



Clinical Factors Associated with the Risks of Depression in Patients with Parkinson's Disease

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Abstract

Objective:

Depression is twice as common among patients with Parkinson's disease (PD) than it is among healthy individuals, and treating the symptoms of depression could help improve the quality of life of patients. A better understanding of the factors associated with depression can lead to a focused screening and clinical examination/interview of this patient population.

Methods:

This study enrolled 93 adult patients with idiopathic PD aged ≥ 55 years. The severity of depression was classified as follows using the Geriatric Depression Scale (GDS) score: No depression (GDS, 0-9), mild depression (GDS, 10-19), and severe depression (GDS, 20-30). Stepwise logistic regression was then used to evaluate the relationships between baseline clinical factors and the presence of depression (both mild and severe depression), after adjusting for potential confounding factors.

Results:

In total, 73 (78%) patients with PD were diagnosed with depression (mild depression, $n=51$; severe depression, $n=22$). Clinical factors associated with the risk of depression were sex, years of education, exercise habituation, mini-mental state examination (MMSE) scores, mean levodopa equivalent dose, and mean Barthel index, unified Parkinson's disease rating scale (UPDRS) score, striatal dopamine transporter uptake ratios, and Hoehn and Yahr staging. Of these risk factors, both female sex and mean UPDRS score remained independently associated with the risk of depression in the stepwise logistic regression analysis. Women had an odds

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ratio of 3.6 compared to that of men, and the cut-off value of the mean UPDRS score for predicting the risk of depression was 38.5 (sensitivity, 75%; specificity, 76.5%).

Conclusion:

Higher mean UPDRS score (>38.5) and female sex are associated with a higher risk of depression. The prevention and evaluation of depressive disorders in the high-risk PD group are important safety issues and are highly relevant to patients' quality of life.

Keywords

Depression, Geriatric depression scale, Idiopathic Parkinson's disease, Quality of life, Risk factors

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease, and is characterized by both motor and non-motor dysfunction [1]. Depression is common in patients with PD, being twice as likely to occur in this population as it is in healthy individuals; it has been reported that an estimated 30%-40% of patients with PD and 20%-25% of patients receiving specialty care are prescribed antidepressants [2-4]. Further, depression may predate the onset of motor impairment [5], and is significantly correlated with performance in daily functional activities, cognitive function, and the caregivers' quality of life [6,7].

Therefore, it is important to adequately recognize and assess depressive symptoms in patients with PD. Routine use of depressive symptom rating scales may improve the detection of depression, but screening tools should be both sensitive and specific to the broad differential diagnosis of the depressed mood characteristic of PD [8]. Moreover, no single scale is recommended for use in the PD population at present [8].

The Geriatric Depression Scale (GDS-30) is a short, self-reported, yes/no screening instrument for depression in the elderly population. It focuses on the psychological aspects and social consequences of depression, avoiding symptom overlap with other medical disorders or aging [9]. The GDS-30 is reported to have adequate discriminating validity for major depressive disorder in PD among patients aged ≥ 55 years, with a cut-off value >9 [9,10].

This hospital-based study aimed to provide accurate information on neuroimaging studies, the severity and duration of PD, daily dose of anti-Parkinsonian agents, and functional outcomes. Given the importance of depression to disease burden, determining the risk factors

associated with depressed mood in patients with PD who should receive preventive intervention is warranted. We aimed to analyze the clinical features and scores to determine potential factors associated with depression; this can lead to focused screening and clinical examination in this population.

Materials and Methods

■ **Study design**

This single-center prospective cross-sectional study was conducted at Chang Gung Memorial Hospital-Kaohsiung, a tertiary medical center and the main referral hospital serving a population of 3 million in southern Taiwan. The Institutional Review Committees on Human Research of the hospital approved the study protocol, and written informed consent was obtained from all the patients or their relatives (if patients had cognitive decline as revealed by their clinical symptoms or a criterion related to the MMSE).

■ **Inclusion and exclusion criteria**

This study evaluated 137 patients with a definitive diagnosis of idiopathic PD [11] who were followed-up at the Neurology Outpatient Clinic for more than 6 months after titration of their daily anti-Parkinsonian agents to a steady dose in accordance with their clinical symptoms. Patients were excluded if (1) they had newly diagnosed PD or were on follow-up for less than 6 months since their daily dose of anti-Parkinsonian agents was adjusted; (2) they showed focal neurological signs that were not related to the diagnostic criteria of PD; (3) they had impaired consciousness, or moderate or severe dementia (Clinical Dementia Rating (CDR) ≥ 2) which could keep patients from following our instructions; (4) were aged <55 years; and (5) they had received anti-depressant therapy for depressive disorder. Finally, 93 patients were included in the analysis.

