.30
				Left leg outstretched	11.4%	1.6%	25.1%	-1.1%	0.30
				Double vision	40.5%	18.9%	5.9%	-12.4%	0.72
Ocular	Eyelid droop	37.9%	11.3%	Ptosis	38.7%	19.6%	7.7%	-13.0%	0.24
				Double vision	40.5%	18.9%	-2.6%	-7.6%	0.31
				Ptosis	38.7%	19.6%	-0.8%	-8.3%	0.59

MG-ADL Myasthenia Gravis Activities of Daily Living, MG-QOL15R Myasthenia Gravis Quality of Life 15, QMG Quantitative Myasthenia Gravis.

Table 3
Spearman correlation rank order coefficients of MG-ADL item scores (N = 3.471).

MG-ADL		Talking	Chewing	Swallowing	Breathing	Brush teeth /comb hair	Rise from chair	Double vision
Bulbar	Chewing	0.43						
	Swallowing	0.36	0.43					
Respiratory	Breathing	0.17	0.30	0.24				
Limb weakness	Brush teeth/comb hair	0.15	0.37	0.23	0.30			
	Rise from chair	0.14	0.28	0.28	0.36	0.40		
Ocular	Double vision	0.11	0.18	0.22	0.17	0.18	0.21	
	Eyelid droop	0.22	0.26	0.19	0.26	0.24	0.23	0.36

MG-ADL Myasthenia Gravis Activities of Daily Living.

problems.

The PCA performed on the eight MG-ADL items alone resulted in a 3-factor solution, with the three bulbar items grouped together in one factor, double vision and eyelid droop in a second factor, and the 2 limb weakness items grouped with breathing in a third factor (Appendix Table 3).

3.9. Association of the MG-ADL items and its total score

Fig. 2 (upper panel) displays the average level scores of each of the eight MG-ADL items by MG-ADL score. This demonstrates how the total score is composed, and which domains gain in importance with more severe disease. By definition, the levels of the items are increasing for higher MG-ADL scores, however the relative importance of each item/domain changes. Bulbar symptoms such as talking and swallowing are the least common across all severity levels, whereas ocular problems are

Table 4

Known groups validity* of MG-ADL score, MG-QOL15r score, EQ VAS and EQ-5D-5L utility (baseline data, N = 671)^a.

MGFA classification	N	MG-ADL score		MG-QOL15r score		EQ VAS		EQ-5D-5L utility (US)	
		Mean	SD	Mean	SD	Mean	SD	Mean	SD
Class I	73	2.8	2.6	5.8	5.5	71.7	21.5	0.85	0.17
Class II	196	5.9	3.5	11.1	6.8	65.5	20.4	0.75	0.19
Class III	283	7.4	3.5	14.7	6.4	59.0	18.7	0.65	0.23
Class IV	80	8.6	3.6	16.3	6.0	49.9	22.4	0.51	0.30
F test		F statistic	P	F statistic	P	F statistic	P	F statistic	P
		37.4	0.00	38.9	0.00	14.8	0.00	29.2	0.00
Gender	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
F	461	6.8	3.8	12.9	7.1	61.1	20.9	0.68	0.24
M	196	5.8	4.0	11.8	7.4	63.2	20.9	0.71	0.24
F test		F statistic	P	F statistic	P	F statistic	P	F statistic	P
		9.3	0.17	3.6	0.37	1.3	0.63	2.1	0.49
AChR	N	Mean	SD	Mean	SD	Mean	SD	Mean	SD
NEGATIVE	172	7.9	3.5	14.7	6.5	58.3	19.6	0.64	0.25
POSITIVE	358	6.4	3.8	12.5	7.4	61.7	21.5	0.69	0.25
F test		F statistic	P	F statistic	P	F statistic	P	F statistic	P
		18.9	0.04	11.1	0.08	3.1	0.38	5.05	0.28

MGFA Myasthenia Gravis Foundation of America, MG-ADL Myasthenia Gravis Activities of Daily Living, MG-QOL15R Myasthenia Gravis Quality of Life 15, AChR Acetylcholine Receptor, BMI body mass index.

