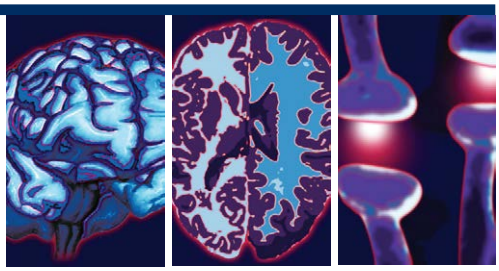

Clinical Factors Associated with the Quality Of Life in Patients with Parkinson's disease

Yun-Ru Lai[1], Yu-Jih Su[2,*], Kuei-Yueh Cheng[3], Chih-Cheng Huang[1], Nai-Wen Tsai[1], Che-Wei Hsu[1], Ya-Ting Chang[1], Hung-Chen Wang[4], Wei-Che Lin[5], Ben-Chung Cheng[2,6], Chia-Te Kung[7], Chih-Min Su[7], Sheng-Yuan Hsiao[6,7], Yi-Fang Chiang[1], Cheng-Hsien Lu[1,6,8,†,*]

Abstract

Purpose: The purpose of this study was to assess the clinical factors which define the quality of life (QOL) in patients with Parkinson's disease (PD), and to investigate the relationships between the main contributory factors of the health profile and the overall QOL.

Methods: This prospective study assessed the QOL using the World Health Organization Quality of Life scale brief version (WHOQOL-BREF) Questionnaire. All patients were tested using the Unified Parkinson's Disease Rating Scale (UPDRS) score, Hoehn and Yahr (HY) stage, Mini-Mental State Examination (MMSE), Schwab and England Activities of Daily Living scale (ADL), Geriatric Depression Scale (GDS), Fatigue Severity Scale (FSS) and the levodopa equivalent dose (LED). Stepwise model of multiple linear regression analysis was used to assess the impact of independent variables on the mean WHOQOL-BREF score.

Results: The mean WHOQOL-BREF score was 11.52 ± 3.94. Total and each domain (physical, psychological, social relationships, and environment domains) WHOQOL-BREF scores were positively correlated with education years, MMSE, and ADL. However, they were negatively correlated with LED; HY stage; UPDRS I, II, and III scores; GDS score; and FSS score (all $p<0.0001$). Multiple linear regression analysis showed that only UPDRS I and II, GDS, and FSS scores were independently associated with the mean WHOQOL-BREF score.

Conclusion: Based on our results, the impairment of non-motor features including activities of daily living and mentation, behavior, and mood and fatigue (UPDRS I and II, FSS, and GDS) affect the QOL in patients with PD. It is crucial to detect non-motor symptoms in the early phases and prompt treatment, which might help to improve the quality of life.

Keywords

Quality of life; Parkinson's disease; WHOQOL-BREF

[1]Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

[2]Department of Internal Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

[3]Department of Nursing, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

[4]Department of Neurosurgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

[5]Department of Radiology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan.

[6]Department of Biological Science, National Sun Yat-Sen University, Kaohsiung, Taiwan

[7]Emergency Medicine, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, Kaohsiung, Taiwan

[8]Department of Neurology, Xiamen Chang Gung Memorial Hospital, Xiamen, Fujian, China

*Contributed equally to corresponding author

†Author for correspondence: Cheng-Hsien Lu, Department of Neurology, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University College of Medicine, No. 123, Ta Pei Road, Niao Sung Hsiang, Kaohsiung City 833, Taiwan, Tel: +886-7-7317123 ext 2283; email: chlu99@ms44.url.com.tw, chlu99@adm.cgmh.org.tw

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease, and both motor and non-motor dysfunctions significantly affect the patient's quality of life (QOL) [1-4]. The QOL means patient-reported outcomes not only included health-related quality of life (HRQOL) but also health status and subjective well-being (SWB) [5]. Therefore, it is important to adequately recognize and assess QOL in patients with PD.

