Qual Life Res (2014) 23:1315–1326
DOI 10.1007/s11136-013-0569-4

Validation and comparison of 15-D and EQ-5D-5L instruments in a Spanish Parkinson's disease population sample

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Accepted: 1 November 2013 / Published online: 22 November 2013

Abstract
Purpose To contribute to the ongoing discussion on the choice of a preference-based health-related quality of life (HRQoL) instrument to be used in cost-effectiveness analysis by studying and comparing the validity, sensitivity and relative efficiency of 15-D and EuroQol 5D 5L (EQ-5D-5L) in a Spanish Parkinson's disease (PD) population sample.
Methods One hundred and thirty-three volunteers were asked to complete an interview using 15-D and EQ-5D-5L. Spearman's rank correlation coefficient (r) was used to test the convergent validity of these instruments with specific PD measures. Sensitivity and efficiency were compared using receiver operating characteristic (ROC) curves and relative efficiency statistic, respectively.
Results A strong correlation ($r > 0.65$; $p < 0.001$) was found between both 15-D and EQ-5D-5L utilities with the summary score of the PDQ-8, and a strong correlation ($r > 0.50$; $p < 0.001$) was found between 15-D and EQ-5D-5L utilities with the EQ-VAS. The areas under the ROC of both instruments all exceeded 0.5 ($p < 0.001$). The 15-D instrument was 4.1–29.8 % less efficient at detecting differences between patients with optimal HRQoL, while this instrument was 11 % more efficient at detecting differences between patients at mild and moderate to strong severity of the PD symptoms.
Conclusions 15-D and EQ-5D-5L are showed to be valid and sensitivity generic HRQoL measures in Spanish PD patients with both instruments showing similar HRQoL dimension coverage and ceiling/floor effects. The 15-D has better efficiency and greater sensitivity to detect clinical changes in PD severity of the symptoms meanwhile the EQ-5D-5L is better to detect clinical HRQoL changes. Additionally, the EQ-5D-5L questionnaire requires less time than 15-D to be administered, and it might be more appropriate for studies conducted in Spain, since a country-specific "value set" is available for this instrument and not for the 15-D.

Keywords Spain · Validation study · Utility · Preference-based instruments · EuroQol-5D-5L · 15-D

Abbreviations

PD	Parkinson's disease
ROC	Receiver operating characteristic
EQ	EuroQol
RE	Relative efficiency
HRQoL	Health-related quality of life
PDQ	Parkinson's disease questionnaire
CUA	Cost-utility analysis
QALY	Quality-adjusted life years
VAS	Visual analogue scale
TTO	Time trade-off
SD	Standard deviation

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IQR Interquartile range
ICC Intraclass correlation coefficient
AUC Area under the curve

Introduction

Parkinson's disease (PD) is a progressive movement disorder that is accompanied by multiple motor or mental symptoms [1] which have an effect upon the health-related quality of life (HRQoL) [2] and well-being [3]. Since the etiology of PD is not known with certainty and no current best treatment exists, the major goal in this population group is to achieve optimal symptom control and to improve the patients' HRQoL. Therefore, HRQoL has been recognized increasingly as an important outcome of health care to be incorporated into the decision-making process of clinicians and policy [4]. Conversely, to undertake a complete patient management approach by including HRQoL as a clinical outcome, the major challenge is to find valid and reliable HRQoL measures.

The most widely used profile-based HRQoL instruments for PD are the 39 or 8 item PD Questionnaire (PDQ-39/PDQ-8) and the 37 item PD Quality of Life Questionnaire (PDQL) [5–7]. Although these specific health profiles can detect clinically important changes in PD, they neither allow HRQoL comparison with other different diseases nor cost-utility analysis (CUA) of healthcare interventions. This is because they are unable to yield preference-based quality weights, also known as preference scores or simply "utilities" [8]. CUA allows health interventions, within and across healthcare programs, to be compared in terms of their cost and the number of quality-adjusted life years (QALYs) they offer, thereby permitting finite healthcare resources to be allocated on a utilitarian "cost per QALY gained" basis [9]. QALY calculations require the elicitation of utilities, and this requirement is covered by various generic preference-based HRQoL measures, reason why their use is recommended alongside with the use of disease-specific instruments in evaluating HRQoL in clinical settings [10].

The 15-D is a 15-dimensional, standardized generic HRQoL instrument that can be used both as a profile and a single preference score measure [11]. The EuroQol 5D (EQ-5D) has been largely validated across the literature in HRQoL assessment [12]. Recently, this instrument has been upgraded to a 5-level version instead of 3-level per dimension in order to improve sensitivity and reduce ceiling effects of the original version [13]. This is because one of the criticisms often made regarding this instrument has been that it is unable to distinguish between health states close to full health, and consequently, many respondents report no problems in some or even all (full health) of its dimensions. Although there is not an established gold standard, the EQ-5D seems to be the preferred HRQoL instrument for CUA[12] and is also recommended as the preferred generic HRQoL instrument in PD [14].

Some studies have been conducted to test the validity of the 15-D [15] and EQ-5D-3L in PD [16, 17]. However, the validity of generic instruments such as 15-D and EQ-5D-5L for HRQoL assessment in PD population is not fully understood. To the best of our knowledge, no studies have been conducted either to validate the EQ-5D-5L or to compare the 15-D and the EQ-5D-5L instruments for use in PD patients in the assessment of HRQoL. Therefore, the aim of this study is to contribute to the ongoing discussion on the choice of a preference-based HRQoL instrument to be used in CUA by studying and comparing the validity, sensitivity and relative efficient (RE) of 15-D and EQ-5D-5L in a Spanish PD population sample.

