Neurol Ther (2025) 14:99–115
https://doi.org/10.1007/s40120-024-00655-0

ORIGINAL RESEARCH

Huntington Disease Health Related Quality of Life, Function and Well Being: The Patient's Perspective

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Received: April 15, 2024 / Accepted: August 7, 2024 / Published online: October 7, 2024

ABSTRACT

Background: Limited information is available on patients' experience living with Huntington's disease (HD). The primary objective of this study was to assess the health-related quality of life and well being of patients with HD.

Methods: A non-interventional, cross-sectional study was conducted in 17 hospitals-based movement disorders units in Spain. Patients aged ≥ 18 years, genetically HD diagnosed [with a diagnostic confidence level score of 4, and an Independence Scale (IS) score ≥ 70] were included. The primary variables were the Huntington's Disease Health-related Quality of Life (HDQLIFE) scores and results of the Satisfaction with Life Scale (SWLS). Secondary outcomes include the Unified HD Rating Scale (UHDRS), Beck Hopelessness Scale (BHS), Stigma Scale for Chronic Illness (SSCI-8), Beck Depression Inventory-Fast Screen (BDI-FS) and Problem Behaviours Assessment for HD short Version (PBA-S).

Results: A total of 102 patients were included. The mean age (SD) was 53.1 (12.1) years and 56% were male. Most of the patients (99.0%) showed motor symptoms (87.3%), behavioural

Prior Publication: This manuscript has not been previously published.

Supplementary Information The online version contains supplementary material available at https://doi.org/10.1007/s40120-024-00655-0.

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and psychiatric disturbances (59.8%), or cognitive impairment (20.6%). HDQLIFE domain score means (SD) includes concern with death and dying 45.97 (9.60) end-of-life planning 37.91 (8.84), and meaning and purpose 44.74 (9.05). SWLS score mean was 24.25 (7.33). Depressive symptoms were found in 37.4% of patients and moderate-to-severe feelings of hopelessness in 32.9%. The prevalence of stigma was 55.9% (n = 57).

***Conclusion*:** HD impacted quality of life, with prevalent motor, psychiatric symptoms and cognitive impairment. Patient perspectives may provide complementary information to implement specific interventions.

Keywords: Huntington disease; Health-related quality of life; Patient-reported outcomes; Satisfaction with Life; Depression; Stigma

Key Summary Points

Why carry out this study?

Huntington's disease (HD) is a slowly progressive autosomal dominant neurodegenerative disorder, usually presented in early middle life, although there is an unusually rare juvenile form, with abnormal movements (chorea) together with psychiatric symptoms and cognitive impairment

HD progresses towards a severe functional decline and dementia, finally causing death. This makes it a complex disease that might require a multidisciplinary approach

The lack of published literature suggests the need of deepening the knowledge of HD's impact on the patient's life along the disease progression, especially in the early stages. The aim of this study is to assess the perception of quality of life (QoL) in patients with HD using a battery of patient-reported measurements

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What was learned from the study?
Stigma, hopelessness, and depressive symptoms have been identified as disease-related factors most strongly correlated with health-related QoL in patients with HD
Understanding patients' perspective of the disease may facilitate the implementation of specific interventions to support their QoL
Clinical approaches could benefit from PROs such as HDQLIFE, SWLS, UHDRS, mood or other scales information in a context where they could give valuable information that it is also related with the early onset of symptoms

INTRODUCTION

Huntington's disease (HD) is an autosomal dominant, neurodegenerative and progressive inherited disorder. [1] The incidence rate reported in a worldwide analysis is 0.38 per 100,000 per year (95%CI: 0.16–0.94) [2]. Higher incidence has been reported in North American, Australian, and European studies compared to the studies in Asia.

The disease tends to affect patients from age 30–50 and manifests motor, cognitive, and emotional symptoms [3]. Usually, this is characterised by motor disorders, functional disability, psychiatric symptoms and cognitive impairment. Cognitive and emotional features can be detected up to 15 years before the appearance of motor symptoms [4]. HD onset is defined when a person who carries a CAG-expanded HTT allele develops "the unequivocal presence of an otherwise unexplained extrapyramidal movement disorder, e.g. chorea, dystonia, bradykinesia or rigidity". HD progresses toward a severe functional decline and dementia, finally causing death, frequently due to comorbid complications such as respiratory infections (pneumonia) and severe trauma after a fall. Finally, at late-stage HD, patients start to experience dysphagia as this contributes to weight loss, and at the end patients lose bowel and bladder control, requiring assistance in all activities of daily living.

Although there is no established treatment to delay the onset or prevent HD progression, symptomatic treatment of chorea may be beneficial in some individuals, as it may have a favourable effect on motor function, quality of life and safety. Thus, education and symptomatic therapies can be effective tools for clinicians to use with patients and families affected by HD.