There are different generic and specific instruments to investigate various aspect of QOL in patients with PD [6-11]. Among generic instruments, the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36) is one of the better known instruments, but it only measures the HRQOL (physical and mental function) [12]. Among specific instruments, the Parkinson's disease Questionnaire (PDQ-39) and Short Form (PDQ-8) are the commonly tested and used QOL questionnaires for PD, although they do not adequately cover nocturnal sleep, sexuality, and fatigue [13]. To have a fair determination of QOL including not only the HRQOL (physical and psychological health) but also the social and environmental status, the World Health Organization Quality of Life Assessment Short Version (WHOQOL-BREF) questionnaire was designed to measure the overall QOL including personal health, access to health care, social network, and safety of the personal environment [14,15]. The WHOQOL-BREF questionnaire is less mentioned in the research articles about PD, despite being a relatively brief (28-item), cross-culture comparison, available in many language versions including the Taiwan version, and measuring a broad range of perception with life. The WHO defined QOL as an individual's perception of their position in life in the context of the culture and value systems in which they live, and in relation to their goals, expectations, standard, and concerns [15]. Routine use of the WHOQOL-BREF questionnaire may be more appropriate in measuring the overall QOL in patients with PD, in daily practice.

This hospital-based study aimed to use the cross-culturally valid instrument, the WHOQOL-BREF Taiwan version questionnaire, to analyze the correlation among clinical factors and the overall QOL in patients with PD. This could aid in focused screening and clinical practice for the improvement of the QOL.

Materials and Methods

■ Study design and participants

This single-center hospital-based prospective study enrolled 119 patients with PD, recruited consecutively from Chang Gung Memorial Hospital-Kaohsiung, a tertiary medical center and the main referral hospital serving a population of 3 million in southern Taiwan.

Patients received a definitive diagnosis of idiopathic PD according to the United Kingdom Parkinson's Disease Society Brain Bank clinical diagnostic criteria [16] and were followed-up at the Neurology Outpatient Clinic for more than 6 months after titration of their daily doses of anti-Parkinsonian medications to a steady dose in accordance with their clinical symptoms [17]; their ability to correctly express their quality of life was assessed based on the Clinical Dementia Rating (CDR) [18].

Exclusion criteria included the following: (1) newly diagnosed PD or follow-up for less than 6 months as the daily dose of anti-Parkinsonian medications were still under titration; (2) presence of focal neurological signs not related to the diagnostic criteria of PD; (3) impaired consciousness or profound cognitive impairment (CDR score more than or equal to 2). All participants received verbal and written information about the purpose and process of our research which was approved by the hospital's institutional Review Committees on Human Research.

■ Clinical data collection

The clinical features included the following: age at disease onset (or age at the time of the first reported symptom attributable to the disease), sex, body height, body weight, body mass index, duration of the disease (time from onset until follow-up), education years, and anti-Parkinsonian medication (levodopa equivalent dose, LED)[19]. An experienced neurology nurse specialist (K.-Y. C) who was blinded to the patients' clinical and biochemical data was trained to measure these functional scores at the time of enrollment.

All participants underwent brain MRI (Magnetic Resonance Imaging) and 99mTc-TRODAT-1 SPECT imaging for confirmation of the diagnosis [20]. The severity of PD was assessed using the Unified Parkinson's Disease Rating Scale (UPDRS) [21], and Hoehn and Yahr stage [22]. The UPDRS total score was computed as

the sum of UPDRS subscales I, II, and III. All participants were evaluated in the morning when they were in the off phase of the medication cycle. Anti-parkinsonism medications were ceased on the day of the study and resumed after the test. The disability was measured using the Schwab and England (S&E) disability score [23]. The Schwab and England Activities of Daily Living (SEADL) scale is a quantitative tool for evaluating the disability of patients with Parkinson's disease, ranging from 100% (completely independent, essentially normal) to 0% (bedridden, vegetative function, completely invalid). A higher score means a better functional status and scores below 80% indicate dependency. The depressive symptoms were measured with a 30-item Geriatric Depression Scale (GDS30)[24]. The Geriatric Depression Scale (GDS) consists of 30 questions, each with 2 possible answers scored either 0 or 1, with a maximum score of 30. The severity of depression was classified as follows: no depression (GDS<10) and depression (GDS≥10). Fatigue was measured using the Fatigue Severity Scale (FSS)[25]. The Fatigue Severity Scale (FSS) consists of 9 statements for evaluating the impact of fatigue. The total score was calculated by combining the mean score of each item. A threshold of FSS mean score ≥ 5 was defined as severe fatigue