Methods

Study design and patient recruitment

A cross-sectional study design was conducted. Patients were recruited (between May 1 and July 15, 2012) from 15 local PD associations belonging to 10 out of 17 different regions of Spain (a 34 % of total PD associations in the country). Out of 190 potentially eligible participants, 157 volunteers with PD diagnoses received detailed information about the aims and study procedures and were included in the study once they gave their written informed consent. Patients were included if they were able to answer the questions independently, aged more than 18 years old and if they were a PD diagnoses. We used the Hoehn and Yahr scale [18] to classify the patients according to disease progression. For the purpose of the study, only data from patients who fully completed the questionnaires were taken into account in the analyses. Twenty-four participants did not meet this criterion, so the final sample consisted of 133 patients (aged 64 ± 10 years). Each patient was interviewed at the local PD association by a trained interviewer, using a standardized questionnaire containing the EQ-5D-5L/visual analogue scale (VAS) and 15-D. Other information solicited from the participants included their sociodemographic data and medical conditions. The symptom severity of the patients was measured using the Hoehn and Yahr scale, while the PDQ-8 was used as specific HRQoL instrument for this population group. The study was approved by the Ethics Committee of the University of Extremadura and was developed following the ethical guidelines of the Declaration of Helsinki as revised in 2000.

Instruments

15-D

The 15-D [11] evaluates 15 dimensions: mobility, vision, hearing, breathing, sleeping, eating, speech, elimination, usual activities, mental function, discomfort and symptoms, depression, distress, vitality and sexual activity, each of them with 5 possible levels from less to more impaired in the dimension. A single score representing the person's health status (1 = full HRQoL, 0 = death) is attached to any of the possible combinations of the dimensions and levels. These scores or "utility indexes" were based on multiattribute utility theory and derived by using a combination of rating scale and magnitude estimation methods from a Finnish population sample [11]. The 15-D has shown good psychometric properties in a number of non-PD populations and also has been partially validated in a PD population [15].

EQ-5D-5L/VAS

The EQ-5D-5L [13] includes five dimensions, each one measuring a different attribute of HRQOL: mobility, self-care, daily activities, pain and discomfort, and anxiety or depression. Five levels for answering are included (no problems, slight problems, moderate problems, severe problems and extreme problems), ranging from 1 to 5. The "utility indexes" or value set (1 = full HRQoL, 0 = death) were originally obtained for the EQ-5D-3L version (which only considers three levels on each dimension) using time trade-off (TTO) values. The value set for the EQ-5D-5L results from a "crosswalk" between the EQ-5D-3L value sets and the new EQ-5D-5L descriptive system. In this study, we used the Spanish value set to assign single scores to the EQ-5D-5L health states [19]. This instrument also includes a VAS. The participants used this vertical 20-cm scale to rate their own health between 0 (worst imaginable health state) and 100 (best imaginable health state), thereby providing an overall numerical estimate of their HRQoL. The EQ-5D correlates with the Unified Parkinson's Disease Rating Scale (UPDRS) scores in PD patients and discriminates PD stages [20]. It has been responsive to therapeutic interventions in PD patients [21, 22].

PDQ-8

The PDQ-8 [7] is a reduced version from the PDQ-39, which includes 8 items representing different dimensions: mobility, activities of daily living, emotional well-being, social support, cognition, communications, bodily discomfort and stigma. The summary index is obtained by summing the 8 items and standardizing on a scale of 0–100; higher scores reflect worse HRQoL. The responsiveness of the PDQ-8 has been tested as well [16].

Hoehn and Yahr scale

The Hoehn and Yahr scale is commonly used to describe disease progression, which defines broad categories (I–V) of motor function in PD [23]. Progression in Hoehn and Yahr stages has been found to correlate with motor decline, deterioration in quality of life and neuroimaging studies of dopaminergic loss [18]. For study purposes, only individuals in stage I–IV were asked to complete the questionnaire.

In all cases, Spanish versions of the instruments were used in the questionnaire. A total of 25 min was the duration on average of the interviews.

Data analyses

Statistical analyses were performed using SPSS version 18.0 (SPSS Inc., Chicago, IL, USA). The significance level was set at $p < 0.05$ for all analyses performed under the study. The data did not follow a normal distribution.

Descriptive statistics of 15-D and EQ-5D-5L

Descriptive statistics were computed to characterize the sample and the distribution of 15-D and EQ-5D-5L/VAS. For continuous variables mean, standard deviation (SD), median, interquartile range (IQR) and range were computed, while categorical variables are shown in the number and proportion of the sample. Based on Hoehn and Yahr scale, we compared those patients in the I or II stage with those in the III or IV stage using Mann–Whitney U or χ^2 tests.

Construct validation

Convergent validity of the 15-D and EQ-5D-5L was assessed by examining their association with PDQ-8 and EQ-VAS at domain and scale level. Validity coefficient was computed as Spearman's rank correlation coefficient (r), with $r > 0.5$ considered as strong correlation, 0.3–0.5 as moderate correlation and 0.2–0.3 as weak correlation [24].

To further extend testing validity, a "known-group" scheme was used to survey the discriminative validity of 15-D and EQ-5D-5L based on its ability to discriminate patients with different level of PD severity and self-reported health status groups alongside with other variables such as social economic status, duration of PD, ongoing therapies and presence of other medical conditions different than PD. Mann–Whitney U tests were used to detect statistically significant effects of the dichotomous variables

on utility scores. The levels of PD severity were defined based on Hoehn and Yahr scale as follows: mild to moderate if Hoehn and Yahr result was equal to I or II and severe if Hoehn and Yahr scale result was equal to III or IV. The EQ-VAS was used to classify individuals into health status groups, covering the range from very poor to very good health, a technique employed in a quite similar study [25]. Definitely, each subject was included in one of six groups according to VAS score: 0–49, 50–59, 60–69, 70–79, 80–89 and 90–100.

Level of agreement between 15-D and EQ-5D-5L

The intraclass correlation coefficient (ICC) and Bland–Altman plot were computed to test the agreement between the two instruments. A value >0.7 in the ICC suggests a strong agreement [26]. In Bland–Altman plot, the average of the two measurements was plotted on the *x*-axis and the difference between the two measurements on the y-axis, where 15-D was the subtrahend. The deviation of difference from 0, which implies total agreement, indicates the degree of agreement of each subject on the plot [27]. Additionally, the 15-D and EQ-5D-5L were compared across the sample as well as for subgroups based on socioeconomic and clinical characteristics by performing paired comparisons with Wilcoxon's signed-rank test and Spearman's rank correlation for the association of them.

