INDEPENDENT VALIDATION OF THE QUALITY OF LIFE IN ESSENTIAL TREMOR QUESTIONNAIRE (QUEST)

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PRINT English http://dx.doi.org/10.18071/isz.70.0193 www.elitmed.hu

Quality of Life in Essential Tremor Questionnaire (QUEST) was specially developed for essential tremor population to measure the health-related quality of life. Besides the development of the Hungarian version, we performed an independent testing of the scale adding further information on its clinimetric properties.
In this study 133 ET patients treated at University of Pécs, Hungary, were enrolled. Besides QUEST, we assessed Patient's Global Impression-Severity (PGI-S) and Fahn-Tolosa-Marin Tremor Rating Scales. After the independent validation in accordance to the Classic Theory of Tests, we evaluated cut-off values for detecting clinically meaningful ET-related disabilities based on receiver operating characteristics analysis.
Cronbach's α was 0.897. QUEST demonstrated high convergent validity with PGI and divergent validity with disease-duration, positive family history, need for deep brain stimulation surgery, and the presence of depression and anxiety. Presence of moderate ET-related disabilities was identified by scores > 11.25 points on QUEST-SI (sensitivity: 77.4%, specificity: 83.3%); whereas scores > 20.35 points indicated severe ET-related disabilities (sensitivity: 83.3%, specificity: 59.1%).
We demonstrated that the fundamental clinimetric properties of the QUEST are satisfactory.

Keywords: *essential tremor, validity, reliability, health-related quality of life*

AZ ÉLETMINŐSÉG ESSZENCIÁLIS TREMORBAN SKÁLA (QUEST) FÜGGETLEN VALIDÁCIÓJA

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Ideggyogy Sz 2017;70(5–6):193–202.

Az Életminőség Esszenciális Tremorban Skálát (Quality of Life in Essential Tremor Questionnaire, QUEST) az esszenciális tremoros populáció egészséggel kapcsolatos életminőségének méréséhez fejlesztették ki. A magyar nyelvi verzió kidolgozása mellett egy olyan független validációt is elvégeztünk, ami a skála klinimetrikus tulajdonságainak kibővítését is megcélozta.
Jelen vizsgálatunkba a Pécsi Tudományegyetemen kezelt 133 esszenciális tremoros beteg került bevonásra. A QUEST mellett a Beteg által Értékelt Globális Összbenyomás-súlyosság (Patient's Global Impression-Severity, PGI-S) és a Fahn–Tolosa–Marin Tremor Pontozóskála került felvételre. A klinikai tesztek klasszikus elmélete szerinti független validációt követően hatásfokmérő karakterisztika eljárás alapján meghatároztuk a különböző mértékű korlátozottsági fokokra jellemző határértékeket.
A skálára jellegzetes Cronbach-α értéke 0,897 volt. A QUEST szoros konvergens validitást mutatott a PGI-S skálával, míg divergens validitást a betegségtartammal, a pozitív családi anamnézissel, a mély agyi stimulációt igénylő súlyossággal, illetve a depresszióval és szorongással. Eredményeink alapján a 11,25 pontot meghaladó értékek a közepes fokú (szenzitivitás: 77,4%, specificitás: 83,3%), míg a 20,35 pontot meghaladó értékek súlyos fokú (szenzitivitás: 83,3%, specificitás: 59,1%) korlátozottságra utalnak. Eredményeink szerint a magyar nyelvű QUEST skála megfelelő klinimetrikus tulajdonságokkal rendelkezik.

Kulcsszavak: *esszenciális tremor, validitás, megbízhatóság, egészséggel kapcsolatos életminőség*

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Érkezett: 2017. január 10. Elfogadva: 2017. február 1.

