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RESEARCH ARTICLE

Determinants of quality of life in Parkinson's disease: a perspective of novel clinical subtypes

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Abstract

Objective: New subtyping classification systems of Parkinson's disease (PD) have been proposed for phenotyping patients into three different subtypes: mild motor-predominant (PD-MMP), intermediate (PD-IM) and diffuse malignant (PD-DM). The quality of life (QoL) underlying the novel PD clinical subtypes is unknown. This study aimed explore the feasibility of the classification in Chinese PD patients and to investigate the potential heterogeneous determinants of QoL among the three subtypes. **Methods**: 298 PD patients were enrolled, including 129 PD-MMP patients, 121 PD-IM patients and 48 PD-DM patients. All patients completed the QoL assessment, clinical evaluations and neuropsychological tests. Univariate linear analysis and multiple stepwise regression analysis were performed to identify determinants of QoL. **Results**: Compared to PD-MMP patients, PD-IM and PD-DM patients had more impaired QoL. The Geriatric Depression Rating Scale (GDS) score, Non-Motor Symptoms Questionnaire (NMSQ) score, Unified Parkinson's Disease Rating Scale part III (UPDRS-III) score and Epworth Sleepiness Score (ESS) were independent contributors to QoL in PD-MMP patients. The GDS score, ESS and sniffin' sticks screening 12 test score were independent contributors to QoL in PD-IM patients. The GDS score and Mini Mental State Examination score were independent contributors to QoL in PD-DM patients. **Interpretation**: The new novel subtyping classification is feasible for Chinese PD patients. Although depression was the most crucial determinant for QoL in PD-MMP, PD-IM and PD-DM patients, the other contributors of QoL in the three subtypes were heterogeneous. These findings may prompt clinicians to target specific factors for improving QoL depending on PD subtypes.

Introduction

Parkinson's disease (PD) is a common and intricate neurodegenerative disorder characterized by a wide range of motor and non-motor symptoms (NMS). Increasing evidence has demonstrated that PD is heterogeneous in its clinical manifestations, pathology and rate of progression, which suggests that it may be divisible into subtypes[1] instead of being a pure entity. In recent decades, subtype classification of PD has been a clinical research priority.[2] Among all kinds of subtype classifications, one of the earliest and classic classifications assigned PD patients into tremor-dominant (TD) and postural instability and gait difficulty dominant (PIGD) subtypes based on the ratio of their mean tremor score and mean PIGD score, assessed by Unified Parkinson's Disease Rating Scale (UPDRS).[3] However, the TD-PD and PIGD-PD subtypes only considered the motor symptoms of PD patients, with

NMS being ignored. More recently, a new clinical PD classification has been proposed by data-driven clustering techniques, which allow patients to be assigned to a specific subtype considering both motor and non-motor symptoms, without any a priori hypothesis.[4] Nonetheless, the validated methods used to evaluate NMS in this study were large practical obstacles to completing the same subtype classification in another cohort. Fereshtehnejad et al. categorized PD patients into three subtypes: mild motor-predominant (PD-MMP), intermediate (PD-IM) and diffuse malignant (PD-DM) subtypes, based on the results of scales and questionnaires used to evaluate motor function, cognition, rapid-eye-movement (REM)-sleep behaviour disorder (RBD) and dysautonomia.[5] Longitudinal assessment has validated the feasibility and accuracy of the subtype classification and demonstrated that the DM subtype not only demonstrated the most severe motor deficits and NMS at baseline but also progressed fastest and had a substantially worse prognosis.[6]

Quality of life (QoL) is a vital outcome indicator for disease management among PD patients, as it not only makes necessary complements to clinical evaluation but also supplies information about disease status and the effects of therapy. One of the most important objectives of the treatment and care in PD is the maintenance or improvement of QoL since it is currently incurable.[7] A large number of studies suggest that both motor dysfunction and NMS have negative effects on QoL in PD.[8] To date, no study has investigated QoL and its determinants among the novel clinical subtypes of PD proposed by Fereshtehnejad et al.[5] To accomplish more precise pharmacological and non-pharmacological interventions to improve or maintain QoL, physician should explore the clinical characteristics and differences of QoL based on subtypes in more detail. In addition, research on the novel clinical subtypes of PD is in its infancy, and its feasibility needs to be confirmed in different cohorts. Therefore, we explored the feasibility of the classification of the novel clinical subtypes in Chinese PD patients and then investigated the possible different determinants of QoL among PD-MMP, PD-IM and PD-DM patients in the current study.