* $p < 0.05$.

^a For age and BMI no significant differences were found.

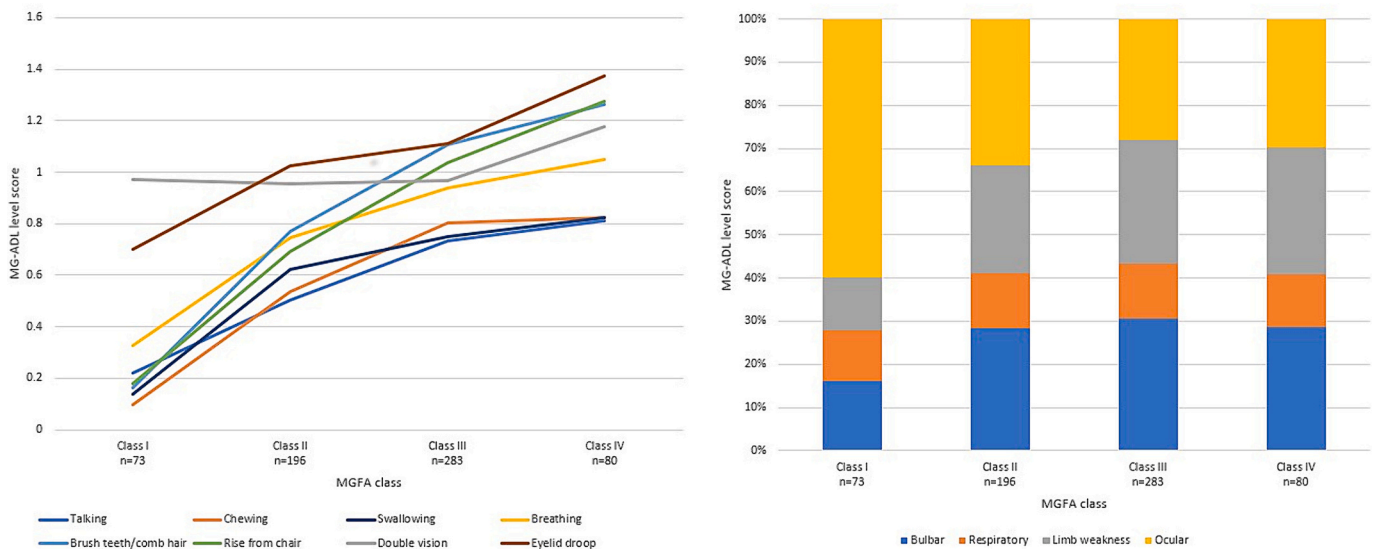


Fig. 1. Mean MG-ADL item level score by MGFA classification (left panel) and relative contribution by domain (right panel) (baseline data, N = 671).

the most frequently occurring symptoms, followed by limb weakness. While breathing issues are one of the most frequently mentioned problems among milder patients, this domain is only contributing to the average level in more severely affected patients.

The relative contribution of MG-ADL domains to the separate MG-ADL scores shows a decreasing contribution of the respiratory domain with increasing MG-ADL score (indicated by the decreasing sub-bars for the respiratory domain in Fig. 2, lower panel), while the contribution of the bulbar domain increases (Fig. 2; lower panel). The contribution of the ocular and limb weakness domains varies with increasing MG-ADL score.

4. Discussion

This study aimed to assess the psychometric properties of the MG-ADL in two large multi-country datasets collected in adult MG patients. Psychometric properties of MG-ADL individual items were generally good, whereas evidence for the MG-ADL score was mixed.