■ Neuropsychiatric assessment

The Mini-Mental State Examination (MMSE) was used to assess general intellectual function [26]; the ability to perform digit forward span was also assessed. Clinical Dementia Rating (CDR) scale was used to assess cognitive function, which was indicative of the functional capacity of participants without physical disability [27]. All of the subjects were assigned a CDR rating score as follows: 0 for no dementia and 0.5, 1, 2, and 3 for questionable, mild, moderate, and severe dementia, respectively.

■ QOL assessment

Participants completed the WHOQOL-BREF questionnaire (Taiwan Version) with answers on a scale of 1 to 5. This is widely used in many countries to assess the QOL of both healthy people and those with disease, and its reliability and validity have been demonstrated [14]. The 28-item questionnaire measures 4 domains: physical health, psychological well-being, social relationships, and environment; and 2 separate items that assess overall QOL and general health satisfaction. The Taiwan version included 2 new national items: being respected/accepted and eating/food [14]. Because the number of items are different for each domain, the mean total score and that of each domain were then multiplied by 4 to allow the total and each domain score to have the same range, from 4 to 20. Higher scores indicate a perceived higher QOL [14].

■ Outcomes assessments and data analysis

The Cronbach reliability coefficient for all questions on the WHOQOL-BREF questionnaire was 0.96. The coefficients for each of its domains were 0.91 for physical health (domain 1), 0.94 for psychological well-being (domain 2), 0.85 social relationships (domain 3), and 0.79 environment (domain 4). These confirm good internal consistency of the instrument.

Spearman's rank correlation coefficient was calculated to assess the correlation between the clinical factors and WHOQOL-BREF scores. P-values of less than 0.05 were accepted as significant. Stepwise model of multiple linear regression analysis was used to assess the impact of independent variables on the mean WHOQOL-BREF score. All statistical analyses were conducted using the SAS software package, version 9.1 (2002, SAS Statistical Institute, Cary, North Carolina).

Results

■ Study patients and their demographic data

The 119 patients with idiopathic PD included 56 males (age range, 32-81 years; mean ± SD, 66.48 ± 1.64 years) and 63 females (age range, 41-82 years; mean ± SD, 66.21 ± 1.25 years) **(Table 1)**. Most (89.1%) of the patients were married, the remaining patients being either single (6.7%), widowed (1.7%) or divorced (1.7%). Mean disease duration was 4.20 ± 3.99 years at the time of enrollment. The mean levodopa equivalent dose was 532.42±519.56 mg/day. The mean education years were 6.81 ± 5.02 and the mean baseline mini-mental status exam score was 23.23 ± 5.78 **(Table 1)**.

The mean total UPDRS score, UPDRS-I (mentation, behavior, and mood) score, UPDRS-II (activities of daily living) score, and UPDRS-III (motor examination) score were 48.17 ± 28.89 (range 5-119). 4.57 ± 3.24 (range 0-14), 13.87± 9.80 (range 1-46), and 31.40 ±

Table 1: Basic characteristics of the patients.