Materials and Methods

Patients

All patients in this study were successively enrolled at Huashan Hospital, Fudan University from March 2011 to February 2019. The diagnosis of PD was made by two neurologists specializing in movement disorders based on the UK Brain Bank criteria.[9] Recruitment criteria included age $\geq$ 30, disease duration $\leq$ 48 months, and Hoehn and Yahr (H&Y) staging I–II.

Standard protocol approvals, registrations, and patient consents

The study was approved by the Human Studies Institutional Review Board, Huashan Hospital, Fudan University. Written informed consent in conformity to the Declaration of Helsinki were acquired from all participated patients in this study.

Clinical assessments and neuropsychological tests

All the clinical assessments and neuropsychological tests were completed by two clinicians specializing in movement disorders. Movement dysfunction was assessed by H&Y staging and the Unified Parkinson's Disease Rating Scale-part III (UPDRS-III) during the off-medication state, which was defined as the withdrawal of anti-PD medications for at least 12 h. NMS were determined by Non-Motor Symptom Questionnaire (NMSQ).[10] In addition, some other specific scales and questionnaires were used to assess the corresponding NMS, including the Geriatric Depression Rating Scale (GDS) for depression,[11] the REM-sleep Behaviour Disorder Screening Questionnaire (RBDSQ) for RBD,[12] the Epworth Sleepiness Scale (ESS) for excessive daytime sleepiness (EDS)[13] and the Sniffin' Sticks Screening Test 12 (SSST-12) for olfaction dysfunction.[14] The levodopa equivalent dose (LED) was calculated as a previous study suggested.[15]

QoL was recorded by the 39-item Parkinson's Disease Questionnaire (PDQ-39) which comprises 39 items that were separated into eight subdomains: mobility, activity of daily living, emotional well-being, stigma, social support cognition, communication, and bodily discomfort.[16] Each item on the PDQ-39 is recorded on a 5-point Likert scale. In the current study, the PDQ-39 summary index (PDQ-39 SI) was standardized from the original PDQ-39 scores by dividing the scored points by the maximum possible points and then multiplying by 100. Hence, a range of 0 to 100 for the PDQ-39 SI was defined, with higher scores meaning worse QoL.

All participants were in the ON condition during cognitive assessment to minimize the confounding impact of motor symptoms. Global cognitive abilities were assessed by the Mini Mental State Examination (MMSE).[17] Other neuropsychological tests included attention and working memory [Symbol Digit Modalities Test (SDMT)][18] and [Trail Making Test A (TMT-A)],[19] executive function [Stroop Color-Word Test (CWT)][20] and [Trail Making Test B (TMT-B)],[19] language [Boston Naming Test (BNT)][21] and [Animal Fluency Test (AFT)],[22] memory [Auditory Verbal Learning Test (AVLT)][23] and [delayed recall of the Rey-Osterrieth Complex Figure Test (CFT-

delay)],[24] visuospatial function[Clock Drawing Test (CDT)][25] and [copy task of the Rey-Osterrieth Complex Figure test (CFT)].[24]

Clinical definition of the three subtypes

Subtypes classification proposed by Fereshtehnejad et al.[5] were adapted in the current study. Notably, we employed scores on the autonomic dysfunction-related items in the NMSQ,[10] including items 1, 4–9, 18–20 and 28, defined as autonomic dysfunction-related items in the NMSQ (NMSQ-AD) score, to evaluate dysautonomia. In addition, we adopted a composite cognitive z score, subtracting the mean test score of the control sample from the individual raw scores and then dividing the difference by the standard deviation (SD) of the score of the control sample, to evaluate the cognitive function of PD patients. Calculations for the z score of each neuropsychological test were z-score = (crude $\text{score}_{\text{patient}} - \text{mean}_{\text{healthy control}}$)/$\text{SD}_{\text{healthy control}}$. The mean score and SD of the neuropsychological tests from an age- and sex-matched healthy control cohort consisting of 100 subjects are shown in Table S1. Four critical clinical features, including motor (UPDRS-III score), cognition (composite cognitive z score), RBD (RBDSQ score), and dysautonomia (NMSQ-AD score), were used to classify patients into subtypes.[5] The corresponding 75th percentile was calculated for each critical clinical feature, and patients were classified into three subtypes according to the following criteria: (1) PD-MMP subtype: both motor and all NMS scores were less than 75th percentile; (2) PD-DM subtype: either (i) motor score >75th percentile and at least 1 NMS score >75th percentile; or (ii) all three NMS scores >75th percentile; (3) PD-IM subtype: those not meeting criteria for PD-MMP or PD-DM subtypes. The corresponding values for the 25th, 50th and 75th percentiles of the main clinical features used for subtype classification are shown in Table S2.