■ Clinical data collection

An experienced and specialized neurology nurse who was blinded to the patients' clinical and biochemical data was trained to measure the functional scores at the time of enrollment. The clinical features recorded were age at disease onset (or age at the time of the first reported symptom attributable to the disease), years of education, disease duration (time from onset until follow-up), and other underlying diseases apart from PD. In this study, exercise habituation was defined as patients engaged in at least 30 minutes of moderately intense physical exercise more than twice a week. The severity of PD was graded using the Unified Parkinson's Disease Rating Scale (UPDRS) and the Hoehn and Yahr staging [12,13].

The daily dose of anti-Parkinsonian agents was converted into the equivalent dose of levodopa [14]. In motor fluctuating cases, the UPDRS and Hoehn and Yahr scales were administered in the off situation (8-10 hours after the patients stopped their usual anti-Parkinsonian treatment) to evaluate the possible influence of disease severity.

■ Neuroimaging

All the patients underwent cranial magnetic resonance imaging (MRI) and ^{99m}Tc-TRODAT-1 single-photon emission computed tomography (SPECT)/computed tomography (CT) scanning; the details of image acquisition and analysis are as follows [15,16].

■ MR Image acquisition

Routine MRI scans were acquired on a GE Signa 3T whole-body MRI scanner (General Electric Healthcare, Milwaukee, WI, USA) using an 8-channel phase array head coil at the Kaohsiung Chang Gung Memorial Hospital in Taiwan. Whole brain three-dimensional T1 weighted images were acquired using an inversion-recovery fluid-attenuated fast spoiled gradient-recalled echo pulse sequence with the following imaging parameters: Repetition time (TR)/ echo time (TE)/ inversion time (TI)=9.5/3.9/450 ms; flip angle=15 degrees; number of excitations (NEX)=1; field of view (FOV)=240*240 mm²; matrix size=512*512; voxel size=0.47*0.47*1.3 mm³; and slice number=110 axial slices (without interslice gap). In order to identify any brain abnormalities, an additional volumetric axial T2-weighted fast spin-echo sequence (TR/TE=4200/102 ms; echo train length=18; NEX=2; FOV=240 mm²; slice thickness=5 mm; matrix size=320*256; and 18 slices) and axial

T2-weighted inversion-recovery fluid-attenuated sequence (TR/TE/TI=8000/100/2000 ms; NEX=1; FOV=240 mm²; slice thickness=5 mm; matrix size=320*256; and 18 slices) were used in the same imaging session. An experienced neuroradiologist blinded to the participants' status visually checked all of the MR scans to evaluate the imaging quality and exclude participants with any organic lesions. None of the participants was excluded on these grounds.

■ ^{99m}Tc-TRODAT-1 SPECT/CT and region of interest (ROI) analysis

Each patient was intravenously injected with a single bolus of 925 MBq (25 mCi) of ^{99m}Tc-TRODAT-1. The image acquisition was performed after 4 h using a dual-head SPECT/CT equipped with low-energy high-resolution collimators (Symbia T, Siemens Medical Solutions, Erlangen, Germany). Emission data were acquired in a 128 x 128 matrix with 1.45 zoom through 360° rotation (180° for each head) at 3° intervals for 30 s per angle step. Transmission data acquired by low-dose CT without the use of contrast medium were used for attenuation correction and functional-anatomical image fusion.

Low-dose CT images were acquired using the following parameters: 130 kV, 45 mAs (maximum), and 5 mm-thick sections. The reconstruction and display of functional-anatomical fusion images were performed on the Syngo™ MI workplace (Siemens Healthcare, Forchheim, Germany). After fast low angle shot (FLASH) 3D (ordered-subset expectation maximization iterative reconstruction method with 3D collimator beam modeling) reconstruction of the emission data, three-dimensional images of trans-axial, coronal, and sagittal slices were obtained. The trans-axial ^{99m}Tc-TRODAT-1 SPECT/CT images were analyzed both visually and semi-quantitatively. With the help of anatomical co-registration of CT images, ROIs of bilateral striata were defined on composite images of the six slices showing the highest striatal activity. The occipital cortex was drawn in the same way, and served as the background area. The ROI radioactivity was counted, and striatal dopamine transporter uptake ratios were calculated as the quotient of the mean counts per pixel in each striatum divided by the mean counts per pixel in the occipital cortex. All images were reviewed by an experienced nuclear physician who was blinded to the patient information.