It seems necessary to deepen the knowledge on the impact that HD causes in the patient's life along with the disease progression, especially in the early stages. Arguably, there is a case to better understand the dimensions of the impact of HD on the lives of patients and time sequence of the different motor, emotional and cognitive signs of the disease and the way in which they affect the patient's daily activity [5]. Several patient-reported outcomes (PROs) have been developed. Those associated with cognitive and emotional disturbances seem to be important contributors to health-related quality of life (HRQoL) and may appear in an earlier disease stage [6, 7].

The WHO defines QoL as "individuals' perception of their position in life in the context of the cultures in which they live and in relation to their goals, expectations, standards, and concerns [8]. The National Institute for Neurological Disorder and Stroke has recommended the assessment of PROs evaluating HRQoL, motor function, emotional/behavioural, cognitive and functional outcomes. It is necessary to better understand the impact that HD causes on the patient's life along with the disease progression, especially in the initial phases. [9] HD is a complex disease that requires a multidisciplinary approach to address the pharmacological, cognitive, physical and psychological therapies, especially in early stages.

The aim of this study is to assess the perception of quality of life in patients with HD through a battery of PRO measurements.

METHODS

Study Design

This study is non-interventional and cross-sectional, conducted in 17 hospitals in Spain.

Participants

The study includes 102 patients aged ≥ 18 years, genetically diagnosed with HD by direct DNA testing, with a diagnostic confidence level score of 4 and an independence scale (IS) score ≥ 70. Patients with juvenile HD or chronic disorders that could significantly affect HRQoL according to the investigator criteria were excluded.

Procedures

Consecutive patients were recruited by neurologists specialised in movement disorders and they attended a single visit. Sociodemographic and clinical data were collected through an electronic Case Report Form (e-CRF) specifically designed for this study. Questionnaires were completed in electronic format through a tablet or touch panel, and paper was used as requested. The informed consent to participate in the study was also collected on paper.

All patients provided written informed consent according to the Declaration of Helsinki. The study was approved by the Ethics Committee Hospital La Fe in Valencia (Spain) (ROC-HUN-2020-01) and notified to all committees of the participating centres (See supplementary material file).

Primary and Secondary Outcomes

The primary objective of this study was to describe the HRQoL and subjective well-being of patients using Huntington's Disease Health-related Quality of Life (HDQLIFE) and Satisfaction with Life (SWLS) questionnaires.

The HDQLIFE it is an instrument developed for individuals living with HD. It is a disease-specific measure used in a wide spectrum of patients with HD from prodromal to later stage disease. It is a Computerized Adaptive Test (CAT) developed by the NeuroQOL group in the US and is psychometrically validated in Spanish. In our study, a paper questionnaire was used. The HDQLIFE contains 6 calibrated item banks that are specific to HD, and 11 additional item banks from PROMIS/Neuro-QoL. All items have Likert-style items. HD-specific domains (t-score) (with a mean of 50 and a standard deviation of 10) assessed in our study were described as follows: Chorea, Speech Difficulties, Swallowing Difficulties, Concern with Death and Dying, End of Life Planning (EoL) and Meaning and Purpose (M&P). Higher scores indicate worse functioning [10].

The SWLS is a 5-item scale designed to measure global cognitive judgments of one's life satisfaction (not a measure of either positive or negative affect. The total SWLS score was obtained as the sum of the 5 items (score range 5–35). The total score was described and grouped into 6 categories: very high score; highly satisfied (30–35); high score (25–29); average score (20–24); slightly below average in life satisfaction (15–19); dissatisfied (10–14); and extremely dissatisfied (5–9) [11].

Secondary objectives include the Unified HD Rating Scale (UHDRS), The Stroop Color Naming, Stroop Word Reading and Symbol Digit Modalities Test (SDMT), Beck Hopelessness Inventory (BHS), Stigma Scale for Chronic Illness 8-item version (SSCI-8), Beck Depression Inventory-Fast Screen (BDI-FS), Huntington's Disease Activities of Daily Living Scale (HD-ADL) and Problem Behaviours Assessment for HD-short Version (PBA-S).

The presence, severity and progression of symptoms and signs were assessed with the Unified HD Rating Scale (UHDRS), which is subdivided into motor, cognitive and functional domains [12]. To assess motor function, part I of the UHDRS was evaluated by the investigator: the motor section is composed of 31 items rating ocular motor function, dysarthria, chorea, dystonia, gait, and postural stability. The Total Motor Score (TMS) is the sum of all the individual items, with higher scores indicating worse motor performance (maximum score = 124) [3].

Huntington's Disease Activities of Daily Living (HD-ADL) is a 17-item scale that evaluates specific domains of functioning including employment, completion of household tasks, personal care, written and phone communications, travel, money management, sociability and general level of activity interest. A score of 0 indicates no difficulty and 3 maximal difficulties. This scale is a companion/caregiver report and valuable when completed by the companion as intended [13].