Statistical analysis

Continuous variables were showed in the form of mean ± standard deviation (SD) or median (25%, 75%) and categorical variables were showed in the form of frequencies (%). The continuous variables were compared among the three subtypes by Kruskal–Wallis test followed by a Dunn–Bonferroni test for post hoc comparisons. The chi-squared test was used for the comparisons of categorical variables among the three subtypes. Univariate linear analyses between the clinical variables, including sex, age, education, disease duration, H&Y, UPDRS-III score, NMSQ, RBDSQ, ESS, GDS score, SSST-12, MMSE, and PDQ-39 were performed for each of the three subtypes. The multiple linear stepwise regression analysis with all variables with $p < 0.2$ in the univariate models included was conducted in the three subtypes,[26] respectively, to identify the main determinants of QoL in PD-MMP, PD-IM and PD-DM patients. A partial R^2 value contributed by each variable was calculated for this multivariate model. The total R^2 value was used to represent the proportion of total variability explained by the independent variables. The variance inflation factor (VIF) was used to evaluate the multicollinearity among independent variables in the multiple linear stepwise regression analysis. The statistically significant differences were defined as two-tailed $p < 0.05$. Data analysis was performed using SPSS (version 22.0).

Data availability statement

The data supporting all the findings of the study are available on request from the corresponding author (wangjian_hs@fudan.edu.cn; tangyilin@fudan.edu.cn).

Results

Demographic and clinical characteristics of the three subtypes

A total of 298 patients (180 males, 118 females), with a mean (SD) age of 52.17 (11.44) years and a mean (SD) disease duration of 22.95 (10.28) months, were recruited for the study. Based on the subtype classification criteria proposed by Fereshtehnejad et al.,[5] 129 (43.28%) patients were assigned to the PD-MMP subtype, 121 patients (40.60%) were assigned to the PD-IM subtype, and 48 (16.11%) patients were assigned to the PD-DM subtype. The demographic and clinical features of the three subtypes are demonstrated in Tables 1 and 2. No differences in sex, disease duration or LED among the three subtypes were observed. PD-MMP and PD-IM patients were significantly younger at diagnosis than PD-DM patients. Tables 1 and 2 details post hoc pairwise comparisons of the three subtypes. In summary, the PD-MMP patients had the lowest H&Y stage, UPDRS-III score, NMSQ score, RBDSQ score, SSST-12 score and the least impaired cognitive scores (all neuropsychological tests except CDT). On the other side of the spectrum, the PD-DM patients had the highest H&Y stage, UPDRS-III score, GDS score, and the worst performance on neuropsychological tests, including the MMSE, SDMT, TMT-A, CWT-C and TMT-B.

QoL in PD subtypes

QoL, which was evaluated using the PDQ-39, is shown in Table 3 for all three subtypes. PD-DM and PD-IM patients demonstrated higher scores on the PDQ-39 SI,

Table 1. Demographic and clinical characteristics of the three subtypes.