■ **Neuropsychiatric testing and outcome**

The Mini-Mental State Examination (MMSE) was used to assess general intellectual function [17], and the ability to perform the digit forward span test was assessed. Cognitive outcomes were assessed using the Clinical Dementia Rating (CDR) scale, which scored the functional capacity of participants without physical disability [18]. 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.

To obtain a patient-based measurement of depression, the Geriatric Depression Scale (GDS-30) was used. The GDS-30 was developed to assess depression in the elderly population [9,10], and is a widely validated questionnaire that is easy to understand and complete without supervision. It consists of 30 questions, each with 2 possible answers (scored 0 or 1), with a maximum score of 30. Depression severity was classified using the Geriatric Depression Scale (GDS-30) as follows: No depression (GDS 0-9), mild depression (GDS 10-19), and severe depression (GDS 20-30).

Two separate statistical analyses were performed. First, the clinical data and manifestations between the two patient groups (with or without depression), were analyzed using the Chi-square test or Fisher's exact test. The mean age, levodopa equivalent dose, and mean functional score between the two patient groups were compared using the Student's t-test. Stepwise logistic regression was then used to evaluate the relationship between baseline clinical factors and the presence of depressive symptoms, while controlling for the effects of potential confounding factors. Receiver operating characteristic (ROC) curves were generated for significant predictor variables. All statistical analyses were conducted using the SAS software package version 9.1 (2002, SAS Statistical Institute, Cary, North Carolina).

Results

■ **Baseline characteristics of the patients**

We enrolled 93 patients with idiopathic PD including 44 men (age range, 57-81 years; mean age, 70.4 years) and 49 women (age range, 55-82 years; mean age, 68.4 years). The mean disease duration was 4.6 ± 2.0 years. While 20 patients had no depression, 51 had mild depression, and the remaining 22 had severe depression

(**Table 1**). The mean (\pm standard deviation [SD]) age of these 3 groups was $66.5 (\pm 7.6)$ years, $70.5 (\pm 7.9)$ years, and $69.3 (\pm 8.2)$ years, respectively ($p=0.16$). The mean levodopa equivalent dose (mg) was 267.7 ± 92.0 , 498.6 ± 350.2 , and 895.7 ± 437.2 , respectively ($p<0.001$); the mean (\pm SD) striatal dopamine transporter uptake ratio was $1.6 (\pm 0.2)$, $1.4 (\pm 0.1)$, and $1.3 (\pm 0.2)$, respectively ($p<0.001$); the mean (\pm SD) MMSE score was $25.2 (\pm 5.2)$, $23.0 (\pm 5.7)$, and $17.5 (\pm 3.7)$, respectively ($p<0.001$); the mean (\pm SD) Barthel index (BI) score was $95.0 (\pm 21.2)$, $79.4 (\pm 25.0)$, and $50.7 (\pm 30.1)$, respectively ($p<0.001$); and the mean (\pm SD) UPDRS score was $30.8 (\pm 23.4)$, $54.4 (\pm 25.9)$, and $78.3 (\pm 23.2)$, respectively ($p<0.001$). Hoehn and Yahr staging of the 93 patients with PD showed that 26 patients were stage I, 21 were stage II, 24 were stage III, 9 were stage IV, and 13 were stage V. Other basic characteristics of the patients are listed in **Table 1**. The mean (\pm SD) MMSE scores of the women and men were $20.7 (\pm 6.1)$ and $23.8 (\pm 5.8)$, respectively ($p=0.012$), and the mean (\pm SD) UPDRS scores of the women and men were $55.2 (\pm 30.9)$, and $52.3 (\pm 27.8)$, respectively ($p=0.639$).