Essential tremor (ET) is one of the most frequent movement disorders with the estimated prevalence of 4–39 per 1.000 inhabitants[1]. Although the most prominent feature of ET is the tremor itself, recent research demonstrated that non-motor symptoms (e.g. sleep problems, depression, anxiety, etc.) are also pertinent[2–4]. Clinical diagnosis is based purely on the neurological features; which can be classified as either possible, probable or definite ET[5]. The spectrum of symptoms is broad and ranges from mild disease to severe disabling condition having an impact on the health-related quality of life (HRQoL)[6]. Therefore, assessment instruments which reflect the broader influence of these motor and non-motor symptoms on the well-being of ET patients are needed. To describe reliably the HRQoL in ET, the Quality of Life in Essential Tremor Questionnaire (QUEST) scale was established as a disease-specific instrument in the English language[7] and has become a standard evaluation tool. The validity of the QUEST scale has been demonstrated by independent groups[8]. QUEST has been recently translated into some languages, including Spanish[8], German[9] and Turkish[10].

The response to pharmacological treatments are variable on the motor and non-motor symptoms of ET[6]. In case of pharmacoresistant tremor, neurosurgical options including ablative surgeries and deep brain stimulation are indicated[11, 12]. To judge the efficacy of these medical treatments, changes not only in the symptoms of ET, but also in the HRQoL have to be assessed. Therefore, it is an important task to translate and validate this ET-specific HRQoL instrument into the native language of patients included in clinical trials.

The QUEST consists of 30 items contributing five different areas including Physical symptoms, Psychosocial symptoms, Communication, Hobbies/Leisure and Work/Finance domains. Each item is scored between 0 (never) and 4 (always). Each dimension score is expressed as the percentage of the achieved score to the maximum possible score, with a higher score indicating higher dissatisfaction with that specific domain. Subsequently, a summary index (QUEST-SI) can be calculated by averaging the five dimensions. As some items may not be appropriate for some patients (e.g. not working anymore), the work-related items may also be reported as "not applicable".

Besides these 30 items, the QUEST consists of a self-evaluation section not contributing to the QUEST-SI. In this part of the QUEST, the patients have to describe their General Health Status, Global HRQoL (each rated from 0 to 100 in five-point increments with a higher value indicating better status). Besides, questions addressing ET-related impact on sexual satisfaction, treatment satisfaction and occupational status. It also includes a self-assessment of tremor occurrence (hours per day with tremor) and tremor severity (in head, voice, and all four extremities) scored from 0 (never) to 4 (severe). This introductory section provides additional self-assessed information on tremor, but it is not part of the total score of QUEST.

The QUEST scale was initially validated on 200 ET patients in the USA. The psychometric properties of the scale was further confirmed in a multicenter Spanish study (n=118)[8] and a single-center German study (n=138)[9]. However, in these independent validation studies dealt with the problem of missing values. Some of the items had 18.6–30.5% absent values[8]. Recently, QUEST was utilized in some clinical trials as an outcome[13]. Furthermore, the threshold values for mild/moderate and moderate/severe disease impact on HRQoL have not been determined yet.

The objective of the present study was to perform an independent validation of the QUEST following the principles of the Classical Test Theory[14] and determine the respective threshold values for moderate and severe disability.

ABBREVIATIONS

EQ-5D: EuroQol Instrument
ET: essential tremor
FTMTRS: Fahn-Tolosa-Marin Tremor Rating Scale
HAS: Hamilton Anxiety Scale
HRQoL: Health-related Quality of Life
ICC: Intra-class Correlation Coefficient
KMO: Kayser-Meyer-Olkin measure of sampling accuracy
MADRS: Montgomery-Asberg Depression Rating Scale
PGI: Patient's Global Impression
QUEST: Quality of Life in Essential Tremor Questionnaire
QUEST-SI: Quality of Life in Essential Tremor Questionnaire Summary Index
ROC: Receiver Operational Characteristic
VAS: Visual Analogue Scale

Materials and methods

PATIENTS

In this cross-sectional study 133 consecutive patients fulfilling the criteria for either definite or

probable ET were enrolled. Each subject gave written consent in accordance with the ethical approval of Regional and Institutional Ethical Committee of the University of Pécs (5624/2015). Each patient was examined by neurologists specialized in movement disorders.