Characteristic	Phenotype I Mild Motor-predominant (n = 129)	Phenotype II Intermediate (n = 121)	Phenotype III Diffuse malignant (n = 48)	p value*	Significant adjusted pairwise comparisons
Sex (M/F)	74/55	73/48	33/15	0.3874[#]	NA
Age at diagnosis(y)	48.48 ± 10.77	52.09 ± 11.56	58.24 ± 9.98	<0.0001	I versus III, II versus III
Education (y)	12.68 ± 3.38	10.40 ± 3.81	9.62 ± 3.85	<0.0001	I versus II, I versus III
Disease duration (M)	22.09 ± 10.18	22.64 ± 10.40	26.00 ± 9.86	0.0727	None
LED (mg/day)	300.00 (168.80, 400.00)	325.60 (200.00, 450.00)	325.00 (200.00, 425.00)	0.0833	None
Motor symptoms and signs					
H&Y	1 (1, 2)	2 (1, 2)	2 (2, 2)	<0.0001	All comparisons
UPDRS-III score	18.05 ± 6.60	22.79 ± 9.51	34.77 ± 8.96	<0.0001	All comparisons
Non-motor symptoms and signs					
ESS	4.35 ± 3.66	5.94 ± 4.59	5.23 ± 3.22	0.0090	I versus II
NMSQ	6.22 ± 3.90	10.83 ± 6.20	11.11 ± 5.24	<0.0001	I versus II, I versus III
NMSQ-AD score	2.39 ± 1.44	4.42 ± 2.60	4.66 ± 2.57	<0.0001	I versus II, I versus III
GDS score	8.31 ± 5.58	9.86 ± 6.85	12.64 ± 6.57	0.0008	I versus III, II versus III
RBDSQ	2.03 ± 1.07	4.03 ± 2.70	4.83 ± 3.05	<0.0001	I versus II, I versus III
SSST-12 score	5.97 ± 2.32	5.20 ± 2.41	4.36 ± 2.50	0.0006	I versus II, I versus III

ESS, Epworth Sleepiness Score; GDS, Geriatric Depression Rating Scale; H&Y, Hoehn and Yahr; LED, levodopa-equivalent daily dose; NMSQ, Nonmotor Symptoms Questionnaire; NMSQ-AD, autonomic dysfunction related items in Nonmotor Symptoms Questionnaire; RBDSQ, Rapid-Eye-Movement Sleep Behavior Disorder Screening Questionnaire; SSST-12, Sniffin' Sticks screening 12 test; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

The data of H&Y and LED are presented as median (25%, 75%), and the other continuous data are presented as mean ± SD.

The continuous variables were compared among the three subtypes by Kruskal–Wallis test followed by a Dunn–Bonferroni test for post hoc comparisons.

*Comparison among the three subtypes.

[#]The categorical variables were compared among the three groups by the chi-squared test.

Table 2. Neuropsychological tests of the three subtypes.

Characteristic	Phenotype I Mild motor-predominant (n = 129)	Phenotype II Intermediate (n = 121)	Phenotype III Diffuse malignant (n = 48)	p value*	Significant adjusted pairwise comparisons
MMSE	28.74 ± 1.29	27.47 ± 2.49	26.42 ± 2.85	<0.0001	All comparisons
SDMT	47.67 ± 12.16	39.88 ± 14.15	28.73 ± 12.94	<0.0001	All comparisons
TMT-A (s)	48.70 ± 16.06	64.45 ± 31.41	82.69 ± 39.13	<0.0001	All comparisons
CWT-C time (s)	66.94 ± 16.17	79.78 ± 21.25	89.80 ± 22.50	<0.0001	All comparisons
CWT-C right	47.78 ± 2.64	45.87 ± 4.92	42.23 ± 8.31	<0.0001	All comparisons
TMT-B (s)	119.30 ± 39.72	152.00 ± 57.49	184.90 ± 66.69	<0.0001	All comparisons
BNT	24.59 ± 3.44	22.21 ± 4.36	21.70 ± 4.90	<0.0001	I versus II, I versus III
AFT	18.46 ± 4.57	15.62 ± 4.97	15.89 ± 3.96	<0.0001	I versus II, I versus III
AVLT-delay recall	6.34 ± 5.36	4.28 ± 2.28	3.33 ± 2.01	<0.0001	I versus II, I versus III
AVLT-T	30.57 ± 9.47	24.11 ± 8.45	20.02 ± 7.71	<0.0001	I versus II, I versus III
CFT-delay recall	17.52 ± 7.19	14.08 ± 7.44	11.05 ± 6.23	<0.0001	I versus II, I versus III
CFT	33.99 ± 2.09	31.82 ± 8.56	29.02 ± 8.75	<0.0001	I versus II, I versus III
CDT	20.66 ± 6.02	19.63 ± 6.55	19.80 ± 5.33	0.3113	None

AFT, Animal Fluency Test; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CDT, Clock Drawing Test; CFT, the Rey-Osterrieth Complex Figure Test; CWT, Stroop Color-Word Test; MMSE, Mini Mental State Examination; SDMT, Symbol Digit Modality Test; TMT, Trail Making Test.