The Stroop Color Naming, Stroop Word Reading and SDMT, which are part of the UHDRS [12], assess cognitive function of HD patients: stroop color, stroop word and stroop color–word scores provided by the investigator were described (total items correct within a given time limit on each scale). And SDMT score (number of correct items produced in 90 s) was also described. Higher scores reflect better cognitive functioning.

The BHS is a 20-items true–false questionnaire to assess expectations for the future. The total score was obtained as the sum of all 20 items (1 or 0), after the inversion of 9 items (items 1, 3, 5, 6, 8, 10, 13, 15, 19), which are inversely scored to prevent acquiescence. Higher scores reflect more intense levels of hopelessness. A cut-off score ≥ 9 indicates moderate-to-severe hopelessness and was associated to suicide risk [14, 15].

To know the level of stigmatisation of patients, the score in the SSCI-8 was described. Accordingly, the raw summed score range for the SSCI-8 was 8–40, with higher scores indicating higher levels of perceived stigma. The SSCI-8 raw score was calculated by summing individual items. A cut-off score > 8 indicates the presence of stigmatisation [16, 17].

The BDI-FS was used to evaluate the possible mood disturbances in terms of depressive symptoms. It is a 7-item questionnaire that assesses dysphoria, anhedonia, suicidal ideation and cognition-related symptoms on a 3-point scale. Scoring is easily accomplished by summing total scores (range from 0 to 21), with higher scores indicating more depressive symptomatology. Cut-off scores ≥ 4 and ≥ 9 are used to define the presence of depression and moderate-to-severe depression, respectively. Scores were interpreted according to the manual guidelines, as follows: 0–3 minimal, 4–6 mild, 7–9 moderate, and 10–21 severe depression [18].

The PBA-S is an 11-item questionnaire that evaluates the severity and frequency of symptoms during the last month. The scores range from 0 (no symptom) to 4 (present all the time). The severity scores range from 0 (symptom absent) to 4 (symptom causing severe problems [19].

All PROs and scale licenses were requested to be used in this study, including the different components of the UHDRS from the Huntington Study Group.

Statistical Analysis

For descriptive analysis, continuous variables were described by the number of patients with valid/missing observations, mean, standard deviation (SD), median, 25 and 75 percentiles (P25 and P75, respectively), minimum and maximum. Categorical variables were described by frequencies and related percentages per class level. In both cases the number of observations (*n*) and number of missing data (*n* missing) were specified. A *p* value lower than 0.05 was considered significant. The statistical analysis was conducted using SAS Enterprise Guide 7.15.

To evaluate the correlation between different scales, univariant and multivariant analyses were carried out by measuring the association of the motor symptoms, cognitive alterations, and emotional/behavioural problems (subjective patient perceptions impact of the disease, the attitude of optimism/pessimism, hopelessness, stigma, depression) with the quality of life and the subjective well-being of Huntington's disease patients.

RESULTS

The patients included were of a mean age of 53.1 (SD 12.1), with just over half married (56.6%) and male (55.9%), and 37% of patients reported university/postgraduate studies. Regarding working status, only 18.2% of the patients were employed, 59.6 were unemployed and 22.2% reported having incapacity.

Table 1 Sociodemographic characteristics

	***n* = 102**
Age (years), mean (SD)	53.1 (12.1)
Gender man (%)	57 (55.9)
Living status (%)	
Single	26 (26.3)
Married	56 (56.6)
Educational level (%)	
Secondary education	36 (36.0)
University study/postgraduate studies	37 (37.0)
Age at HD diagnosis, mean (SD)	46.3 (13.6)
Years since HD diagnosis, mean (SD)	6.9 (6.2)
Concomitant disease* (%)	80 (78.4)
Hypertension	17 (16.7)
Type II diabetes	6 (5.9)
Depression	23 (22.5)
Anxiety	12 (11.8)
Active smoking habit (%)	28 (27.5)
Working status (%)	
Employed	18 (18.2)
Not employed	59 (59.2)
Incapacity	22 (22.2)
Caregiver (%)	
Yes	24 (24.2)
No	75 (75.8)

A total of 24 patients (24.2%) reported the necessity of a caregiver (Table 1).

A total of 81 (79.4%) patients reported having received treatment since the diagnosis of HD. The treatment was mainly based on antidepressants (63.2%), other nervous system drugs (38.2%), anxiolytics (36.8%), pyknoleptic (27.6%) and dopaminergic agents (22.4%), and hypnotics and sedatives (11.8%). Some patients (27.3%) reported having discontinued the treatment. The reason was toxicity (3.6%), lack of efficacy (19.6%), and others (76.8%).