	n=119
Age (years)	66.34 ± 11.04
Sex (male/female)	56/63
Body Height (m^2)	158.98 ± 8.01
Body Weight (kg)	61.13 ± 9.62
Body mass Index (kg/m^2)	24.16 ± 3.43
Disease duration (years)	4.20 ± 3.99
Education (years)	6.81 ± 5.02
Striatal dopamine transporter uptake ratios	1.44 ± 0.20
The levodopa equivalent dose (mg/day)	532.42 ± 519.56
Unified Parkinson's Disease Rating Scale	
Total UPDRS[α]	48.17 ± 28.89
UPDRS I[β]	4.57 ± 3.24
UPDRS II[γ]	13.87 ± 9.80
UPDRS III[δ]	31.40 ± 17.35
Hoehn and Yahr stage (n (%))	
Stage I	37(31%)
Stage II	33(28%)
Stage III	26(21%)
Stage IV	9(8%)
Stage V	14(12%)
Geriatric Depression Scale	13.95 ± 6.08
Mini-mental state examination score	23.23 ± 5.78
Schwab and England Activities of Daily Living scale	74.96 ± 23.47
Fatigue Severity Scale	5.86 ± 3.12
The World Health Organization Quality of Life scale brief Version (Taiwan Version)	
Score of overall quality of life (range from 1 to 4)	2.67 ± 1.17
Score of overall health (range from 1 to 4)	2.51 ± 1.01
Score of physical health domain (range from 4 to 20)	10.54 ± 4.04
Score of psychological domain (range from 4 to 20)	10.11 ± 4.37
Score of social relationships domain (range from 4 to 20)	11.94 ± 4.06
Score of environmental domain (range from 4 to 20)	13.40 ± 3.78
Total WHOQOL score (range from 4 to 20)	11.52 ± 3.94

UPDRS: Unified Parkinson's Disease Rating Scale

α="Total UPDRS" score is the combined sum of parts I, II, and III. Theoretical minimum and maximum values are 0 and 176, respectively (176 represents the worst disability and 0 no disability)

β= I. Mentation, behavior, and mood. Theoretical minimum and maximum values are 0 and 16, respectively. (16 represents the worst disability and 0 no disability)

γ= II. Activities of daily living (ADL). Theoretical minimum and maximum values are 0 and 52, respectively. (52 represents the worst disability and 0 no disability)

δ= III. Motor examination. Theoretical minimum and maximum values are 0 and 108, respectively. (108 represents the worst disability and 0 no disability)

17.35 (range 5-81), respectively. The Hoehn and Yahr staging of the 119 patients with PD were as follows: 37 were stage I, 33 stage II, 26 stage III, 9 stage IV, and 14 Stage V. The mean SEADL, GDS, and FFS scores are listed in **Table 1**. The mean total WHOQOL-BREF score, overall QOL score, mean overall health score, physical health (domain 1) score, psychological well-being (domain 2) score, social relationships (domain 3) score, and environment (domain 4) score were 11.52 ± 3.94, 2.67 ± 1.17, 2.51 ± 1.01, 10.54 ± 4.04, 10.11 ± 4.37, 11.94 ± 4.06 and 13.40 ± 3.78, respectively **(Table 1)**.

■ Effects of risk factors on the total score and that of each domain of WHOQOL-BREF

A correlation analysis was used to test the influence of age, disease duration, education years, LED, the striatal 99mTc-TRODAT-1 uptake, HY stage, UPDRS I (Mentation, behavior, and mood) score, UPDRS II (Activities of daily living) score, UPDRS III (Motor examination) score, MMSE, SEADL score, GDS score, and FSS score on the total WHOQOL-BREF score and that of each domain (physical, psychological, social relationships, and environment) **(Table 2)**. Based on the statistical analyses (correlation coefficient, p value), the total WHOQOL-BREF score and that of each domain (physical, psychological, social relationships, and environment) were positively correlated with education years, MMSE, and ADL. However, they were negatively correlated with LED; HY stage; UPDRS I, II, and III scores; GDS score; and FSS score (all $p<0.0001$) **(Table 2)**.

■ Clinical factors associated with mean total WHOQOL-BREF score

Variables that were significantly correlated with the total WHOQOL-BREF score were selected in stepwise model of multiple linear regression analysis, and showed that the GDS score ($P<0.0001$), UPDRS-I score ($P=0.019$), UPDRS-II score ($P<0.0001$), and FFS score ($p=0.024$) were independently associated with the total WHOQOL-BERF score. Stepwise model of multiple linear regression formula was calculated as follows: WHOQOL-BREF total score =17.597-0.185× (GDS)-0.093× (UPDRS II)-0.125× (UPDRS I)-0.148× (FSS) **(Table 3)**.