■ **Effects of risk factors on the geriatric depression score and UPDRS I (depressive item) score**

A correlation analysis was used to test the influence of age, education (years), disease duration, levodopa equivalent dose (mg), striatal dopamine transporter uptake ratios, MMSE score, and UPDRS (total, UPDRS I, UPDRS II, and UPDRS III) scores on the GDS-30 scores (**Table 2**). Based on the statistical analyses (correlation coefficient, p value), disease duration ($r=0.282$, $p=0.006$), mean levodopa equivalent dose (mg) ($r=0.576$, $p<0.001$), and the UPDRS ($r=0.665$, $p<0.001$), UPDRS I ($r=0.684$, $p<0.001$), UPDRS II ($r=0.638$, $p<0.001$), and UPDRS III ($r=0.614$, $p<0.001$) scores were positively correlated with the GDS-30 score, while education (years) ($r=-0.273$, $p=0.003$), mean striatal dopamine transporter uptake ratios ($r=-0.471$, $p=0.002$), and mean MMSE score ($r=-0.467$, $p<0.001$) were negatively correlated with the GDS-30 score. Furthermore, the disease duration ($r=0.213$, $p=0.04$), mean levodopa equivalent dose (mg) ($r=0.489$, $p<0.001$), and UPDRS ($r=0.576$, $p<0.001$), UPDRS II ($r=0.538$, $p<0.001$), and UPDRS III ($r=0.508$, $p<0.001$) scores were positively correlated with the score of the depressive items of the UPDRS I (average) score; while education (years) ($r=-$

0.224, $p=0.016$), mean striatal dopamine transporter uptake ratios ($r=-0.405$, $p=0.008$), and mean MMSE score ($r=-0.3$, $p=0.003$) were negatively correlated.

Outcome and risk factors associated with depression

The risk factors associated with depression are listed in **Table 3**. Statistical analysis of the baseline clinical manifestations and functional scores between the depressed and non-depressed groups revealed that sex ($p=0.033$), education (years) ($p=0.016$), mean levodopa equivalent dose ($p=0.022$), mean Barthel index score ($p=0.002$), mean UPDRS score ($p=0.005$), and mean striatal dopamine transporter uptake ratios ($p=0.015$) were significant variables. These variables were then used in the stepwise logistic regression model, which revealed that sex ($p=0.035$, odds ratio [OR]=3.66, 95% confidence interval [CI]=1.09-12.24) and mean UPDRS score ($p=0.011$, OR=1.04, 95% CI=1.009-1.072) remained independently associated with the risk of depression. An increase of 1 point in the mean UPDRS score increased the depression rate by 4%. The area under the ROC curve for the mean UPDRS score was 0.760 (95% CI=0.618-0.902, $p=0.001$) and the cut-off value for the mean UPDRS score to predict the risk of depression was 38.5 (sensitivity=75%, specificity=76.5%).

Discussion

Differences in the relative prevalence and risk factors of depression in patients with idiopathic PD vary with case determination and inclusion criteria, depression rating scales, disease severity and duration, length of follow-up, PD-related complications (e. g., neuromuscular disorders like frozen shoulder, cervical and lumbo-sacral radiculopathy, and spinal compressive fracture), and PD medication-related complications (e.g., constipation, dry eyes, dry mouth, drowsiness, cardiac arrhythmia, or orthostatic hypotension) [2-9,19-21]. In the present study, the frequency of depression in patients with PD was 78% (73 out of 93), including mild depression in 51 (55%) patients and severe depression in 22 (23%) patients.

The present study examined the risk of depression and produced three major findings. First, sex, exercise habituation, the mean levodopa equivalent dose (mg), striatal dopamine transporter uptake ratios, MMSE score, Barthel index score, Hoehn and Yahr staging, and UPDRS scores were significantly

Table 1: Basic characteristics of patients with Parkinson's disease[†].

	No depression n=20	Mild depression n=51	Severe depression n=22	p value
Age (years)	66.5 ± 7.6	70.5 ± 7.9	69.3 ± 8.2	0.16
Sex (women/men)	8/12	23/28	18/4	0.007
Education (years)	7.0 ± 4.6	6.6 ± 5.2	4.8 ± 3.3	0.23
Exercise habituation	17	40	8	<0.001
Body mass index (kg/m ²)	25.4 ± 3.5	23.9 ± 3.3	24.1 ± 3.7	0.23
Disease duration (years)	3.3 ± 2.9	4.8 ± 4.1	5.8 ± 4.7	0.11
Levodopa equivalent dose (mg)	267.7 ± 92.0	498.6 ± 350.2	859.7 ± 437.2	<0.001
Striatal dopamine transporter uptake ratios	1.6 ± 0.2	1.4 ± 0.1	1.3 ± 0.2	0.001
Mini-Mental State Examination	25.2 ± 5.2	23.0 ± 5.7	17.5 ± 3.7	<0.001
CDR				
0	15	21	0	
0.5	3	27	14	<0.001
1	2	3	8	
Barthel Index	95.0 ± 21.2	79.4 ± 25.0	50.7 ± 30.1	<0.001
Unified Parkinson's Disease Rating Scale (UPDRS) ^a	30.8 ± 23.4	52.4 ± 25.9	78.3 ± 23.2	<0.001
UPDRS I ^b	2.0 ± 1.1	5.1 ± 2.4	8.2 ± 2.9	<0.001
UPDRS II ^c	8.6 ± 4.9	14.4 ± 9.3	24.2 ± 8.2	<0.001
UPDRS III ^d	20.3 ± 14.5	32.8 ± 16.1	45.9 ± 14.2	<0.001
Hoehn and Yahr staging				
Stage I	16	10	0	
Stage II	1	19	1	<0.001
Stage III	2	12	10	
Stage IV	0	8	1	
Stage V	1	2	10	