Regarding HDQLIFE, data are shown in Fig. 1. Patients with chorea presented a raw score of mean 11.53 (SD 6.23) and T-score mean 52.23 (SD 8.75); speech [raw score mean 11.33 (SD 5.30) and T-score mean 48.84 (SD 8.21)]; swallowing [raw score mean 9.87 (SD 5.40) and T-score mean 49.76 (SD 8.77)]; concern with death and dying presented [raw score of mean 9.93 (SD 4.53) and T-score mean 45.97 (SD 9.60)]. Patients with HDQLIFE EoL planning presented [a raw score of mean 24.30 (SD 7.56) and T-score mean 37.91 (SD 8.84)]; M&P presented raw score of mean 14.68 (SD 3.85) and T-score mean 44.74 (SD 9.05). On the other hand, the SWLS score presented a mean of 24.25 (SD 7.33) with the main categories: highly satisfied (30–35) (26.7%), high score (25–29) (26.7%), and average score (20–24) (25.7%).

TMS (as part I of UHDRS) had a mean of 25.56 (SD 15.01), and, overall, the patients in our study reported predominant symptomatology or complications associated with HD in 99% of the cases. In those patients, motor symptoms were more frequent than behavioural and psychiatric disturbances or cognitive impairment. Involuntary movements were the principal motor symptoms, but akinesia, bradykinesia, eye movements, difficulty speaking, difficulty swallowing, balance problems and falls were also commonly reported symptoms, as described in Table 2. Mixed anxiety–depression was the concomitant disease reported more frequently (23.5%).

The Stroop test results showed that the highest mean was reported by word score [mean 66.79 (SD 20.52)], followed by colour score [mean 45.59 (SD 16.79)], and word–colour score [mean 27.62 (SD 11.19)]. SDMT scores showed that the total number of answered items [mean 34.76 (SD 22.52)] and total number of correct items [mean 33.62 (SD 21.82)] have similar mean distributions. The symbol digit (90-s matching of as many symbols and numbers as quickly as possible); and colour and word Stroop tests (45 s naming the coloured boxes, read, and name the words and name the ink colours in a word. According to those tests, we can see that the patient population showed

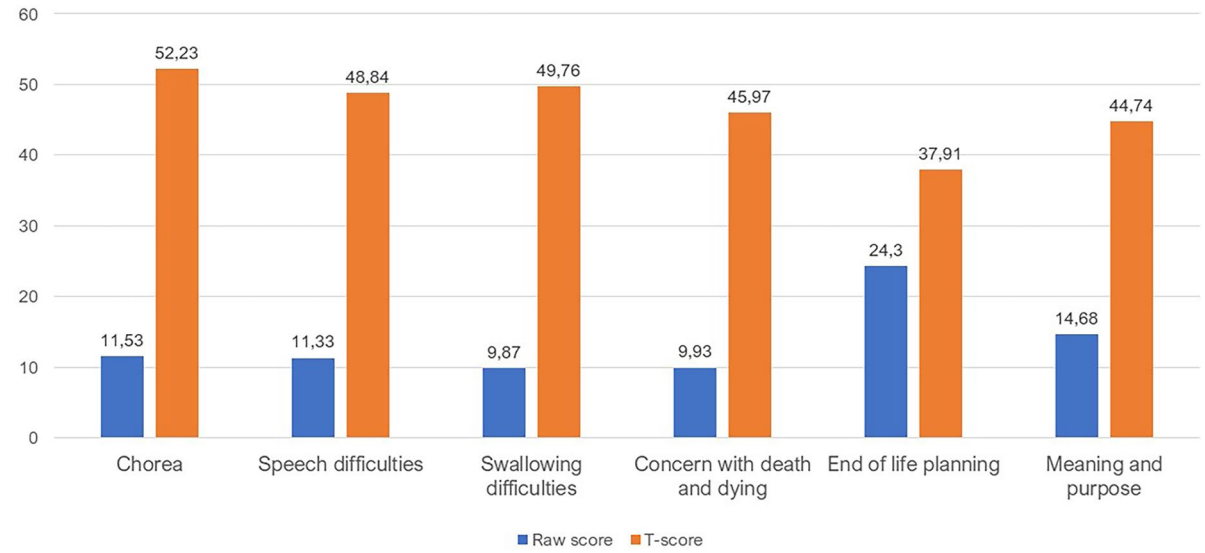

Fig. 1 Description of HDQLIFE scores in the defined domains

cognitive function damage. The HD-ADL score showed a mean (SD) of 15.36 (10.56).

Regarding PBA-S, problem behaviours showed high score means such as apathy (mean 2.47); depressed mood (mean 2.33); anxiety (mean 2.13); irritability (mean 2.11); and perseveration (mean 1.88). Instead, the rest of the behaviours showed PBA-S score means lower than 1.

Depressive symptoms were found in 37.4% (n = 33/99) of patients and moderate-to-severe feelings of hopelessness in 32.9% (n = 32/97). The prevalence of stigma was 55.9% (n = 57/102) with low-to-moderate severity (Table 2).