OBTAINED RATING SCALES

Severity of ET-related problems were globally characterized by a Patient's Global Impression Scale (PGI) adjusted for ET: no ET-related disabilities (0), borderline/mild ET-related disabilities (1), moderate ET-related disabilities (2), marked ET-related disabilities (3) and severe ET-related disabilities that prevents subjects from performing some activities of daily living (4).

Severity of tremor was objectively assessed by the Fahn-Tolosa-Marin Tremor Rating Scale (FTMTRS)[15]. FTMTRS has three parts, Part A describing the magnitude of tremor on face, voice, tongue, head, trunk and the four extremities from 0 to 4. The score of FTMTRS Part A can be between 0 and 84. Part B describes the disability caused by tremor during five different tasks including handwriting, drawing small and large spirals, drawing a straight line and pouring water with a maximum score of 36 points. Part C of FTMTRS describes the impact of tremor on seven everyday activities including speech, eating, drinking, hygienic activities, dressing, handwriting and working with a maximum score of 28. The total score of FTMTRS is the sum of the subscores of Part A, B and C with higher values indicating more severe tremor.

To assess depression and anxiety, the Montgomery-Asberg Depression Rating Scale (MADRS)[16, 17] and the Hamilton Anxiety Scale (HAS) were used. For assessing the neurocognitive profile, the Hungarian validated version of the Montreal Cognitive Assessment (MoCA) was used[18, 19].

ET-specific HRQoL was evaluated by the Hungarian version of QUEST[7]. The QUEST was translated according to approved translation standards into Hungarian and back-translated into English. Subsequently the original English and the back-translated English versions were compared[20].

For evaluating general HRQoL among movement disorder patients[21], the EuroQol Instrument (EQ-5D) was assessed[22]. EQ-5D had been previously validated and utilized in the evaluation of different therapeutic approaches in ET[8, 9]. Moreover, it can also be applied for health-related economical calculations[23]. EQ-5D consists of two major parts: a five item questionnaire and a visual analogue scale (VAS). The first part of EQ-5D maps five different domains of HRQoL: Mobility, Self-care, Usual activities, Pain/Discomfort and Anxiety/Depression[22]. Based on the responses for the five domains questionnaire, an index value can be calculated. The EQ-5D index can be in the range from –0,52 to +1, the former representing a state worse than death and the later representing the best health-related status[22]. The response on VAS can range from 0 to 100, the higher values meaning better HRQoL[22].

DESCRIPTIVE DATA ANALYSIS

Because a score of 0 means symptom-free condition, the prevalence of each item was based on the portion of subjects having the score > 0 point on that particular item. For variables following the normal distribution (e.g. age, disease-duration), medians ± standard deviations (SD) were calculated.

Data quality was defined as the proportion of computable data. The criterion for acceptable amount of missing data[24] is < 10%. For acceptability the floor and ceiling effect[25] should be kept < 15% and the skewness should range[26] between –1 and +1.

FACTOR ANALYSIS

Before the structure of the scale was explored by a factor analysis, the value of Kayser-Meyer-Olkin measure of sampling accuracy (KMO) was calculated. A KMO > 0.60 is a minimum requirement; whereas, KMOs > 0.90 are considered as excellent for factor analysis. We accepted only those factors having an eigenvalue > 1 and a Scree test for factor analysis.

RELIABILITY

In the clinimetrics, reliability is the overall consistency of a measure. A measure is said to have a high reliability if it produces similar results under consistent conditions[14]. In our study the internal consistency was evaluated by four different approaches[20]:

– Cronbach's α (should be > 0.70)[27]

– corrected item-total correlation (should be > 0.30 for each item)

– item homogeneity coefficient (should be > 0.30)

– test-retest properties (Intra-class Correlation Coefficient, ICC should be > 0.6)[28]. The retest properties of the QUEST were analyzed on a subset of patients (n=32) one day after the initial examination.