[†]Figures are mean +/-SD or number (%)
^a"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)
^bIMentation, behavior, and mood. Theoretical minimum and maximum values are 0 and 16, respectively (16 represented the worst disability and 0 no disability).
^cIIActivities of daily living (ADL). Theoretical minimum and maximum values are 0 and 52, respectively (52 represented the worst disability and 0 no disability).
^dIIIMotor examination. Theoretical minimum and maximum values are 0 and 108, respectively (108 represented the worst disability and 0 no disability).

different among the three groups (no depression, mild depression, and severe depression). Second, the disease duration, mean levodopa equivalent dose (mg), and mean UPDRS score were positively correlated with the GDS-30 score; while the education (years), mean striatal dopamine transporter uptake ratios, and mean MMSE score were negatively correlated with the GDS-30 score. Third, both female sex and the mean UPDRS score remained independently associated with the risk of depression. There were 3.6 times more women than men with the risk of depression, and an increase of one point in the mean UPDRS score increased the depression rate by 4%; the cut-off value for the mean UPDRS score to predict the risk of depression

Table 2: Correlation analysis of the effects of risk factors on both geriatric depression score and UPDRS I depressive item on patients with PD.

Variables	Geriatric depression score		Depressive item of UPDRS I	
	r	p value	r	p value
Age (years)	0.109	0.303	0.065	0.535
Education (years)	-0.273	0.003	-0.224	0.016
Body mass index (kg/m ²)	-0.149	0.156	-0.10	0.339
Disease duration (years)	0.282	0.006	0.213	0.04
Levodopa equivalent dose (mg)	0.576	<0.001	0.489	<0.001
Striatal dopamine transporter uptake ratios	-0.471	0.002	-0.405	0.008
Mini-Mental State Examination	-0.467	<0.001	-0.3	0.003
UPDRS ^a	0.665	<0.001	0.576	<0.001
UPDRS I ^β	0.684	<0.001	---	---
UPDRS II ^γ	0.638	<0.001	0.538	<0.001
UPDRS III ^δ	0.614	<0.001	0.508	<0.001

Abbreviations
 r: Correlation coefficient
 UPDRS: Unified Parkinson’s disease Rating Scale
[†] Figures are mean +/- SD or number (%)
^a“Total UPDRS” score is the combined sum of parts I, II, and III. Theoretical minimum and maximum values are 0 and 176, respectively (176 represented the worst disability and 0 no disability).
^βIMentation, behavior, and mood. Theoretical minimum and maximum values are 0 and 16, respectively (16 represented the worst disability and 0 no disability).
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^δIIIMotor examination. Theoretical minimum and maximum values are 0 and 108, respectively (108 represents the worst disability and 0 no disability).

was 38.5 (sensitivity=75%, specificity=76.5%). A higher mean UPDRS score, which may imply an increase in the severity of PD, was associated with a higher risk of depression.

The GDS has been validated in subjects aged 55 years and older, and it is also useful in patients with mild to moderate cognitive impairment [22-24]. The data on its validity in moderately to severely cognitively impaired patients are conflicting [23,25]. Although the mean MMSE score was low in our patients with severe depression, it is well known that this score significantly declines with age and lower education level [26], and low MMSE scores could also be a result of depression (e.g. because of poor attention). Moreover, the CDR scores in our group indicated mild to moderate dementia. Therefore, the GDS could be valid in our study. Although one study demonstrated that there was no significant difference in the prevalence of depression between men and women [27], our study showed that female sex is a risk factor for depression. There could be because women had a lower MMSE score and higher UPDRS score than men.