A considerable average ceiling was observed across all four instruments, which may be caused by the episodic nature of MG. The ceiling for the MG-specific instruments was highest for MG-ADL, which may further be explained by a lack in content validity, which has been demonstrated before in a comparative study with the QMG [32]. A way of increasing content validity would be to add items to the MG-ADL, e.g. items that tap into other domains or items that capture other aspects of the existing MG-ADL domains, although this might compromise the internal structure of the instrument. Overall absolute informativity was higher for MG-ADL when compared to other instruments, while relative informativity was comparable to the QMG but lower than for the MG-QOL15r. This implies that the absolute amount of information captured is highest for the MG-ADL, while when just looking at distributional evenness MG-QOL15r performs better. Taking both absolute and relative informativity into account, it can be concluded that MG-ADL performs best overall. Differences in distributional characteristics and correlations of similar MG-ADL items with the items of other instruments were considerable and in mixed directions, likely due to

Table 5Principal components analysis of MG-ADL, QMG, MG-QOL15r and EQ-5D-5L items (item loadings of ≥ 0.3) with a nine factor solution (ADAPT dataset, N = 2.963).

		Daily activities	Limbs	Bulbar	Emotions	Function-ing/ pain	Self-care /vital	Hand grip	Ptosis	Eye problems	
Instrument	Item	Factor1	Factor2	Factor3	Factor4	Factor5	Factor6	Factor7	Factor8	Factor9	Uniqueness
MG-ADL	Talking			0.81							0.35
	Chewing			0.55							0.44
	Swallowing			0.75							0.40
	Breathing					0.31					0.70
	Brush teeth or comb hair						0.39				0.51
	Rise from chair					0.59					0.42
	Double vision									0.92	0.19
	Eyelid droop								0.87		0.22
	Double vision									0.85	0.26
	Ptosis								0.84		0.25
	Facial muscles							0.43			0.50
	Swallowing			0.72							0.50
	Speech			0.67							0.49
	Right arm outstretched			0.85							0.23
	Left arm outstretched			0.85							0.22
	QMG	Vital capacity						0.96			
Right hand grip								0.93			0.18
Left hand grip								0.93			0.17
Head lifted			0.74								0.35
Right leg outstretched			0.95								0.20
Left leg outstretched			0.93								0.22
Frustrated		0.32			0.55						0.38
Eye problems										0.74	0.31
Eating		0.33		0.66							0.32
Social activity		0.92									0.23
Enjoying leisure		0.89									0.26
Meeting needs of family		0.86									0.30
Planning around illness		0.83									0.31
Performing work		0.81									0.27
Speaking				0.73							0.34
Independence		0.77									0.31
Depressed				0.83						0.26	
Walking	0.65					0.48				0.27	
Getting around	0.72					0.32				0.27	
MG-QOL15r	Feeling overwhelmed				0.73						0.36
	Personal grooming	0.39					0.30				0.38
	Mobility	0.50				0.62					0.22
	Self-care	0.33				0.39	0.35				0.26
	Usual activities	0.63				0.33					0.25
EQ-5D-5L	Pain/discomfort				0.42	0.54					0.51
	Anxiety/depression				0.91						0.30

MG-ADL Myasthenia Gravis Activities of Daily Living, MG-QOL15r Myasthenia Gravis Quality of Life 15, QMG Quantitative Myasthenia Gravis.

different operational properties of items across instruments (e.g. the MG-ADL measures MG symptoms and functional status, while the MG-QOL15r assessed the impact of MG on HRQoL). Inter-item correlation within MG-ADL domains was moderate, whereas correlations between domains were mostly weak, reflecting the multidimensional and heterogeneous nature of MG. Interesting was the low correlation (0.20) between the MG-ADL breathing and QMG vital capacity items, as we expected a strong correlation (>0.50). Apparently subjective shortness of breath as reported with the MG-ADL is quite different from objectively measuring vital capacity using a spirometer as part of the QMG. Also, previously it was demonstrated that the QMG vital capacity item did not have good discriminative properties between patients [33]. Known groups validity of MG-ADL scores was confirmed for MGFA and AChR, but not for age, gender or BMI. There being no effect for age could be explained through the different ages of onset of MG in our study samples. For BMI, the hypothesized differences in outcomes could have been cancelled out by prevailing MG symptoms. Moreover, if age and BMI are not considered to be drivers of MG symptoms, the lack of significant results could also indicate a strong property of the MG-ADL score. The factor structure resulting from the PCA across the four measures