VALIDITY

Validity of an assessment is the degree to which it measures what it is supposed to measure. Therefore, it corresponds to how a measurement is well-founded and accurately describes the real world[14]. In our study the construct validity was evaluated by three different methods:

– Convergent validity: Convergent validity refers to the degree to which a measure is correlated with other measures that it is theoretically predicted to correlate with[14]. The total score and the subscores of QUEST were compared to the PGI, EQ-5D, FTMTRS, MADRS and HAS. For correlation, Spearman's rank correlation coefficients were calculated. The values of correlation coefficients can indicate weak (0–0.299), moderate (0.300–0.599) and high (0.600–1.000) association[29].

– Internal validity. The correlation between the domains (subscales) should not be too low ($r_S < 0.300$) or too high ($r_S > 0.700$) either.

– Discriminative validity. Discriminative validity tests whether concepts or measurements that are supposed to be unrelated are, in fact, unrelated[14]. It is well-known, that the prevalence and/or the severity of tremor-related problems depend on disease-duration, depression, anxiety[30]. Therefore, we tested the discriminative validity of QUEST against these factors.

PRECISION

Precision of the QUEST was estimated by standard error of measurement (SEM), where the value of SEM should be less than the half of the standard deviation.

RECEIVER OPERATING CHARACTERISTIC (ROC) CURVE

In order to establish a cut-off value for the total score of QUEST, which can reliably differentiate the clinically irrelevant vs. relevant problems, we applied ROC analysis. Patients were categorized by the PGI value (no ET-related disabilities at all vs. presence of ET-related disabilities with any degree). This categorization served as the state variable and the QUEST total score as the test variable. The best cut-off value was estimated as the point on the ROC curve closest to the point of (0,1). It was calculated as the minimum value of the square root of $(1–\text{sensitivity})^2+(1–\text{specificity})^2$. Besides, area under the curve, specificity, sensitivity, positive and negative likelihood ratios were calculated for the best cut-off value. Subsequently, we also established a threshold value for discriminating marked tremor-related disabilities from mild-moderate tremor-related problems based on the PGI value (having marked and severe tremor-related disabilities problems vs. having mild and moderate tremor-related disabilities).

STATISTICAL ANALYSIS

All statistical analyses were carried out using IBM SPSS software package (version 21.0.1, IBM Inc., Chicago, USA). Statistical significance level was set to 5%. Because the SPSS Suite did not have built-in functions for calculating positive and negative likelihood ratios, we utilized the syntax available on the IBM website (http://www-01.ibm.com/support/docview.wss?uid=swg21483380, assessed on Jan 15, 2013).

Results

DEMOGRAPHIC AND ET-RELATED CLINICAL DATA

The subject population consisted of 133 ET patients. The clinical characteristics are demonstrated in **Table 1**.

DESCRIPTIVE MEASUREMENTS

Based on the PGI scale, 31 patients (23.3%) did not report any ET-related disabilities; whereas, 27 patients (20.3%) had mild/borderline, 38 (28.6%) had moderate, 22 (16.5%) had marked and 15 (11.3%) had severe tremor-related disabilities **(Table 1)**.

Six patients had a total score of 0 on QUEST (4.5%). The prevalence of QUEST items varied differently: Item 13 (being depressed because of tremor) had the lowest prevalence (21.8%), whereas, item 7 (tremor interferes with eating) had the highest (87.2%, **Table 2**). Data on self-evaluation of tremor is shown in **Table 2**. Data quality was excellent for all QUEST items **(Table 3).**

FACTOR ANALYSIS

The KMO value was sufficiently high (0.914) to enable a factor analysis. The Scree-test supported a five-factor solution explaining 68.9% of the variance. Using Principal Component Analysis extraction method with Varimax rotation, we identified almost the same factor structure as it was originally described.