Discussion

This prospective study evaluated the overall QOL in patients with PD using the WHOQOL-

Table 2: Coefficients analysis of the total score and score of each domain of the WHOQOL-BREF questionnaire in patients with Parkinson's disease.

Variables	Total Score		Physical		Psychological		Social		Environment	
	r	P value	r	P value	r	P value	r	P value	r	P value
Age	-0.20*	0.034	-0.15	0.097	-0.14	0.143	-0.27**	0.003	-0.27**	0.004
Disease Duration	-0.46**	<0.0001	-0.47**	<0.0001	-0.39**	<0.0001	-0.48**	<0.0001	-0.42**	<0.0001
Education years	0.34**	<0.0001	0.33**	<0.0001	0.29**	0.001	0.33**	<0.0001	0.44**	<0.0001
LED	-0.42**	<0.0001	-0.42**	<0.0001	-0.38**	<0.0001	-0.37**	<0.0001	-0.35*	<0.0001
Trodat uptake	0.28*	0.027	0.22	0.077	0.25*	0.043	0.27*	0.031	0.25*	0.042
HY stage	-0.74**	<0.0001	-0.70**	<0.0001	-0.69**	<0.0001	-0.70**	<0.0001	-0.67**	<0.0001
UPDRS I	-0.73**	<0.0001	-0.68**	<0.0001	-0.70**	<0.0001	-0.66**	<0.0001	-0.70**	<0.0001
UPDRS II	-0.73**	<0.0001	-0.72**	<0.0001	-0.63**	<0.0001	-0.70**	<0.0001	-0.66**	<0.0001
UPDRS III	-0.70**	<0.0001	-0.67**	<0.0001	-0.63**	<0.0001	-0.68**	<0.0001	-0.64**	<0.0001
MMSE	0.53**	<0.0001	0.53**	<0.0001	0.54**	<0.0001	0.58**	<0.0001	0.66**	<0.0001
S&E ADL	0.73**	<0.0001	0.70**	<0.0001	0.66**	<0.0001	0.71**	<0.0001	0.67**	<0.0001
GDS	-0.84**	<0.0001	-0.78**	<0.0001	-0.88**	<0.0001	-0.74**	<0.0001	-0.73**	<0.0001
FSS	-0.51**	<0.0.001	-0.49**	<0.0.001	-0.44**	<0.0.001	-0.47**	<0.0001	-0.46**	<0.0001
Overall QoL	0.90**	<0.0001	0.81**	<0.0001	0.87**	<0.0001	0.79**	<0.0001	0.80**	<0.0001
Overall Health	0.87**	<0.0001	0.81**	<0.0001	0.86**	<0.0001	0.77**	<0.0001	0.73**	<0.0001

r: correlation coefficient. * indicates that p value <0.05. ** indicates that p value <0.0001.
Abbreviations: LED, the levodopa equivalent dose; Trodat uptake, The striatal 99mTc-TRODAT-1 uptake; HY stage, Hoehn and Yahr stage; UPDRS I, Mentation, behavior, and mood; UPDRS II. Activities of daily living (ADL); UPDRS III, Motor examination; MMSE Mini-Mental Status Examination; S&E ADL, Schwab and England Activities of Daily Living; GDS, Geriatric Depression Scale; FSS, Fatigue Severity Scale.

Table 3: Effects of the variables on the total score of the WHOQOL-BREF questionnaire in patients with Parkinson's disease according to correlation analysis.

	F (P value)	Adjusted R^2	Regression coefficient	Standard error	P value
WHOQOL-BREF (Total score)	**152.83 (P<0.0001)**	**0.85**			
Constant			17.597	0.281	<0.0001
GDS			-0.185	0.028	<0.0001
UPDRS II			-0.093	0.019	<0.0001
UPDRS I			-0.125	0.052	0.019
FSS			-0.148	0.065	0.024

Regression coefficient for each individual variable.