included in ADAPT largely confirmed the dimensional structure applied in MG-ADL, but also in QMG and MG-QOL15r. The PCA again confirms the multidimensional heterogeneous nature of MG, even within domains, as ptosis and eyelid droop were identified as separate factors. From the PCA conducted on the MG-ADL items alone it was apparent that breathing was not identified as a separate factor as it is conceived in the design of MG-ADL, although this could be caused by the limited number of 8 items included in the PCA. It was striking that there was a relatively high contribution of patients scoring non-ocular items in the MGFA class I patients (Fig. 1), while class I describes ocular problems only. This could be explained by the fact that a proportion of patients in MRW (Class I was observed in MRW only) transcribed their MGFA status from their medical file, while at the time of measurement could have progressed into a different MGFA class. Also, as disease classification, MGFA is rather static, and it could be that MGFA Class I patients reported temporary problems in other domains. The relative contribution of MG-ADL domains to the MG-ADL score showed that with increasing disease severity (assessed either by MGFA or MG-ADL score), the contribution of the ocular, bulbar and limb weakness domains was about equal (roughly 30%), while the contribution of the respiratory domain

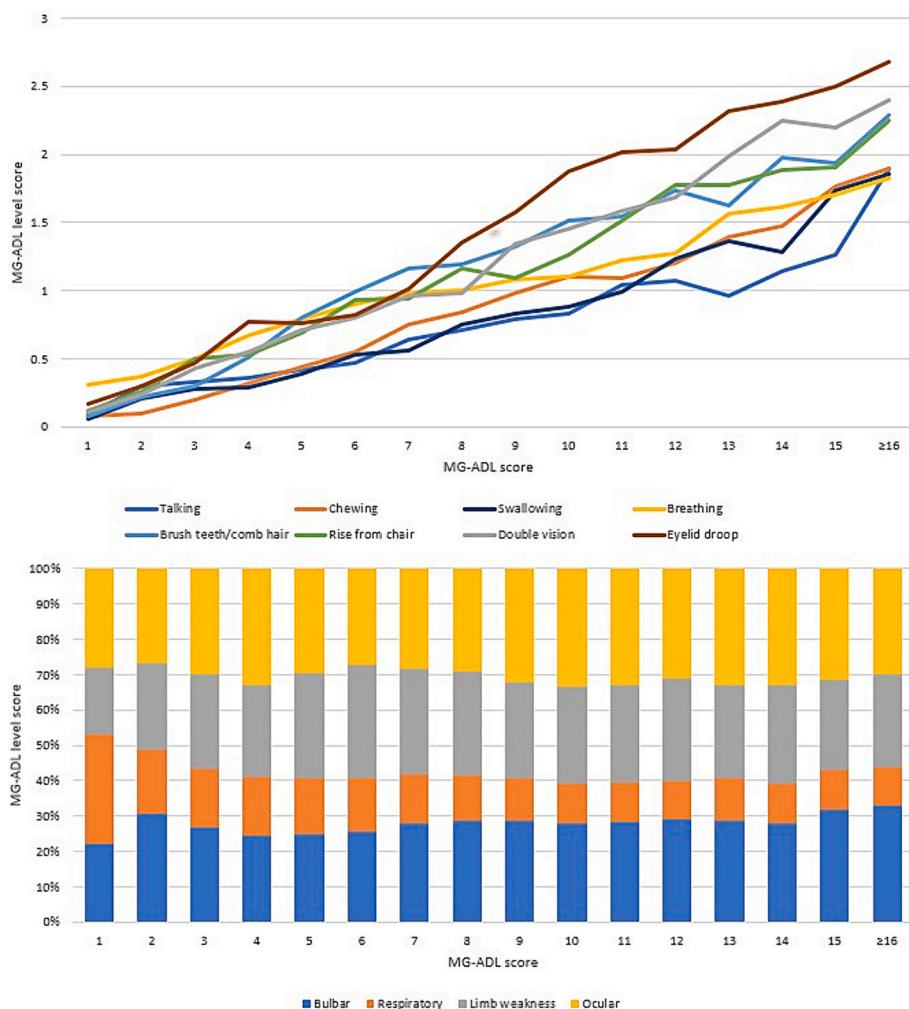


Fig. 2. Mean MG-ADL item level score by MG-ADL score (upper panel) and relative contribution by domain (lower panel) (baseline data, N = 671).

was considerably smaller (about 10%), which is partly explained by there being only one respiratory item in the MG-ADL.

The result we observed in terms of convergent validity of the MG-ADL score with the QMG score (Pearson correlation of 0.66) fits well in the range of correlation coefficients found in other studies (0.33–0.85). This was also the case for the correlation we found with the MG-QOL15r score (0.64) and those found in other studies (0.62–0.85) [14].

A main strength of this study is that it was based on two large multi-country datasets, collected in diverse populations of MG patients, enhancing generalizability of study results and conclusions. Most studies assessing psychometric properties of MG-ADL were conducted in smaller samples [14]. The multinational nature of our study ensures that any effects due to differences in culture, language (translations of the instruments) or differences caused by different healthcare systems or other environmental factors are cancelled out to a large extent, which