Table 1. *Clinical characteristics of the study cohort (n=133)*

		Mean or count	Standard deviation or percentage
Age		57.4	17.4
Age at disease onset		44.0	21.4
Age at disease onset (Binned)	<20	27	20.3%
	20–39	32	24.1%
	40–59	34	25.6%
	>60	40	30.1%
Disease duration (years)		11.8	11.3
Disease duration (Binned)	<5	58	46.0%
	6–10	16	12.7%
	11–15	24	19.0%
	16–20	5	4.0%
	21–25	8	6.3%
	>25	15	11.9%
Education years		12.0	3.2
Positive family history		87	65.4%
Medication usage for ET		79	59.4%
Being referred for deep brain surgery		17	12.8%
Montgomery-Asberg Depression Rating Scale		11.8	8.0
Hamilton Anxiety Scale		13.4	9.3
Patient's Global Impression	none	31	23.3%
	mild/borderline	27	20.3%
	moderate	38	28.6%
	marked	22	16.50%
	severe	15	11.3%
EQ-5D VAS		61.2	22.9
EQ-5D index		0.823	0.182
FTMTRS Part A		13.3	9.2
FTMTRS Part B		15.3	8.9
FTMTRS Part C		7.2	5.1
FTMTRS Total score		35.8	21.7

EQ-5D: EuroQol Instrument, FTMTRS: Fahn-Tolosa-Marin Tremor Rating Scale, VAS: Visual Analogue Scale

Table 2. *Self-evaluation of tremor severity*

	Individual scores						
	0	1	2	3	4	Mean	Standard deviation
Head	68	27	19	10	9	0.8	1.1
Voice	85	28	8	6	6	0.4	0.7
RUL	16	31	36	33	17	1.9	1.2
LUL	19	30	35	33	16	1.9	1.2
RLL	83	23	11	10	6	0.5	0.9
LLL	83	26	9	9	6	0.5	0.8

LLL: left lower limb, LUL: left upper limb, RLL: right lower limb, RUL: right upper limb

RELIABILITY ANALYSIS

The value of Cronbach's α for the domains of the QUEST varied between 0.798–0.915 **(Table 3)**. All the items reached the 0.30 threshold value for item-total correlation **(Table 3)**. Item homogeneity index values were acceptable for all subdomains and the total score of QUEST.

VALIDITY AND PRECISION

Table 4 shows the convergent validity for QUEST. The total score of QUEST demonstrated high (>0.600) Spearman's rank correlation coefficient with both FTMTRS Part C and PGI describing the disability caused by tremor. Whereas, it had moderate correlation with other scales (other parts

Table 3. *Acceptability, reliability and precision of the QUEST*

	Physical	Psychosocial	Communi-cation	Hobbies/ Leisure	Work/ Finance	QUEST-SI
Data quality (%)	100	100	100	100	100	100
Skewness	0.257	0.817	0.925	0.672	0.971	0.783
Floor effect (%)	11.3	9.8	41.4	46.6	45.1	4.5
Ceiling effect (%)	1.5	1.5	0.8	8.3	0.0	0.0
Cronbach's α	0.868	0.915	0.798	0.885	0.882	0.897
Item-total correlation	0.302–0.678	0.439–0.699	0.468–0.564	0.614–0.784	0.365–0.782	NA
Item homogeneity	0.420	0.340	0.556	0.598	0.374	NA
Mean	39.6	30.5	21.1	32.2	13.2	27.4
Standard deviation	29.9	26.1	26.7	39.8	19.7	24.2
Precision (standard error of measurement)	2.7	2.3	2.4	3.6	1.7	2.2
Intra-class Correlation Coefficient	0.798	0.787	0.623	0.514	0.598	0.798