R^2 is the proportion of the WHOQOL-BREF variation explained by the model taking into account the listed factors cumulatively.
Abbreviations: WHOQOL-BREF, The World Health Organization Quality of Life scale brief Version; UPDRS II. Activities of daily living (ADL); UPDRS I, Mentation, behavior, and mood; FSS, Fatigue Severity Scale; GDS, Geriatric Depression Scale. This model is controlled for age, sex, education years, disease duration, LED, MMSE and UPDRS III but only significant variables are shown for clear visualization.

BREF questionnaire and demonstrated two major findings. First, total and each domain (physical, psychological, social relationships and environment) WHOQOL-BREF scores were positively correlated with education years, MMSE and ADL. However, they were negatively correlated with LED; HY stage; UPDRS I, II, and III scores; GDS score; and FSS score (all p<0.0001). One study evaluated QOL in patients with PD using WHOQOL-BREF questionnaire, and found a negative correlation between the psychological domain score and disease duration (p = 0.01), as well as the social domain score and disease severity (p = 0.001) [28]. Another study evaluated QOL in patients with PD using the 100-item version of WHOQOL (WHOQOL-100) and found the level of all facets of independence domain, energy and fatigue of physical domain, and three facets of the environment domain were negatively associated with QOL [29]. Second, a stepwise model of multiple linear regression analysis showed that only UPDRS I and II, GDS, and FSS scores were independently associated with the mean WHOQOL-BREF score. Our study demonstrated that non-motor features (UPDRS I and II , GDS, and FSS) have a greater effect on the QOL in patients with PD than do motor features (UPDRS III), and these findings are consistent with those of our previous studies [2,30].

One study demonstrated that depression is a major contributor to the QOL in patients with

PD [31], and this conclusion was consistent with that of our previous study and other studies using different QOL instruments (EQ-5D and Medical Outcome Study 36-item short-form Health Survey)[1,2,32,33]. Our recent study also demonstrated that higher mean UPDRS scores (>38.5) are associated with a higher risk of depression which is often unrecognized and untreated. The prevention and evaluation of depressive disorders in the high-risk group are important safety issues and are highly relevant to patients' QOL [34].

Fatigue, the major non-motor symptom, is one of most debilitating symptoms of PD, and is also associated with other non-motor symptoms (e.g. depression, dementia, and sleep disorders) [35-38]. Our study demonstrated that the presence of fatigue could affect the QOL in patients with PD. Furthermore, our recent study also showed that a higher mean UPDRS score (>41.5), which may imply an increase in the severity of PD, was associated with a higher risk of fatigue [39].

However, the present study has several limitations. First, as a prospective observational study, it may be subject to the bias of unmeasured factors. Second, these results may not adequately reflect the general populations of PD because we excluded the patients who had severe dementia (CDR equal or more than two) and co-morbidity with other neurological disorders. Second, PD is a slowly progressive neurodegenerative disorder and we did not assess both the effects of dopaminergic therapy and antidepressants, and endurance exercise training. If the changes in function scores, clinical features, and imaging studies followed a standard pattern and temporal relationship, our ability to assess the impact of QOL scale in patients with PD would improve.

Conclusion

Based on our results, routine use of the WHOQOL-BREF questionnaire may be more appropriate into measuring the overall QOL in patients with PD, in daily practice in PD. The impairment of non-motor features including activities of daily living and mentation, behavior, and mood and fatigue (URDRS I and II, FSS and GDS) affect the QOL in patients with PD. It is crucial to detect non-motor symptoms in the early phases and prompt treatment, which might help to improve the quality of life.

Acknowledgements:

The authors thank all the subjects who participated in this study.

Competing interests

The authors declare that they have no competing interests.

Ethics approval

The study was approved by Chang Gung Memorial Hospital's Institutional Review Committee on Human Research.