Efficiency and sensitivity of 15-D and EQ-5D-5L

The RE statistic was used to test the efficiency of the 15-D and EQ-5D-5L to detect clinically relevant differences of PD patients. RE is defined as the ratio of the square of the *t* statistic of the comparator instrument (assumed to be the 15-D utility score for the purposes of this study) over the square of the *t* statistic of the reference instrument (assumed to be the EQ-5D-5L utility score for the purposes of this study) [26]. The coefficient >1 suggests that 15-D is more sensitive than EQ-5D at detecting clinically relevant differences with the given sample size, while the coefficient <1 means less sensitive. The

Table 1 Characteristics of participants and distribution of EQ-5D-5L and 15-D utility scores

Variables	Total ($n = 133$)	Hoehn and Yahr (stages I–II) ($n = 49$)	Hoehn and Yahr (stages III–IV) ($n = 84$)	p value
Age (years)				
Median (IQR)	65.00 (13.00)	65.00 (14.00)	66.00 (12.00)	0.134[a]
Mean (SD)	64.33 (9.74)	62.24 (10.10)	65.55 (9.37)	
Range	34–86	34–78	38–86	
Gender				
Male	95 (71.4)	35 (71.4)	60 (71.4)	0.582[b]
Female	38 (28.6)	14 (28.6)	24 (28.6)	
Level of studies				
Primary studies	65 (48.9)	18 (36.7)	47 (56.0)	0.065[b]
Secondary studies	31 (23.3)	16 (32.7)	15 (17.9)	
University studies	37 (27.8)	15 (30.6)	22 (26.2)	
Occupational status				
Self-employee	3 (2.3)	1 (2.0)	2 (2.4)	0.417[b]
Government employee	5 (3.8)	3 (6.1)	2 (2.4)	
Employee	4 (3.0)	3 (6.1)	1 (1.2)	
Housewife	11 (8.3)	4 (8.2)	7 (8.3)	
Retired	110 (82.7)	38 (77.6)	72 (85.7)	
Household size[c]				
Median (IQR)	2.00 (1.00)	2.00 (1.00)	2.00 (1.00)	0.064[a]
Mean (SD)	2.42 (1.13)	2.67 (1.21)	2.28 (0.06)	
Range	1.00–6.00	1.00–6.00	1.00–5.00	
Household income, €[c]				
Median (IQR)	1,700.00 (1,492.00)	1,900.00 (1,750.00)	1,600.00 (2,294.00)	0.961[a]
Mean (SD)	2,087.89 (1,369.13)	2,097.00 (1,424.00)	2,052.00 (1,330.00)	
Range	400.00–5,000.00	400.0–5,000.00	1,008.00–4,000.00	
Other medical conditions[d]				

Table 1 continued

Variables	Total ($n = 133$)	Hoehn and Yahr (stages I–II) ($n = 49$)	Hoehn and Yahr (stages III–IV) ($n = 84$)	p value
Median (IQR)	0.00 (1.00)	0.00 (1.00)	0.00 (1.00)	0.680[a]
Mean (SD)	0.54 (0.71)	0.47 (0.58)	0.58 (0.77)	
Range	0.00–3.00	0.00–2.00	0.00–3.00	
Ongoing therapies[e]				
Median (IQR)	3.00 (2.00)	3.00 (1.00)	3.00 (2.75)	0.811[a]
Mean (SD)	2.44 (1.38)	2.51 (1.26)	2.40 (1.45)	
Range	0.00–6.00	0.00–6.00	0.00–6.00	
Years since clinical diagnosis[c]				
Median (IQR)	6.00 (10.00)	3.00 (4.00)	8.00 (10.50)	<0.001[a]
Mean (SD)	7.70 (6.44)	4.39 (4.05)	9.74 (6.80)	
Range	0.50–32.00	0.50–21.00	0.50–32.00	
$PDQ\text{-}8_{summary\ score}$				
Median (IQR)	21.87 (26.56)	18.75 (14.06)	29.68 (33.59)	<0.001[a]
Mean (SD)	26.69 (18.24)	18.30 (11.83)	31.58 (19.56)	
Range	0.00–87.00	0.00–56.00	3.13–87.50	
$EQ\text{-}5D\text{-}5L_{utility}$				
Median (IQR)	0.64 (0.28)	0.72 (0.24)	0.59 (0.41)	<0.001[a]
Mean (SD)	0.59 (0.26)	0.70 (0.18)	0.53 (0.28)	
Range	−0.25 to 1.00	0.50–1.00	−0.25 to 1.00	
EQ-5D-5L-VAS				
Median (IQR)	60.00 (22.50)	70.00 (30.00)	50.00 (20.00)	<0.001[a]
Mean (SD)	57.63 (19.67)	66.57 (16.60)	52.42 (19.53)	
Range	10–100	30–95	10–100	
$15\text{-}D_{utility}$				
Median (IQR)	0.79 (0.24)	0.83 (0.13)	0.76 (0.29)	0.001[a]
Mean (SD)	0.74 (0.16)	0.81 (0.10)	0.70 (0.17)	
Range	0.31–1.00	0.51–0.98	0.31–1.00	

Values are presented as n (%), unless otherwise indicated, Hoehn and Yahr: Hoehn and Yahr scale

[a] p value from Mann–Whitney U test

[b] p value from χ^2 test

[c] Lost values [household size $n = 4$ (3.00 %), household income $n = 114$ (85.71 %), years since clinical diagnosis $n = 7$ (5.30 %)]