The results of neuropsychological tests are presented as mean ± SD.

The continuous variables were compared among the three subtypes by Kruskal–Wallis test followed by a Dunn–Bonferroni test for post hoc comparisons.

*Comparison among the three subtypes.

Table 3. Quality of life assessment in the three subtypes.

	Phenotype I Mild motor-predominant (n = 129)	Phenotype II Intermediate (n = 121)	Phenotype III Diffuse malignant (n = 48)	p value*	Significant adjusted pairwise comparisons
PDQ-39 SI	11.79 ± 8.11	16.21 ± 11.49	20.21 ± 13.20	<0.0001	I versus II, I versus III
Mobility SI	9.61 ± 12.12	12.65 ± 14.18	18.85 ± 15.78	<0.0001	I versus III, II versus III
Activity of daily living SI	8.74 ± 12.15	10.78 ± 12.30	16.84 ± 18.67	0.0121	I versus III
Emotional well-beings SI	17.21 ± 15.21	19.68 ± 18.02	23.87 ± 18.07	0.0686	None
Stigma SI	17.67 ± 21.09	22.06 ± 22.19	22.40 ± 24.01	0.1367	None
Social support SI	3.77 ± 7.95	10.01 ± 18.11	8.16 ± 11.34	0.0060	I versus II, I versus III
Cognitions SI	13.78 ± 13.08	23.84 ± 17.99	27.60 ± 19.12	<0.0001	I versus II, I versus III
Communication SI	5.81 ± 10.87	10.29 ± 15.33	15.45 ± 21.12	0.0007	I versus II, I versus III
Bodily discomfort SI	17.69 ± 18.07	26.12 ± 21.29	28.13 ± 20.60	0.0005	I versus II, I versus III

PDQ-39, 39-item Parkinson's disease questionnaire; SI, summary index
*Comparison among the three subtypes.

indicating worse quality of life than PD-MMP patients. The most affected subdomains of the PDQ-39 were bodily discomfort (17.69 ± 18.07), stigma (17.67 ± 21.09) and emotional well-beings (17.21 ± 15.21) in PD-MMP patients, while the most affected subdomains were bodily discomfort (26.12 ± 21.29), cognition (23.84 ± 17.99) and stigma (22.06 ± 22.19) in PM-IM patients and bodily discomfort (28.13 ± 20.60), cognition (27.60 ± 19.12) and emotional well-beings (23.87 ± 18.07) in PD-DM patients.

Determinants of QoL in PD subtypes

To find out the determinants of QoL in the three subtypes, we firstly performed univariate linear analyses between the clinical variables, including sex, age, education, disease duration, H&Y, UPDRS-III score, NMSQ, RBDSQ, ESS, GDS score, SSST-12 and MMSE, and PDQ-39 in the three subtypes, respectively, and the results are shown in Table 4. Next, we conducted the multiple linear stepwise regression analysis with all variables with $p < 0.2$ in the univariate models to reveal the determinants of QoL in the three subtypes (Table 5). All VIFs of the variables included in the multiple linear stepwise regression of the three subtypes were less than 10 (Table S3), which indicated that multicollinearity didn't exist between one independent variable and the other independent variables. In PD-MMP patients, the most important determinants of QoL were GDS score ($R^2 = 0.336$, $\beta = 0.682$, $p = 0.000$), NMSQ ($R^2 = 0.059$, $\beta = 0.703$, $p = 0.007$), UPDRS-III score ($R^2 = 0.041$, $\beta = 0.369$, $p = 0.004$) and ESS ($R^2 = 0.033$, $\beta = 0.606$, $p = 0.009$). In PD-IM patients, the most important determinants of QoL were GDS score ($R^2 = 0.494$, $\beta = 1.696$, $p = 0.000$), followed by ESS ($R^2 = 0.024$, $\beta = 0.689$, $p = 0.011$) and SSST-12 ($R^2 = 0.022$, $\beta = -1.162$, $p = 0.021$). In PD-DM patients, the most vital determinants of QoL were GDS score ($R^2 = 0.429$, $\beta = 1.737$, $p = 0.000$), followed by MMSE ($R^2 = 0.098$, $\beta = -2.437$, $p = 0.006$).