Several studies have indicated that depression disorders in PD are associated with an increased illness severity [19, 20], younger age at PD onset [19-21], longer disease duration [20,21], motor fluctuations and H/Y stage [28,29], and severe autonomic symptoms [30]. Pathology studies have demonstrated that brain nuclei known to be involved in the production of dopamine, serotonin, and norepinephrine—the main chemical targets for the pharmacological treatment of anxiety and depression—are systematically affected as the symptoms of PD progress [31].

In vivo functional neuroimaging studies have shown deficits in the same chemical pathways in subjects with PD [32]. In the present study, sex (male predominance), higher mean education (years), mean lower MMSE score, higher mean levodopa equivalent dose, lower mean Barthel index, higher mean UPDRS score, and lower mean striatal dopamine transporter uptake ratios were determined to be significant risk factors for depression.

However, the present study had several limitations. First, as a cross-sectional observation study, it may have been subject to the bias of unmeasured factors. For example, the etiologies of depression in PD may be multi-factorial, including underlying PD, medical co-morbidity, and drug-related complications. Since PD is a slowly progressing neurodegenerative disorder, patients who enrolled in this study were followed-up at the Neurology Outpatient Clinic for more than 6 months after titration of their daily anti-Parkinsonian agents to a steady dose in accordance with their clinical symptoms. There may have been changes in the data of functional imaging studies (99mTc-TRODAT-1 SPECT/CT) at baseline after enrollment in the same patient. Second, patients who were both less than 55 years old and received anti-depressant therapy for depressive disorder were excluded from the study. Further, our hospital is a medical center, which provides tertiary referral care of patients. Several patients with PD, who were either depressed or cognitively impaired, were initially treated at other hospitals and subsequently transferred to our hospital for further therapy. Thus, there is continued uncertainty in assessing the incidence of depression in patients with PD. Third, this was a cross-sectional study. Depression almost inevitably emerges with disease progression that may dominate the clinical picture of advanced PD, which contributes to severe disability and impaired quality of life

[32]. Thus, the proportion of depression in these patients may have been underestimated during the follow-up period. A long-term longitudinal study is needed to identify the course, predictors, and prognostic significance of depression in patients with PD. Lastly, the sample size was not large. Based on the stepwise procedures, only two variables were selected as important variables capable of predicting the outcome. As such, the maximum likelihood estimates of the coefficients were valid in the analysis [33].

Depression disorders are often unrecognized and untreated, and co-morbidities of these disorders with PD greatly exacerbate PD symptoms. The identification of factors associated with the development of depression disorders may help in designing preventive interventions that will decrease the risk and burden on patients with idiopathic PD. Thus, preventing and evaluating depressive disorders should be considered in high-risk patients with PD. These are important issues for patient safety and are highly relevant for addressing the quality of life of these patients in terms of their ability to perform daily activities.

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Competing interests

The authors declare that they have no competing interests.

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Table 3: Risk factors associated with depression[†].

	Non-depression (n=17)	Depression (n=76)	OR [§]	95 % CI [§]	p value [§]
Sex (women/men)	5/12	44/32	3.3	1.06-10.30	0.033
Body mass index (kg/m ²)	24.8 ± 3.1	24.1 ± 3.5	0.92	0.81-1.06	0.45
Age (years)	66.6 ± 8.1	70.0 ± 7.8	1.05	1.0-1.11	0.12
Knee osteoarthritis	3	18	1.45	0.37-5.61	0.574
Exercise habituation	13	52	0.67	0.20-2.26	0.51
Disease duration (years)	3.2 ± 2.8	5.0 ± 4.2			0.06
Education, years	8.1 ± 4.3	5.4 ± 4.7			0.016
Levodopa equivalent dose	206.9 ± 233.2	481.3 ± 4 12.0			0.022
Striatal dopamine transporter uptake ratios	1.5 ± 0.2	1.4 ± 0.2			0.015
Mini-Mental State Examination	24.6 ± 5.5	21.6 ± 6.0			0.067
Barthel Index	90.8 ± 25.8	72.6 ± 29.5			0.002
UPDRS	36.1 ± 27.8	57.8 ± 28.4			0.005
UPDRS I	2.5 ± 1.2	5.8 ± 3.1			<0.001
UPDRS II	9.8 ± 8.0	16.7 ± 10.1			0.01
UPDRS III	23.9 ± 17.6	35.3 ± 16.8			0.014
Hoehn and Yahr staging					
Stage I	12	14			
Stage II	1	20			0.001
Stage III	2	22			
Stage IV	1	8			
Stage V	1	12			

Abbreviations:

OR, odds ratio;

CI, confidence interval

[†]Figures are mean+/-SD or number (%)

Ethics approval

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

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