[d] Number of self-reported medical conditions Parkinson's disease apart

[e] Number of self-reported ongoing therapies for the control of the Parkinson's disease, $EQ\text{-}5D\text{-}5L_{utility}$ utility from the European Quality of Life Questionnaire 5 dimensions 5 levels, *EQ-5D-5L-VAS* visual analogical scale from the EQ-5D-5L, $15\text{-}D_{utility}$ utility from the 15 dimensions Health-Related Quality of Life Questionnaire, $PDQ\text{-}8_{summary\ score}$ summary score from the Parkinson's disease questionnaire 8 items

sensitivity of the 15-D and EQ-5D-5L instruments was compared and tested using receiver operating characteristic (ROC) curves [28]. The utility measure that generates the largest area under the ROC curve is regarded as the most sensitive at detecting differences in the external indicator. A measure with perfect discrimination would generate an area under the curve (AUC) score of 1.0, while a measure with no discriminatory power would generate an AUC score of 0.5. Self-reported health status (PDQ-8) and severity of the symptoms (Hoehn and Yahr scale) were used as external indicators. For the purposes of RE and AUC analysis, different "cutoff" points for the self-reported health status were selected for PDQ-8 (5.8 and 7.4 based on the literature [29] and 21.87 based on the PDQ-8 median) and a "cutoff" point differentiating between patients in the I or II stage and those in the III or IV stage was used for the severity of the symptoms.

Results

Descriptive statistics of 15-D and EQ-5D-5L

Table 1 shows the descriptive statistics across the sample and stratified by severity of the symptoms. Of the total 133

patients, the mean (SD) utility score and the median (IQR) of 15-D were 0.74 (0.16) and 0.79 (0.24), respectively, and those of EQ-5D-5L-VAS were 57.63 (19.67) and 60.00 (22.50).

While we did not detect statistically significant differences between the Hoehn and Yahr scale groups for socioeconomical or clinical variables, 15-D and EQ-5D-5L utilities were found to be higher in the lower severity group ($p < 0.05$). We also found greater scores for the EQ-VAS in the lower severity group, whereas PDQ-8 scores and the number of years since clinical diagnosis were lower for the same group ($p < 0.05$).

Table 2 displays the distribution of 15-D and EQ-5D-5L results within each domain. We observed the highest ceiling effects (i.e., most of respondents declaring no problems in a certain dimension) in the 15-D at mobility (46.6 %), vision (56.6 %), hearing (70.7 %), elimination (73.3 %) and distress (46.6 %), while no floor effects (i.e., most of respondents located at the bottom level in a certain dimension) were observed in almost all domains. Similarly, we detected ceiling effects in the self-care domain (39.8 %) of the EQ-5D-5L. Only 0.8 % in the 15-D and 5.3 % in the EQ-5D-5L had a 1 score, whereas no patients had a 0 score in both instruments.

Construct validity

A strong correlation was achieved between both 15-D and EQ-5D-5L utilities with the summary score of the PDQ-8 (-0.710; $p < 0.001$ and -0.679; $p < 0.001$, respectively), and a moderate correlation was found between 15-D and EQ-5D-5L utilities with the EQ-VAS (0.542; $p < 0.001$

Table 2 Distribution of 15-D and EQ-5D-5L results within each domain ($n = 133$)

15-D (%)															
Level	MO	V	H	B	SL	E	SP	EL	UA	MF	DI	DE	DIS	VI	Sex
1	**46.6**	**56.6**	**70.7**	**56.4**	24.4	**73.7**	33.1	32.3	18.8	36.1	**46.6**	**36.8**	25.6	25.6	24.8
2	32.3	23.3	18.0	24.8	**38.3**	18.0	**45.9**	**43.6**	**51.9**	**42.1**	30.8	33.1	**45.1**	**42.9**	27.1
3	11.3	15.0	9.0	12.8	15.8	7.5	14.3	20.3	14.3	19.5	15.0	25.6	23.3	18.8	**29.3**
4	9.8	5.3	2.3	4.5	18.8	0.8	6.0	3.0	8.3	1.5	5.3	4.5	4.5	8.3	6.0
5	0.0	0.0	0.0	1.5	2.3	0.0	0.8	0.8	6.8	0.8	2.3	0.0	1.5	4.5	12.8

Health status, *n* (%)	
Maximum score (the worst)	0 (0.0)
Minimum score (the best)	1 (0.8)

15-D index, *n* (%)	
Maximum score (the best)	1 (0.8)
Minimum score (the worst)	0 (0.0)

EQ-5D-5L (%)					
Level	M	SC	UA	PD	AD
1	24.1	**39.8**	24.1	24.1	33.8
2	**34.6**	33.8	**36.1**	30.1	**35.3**
3	28.6	13.5	25.6	**33.1**	27.8
4	12.8	10.5	11.3	7.5	0.0
5	0.0	2.3	3.0	4.5	3.0

EQ-5D index, *n* (%)	
Maximum score (the best)	7 (5.3)
Minimum score (the worst)	0 (0.0)

15-D dimensions: *MO* mobility, *V* vision, *H* hearing, *B* breathing, *SL* sleeping, *E* eating, *SP* speech, *EL* elimination, *UA* usual activities, *MF* mental function, *DI* discomfort and symptoms, *DE* depression, *DIS* distress, *VI* vitality, *Sex* sexual activities. EQ-5D-5L dimensions: *M* mobility, *SC* self-care, *UA* usual activities PD, pain/discomfort, *AD* anxiety/depression

Level in mold is in bold

15-D 15 dimensions Health-Related Quality of Life Questionnaire, *EQ-5D-5L* European Quality of Life Questionnaire 5 dimensions 5 levels

Table 3 Spearman's rank correlation coefficient between EQ-5D-5L or 15-D and PDQ-8 or EQ-5D-5L-VAS ($n = 133$)