Table 3 shows the correlation of HDQLIFE domains and the different PROs and study scales. SWLS scores showed a significant positive correlation with all HDQLIFE domains ($p < 0.05$) (a moderate significant correlation with the impact of M&P HDQLIFE on QoL: rho 0.60942; $p < 0.000$), except for the EoL planning ($p = 0.1106$); BHS and BDI-FS scores showed significant positive correlations with the impact that concerns and preoccupation with death and dying had on QoL (death and dying HDQLIFE score): rho 0.439 and 0.470, respectively; $p < 0.0001$; and stigma scores showed a moderate significant correlation with chorea, speech and swallowing difficulties: rho 0.42010, 0.45106 and 0.41689, respectively; $p < 0.0001$.

SWLS scores showed a moderate significant correlation with the impact of M&P HDQLIFE on QoL: rho 0.60942; $p < 0.0001$.

DISCUSSION

The purpose of the present study is to describe the HRQoL and subjective well-being of Huntington's disease patients using the HDQLIFE and SWLS, respectively. Moreover, we have evaluated other important PROs which are considered as key measures to guide treatment recommendations [20, 21].

The mean reported age of our patients was 53, slightly superior to the usual range of ages of patients with the disease from 30 to 50 [22]. According to inclusion criteria, patients had an early HD stage, which was confirmed through the mean of 6.8 years registered from HD diagnosis. In our study, patients showed limitations in working status and required partial support from caregivers. However, requirements for help and assistance were minor.

Our study population had a high level of education. Earlier recognition of symptoms and manifestations among the more educated patients could explain the earlier estimated age at onset in this group [23]. Furthermore,

Table 2 Clinical characteristics

Type of symptoms (n = 102)	Motor symptoms	89 (87.3%)
	Behavioural and psychiatric disturbances	61 (59.8%)
	Cognitive impairment	21 (20.6%)
	Other	9 (8.8%)
Motor symptoms (n = 102)	Involuntary movements	83 (81.4%)
	Eye movements	10 (9.8%)
	Akinesia, Bradykinesia	15 (14.7%)
	Difficulty speaking	13 (12.7%)
	Difficulty to swallow	9 (8.8%)
	Balance problems and falls	12 (11.8%)
	Dystonia	7 (6.9%)
Behavioural and psychiatric disturbances (n = 102)	Personality changes	7 (6.9%)
	Depression	34 (33.3%)
	Anxiety	20 (19.6%)
	Irritability	16 (15.7%)
	Apathy	13 (12.7%)
	Involuntary movements	54 (52.9%)
	Balance problems and falls	3 (2.9%)
	Personality changes	6 (5.9%)

Table 2 continued

Cognitive impairment (n = 102)	Speech disorders (aphasia)	0 (0%)
	Slowing down of mental processes (bradyphrenia or bradypsychia)	7 (6.9%)
	Recent memory alterations—mainly the information retrieval processes are altered	7 (6.9%)
	Attention problems, visuospatial alterations and executive functions (planning and sequencing deficit)	9 (8.8%)
Satisfaction with Live Scale (n = 101)		
SWLS score, mean (SD)		24.25 (7.33)
SWLS score (n, %)	Highly satisfied (30–35)	27 (26.7%)
	High score (25–29)	27 (26.7%)
	Average score (20–24)	26 (25.7%)
	Slightly below average in life satisfaction	6 (5.9%)
	Dissatisfied (10–14)	11 (10.9%)
	Extremely dissatisfied (5–9	4 (4.0%)
Beck Hopelessness Inventory (n = 97)		
BHS score, mean (SD)		6.59 (4.97)
BHS score, (n, %)	0–3 normal range	33 (34.0%)
	4–8 mild	32 (33.0%)
	9–14 moderate	20 (20.6%)
	15–20 severe	12 (12.4%)
Stigma Scale (n = 102)		
SSCI-8 (raw score), mean (SD)		10.8 (4.2)
SSCI-8 (ITR score), mean (SD)		45.7 (6.8)

Table 2 continued

SCCI-8 categorised	No presence of stigma (SSCI-8 = 8)	45 (44.1%)
	Presence of stigma (SSCI-8 > 8)	57 (55.9%)
Beck Depression Inventory-Fast Screen (n = 99)		
BDI-FS score, mean (SD)		2.95 (3.5%)
	0–3 minimal depression	62 (62.6%)
	4–6 mild depression	22 (22.2%)
	7–9 moderate depression	10 (10.1%)
	10–21 severe depression	5 (5.1%)
Problem Behaviours Assessment for HD short Version (n = 102)		
	Severity mild[a]	Mean (SD)
Depressed mood	28 (27.7%)	2.3 (3.5)
Suicidal ideation	3 (3.0%)	0.2 (1.0)
Anxiety	25 (24.8%)	2.1 (3.3)
Irritability	30 (29.7%)	2.1 (2.8)
Angry/aggressive behaviour	12 (11.9%)	0.9 (2.6)
Apathy	24 (23.8%)	2.5 (3.7)
Perseveration	25 (24.5%)	1.9 (2.8)
Obsessive–compulsive behaviours	8 (8.0%)	0.6 (1.9)
Delusions/paranoid thinking	0	0.10 (0.90)
Hallucinations	0	0.1 (0.9)
Disoriented behaviour	3 (3.0%)	0.34(1.0)

[a]0 symptom absent; 1 questionable/trivial; 2 mild (definitely present, but not causing a problem); 3 moderate (causing a problem and/or distress); 4 severe (causing intolerable distress/making normal life impossible)

education could improve the interest to participate in physiotherapy programs [24].