Table 4. *Convergent validity and internal validity of PDSS-2*

		Physical	Psychosocial	Communi-cation	Hobbies/ Leisure	Work/ Finance	QUEST-SI
External scales	PGI	0.467**	0.552**	0.379**	0.487**	0.429**	0.647**
	EQ-5D VAS	–0.332**	–0.484**	–0.308**	–0.393**	–0.320**	–0.432**
	ED-5D index	–0.547**	–0.495**	–0.424**	–0.533**	–0.419**	–0.595**
	MADRS score	0.395**	0.639**	0.434**	0.557**	0.493**	0.589**
	HARS score	0.414**	0.407**	0.286**	0.431**	0.343**	0.545**
	FTMTRS Part A	0.660**	0.403**	0.354**	0.382**	0.347**	0.542**
	FTMTRS Part B	0.665**	0.377**	0.245**	0.339**	0.261**	0.501**
	FTMTRS Part C	0.727**	0.518**	0.338**	0.477**	0.412**	0.639**
	FTMTRS Total score	0.721**	0.454**	0.331**	0.415**	0.358**	0.588**
Internal validity	Physical domain		0.612**	0.512**	0.695**	0.570**	0.669**
	Psychosocial domain	0.612**		0.562**	0.689**	0.677**	0.690**
	Communication domain	0.512**	0.562**		0.584**	0.583**	0.635**
	Hobbies/Leisure domain	0.695**	0.689**	0.584**		0.659**	0.681**
	Work/Finance domain	0.570**	0.677**	0.583**	0.659**		0.664**
	QUEST-SI	0.669**	0.690**	0.635**	0.681**	0.664**	
	Health Status item	–0.445**	–0.512**	–0.428**	–0.433**	–0.354**	–0.530**
	Overall Quality of Life item	–0.407**	–0.506**	–0.323**	–0.452**	–0.344**	–0.485**
	Tremor hours	0.589**	0.481**	0.296**	0.439**	0.387**	0.542**
	Tremor head	0.263**	0.407**	0.424**	0.316**	0.225*	0.384**
	Tremor voice	0.390**	0.364**	0.466**	0.325**	0.358**	0.433**
	Tremor RUL	0.691**	0.528**	0.396**	0.438**	0.356**	0.616**
	Tremor LUL	0.654**	0.563**	0.341**	0.433**	0.386**	0.597**
	Tremor RLL	0.406**	0.317**	0.404**	0.392**	0.369**	0.429**
	Tremor LLL	0.358**	0.362**	0.430**	0.370**	0.312**	0.426**

The table reports Spearman's rank correlation coefficients. *p<0.05, **p<0.01, ***p<0.001.

and total score of FTMTRS, EQ-5D, MADRS and HAS). The internal validity for the subdomains of QUEST was acceptable (r_s values in the range of 0.300–0.700, **Table 4**). As far as the discriminative properties were considered, all the domains and the total score significantly differed between depressed and non-depressed, anxious and non-anxious groups **(Table 5)**. Many subdomains and the QUEST-SI differed based on disease-duration, presence of family history and the need for deep brain surgery treatment. As we expected, QUEST had an excellent discriminant validity based on the PGI scores **Table 5**).

The precision were acceptable for both the domains and the total score of QUEST **(Table 3)**.