	PDQ-8									EQ-5D-5L-VAS
	MO	AD	EW	ST	SS	CG	C	BD	SSc	
15-D										
Utility	−0.428**	−0.501**	−0.539**	−0.295**	−0.448**	−0.569**	−0.473**	−0.498**	−0.710**	0.542**
MO	−0.502**	−0.502**	−0.318**	−0.136	−0.329**	−0.483**	−0.355**	−0.403**	−0.564**	−0.502**
V	−0.374**	−0.386**	−0.237**	−0.111	−0.345**	−0.404**	−0.362**	−0.337**	−0.458**	−0.355**
H	−0.212*	−0.182*	−0.285**	−0.136	−0.209*	−0.313**	−0.392**	−0.138	−0.296**	−0.152
B	−0.135	−0.239**	−0.283**	−0.207*	−0.300**	−0.370**	−0.358**	−0.267**	−0.371**	−0.294**
SL	−0.078	−0.208*	−0.306**	−0.117	−0.178*	−0.276**	−0.193*	−0.327**	−0.301**	−0.258**
E	−0.448**	−0.432**	−0.401**	−0.288**	−0.355**	−0.210*	−0.309**	−0.303**	−0.492**	−0.345**
SP	−0.382**	−0.290**	−0.193*	−0.266**	−0.303**	−0.282**	−0.543**	−0.172*	−0.449**	−0.260**
EL	−0.322**	−0.430**	−0.366**	−0.134	−0.309**	−0.390**	−0.333**	−0.365**	−0.496**	−0.422**
UA	−0.441**	−0.528**	−0.464**	−0.238**	−0.360**	−0.333**	−0.319**	−0.357**	−0.576**	−0.583**
MF	−0.211*	−0.236**	−0.334**	−0.161	−0.265**	−0.543**	−0.432**	−0.235**	−0.431**	−0.164
DI	−0.336**	−0.381**	−0.346**	−0.184*	−0.315**	−0.418**	−0.200*	−0.454**	−0.498**	−0.427**
DE	−0.190*	−0.299**	−0.749**	−0.246**	−0.361**	−0.389**	−0.315**	−0.400**	−0.564**	−0.370**
DIS	−0.157	−0.291**	−0.568**	−0.351**	−0.232**	−0.410**	−0.265**	−0.300**	−0.510**	−0.333**
VI	−0.380**	−0.435**	−0.509**	−0.337**	−0.423**	−0.442**	−0.307**	−0.470**	−0.623**	−0.527**
Sex	−0.180*	−0.260**	−0.414**	−0.096	−0.417**	−0.372**	−0.262**	−0.235**	−0.429**	−0.309**
EQ-5D-5L										
Utility	−0.496**	−0.612**	−0.516**	−0.283**	−0.344**	−0.458**	−0.315**	−0.470**	−0.679**	0.609**
MO	0.587**	0.573**	0.331**	0.274**	0.374**	0.411**	0.358**	0.318**	0.605**	−0.531**
SC	0.534**	0.688**	0.389**	0.320**	0.385**	0.356**	0.342**	0.365**	0.614**	−0.509**
UA	0.554**	0.594**	0.376**	0.332**	0.298**	0.394**	0.325**	0.350**	0.602**	−0.591**
PD	0.285**	0.403**	0.410**	0.162	0.280**	0.345**	0.138	0.473**	0.500**	−0.507**
AD	0.195*	0.338**	0.705**	0.324**	0.302**	0.397**	0.273**	0.448**	0.582**	−0.448**

15-D dimensions: *MO* mobility, *V* vision, *H* hearing, *B* breathing, *SL* sleeping, *E* eating, *SP* speech, *EL* elimination, *UA* usual activities, *MF* mental function, *DI* discomfort and symptoms, *DE* depression, *DIS* distress, *VI* vitality, *Sex* sexual activities. EQ-5D-5L dimensions: *M* mobility, *SC* self-care, *UA* usual activities, *PD* pain/discomfort, *AD* anxiety/depression. PDQ-8: *MO* mobility, *AD* activities of daily living, *EW* emotional well-being, *ST* stigma, *SS* social support, *CG* cognition, *C* communications, *BD* bodily discomfort, *SSc* summary score

15-D 15 dimensions Health-Related Quality of Life Questionnaire, *EQ-5D-5L* European Quality of Life Questionnaire 5 dimensions 5 levels, *EQ-5D-5L-VAS* visual analogical scale from EQ-5D-5L, *PDQ-8* Parkinson's disease questionnaire 8 items

Continuous variables were transformed in categorical variables

* $p < 0.05$ (two-tailed); ** $p < 0.001$ (two-tailed)

and 0.609; $p < 0.001$). We observed as well in almost all domains from 15-D and EQ-5D-5L a moderate to high correlation with both PDQ-8 domains and EQ-VAS (Table 3).

Univariate analyses for 15-D show that utility score decreases monotonically with increasing PDQ-8, however, 15-D utility score increase monotonically with EQ-VAS and Hoehn and Yahr stage. Although this fact is true for the utility derived from EQ-5D-5L as well, this instrument does not discriminate across PDQ-8 or Hoehn and Yahr stages. With the exception of years since PD diagnoses, level of education and gender, no significant difference in utility scores was observed among variables of social economic status in univariate analyses for both instruments (Tables 4, 5).

Level of agreement between 15-D and EQ-5D-5L

Although statistically significant differences were detected between 15-D and EQ-5D-5L in almost all subgroups, a strong agreement between the two instruments was found as shown by the high ICCs obtained (from 0.67 to 0.87) and by the Spearman's correlation coefficients (from 0.691 to 0.844; $p < 0.001$) for both across the sample and according to different social economical and clinical factors (Table 4). However, Bland–Altman analysis indicated that the 95 % limits of agreement between 15-D and EQ-5D-5L ranged from −0.47 to 0.17 [−0.15 (0.16) bias (SD)] and over 95 % points lies within limits. Additionally, a systematic discrepancy in the utility difference of 15-D and

Table 4 Univariate analyses and comparison of 15-D and EQ-5D-5L utility scores for all patients and for several sociodemographic or health characteristic-based subgroups