Table 4. The results of univariate linear analyses of clinical characteristics and PDQ-39 in the three subtypes.

	PDQ-39					
	PD-MMP		PD-IM		PD-DM	
Variables	β	p value	β	p value	β	p value
Sex[1]	−0.351	0.880	−0.718	0.832	−1.824	0.779
Age (y)	−0.029	0.785	−0.201	0.179*	−0.505	0.100*
Education (y)	0.014	0.967	−0.950	0.029*	−1.704	0.037*
Disease duration (y)	0.194	0.086*	0.023	0.886	0.388	0.207
LED (mg/day)	−0.008	0.356	−0.007	0.347	−0.005	0.792
H&Y	1.039	0.655	2.227	0.508	11.981	0.205
UPDRS−III score	0.655	0.000*	0.089	0.624	−0.071	0.834
NMSQ	1.855	0.000*	0.780	0.003*	1.951	0.000*
RBDSQ	−0.077	0.939	−0.052	0.933	0.163	0.873
ESS	1.200	0.000*	1.331	0.000*	0.638	0.507
GDS score	1.343	0.000*	1.834	0.000*	2.054	0.000*
SSST-12	0.096	0.846	−1.614	0.020*	−0.306	0.814
MMSE	−0.409	0.643	−0.865	0.193*	−3.475	0.001*

ESS, Epworth Sleepiness Score; GDS, Geriatric Depression Rating Scale; H&Y, Hoehn and Yahr; LED, levodopa-equivalent daily dose; MMSE, Mini Mental State Examination; NMSQ, Nonmotor Symptoms Questionnaire; PDQ-39, 39-item Parkinson's disease questionnaire; PD, Parkinson's disease; PD-MMP, Phenotype I Mild motor-predominant; PD-IM, Phenotype II Intermediate; PD-DM, Phenotype III Diffuse malignant; RBDSQ, Rapid-Eye-Movement Sleep Behavior Disorder Screening Questionnaire; SSST-12, Sniffin' Sticks screening 12 test score; UPDRS- III, Unified Parkinson's Disease Rating Scale part III.
[1]Male as reference.
*Included in stepwise multiple linear regression analysis ($p < 0.2$).

Table 5. Determinants of life quality according to the stepwise multiple linear regression analysis in the three subtypes.

	Partial R^2	β	95% CI	p value
PD-MMP (total R^2 = 0.469)				
GDS score	0.336	0.682	(0.328, 1.035)	0.000
NMSQ	0.059	0.703	(0.193, 1.214)	0.007
UPDRS-III score	0.041	0.369	(0.123, 0.615)	0.004
ESS	0.033	0.606	(0.155, 1.058)	0.009
PD-IM (total R^2 = 0.540)				
GDS score	0.494	1.696	(1.340, 2.051)	0.000
ESS	0.024	0.689	(0.161, 1.216)	0.011
SSST-12	0.022	−1.162	(−2.143, −0.180)	0.021
PD-DM (total R^2 = 0.527)				
GDS score	0.429	1.737	(1.006, 2.468)	0.000
MMSE	0.098	−2.437	(−4.128, −0.745)	0.006

β, standardized beta coefficient; CI, confidence interval; ESS, Epworth Sleepiness Score; GDS, Geriatric Depression Rating Scale; MMSE, Mini Mental State Examination; NMSQ, Nonmotor Symptoms Questionnaire; PD, Parkinson's disease; PD-MMP, Phenotype I Mild motor-predominant; PD-IM, Phenotype II Intermediate; PD-DM, Phenotype III Diffuse malignant; SSST-12, Sniffin' Sticks screening 12 test; UPDRS-III, Unified Parkinson's Disease Rating Scale part III.