Individuals suffering from Huntington's disease (HD) have been shown to present with poor self-awareness of a variety of symptoms especially in the early stage, where they may have limited consciousness of their motor disturbances [25]. However, the patients in our study reported the development of predominant symptomatology or complications

Table 3 Pearson correlation coefficients between HDQLIFE domains and study PROs

	Chorea HDQLIFE	Speech difficulties HDQLIFE	Swallowing difficulties HDQLIFE	Concern with death and dying HDQLIFE	End of life planning HDQLIFE	Meaning and purpose HDQLIFE
SWLS	− 0.29763 0.0028 99	− 0.32070 0.0018 92	− 0.21713 0.0309 99	*− 0.40442* 0.0001 87	− 0.16654 0.1106 93	*0.60942* < .0001 99
Total motor score (UHDRS)	*0.57981* < 0.0001 100	0.31941 0.0018 93	*0.45128* < .0001 100	0.01071 0.9211 88	0.09851 0.3475 93	− 0.00384 0.9698 100
Independence scale	*− 0.62192* < .0001 100	*− 0.43845* < .0001 93	*− 0.53236* < .0001 100	− 0.08433 0.4347 88	0.00895 0.9322 93	0.09201 0.3626 100
HD-ADL	*0.62092* < .0001 58	0.37617 0.0051 54	0.35752 0.0059 58	0.22096 0.1155 52	0.03058 0.8296 52	− 0.25551 0.0488 60
Word score (Stroop)	*− 0.63087* < .0001 98	*− 0.41615* < .0001 92	*− 0.49058* < .0001 98	− 0.15648 0.1502 86	− 0.10737 0.3110 91	0.06882 0.5007 98
Color score (stroop)	*− 0.58700* < .0001 99	− 0.39376 0.0001 92	*− 0.44332* < .0001 99	− 0.15462 0.1527 87	− 0.06367 0.5466 92	0.14942 0.1399 99
Word-color score (stroop)	*− 0.50006* < .0001 99	− 0.31561 0.0022 92	− 0.35866 0.0003 99	− 0.04355 0.6888 87	0.00519 0.9608 92	0.02823 0.7815 99
Total number of correct items (SDMT)	− 0.37093 0.0002 99	− 0.16469 0.1147 93	− 0.36768 0.0002 99	− 0.14021 0.1952 87	− 0.08449 0.4233 92	0.20269 0.0442 99
BDI-FS	0.20156 0.0477 97	0.27611 0.0084 90	0.19306 0.0581 97	*0.47082* < .0001 85	0.24884 0.0180 90	*− 0.41775* < .0001 97
Depressed mood (PBA-S)	0.10797 0.2875 99	0.22422 0.0317 92	0.02408 0.8130 99	*0.43554* < .0001 87	0.16572 0.1144 92	− 0.30925 0.0018 99
Suicidal ideation (PBA-S)	− 0.04844 0.6340 99	0.01959 0.8530 92	0.02393 0.8141 99	0.30164 0.0045 87	0.20844 0.0462 92	− 0.28180 0.0047 99
Anxiety (PBA-S)	0.08936 0.3791 99	0.25355 0.0147 92	− 0.02603 0.7981 99	0.17700 0.1010 87	0.03871 0.7141 92	− 0.20831 0.0385 99