Variable-based subgroups	*n* (%)	Mean (SD)		Median (IQR)		*p* value[a]	ICC	Spearman's rank correlation coefficient
		$15\text{-}D_{utility}$	EQ-5D-$5L_{utility}$	$15\text{-}D_{utility}$	EQ-5D-$5L_{utility}$			
All patients	133	0.74 (0.16)	0.59 (0.26)	0.79 (0.24)	0.64 (0.28)	<0.001	0.83	0.812**
Age (years)								
34–65	67 (50.40)	0.75 (0.15)	0.58 (0.25)	0.79 (0.23)	0.60 (0.25)	<0.001	0.79	0.785**
66–90	66 (49.60)	0.74 (0.17)	0.61 (0.28)	0.63 (0.15)	0.69 (0.37)	<0.001	0.87	0.841**
Gender								
Male	95 (71.40)	0.76 (0.15)	0.65 (0.21)	0.80 (0.22)	0.67 (0.75)[b]	<0.001	0.82	0.800**
Female	38 (28.60)	0.70 (0.17)	0.45 (0.32)	0.75 (0.20)	0.52 (0.61)	<0.001	0.80	0.819**
Level of studies								
Non-university studies	96 (72.20)	0.72 (0.16)	0.55 (0.28)	0.77 (0.24)	0.60 (0.41)	<0.001	0.82	0.820**
University studies	37 (27.80)	0.81 (0.13)	0.70 (0.17)	0.81 (0.18)[b]	0.67 (023)	<0.001	0.82	0.752**
Occupational status								
Employee	23 (17.30)	0.76 (0.12)	0.53 (0.28)	0.79 (0.14)	0.59 (0.28)	<0.001	0.76	0.659**
Retired	110 (82.70)	0.74 (0.17)	0.61 (0.26)	0.78 (0.27)	0.65 (0.32)	<0.001	0.85	0.823**
Other medical conditions[c]								
Yes	60 (45.10)	0.73 (0.16)	0.59 (0.27)	0.78 (0.20)	0.63 (0.22)	<0.001	0.82	0.810**
No	73 (54.90)	0.76 (0.16)	0.60 (0.26)	0.79 (0.25)	0.65 (0.32)	<0.001	0.84	0.816**
Ongoing therapies[d]								
Yes	120 (90.20)	0.75 (0.15)	0.61 (0.26)	0.79 (0.23)	0.65 (0.22)	<0.001	0.83	0.813**
No	13 (9.80)	0.66 (0.19)	0.47 (0.30)	0.73 (0.41)	0.51 (0.54)	0.004	0.75	0.729**
Years since clinical diagnosis[e]								
≤10	91 (68.40)	0.77 (0.13)	0.63 (0.25)	0.81 (0.19)[b]	0.66 (0.27)	<0.001	0.83	0.753**
>10	35 (26.30)	0.67 (0.20)	0.50 (0.28)	0.72 (0.35)	0.57 (0.47)	<0.001	0.78	0.837**
EQ-5D-5L-VAS								
<65	86 (64.70)	0.69 (0.16)	0.49 (0.16)	0.73 (0.26)	0.57 (0.33)	<0.001	0.82	0.799**
≥65	47 (35.30)	0.84 (0.10)	0.78 (0.18)	0.86 (0.13)[b]	0.83 (0.22)	<0.001	0.73	0.620**
$PDQ\text{-}8_{summary\ score}$								
≤5.43	8 (6.01)	0.91 (0.06)	0.90 (0.09)[b]	0.93 (0.09)[b]	0.91 (0.12)	0.344	0.83	0.553
>5.43	125 (93.99)	0.73 (0.16)	0.57 (0.26)	0.78 (0.23)	0.63 (0.29)	<0.001	0.82	0.793**
≤7.44	15 (11.27)	0.91 (0.06)	0.87 (0.11)[b]	0.91 (0.07)[b]	0.91 (0.12)	0.039	0.75	0.501
>7.44	118 (88.73)	0.72 (0.16)	0.56 (0.26)	0.77 (0.23)	0.60 (035)	<0.001	0.82	0.779**
Hoehn and Yahr								
Stages I–II	49 (36.84)	0.81 (0.10)	0.70 (0.18)[b]	0.83 (0.13)[b]	0.72 (0.24)	<0.001	0.85	0.844**
Stages III–IV	84 (63.16)	0.70 (0.17)	0.53 (0.28)	0.76 (0.29)	0.59 (0.41)	<0.001	0.67	0.691**

Values are presented as *n* (%), unless otherwise indicated

* $p < 0.05$ (two-tailed); ** $p < 0.001$ (two-tailed)

[a] Paired comparisons of 15-D and EQ-5D-5L utilities scores were made with Wilcoxon's signed-rank test

[b] Independent comparisons of 15-D and EQ-5D-5L utilities scores were made with Mann–Whitney *U* test

[c] Self-reported medical conditions Parkinson's disease apart

[d] Self-reported ongoing therapies for the control of the Parkinson's disease, $EQ\text{-}5D\text{-}5L_{utility}$ utility index from the European Quality of Life Questionnaire 5 dimensions 5 levels, *EQ-5D-5L-VAS* visual analogical scale from the EQ-5D-5L, $15\text{-}D_{utility}$ utility index from the 15 dimensions Health-Related Quality of Life Questionnaire, $PDQ\text{-}8_{summary\ score}$ summary score from the Parkinson's disease questionnaire 8 items, Hoehn and Yahr: Hoehn and Yahr scale, *ICC* intraclass correlation coefficient, *IQR* interquartile range

[e] Lost values: years since clinical diagnosis $n = 7$ (5.3 %)

Table 5 Comparison of the 15-D and EQ-5D-5L utilities across the VAS-based health groups