Discussion

The current study validated the feasibility of the classification of novel clinical subtypes in Chinese PD patients. Our results showed that depression was the most crucial determinant for QoL in PD-MMP, PD-IM and PD-DM patients, and the other contributors of QoL in the three subtypes were heterogeneous.

The subtype classifications in this cross-sectional cohort were performed according to the definition proposed by Fereshtehnejad et al.[5] Although our subtypes corresponded to their criteria as closely as possible, there were some differences in the kinds of scales used for the assessments of the four critical features (motor, cognition, RBD and dysautonomia) between our study and the reference Parkinson's Progression Markers Initiative (PPMI) group as the above "Materials and methods" described. However, our study did not differ in PD subtype distribution (PD-MMP/PD-IM/PD-DM: 43.29%, 40.60%, and 16.11%, respectively, vs. 52.97%, 34.68%, and 12.35%, respectively; $\chi^2 = 2.09$; $p = 0.35$) in comparison with the reference PPMI group.[5] Furthermore, in agreement with the PPMI and the Queen Square Brain Bank (QSBB) cohort,[5,6] the PD-DM subtype showed almost the most severe clinical symptoms and signs, followed by PD-IM patients, while the PD-MMP subtype presented the lightest clinical manifestations.

The assessment of QoL for PD patients is necessary in clinical practice given its important role as an outcome indicator in PD. With increasing evidence indicating that PD incorporates different subtypes, a growing number of studies have investigated QoL in different PD subtypes. For instance, previous studies reported that PD patients with the PIGD subtype suffered from poorer QoL than PD patients with the TD subtype.[27–29] However, the QoL in the new clinical subtypes has yet to be evaluated. Our study demonstrated that in comparison with PD-MMP patients, QoL was more impaired in PD-IM and PD-DM patients. In detail, except for emotional well-beings and the stigma subdomain, the scores of the remaining six subdomains of the PDQ-39 in PD-DM patients were remarkably higher than those in PD-MMP patients. Both motor and non-motor dysfunction contribute to poor QoL in PD.[8,30] PD-DM and PD-IM patients suffered more severe motor function and most NMS than PD-MMP patients, which could explain the findings that PD-DM and PD-IM patients had a worse QoL than PD-MMP patients.

PD is generally recognized by motor dysfunctions, mainly manifested as rigidity, bradykinesia, and resting tremor.[31] There are still debates about whether motor function is an independent determinant of QoL in PD. Studies have suggested that the UPDRS-III score, a classical scale used for the measurements of motor deficits in PD, is a vital contributor to QoL in PD.[8,30,32,33] In contrast, a broad list of studies supported that the UPDRS-III score had no impact on the QoL of PD patients.[34–36] Interestingly, our results showed that the UPDRS-III score was the third strongest contributor of QoL in the PD-MMP subtype, while it had no influence on QoL for either PD-IM or PD-DM patients. The findings suggest that the discrepancy results of the previous studies could be attributed to the fact that the participants were enrolled in these studies without considering the substantial heterogeneity among PD patients. The contribution of motor function varies among PD patients with a spectrum of heterogeneous motor and NMS.

NMS in PD have received a great deal of attention in recent decades because it could be predominant as the disease progresses and has a detrimental impact on QoL for PD patients.[37] The NMSQ and the Non-Motor Symptoms Scale (NMSS) addressing NMS as a whole were developed for the assessments of NMS in PD.[10,38] NMSQ and NMSS were the most predominant contributors to QoL in several studies.[39–41] In our study, we illustrated that NMSQ was an independent determinant of QoL and even explained more of the variability than UPDRS-III score (R^2 change, 5.9% vs. 4.1%, respectively) in PD-MMP patients. This result suggested that NMS, as a whole, had a greater impact on QoL than motor function in the PD-MMP subtype. However, NMSQ is not the determinant of QoL in either PD-IM or PD-DM subtypes. The results suggest that the frequency and severity

of NMS as a whole is not the vital determinant for PD-IM and PD-DM patients, but this may not be the case with each single non-motor symptom.