Table 3 continued

	Chorea HDQLIFE	Speech difficulties HDQLIFE	Swallowing difficulties HDQLIFE	Concern with death and dying HDQLIFE	End of life planning HDQLIFE	Meaning and purpose HDQLIFE
Irritability (PBA-S)	− 0.02953 0.7717 99	0.10632 0.3131 92	− 0.10771 0.2886 99	0.06411 0.5552 87	0.02207 0.8346 92	− 0.27889 0.0052 99
Angry/aggressive behaviour (PBA-S)	− 0.01841 0.8565 99	0.13125 0.2123 92	− 0.07495 0.4609 99	0.06280 0.5634 87	− 0.11395 0.2794 92	− 0.23151 0.0211 99
Apathy (PBA-S)	0.17074 0.0911 99	0.19822 0.0582 92	0.06389 0.5298 99	0.32197 0.0024 87	0.10807 0.3052 92	− 0.34165 0.0005 99
Perseveration (PBA-S)	0.18340 0.0678 100	0.17149 0.1002 93	− 0.00544 0.9572 100	− 0.00018 0.9987 88	0.01037 0.9214 93	− 0.20463 0.0411 100
Obsessive–compulsive behaviours (PBA-S)	0.00671 0.9477 98	0.10879 0.3046 91	− 0.10319 0.3120 98	− 0.08225 0.4515 86	− 0.09789 0.3559 91	− 0.06410 0.5306 98
Delusions/paranoid thinking (PBA-S)	0.02490 0.8077 98	0.05119 0.6299 91	0.04360 0.6699 98	− 0.09275 0.3957 86	− 0.13378 0.2062 91	0.05694 0.5776 98
Hallucinations (PBA-S)	98	0.05226 0.6227 91	0.03943 0.6999 98	− 0.09341 0.3923 86	− 0.13105 0.2156 91	0.06220 0.5429 98
Disoriented behaviour (PBA-S)	0.11765 0.2486 98	0.12114 0.2527 91	0.03895 0.7034 98	− 0.10537 0.3343 86	0.14112 0.1821 91	− 0.04407 0.6666 98
SSCI-8	*0.42010* < .0001 100	*0.45106* < .0001 93	*0.41689* < .0001 100	0.20999 0.0496 88	0.09947 0.3428 93	− 0.11714 0.2458 100
BHS	0.29566 0.0034 96	0.28842 0.0061 89	0.26094 0.0106 95	*0.43895* < .0001 83	0.14368 0.1817 88	*− 0.40559* < .0001 96

Pearson correlation coefficients in italics indicate a correlation (positive or negative) between scales

Prob >|*r*| under H0: Rho = 0

Number of observations

associated with HD in 99% of the cases. The most important motor symptoms were involuntary movements (81.4%) and depression was reported by 33.4%. In the early stage, patients may have limited awareness of their motor disturbances; however, chorea symptoms are one

of the most sensitive signs and highly associated with early diagnosis [25, 26].

The literature supports the use of the HDQLIFE as an adequate tool/PRO to assess the impact of HD [10, 27]. In our study, the highest domain was chorea and the lowest was EoL. A higher T-score represents more of the concept being measured.

Carlozzi et al. assessed the EoL domain and found a mean score of 48.68, higher than ours [28]. Longitudinal studies have shown that HDQLIFE is more sensitive to change over time, and our study's characteristics, with a cross-sectional design and a lower sample size, could explain this lower score. Nevertheless, these new assessment tools might be used to capture patient preferences about EoL and the goal is to reduce family stress, anxiety, and depression [27, 29].

Regarding the M&P, our population score is slightly superior to the mean. Meaning these individuals have greater feelings of meaning and purpose. Sokol et al. reported that this domain was associated with positive affect and well being regardless of the magnitude of symptoms burden among a cohort of people with pre-, early, and late-stage HD. The M&P score mean was 50.3, slightly higher than ours [7]. These results might highlight patients not being conscious about their pathology, which may be due to the early stage of the disease and the lack of aware of the concept of progressive disease.

Ho et al. found that convergent and discriminant validity was demonstrated by correlations between specific HDQoL domains and corresponding clinical assessments and supports the contribution of PROs to improve clinical management by promoting a more patient-centred approach in HD [21].

The SWLS scale allows access to the positive side of the individual experience by responding to a self-assessment [11]. Data by intervals showed 33.9% of patients were satisfied (25–29 interval) and 28.7% of subjects with an average score (20–24 interval) compared to our 26.7% and 25.7%, respectively. Results of our study show that satisfaction in our population is similar to satisfaction in the general population [30]. One reason could be lack of awareness or perception of the disease due to the early stage in our study group.

The adaptative function in our population, assessed through the HD-ADL completed by caregivers, showed that HD has a lower impact in performing patients' daily activities, confirming the ability of patients to perform specific activities, to cover the domains of personal care, household care and social relationships. It should be note that, although our population was young and in an early stage, nearly 25% stated the necessity of a caregiver and the need of help. This highlights the relevant role and the involvement of caregivers as contributors in partnerships with healthcare professionals. Facilitating the mutual sharing of knowledge may improve the coordination of care [31, 32].

In our study, there was a high reported level of stigma. Stigmatisation is often attributed to ignorance, and knowledge in the context of values can help overcome prejudice [33]. This is in line with the literature that shows that HD has been one of the most stigmatised disorders [34]. This study highlights the need for further medical education in rare diseases, such as Huntington disease, to minimise the impact of the disease to the patient itself. Self-stigma is common in those patients, which may lead to social isolation and delayed search for medical help. The stigma and discrimination faced by people who, through no fault of their own, are at risk of HD intensify the anguish that these individuals face and make it much more difficult to address their real needs [25]. These findings indicate that physical, emotional and cognitive health are associated with perceived stigma. Other studies have found that chorea contributes to social isolation, and stigma was observed among respondents with higher chorea scores. Other important sources of psychological burdens described include loss of independence, fear of their symptoms worsening, fear of falling and anxiety [35].