Range	Health status groups			Utility comparisons			
	n (%)	Age mean (SD)	15-$D_{utility}$ mean (SD)	EQ-5D-5L$_{utility}$ mean (SD)	15-$D_{utility}$ median (IQR)	EQ-5D-5L$_{utility}$ median (IQR)	Median difference[a]
0–100	133 (100)	64.33 (9.74)	0.74 (0.16)	0.59 (0.26)	0.79 (0.24)	0.64 (0.28)	−0.21**
0–49	33 (24.81)	65.58 (8.35)	0.60 (0.15)	0.37 (0.28)	0.64 (0.22)	0.48 (0.45)	−0.16**
50–59	32 (24.06)	65.19 (9.90)	0.77 (0.13)	0.61 (0.18)	0.79 (0.15)	0.66 (0.22)	−0.13**
60–69	24 (18.04)	61.13 (9.87)	0.71 (0.16)	0.55 (.21)	0.74 (0.24)	0.60 (0.37)	−0.14**
70–79	15 (11.27)	61.60 (12.12)	0.82 (0.13)	0.74 (0.24)	0.84 (0.11)	0.76 (0.20)	−0.08
80–89	19 (14.28)	66.74 (9.35)	0.83 (0.07)	0.77 (0.16)	0.84 (0.08)	0.83 (0.20)	−0.01
90–100	10 (7.51)	64.70 (9.56)	0.91 (0.04)	0.87 (0.07)	0.87 (0.08)	0.94 (0.09)	−0.07
Explained variance[b]	0.294			0.329			

* $p < 0.05$; ** $p < 0.001$

[a] Median difference. Paired comparisons of 15-D and EQ-5D-5L utility scores were made with Wilcoxon's signed-rank test

[b] Expressed as R^2 and corresponds to the % of variance in the 15-$D_{utility}$ and the EQ-5D-5L$_{utility}$ explained by the EQ-5D-5L VAS-based health status groups

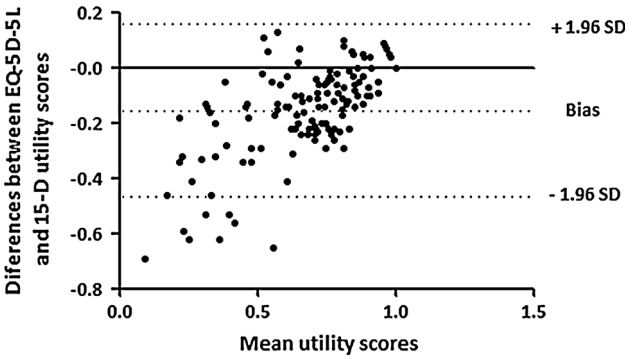

Fig. 1 Bland–Altman plot for all 133 individuals who completed both the EQ-5D-5L and 15-D

EQ-5D-5L scores was detected, with higher 15-D at lower mean utility, and lower 15-D at higher mean utility scores (Fig. 1).

Efficiency and sensitivity of 15-D and EQ-5D-5L

RE statistic calculations showed that 15-D was 29.8 % less efficient at detecting difference between patients with optimal HRQoL when the selected "cutoff" point was 5.8 PDQ-$8_{summary\ score}$ points; meanwhile, this efficiency lies at 4.1 % lower when compared with the EQ-5D-5L when the selected "cutoff" point was fixed at 7.4 PDQ-$8_{summary\ score}$ points. Moreover, AUC scores above 0.5 ratify the capacity of the two instruments to detect clinical differences on HRQoL in PD patients as well as the greater ability of the EQ-5D-5L for this fact. Conversely, the 15-D was 11 % more efficient at detecting differences between patients at mild and moderate to strong severity of the symptoms as measured by Hoehn and Yahr scale (Table 6).

Discussion

The current study has delivered the evidence of validity and sensitivity of the 15-D and the EQ-5D-5L, where these two instruments were compared through PD patients varying in socioeconomical, clinical characteristics and EQ-VAS-based health status. Therefore, the use of these two instruments is feasible and acceptable to elicit the utility score under the population of study. Although showing similar performance of these two instruments, there is still difference at individual level. We have therefore provided some insights on the choice of preference-based HRQoL instruments for PD patients. To our knowledge, this is the first study testing and comparing the validity and performance of 15-D and EQ-5D-5L HRQoL measures in PD patients.

The convergent validity for 15-D and EQ-5D-5L was demonstrated through their moderate to strong correlations with PDQ-8, a validated instrument for PD patients, and "known-group" validation further supports the discriminative validation of 15-D and EQ-5D-5L. Previous studies have verified the validity in both the 15-D [15] and EQ-5D-3L [16, 17]. Because EQ-5D is shorter and therefore easier and faster to complete, it seems to be expected to use in the assessment of PD [20]. Nevertheless, 15-D instrument seems to be more comprehensible and covers other areas than EQ-5D such leisure activities, housework, walking ability, communication, worries about the future and bodily aches and pains, important in PD patients [30]. Therefore, utility score from 15-D has a stronger correlation than EQ-5D-5L utility score with the summary score from the PDQ-8, as showed in our patients (Table 3).

The two instruments seemed to correlate strongly in all tested cased, as Spearman's rank correlation (>0.5) and

Table 6 Efficiency of 15-D and EQ-5D-5L to detect clinically relevant difference in quality of life and in the severity of the symptoms

Quality of life							
Measure	$PDQ\text{-}8_{summary\ score}$	*n*	Mean (SD)	*t* test	RE	ROC curve	
				t statistic (*p* value)		AUC	95 % CI
$15\text{-}D_{utility}$	≤5.8	8	0.91 (0.06)	6.698 (<0.001)	0.702[a]	0.87*	(0.77–0.98)
	>5.8	125	0.73 (0.16)				
$EQ\text{-}5D\text{-}5L_{utility}$	≤5.8	8	0.90 (0.09)	7.982 (<0.001)	1.000	0.91*	(0.82–0.99)
	>5.8	125	0.57 (0.26)				
$15\text{-}D_{utility}$	≤7.4	15	0.91 (0.06)	7.995 (<0.001)	0.959[a]	0.87*	(0.79–0.96)
	>7.4	118	0.72 (0.16)				
$EQ\text{-}5D\text{-}5L_{utility}$	≤7.4	15	0.87 (0.11)	8.161 (<0.001)	1.000	0.88*	(0.80–0.96)
	>7.4	118	0.56 (0.26)				
$15\text{-}D_{utility}$	≤21.87	59	0.83 (0.11)	6.427 (<0.001)	1.084[a]	0.79*	(0.72–0.87)
	>21.87	74	0.67 (0.16)				
$EQ\text{-}5D\text{-}5L_{utility}$	≤21.87	59	0.74 (0.20)	6.172 (<0.001)	1.000	0.80*	(0.73–0.88)
	>21.87	74	0.48 (0.26)				
Severity of the symptoms							
Measure	Hoehn and Yahr	*n*	Mean (SD)	*t* test	RE	ROC curve	
				t statistic (*p* value)		AUC	95 % CI
$15\text{-}D_{utility}$	Stages I–II	49	0.81 (0.10)	4.405 (<0.001)	1.110[a]	0.67*	(0.58–0.76)
	Stages III–IV	84	0.70 (0.17)				
$EQ\text{-}5D\text{-}5L_{utility}$	Stages I–II	49	0.70 (0.18)	4.180 (<0.001)	1.000	0.68*	(0.59–0.77)
	Stages III–IV	84	0.53 (0.28)				