Depression is one of the most common NMS in PD, and it was reported that PD patients were twice as likely to develop depression than PD-free individuals.[42] A large number of studies have revealed that depression has a great negative impact on QoL in PD patients.[8,33,34,43,44] Moreover, quite a few studies have shown that depression is the most important contributor to poor QoL in PD patients.[35,45–47] Consistent with these findings, the present study revealed that whichever subtype of PD patients were, the greatest determinant of their QoL was depression, assessed by GDS. The GDS score accounted for 33.6% to 49.2% of the variability of the PDQ-39 SI in the three subtypes, highlighting the influences of depression. Nonetheless, depression in PD patients did not acquire deserved recognition and was frequently underreported in clinical practice,[48,49] which partially results from the fact that there are large overlaps between the characteristics of depression and the main symptoms of PD, such as psychomotor retardation, sleep disturbance and fatigue.[37] In addition, only a few depressed PD patients received antidepression treatment.[50,51] Therefore, more attention should be devoted to depression in PD patients for their QoL.

Excessive daytime sleepiness (EDS) is another common NMS in PD and affects 20%–60% of patients,[52] with a growing prevalence ratio as the disease advances.[53] It is well recognized that EDS, measured by ESS, negatively impacts QoL in PD.[47,54] In this study, we found that ESS was an independent determinant of QoL in both PD-MMP and PD-IM patients, while it had no significant impact on QoL in PD-DM patients. Except for male sex, the use of dopamine agonists is the greatest independent risk factor for EDS[37], and it seems to increase EDS in a dose-dependent manner.[54,55] Therefore, it is imperative for physicians to identify EDS and make appropriate choices in the treatment of PD, considering the association of dopamine agonists with ESS, particularly for the PD-MMP and PD-IM subtypes.

Cognitive dysfunction, with mild cognitive impairment (MCI) and dementia included, is another cardinal NMS in PD and is one of the four most predominant clinical features used for the assignment of novel clinical subtypes of PD.[5] Both MCI and dementia were shown to be independent contributors to QoL in PD.[30,33] Nonetheless, there is controversy regarding whether global cognitive function, assessed by MME or Montreal Cognitive Assessment (MoCA), has a strong impact on QoL in PD. Several studies reported that the MoCA or MMSE score was not a contributor to QoL,[34,41] while few studies demonstrated that the MMSE score was closely correlated with PDQ-39 SI and was an unignorable determinant of QoL for PD patients.[46,56] Interestingly, our study showed that MMSE score is an unignorable contributor to QoL in PD-DM patients, accounting for approximately 10% of the variability of PDQ-39 SI with a considerable standardized beta coefficient (Table 5, $\beta = -2.437$), while it was not a determinant of QoL in either PD-MMP or PD-IM patients. The controversy mentioned above in previous studies may also be partially explained by the heterogeneity in the varied subtypes in PD. Considering the central role of the MMSE score in the QoL of PD-DM patients, extra attention to cognitive dysfunction is highly recommended even in the early course of disease.

Some limitations are observed in this study. First, the cross-sectional design which is inability to analyse the longitudinal effects of these variables on QoL and make causal inferences is the major limitation of this study. Longitudinal studies that aim to investigate whether QoL could be enhanced through interventions targeting these specific factors are needed in the future. Second, the subjects selected for this study were at an early stage of disease, and it needs to be explored whether the same results of this study are replicable in PD populations that are at middle and late courses of disease. Finally, although potential factors impacting QoL were screened by univariate linear analyses in this study, including sex, age, education, disease duration, H&Y, UPDRS-III score, NMSQ, RBDSQ, ESS, GDS score, SSST-12 and MMSE, the effect of non-observed confounding factors could not be completely excluded. Future studies with information on these potentially important factors will need to minimize potential biases.

Conclusion

In conclusion, the present study indicated that clinical subtyping of PD based on motor symptoms, RBD, and autonomic and cognitive dysfunction at diagnosis is feasible in clinical practice. Depression was shown to be the most critical determinant of QoL in all three subtypes. Nonetheless, the other determinants of QoL were heterogeneous among the three subtypes. To improve QoL in PD patients, physicians might need to pay attention to specific factors according to clinical subtypes.

Conflict of Interest

The authors have no conflict of interest to report.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Cognitive profile of healthy controls.

Table S2. The corresponding values for the 25th, 50th and 75th percentile of the main clinical features used for subtype classification.

Table S3. VIF of variables in the multiple linear stepwise regression analysis of the three subtypes.