References

1. Rahman S, Griffin HJ, Quinn NP, *et al.* Quality of life in Parkinson's disease: the relative importance of the symptoms. *Move. Diso* 23(10), 1428-1434 (2008).
2. Schrag A, Jahanshahi M, Quinn N. What contributes to quality of life in patients with Parkinson9s disease? *J. Neurol. Neurosurg. Psychiatry* 69(3), 308-312 (2000).
3. Marinus J, Ramaker C, van Hilten JJ, et al. Health related quality of life in Parkinson's disease: a systematic review of disease specific instruments. *J. Neurol. Neurosurg Psychiatry* 72(2), 241-248 (2002).
4. Soh S-E, Morris ME, McGinley JL. Determinants of health-related quality of life in Parkinson's disease: a systematic review. *Parkinsonism. Relat. Disord* 17(1), 1-9 (2011).
5. Patrick DL, Chiang Y-p. Measurement of health outcomes in treatment effectiveness evaluations: conceptual and methodological challenges. *Medical. Care* 38(9), II-14-II-25 (2000).
6. Nutt J, Siderowf A, Guttman M, et al. Mobility, mood and site of care impact health related quality of life in Parkinson's disease. *Parkinsonism. Relat. Disord* 20(3), 274-279 (2014).
7. Chrischilles EA, Rubenstein LM, Voelker MD, et al. Linking clinical variables to health-related quality of life in Parkinson's disease. *Parkinsonism. Relat. Disord* 8(3), 199-209 (2002).
8. Müller B, Assmus J, Herlofson K, et al. Importance of motor vs. non-motor symptoms for health-related quality of life in early Parkinson's disease. *Parkinsonism. Relat. Disord*, 19(11), 1027-1032 (2013).
9. Klepac N, Hajnšek S, Trkulja V. Impact of pre-morbid depression on health-related quality of life in non-demented Parkinson's disease patients. *Parkinsonism. Relat. Disord* 16(1), 21-27 (2010).
10. Hackney ME, Earhart GM. Health-related quality of life and alternative forms of exercise in Parkinson disease. *Parkinsonism. Relat. Disord* 15(9), 644-648 (2009).
11. Qin Z, Zhang L, Sun F, et al. Health related quality of life in early Parkinson's disease: impact of motor and non-motor symptoms, results from Chinese levodopa exposed cohort. *Parkinsonism. Relat. Disord*, 15(10), 767-771 (2009).
12. Huang I-C, Wu AW, Frangakis C. Do the SF-36 and WHOQOL-BREF measure the same constructs? Evidence from the Taiwan population. *Quality. Of. Life. Research* 15(1), 15-24 (2006).
13. Martinez-Martin P, Jeukens-Visser M, Lyons KE, et al. Health-related quality-of-life scales in Parkinson's disease: critique and recommendations. *Movement. Disorders*, 26(13), 2371-2380 (2011).