strengthens generalizability. Further, a wide array of psychometric properties was assessed, performed on the item level as well as on the MG-ADL score, allowing for a thorough investigation and detailed overview of the MG-ADL instrument. To our knowledge this is the first study assessing detailed distributional characteristics, inter-item correlations, known groups validity, construct validity and PCA on the MG-ADL. Moreover, we demonstrated the relative contribution of the MG-ADL domains to the MG-ADL score.

The MG-ADL score is an equally weighted level sum score across the 8 items included in the MG-ADL. Considering the heterogeneous nature

of MG, and that different symptoms might not affect patients to the same degree, the equal weights of the MG-ADL score might not be suitable or optimal. For instance, the simultaneous occurrence of occasional problems with double vision and occasional eyelid droop will result in the same score as frequent choking, or as shortness of breath at rest. These different clinical manifestations are not likely to be felt or valued the same by patients or clinicians and in turn affect the psychometric performance of the MG-ADL score.

There are a number of limitations that need to be addressed. The digital data collection in the MRW-MG study might have incurred selection bias, as only patients able to use the smartphone app could enroll. The ADAPT data may also have been prone to selection bias due to the inclusion and exclusion criteria [18]. However, as our focus was on psychometric properties of MG-ADL, representativeness of MG patients was not of crucial importance. Moreover, any selection would be largely mitigated by combining our two datasets, based on clinical trial data and real-world data. A potential critical issue is that MG-ADL was scored by physicians in ADAPT and self-reported by patients in MRW-MG. A separate study investigating the agreement between physician versus patient-reported MG-ADL assessments, however, indicated very high concordance of MG-ADL items and total scores [34], confirming earlier evidence [35].

5. Conclusion

This study showed that the MG-ADL captures the multidimensional

heterogeneous nature of MG well. This is, however, accompanied by mixed performance in terms of psychometric properties of the MG-ADL score, which may also complicate health economic modelling. Future research could explore alternative weighted approaches to the MG-ADL score, or to explore the effect of adding items to the MG-ADL on its psychometric performance.

Funding

This study was funded by Argenx, Ghent, Belgium.