Physical therapy, emotional support and cognitive rehabilitation should be included as therapy to ease the burden of perceived stigma; nonetheless, more research is needed in this area [36].

Depression, apathy and irritability, as neuropsychiatric symptoms, may already be present

many years before motor symptoms appear and begin before the onset of motor symptoms [37]. In our study, apathy symptoms were measured by the Behavioural Assessment of the UHDRS and PBA-S, while depressive symptoms by the BDI. We found that depressed mood, anxiety, irritability, apathy and perseveration were the more frequent symptoms reported, which is similar to what has been found in other studies in Spain in patients with manifest HD [38].

There is an important association between carrying the huntingtin gene mutation and prevalence of anxiety symptoms, hopelessness and depression: wigh these two last being more prevalent in individuals with the gene mutation than in individuals who were tested but with no specific mutation. These results underline the importance of timely diagnosis and treatment of psychiatric comorbidities in individuals affected by Huntington's disease [39]. Since one of the main goals of treating patients with HD is to prevent the worsening of their own and their family's quality of life, treatment of comorbid depression should be crucial [40].

This study has some limitations. First, the cross-sectional design restricts the ability to establish causal relationships between outcome measures, emphasising the need for future longitudinal studies. Second, the study included patients with an IS score equal to or greater than 70, indicating that they might be individuals with a moderate level of functional impairment, requiring support in household management and financial matters. Future studies should utilise the new Huntington's Disease Integrated Staging System, which employs an integrated approach combining various objective measures such as the TMS, SDMT, Total Functional Capacity, and IS to secure earlier detection [41]. Third, the study population consisted of patients attending specialised HD clinics and may not represent the broader HD population. Fourth, patients reported a highly educated status and may have more interest and easier access to health assistance. Finally, there may be cultural or regional differences regarding other populations as Spanish centres and healthcare professionals are involved in HD research.

In conclusion, PROs offer valuable information on the status of patients with HD. By integrating these instruments into clinical practice, clinicians can gain complementary insights into patient perspectives and enable tailored approaches to HD care [42]. Furthermore, future studies should investigate the relationship between the presence of neuropsychiatric symptoms and other markers of disease progression, including neuroanatomical changes.

ACKNOWLEDGEMENTS

The authors would like to thank Huntington's disease patients and their caregivers whose support and collaboration made the Perspectives-HD study possible. Pilar Sánchez for the literature review provided. Laura Muñoz-Delgado, Astrid D. Adarmes-Gómez, Santiago Fernández Menéndez, Patricia Prendes Fernández, Francisco Casterá Brugada and all co-investigators for their work in the study.

Medical Writing/Editorial Assistance. Anna de Prado and Sofía García-López wrote the manuscript and authors reviewed it.

Author Contributions. Jose Luis López-Sendón and Jesús Pérez Pérez are both the study coordinators. Jose Luis López Sendón, Jesus Pérez Pérez and Jorge Maurino conceptualised the study. Jose Luis López Sendón, Jesús Pérez Pérez, Anna de Prado and Sofía García-López wrote the first draft of the manuscript. Jesús Pérez Pérez, Sofía García López, Tamara Fernández Valle, Cèlia Painous, María Rosa Querol Pascual, Pedro García-Ruiz Espiga, Elena Bellosta Diago, Esther Cubo Delgado, Bárbara Vives Pastor, María Carmen Peiró Vilaplana, Idaira Martín Santana, Marta Blázquez Estrada, Matilde Calopa Garride, Pablo Mir, Carmen Álvarez, Jorge Mauriño, Anna de Prado and José Luis López-Sendón made significant contributions to the study results, critically revised and approved the manuscript.

Funding. This study and the journal's Rapid Service fee is funded by Roche.

Data Availability. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Conflict of Interest. Sofía García-López, Carmen Álvarez and Jorge Maurino are Roche employees. Jesús Pérez Pérez, Tamara Fernández Valle, Cèlia Painous, María Rosa Querol Pascual, Pedro García-Ruiz Espiga, Elena Bellosta Diago, Esther Cubo Delgado, Bárbara Vives Pastor, María Carmen Peiró Vilaplana, Idaira Martín Santana, Marta Blázquez Estrada, Matilde Calopa Garride, Pablo Mir, Anna de Prado and José Luis López-Sendón declare no conflict of interest. JLS has served as a consultant or as an advisory committee member, unrelated to this research, from: La Roche ltd, Novartis ltd and UCB.

Ethical Approval. The study was approved by the independent ethics committee CEIM of Hospital La Fe in Valencia. Code: ROC-HUN-2020-01 for Clinical Research and all patients provided written informed consent according to the Declaration of Helsinki.

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