$15\text{-}D_{utility}$ utility index from the 15 dimensions Health-Related Quality of Life Questionnaire, *$EQ\text{-}5D\text{-}5L_{utility}$* utility index from the European Quality of Life Questionnaire 5 dimensions 5 levels, *$PDQ\text{-}8_{summary\ score}$* summary score from the Parkinson's disease questionnaire 8 items, *Hoehn and Yahr* Hoehn and Yahr scale, *AUC* area under ROC curves, *CI* confidence interval, *RE* relative efficiency, *ROC* receiver operating characteristic

* $p < 0.001$ indicates that AUC statistically significantly >0.5

[a] Reference is $EQ\text{-}5D\text{-}5L_{utility}$

ICCs (>0.67) show in all tested cases. Nevertheless, the level of agreement between 15-D and EQ-5D-5L was not high across the sample, as denoted by Bland–Altman plot and further supported by the statistically significant differences between the utilities from each instruments (15-D utility score exceeding EQ-5D-5L utility score), according to Wilcoxon's signed-rank test performed in the study. Since different valuation systems are used in each instrument, it is also be expected to find differences on derived utilities between each them. These differences have been therefore accounted in other study comparing utilities form 15-D and health states valued using the TTO method [31], as in the EQ-5D value system is used. It has been shown that 15-D value system produces therefore higher utility scores than EQ-5D value system [32]. According to the results obtained in this study (Table 5), differences between 15-D and EQ-5D-5L utilities are more likely to be accounted in PD patients with a poorer health condition—attending to EQ-VAS scores. This result could have potential implications in CUA as far as QALY gains valuations might differ depending on utility at baseline.

Although both 15-D and EQ-5D-5L were demonstrated to be valid and sensitive in PD patients, some comments need to be made about the relative merits of each one. Although both measures can discriminate patients with different self-reported health status and severity of symptom, RE and ROC analysis showed EQ-5D-5L is more efficient to detect clinically relevant difference of PD patients regarding HRQoL; meanwhile, 15-D was more effective at distinguishing patients according to disease severity, as assessed using the Hoehn and Yahr staging. Overall, there is no strong evidence for the superiority of either instrument, so it can be concluded that both instruments are similarly efficient in our sample of PD patients.

Nevertheless, there are two aspects which are favorable to the EQ-5D-5L. First, this instrument is much shorter (up to three times) than the 15-D. Consequently, if both instruments are equivalent in terms of efficiency, the

shorter questionnaire (EQ-5D-5L) should be preferred. Second, in the context of studies conducted in Spain, there is a good reason to use the EQ-5D-5L because a country-specific value set exists for this instrument (as it does for some other countries) and not for the 15-D.

The current study need to be understood under different limitations to achieve a logical interpretation of results. Since non-longitudinal design was used, fully responsiveness of these two instruments cannot be provided for PD patients. Although sensitive measures are usually considered to be reliable [26], longitudinal study is necessary for the validation of them in PD patients, as this is a chronic disease. Furthermore, clinical conditions were self-reported, and it has been shown that the reliance on such data may result in biased estimates of the prevalence of some conditions [33]. Despite this, EQ-VAS has shown to be valid as a discriminator of overall perceived health, also in specific health conditions [34]. Two other limitations associated with the characteristics and the size of the sample need to be acknowledged. First, although the sample was collected from 15 different local PD associations representing Spain, we could not perform a population-based study with randomized and stratified sample distribution, so the voluntariness of the participation in the study could introduce a selection bias. Second, the relative small sample size does not allow separating Hoehn and Yahr stages in the four levels measured hence this could potentially introduce systematic bias resulting from the possible differences of patients' experience. Further research with larger sample size selected under population-based studies and more strict diagnosis criteria is needed to ratify the results in this study and determine other psychometric properties, such as longitudinal response and reliability.

Conclusion

Both 15-D and EQ-5D-5L are showed to be valid and sensitivity generic HRQoL measures in Spanish PD patients with both instruments showing similar HRQoL dimension coverage and ceiling/floor effects. The 15-D has better efficiency and greater sensitivity to detect clinical changes in PD severity of the symptoms; meanwhile, the EQ-5D-5L is better to detect clinical HRQoL changes. The EQ-5D-5L has the advantage of being substantially shorter than the 15-D. Moreover, the EQ-5D-5L might be preferable because of the availability of country-specific value sets for Spain and other countries.

Acknowledgments Our gratitude extends to the following Parkinson associations: Albacete, Aragón, Astorga, Asturias, Bahía de Cádiz, Córdoba, Elche, Extremadura, Gran Canaria, Granada, Lorca, Málaga, Mallorca, Sevilla and Valencia. We also acknowledge the technical support offered by José Ángel Miguel Dávila, Jorge Eduardo Martínez Pérez and the Universities of Murcia and Extremadura. José María Abellán-Perpiñán and Fernando Ignacio Sánchez-Martínez gratefully acknowledge the financial support from Ministerio de Economía y Competitividad grant ECO2010-22041-C02-02 and from Fundación Séneca-Agencia de Ciencia y Tecnología de la Región de Murcia grant 15357/PHCS/10.

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