CRedit authorship contribution statement

Mathieu F. Janssen: Writing – review & editing, Writing – original

draft, Methodology, Funding acquisition, Formal analysis, Data curation, Conceptualization. **Sarah Dewilde:** Writing – review & editing, Funding acquisition, Conceptualization. **Gil I. Wolfe:** Writing – review & editing. **Srikanth Muppidi:** Writing – review & editing. **Glenn Phillips:** Writing – review & editing, Conceptualization.

Acknowledgements

The authors would like to thank all the participants of the MyRealWorld-MG study for sharing their data.

Appendix A

Appendix Table 1

Distributional comparison of the MG-ADL with the MG-QOL15r (N = 3.471).

Dimension	MG-ADL (4 levels)			MG-QOL15r (3 levels)			Δ Shannon H'	Δ Shannon J'
	Item	Shannon H'	Shannon J'	Item	Shannon H'	Shannon J'		
Bulbar/oropharyngeal	Talking	1.33	0.66	Eating	1.31	0.83	0.02	-0.16
				Speaking	1.31	0.83	0.02	-0.16
	Chewing	1.38	0.69	Eating	1.31	0.83	0.07	-0.14
				Speaking	1.31	0.83	0.07	-0.14
				Eating	1.31	0.83	0.03	-0.16
	Swallowing	1.34	0.67	Speaking	1.31	0.83	0.03	-0.16
				Meeting needs of family	1.50	0.95	0.12	-0.95
	Brush teeth or comb hair	1.62	0.81	Performing work	1.48	0.93	0.14	-0.12
				Independence	1.50	0.95	0.12	-0.14
				Meeting needs of family	1.46	0.92	0.15	-0.92
Performing work				1.48	0.93	0.13	-0.13	
Independence				1.50	0.95	0.11	-0.14	
Limb weakness	1.61	0.81	Walking	1.41	0.89	0.21	-0.08	
			Getting around	1.47	0.93	0.15	-0.12	
Ocular	1.77	0.88	Eye problems	1.46	0.92	0.30	-0.04	
			Eye problems	1.46	0.92	0.42	0.02	

Appendix Table 2

Distributional comparison^a of the MG-ADL with the QMG (ADAPT dataset, N = 2.963).

Dimension	MG-ADL (4 levels)		QMG (4 levels)		Δ Shannon J'
	Item	Shannon J'	Item	Shannon J'	
Bulbar/oropharyngeal	Talking	0.67	Facial muscles	0.79	-0.12
			Swallowing	0.49	0.18
	Chewing	0.69	Speech	0.71	-0.04
			Facial muscles	0.79	-0.09
			Swallowing	0.49	0.21
	Respiratory	0.67	Speech	0.71	-0.01
			Facial muscles	0.79	-0.11
	Brush teeth or comb hair	0.81	Swallowing	0.49	0.19
			Speech	0.71	-0.03
			Vital capacity	0.71	-0.02
Right arm outstretched			0.82	-0.01	
Left arm outstretched			0.80	0.01	
Limb weakness	0.81	Right hand grip	0.50	0.31	
		Left hand grip	0.63	0.18	
Double vision	0.88	Right leg outstretched	0.75	0.06	
		Left leg outstretched	0.74	0.06	
		Double vision	0.96	-0.08	
Ocular	0.95	Ptosis	0.93	-0.05	
		Double vision	0.96	-0.01	
			Ptosis	0.93	0.01

^a Only Shannon's J' was assessed as the number of levels between MG-ADL and QMG was identical.

Appendix Table 3Principal components analysis of MG-ADL (item loadings of ≥ 0.3) with a three factor solution (ADAPT dataset, N = 2.963)

Item	Breathing/limb weakness	Bulbar	Ocular	Uniqueness
	Factor1	Factor2	Factor3	
Talking		0.89		0.30
Chewing		0.70		0.36
Swallowing		0.71		0.43
Breathing	0.66			0.53
Brush teeth or comb hair	0.78			0.41
Rise from chair	0.82			0.37
Double vision			0.88	0.26
Eyelid droop			0.75	0.36

MG-ADL Myasthenia Gravis Activities of Daily Living.

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