Table 5. *Discriminative validity of QUEST*

		Physical		Psychosocial		Commu nication		Hobbies/Leisure		Work/Finance		QUEST-SI	
		Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation	Mean	Standard Deviation
Age at disease onset	<20	0.539	0.277	0.321	0.245	0.279	0.258	0.405	0.383	0.229	0.239	0.356	0.224
	20–39	0.347	0.313	0.306	0.285	0.229	0.293	0.256	0.356	0.124	0.223	0.252	0.254
	40–59	0.382	0.301	0.345	0.288	0.279	0.311	0.368	0.430	0.153	0.208	0.305	0.282
	≥60	0.364	0.289	0.264	0.231	0.098	0.164	0.282	0.408	0.065	0.101	0.215	0.193
	Statistics (p-value)	0.085		0.666		0.010		0.488		0.045		0.119	
Disease duration	<5	0.289	0.282	0.233	0.234	0.111	0.214	0.254	0.394	0.061	0.108	0.190	0.211
	6–10	0.427	0.236	0.350	0.255	0.179	0.209	0.244	0.356	0.112	0.207	0.263	0.207
	11–15	0.370	0.287	0.331	0.277	0.303	0.258	0.311	0.402	0.155	0.190	0.294	0.246
	16–20	0.461	0.398	0.417	0.283	0.283	0.342	0.350	0.418	0.242	0.235	0.351	0.315
	21–25	0.733	0.261	0.465	0.404	0.531	0.391	0.615	0.434	0.359	0.345	0.541	0.329
	>25	0.603	0.193	0.378	0.217	0.301	0.273	0.468	0.356	0.260	0.248	0.402	0.168
	Statistics (p-value)	0.000		0.091		0.000		0.142		0.002		0.001	
Family history	None	0.370	0.307	0.247	0.234	0.105	0.191	0.250	0.384	0.087	0.171	0.212	0.206
	Positive	0.411	0.297	0.337	0.272	0.267	0.285	0.360	0.403	0.156	0.207	0.307	0.255
	Statistics (p-value)	0.413		0.088		0.000		0.173		0.037		0.045	
Need for deep brain stimulation	No	0.382	0.296	0.294	0.264	0.196	0.266	0.302	0.397	0.119	0.185	0.259	0.244
	Yes	0.519	0.313	0.404	0.229	0.340	0.246	0.487	0.379	0.240	0.265	0.398	0.194
	Statistics (p-value)	0.131		0.079		0.019		0.057		0.078		0.019	
Depression	No	0.348	0.293	0.229	0.218	0.174	0.247	0.225	0.349	0.094	0.160	0.214	0.215
	Yes	0.559	0.277	0.603	0.214	0.347	0.314	0.712	0.354	0.285	0.263	0.501	0.228
	Statistics (p-value)	0.002		0.000		0.006		0.000		0.000		0.000	
Anxiety	No	0.296	0.274	0.211	0.206	0.140	0.213	0.190	0.333	0.080	0.154	0.184	0.200
	Yes	0.570	0.268	0.481	0.273	0.335	0.316	0.575	0.399	0.233	0.238	0.440	0.238
	Statistics (p-value)	0.000		0.000		0.000		0.000		0.000		0.000	
PGI	1: no disability. normal	0.134	0.153	0.071	0.073	0.063	0.127	0.026	0.104	0.016	0.037	0.062	0.081
	2: borderline or mild disability	0.218	0.266	0.141	0.148	0.054	0.101	0.137	0.290	0.015	0.045	0.113	0.137
	3: moderate disability	0.484	0.267	0.360	0.259	0.266	0.300	0.433	0.412	0.144	0.191	0.338	0.232
	4: marked disability	0.561	0.295	0.520	0.272	0.383	0.305	0.628	0.387	0.322	0.226	0.483	0.245
	7: severe disability	0.611	0.326	0.167	0.245	0.505	0.389	0.568	0.458	0.215	0.159	0.658	0.235
	Statistics (p-value)	0.000		0.000		0.002		0.000		0.000		0.000	

The cut-off value which best discriminated the presence of ET-related disabilities from the absence of ET-related disabilities was 11.25 points. Therefore a QUEST-SI score >11.25 points may suggest the presence of clinically meaningful tremor-related disabilities in ET. This cut-off value has the sensitivity of 77.4%, specificity of 83.3%, positive likelihood ratio of 4.645 and negative likelihood ratio of 0.271. The area under the curve was 0.829 whereas the ROC analysis yielded the statistical significance level ($p<0.001$).

The cut-off value which best discriminated the presence of moderate ET-related disabilities from severe ET-related disabilities was 20.35 points. Therefore a QUEST-SI score >20.35 points may suggest the presence of severe tremor-related disabilities in ET. This cut-off value has the sensitivity of 83.3%, specificity of 59.1%, positive likelihood ratio of 2.039 and negative likelihood ratio of 0.282. The area under the curve was 0.731 whereas the ROC analysis yielded the statistical significance level ($p<0.001$).

Discussion

The aim of the present study was to develop the cross-cultural adaptation of the QUEST and assess the fundamental clinimetric properties of the scale according to the principles of the Classical Test Theory.

After a standardized translation and back-translation of the scale, we initiated a hospital-based validation study on a large diversity of patients having disease severity from minimal to severe.