14. Yao G, Chung CW, Yu C-F, et al. Development and verification of validity and reliability of the WHOQOL-BREF Taiwan version. *J. Formos. Med. Assoc*, 101(5), 342-351 (2002).
15. Group W. The World Health Organization quality of life assessment (WHOQOL): position paper from the World Health Organization. *Social. Science. & Medicine*, 41(10), 1403-1409 (1995).
16. Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. *J. Neurol. Neurosur. & Psychiatry* 55(3), 181-184 (1992).
17. O'connell B, Myers H. The sensitivity and specificity of the Morse Fall Scale in an acute care setting. *J. Clin. Nurs* 11(1), 134-136 (2002).
18. Morris JC. The Clinical Dementia Rating (CDR): current version and scoring rules. *Neurology* (1993).
19. Tomlinson CL, Stowe R, Patel S, et al. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Movement. Disorders*, 25(15), 2649-2653 (2010).
20. Weng Y-H, Yen T-C, Chen M-C, et al. Sensitivity and specificity of 99mTc-TRODAT-1 SPECT imaging in differentiating patients with idiopathic Parkinson's disease from healthy subjects. *J. Nucl. Med* 45(3), 393-401 (2004).
21. Martínez-Martín P, Gil-Nagel A, Gracia LM, et al. Unified Parkinson's disease rating scale characteristics and structure. *Movement. Disorders* 9(1), 76-83 (1994).
22. Hoehn MM, Yahr MD. Parkinsonism onset, progression, and mortality. *Neurology*, 17(5), 427-427 (1967).
23. Schwab RS. Projection technique for evaluating surgery in Parkinson's disease. E&S Livingstone 152-157 (1969).
24. Schrag A, Barone P, Brown RG, et al. Depression rating scales in Parkinson's disease: critique and recommendations. *Movement. Disorders* 22(8), 1077-1092 (2007).
25. Fereshtehnejad S-M, Hadizadeh H, Farhadi F, et al. Reliability and validity of the persian version of the fatigue severity scale in idiopathic Parkinson's disease patients. *Parkinson's. Disease* (2013).
26. Dick J, Guiloff R, Stewart A, et al. Mini-mental state examination in neurological patients. *J. Neurol. Neurosurg. Psychiatry*, 47(5), 496-499 (1984).
27. Chang CC, Lee YC, Chang WN, et al. Damage of white matter tract correlated with neuropsychological deficits in carbon monoxide intoxication after hyperbaric oxygen therapy. *J. Neurotrauma* 26(8), 1263-1270 (2009).
28. Schestatsky P, Zanatto VC, Margis R, et al. Quality of life in a Brazilian sample of patients with Parkinson's disease and their caregivers. *Revista. Brasileira. de .Psiquiatria* 28(3), 209-211 (2006).
29. Valeikiene V, Ceremnych J, Alekna V, et al. Differences in WHOQOL-100 domain scores in Parkinson's disease and osteoarthritis. *Medical. Science. Monitor*, 14(4):CR221-CR227 (2008).
30. Skorvanek M, Rosenberger J, Minar M, et al. Relationship between the non-motor items of the MDS–UPDRS and Quality of Life in patients with Parkinson's disease. *J. Neurol Sci* 353(1), 87-91 (2015).
31. Sławek J, Derejko M, Lass P. Factors affecting the quality of life of patients with idiopathic Parkinson's disease-a cross-sectional study in an outpatient clinic attendees. *Parkinsonism. Relat. Disord* 11(7), 465-468 (2005).
32. Carod-Artal FJ, Vargas AP, Martinez-Martin P: Determinants of quality of life in Brazilian patients with Parkinson's disease. *Movement. Disorders* 22(10), 1408-1415 (2007).
33. Kuopio AM, Marttila RJ, Helenius H, Toivonen M, Rinne UK: The quality of life in Parkinson's disease. *Movement. Disorders* 15(2), 216-223 (2000).
34. Shao H-C, Chen C-T, Chang H-W, *et al*. Clinical Factors Associated with the Risks of Depression in Patients with Parkinson's Disease. *Neuropsychiatry (London)* 7(1), 416-423 (2017).
35. Schifitto G, Friedman J, Oakes D, et al. Fatigue in levodopa-naive subjects with Parkinson disease. *Neurology* 71(7), 481-485 (2008).
36. Miwa H, Miwa T: Fatigue in patients with Parkinson's disease: impact on quality of life. *Internal. Medicine* 50(15), 1553-1558 (2011).
37. Karlsen K, Larsen JP, Tandberg E. Fatigue in patients with Parkinson's disease. *Movement. Disorders* 14(2), 237-241 (1999).
38. Havlikova E, Rosenberger J, Nagyova I, et al. Impact of fatigue on quality of life in patients with Parkinson's disease. *Eur. J. Neurol* 15(5), 475-480 (2008).
39. Chen C-T, Kuei-Yueh C, Wen-Neng C, *et al*. Clinical Factors Associated with Fatigue in Parkinson's Disease. *Neuropsychiatry (London)* 7(1), 640-652 (2017).