The strength of our study compared to the previous validation studies is the excellent (100%) data quality. In the development study and the following independent validation studies a high portion of patients (up to 40%) had at least one missing value preventing full data computation[8, 9]. As a consequence in their study the percentage of fully computable questionnaires was clearly under the minimum acceptable threshold of 95%. Furthermore, in the original development study, only 44% of patients completed fully the questionnaire[7].

Concerning the descriptive properties, the obtained data quality was excellent and skewness was satisfactory for all subdomains of the scale. The ceiling effect was also negligible for all the domains of the QUEST. While the Communication, Hobbies/Leisure and Work/Finance subscales had relatively high, the Physical and Psychosocial subdomains and the QUEST-SI had acceptable floor-effect. Although the presence of a high floor or ceiling effect may be an indicator for poor acceptability or faulty content validity and may also negatively influence the reliability and sensitivity of the measurement, we suspect other issue in the background. Because many patients (n=31, 23.3% of the examined population) did not report any degree of ET-related disability on PGI and 76 patients (57.1%) were retired at the time of examination, these moderately high floor-effect values (41.4-46.6%) might be due the characteristics of the studied sample and not attributable to the scale itself. This assumption is further supported by the fact that the whole QUEST scale (the QUEST-SI) had only a negligible floor effect (4.5%).

Based on the sufficiently high KMO value, the performed factor analysis revealed almost an identical factor structure reported in the original validation study of QUEST.

Concerning the reliability of the scale, we obtained satisfactory results. The internal consistency of the QUEST was acceptable with α indexes clearly exceeding the threshold value of 0.70. Total score reached an α value higher than 0.8 indicating its usefulness for individual comparisons. All items surpassed the threshold value of 0.30 for the item-correlations. The test-retest validity based on the Intra-class Correlation Coefficients demonstrated good reproducibility for QUEST-SI.

As assumed, the convergent validity between the QUEST and other scales measuring similar constructs was satisfactory. The Spearman's rank correlation coefficients indicated sufficiently high correlation with the PGI, FTMTRS, MADRS and HAS. Similarly to the Spanish validation study[8], we also observed acceptable correlation between QUEST and EQ-5D index value, an indicator of the general health-related quality of life.

QUEST showed satisfactory discriminative ability to differentiate based on the presence of anxiety, depression, disease-duration, family history, need for deep brain stimulation and PGI **(Table 5)**.

The QUEST subscales also correlated with each other to a moderate/high level into the standard limits for internal validity (r_S=0.3–0.7, **Table 4**). The standard error of measurement values were suggestive of a high precision for all components of the scale.

As far as the authors are aware of, there is no other study published on the cut-off value for QUEST-SI differentiating the presence of clinically meaningful tremor-related disability. Based on findings, QUEST-SI > 11.25 indicates the presence of clinically pertinent, whereas, QUEST-SI > 20.35 severe ET-related disability.

Conclusions

Patient reported outcomes and self-completed questionnaires are widely used for patient assessments, follow-ups and making clinical decisions in both clinical practice and research. Validation of adapted scales is important to assure the usefulness of the instrument in the setting in which it will be applied. The most important indicators for the quality of a scale are the reliability, validity and responsiveness. Because the replication of outcomes is a highly desirable scientific need, the independent validation of patient reported outcomes is essential to confirm or reject the findings obtained by the developers of the scale. Our results demonstrate that the fundamental clinimetric properties of the Hungarian validated version of QUEST are satisfactory and confirm those of the original study. Our threshold values for separating mild/moderate and moderate/severe ET-related impact on HRQoL may also be utilized in further studies and categorizing the ET patients.

FUNDING AND ETHICAL APPROVAL

Our study was supported by the Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-II/10 government-based funds. NK was supported by the New National Excellence Program of the Ministry of Human Capacities, Hungary. The present scientific contribution is dedicated to the 650th anniversary of the foundation of the University of Pécs, Hungary. Informed consent was obtained from all individual participants included in the study as approved by the Regional and Institutional Ethical Committee of the University of Pécs (5624/2015).

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