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ORIGINAL ARTICLE

# Association of Depression With Early Occurrence of Postural Instability in Parkinson's Disease

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## ABSTRACT

**Objective** Depression in Parkinson's disease (PD) affects the quality of life of patients. Postural instability and gait disturbance are associated with the severity and prognosis of PD. We investigated the association of depression with axial involvement in early-stage PD patients.

**Methods** This study involved 95 PD patients unexposed to antiparkinsonian drugs. After a baseline assessment for depression, the subjects were divided into a depressed PD group and a nondepressed PD group. Analyses were conducted to identify an association of depression at baseline with the following outcome variables: the progression to Hoehn and Yahr scale (H-Y) stage 3, the occurrence of freezing of gait (FOG), levodopa-induced dyskinesia, and wearing-off. The follow-up period was 53.40 ± 16.79 months from baseline.

**Results** Kaplan–Meier survival curves for H-Y stage 3 and FOG showed more prominent progression to H-Y stage 3 and occurrences of FOG in the depressed PD group than in the nondepressed PD group (log-rank $p = 0.025$ and 0.003, respectively). Depression in drug-naïve, early-stage PD patients showed a significant association with the progression to H-Y stage 3 (hazard ratio = 2.55; 95% confidence interval = 1.32–4.93; $p = 0.005$), as analyzed by Cox regression analyses. In contrast, the occurrence of levodopa-induced dyskinesia and wearing-off did not differ between the two groups (log-rank $p = 0.903$ and 0.351, respectively).

**Conclusion** Depression in drug-naïve, early-stage PD patients is associated with an earlier occurrence of postural instability. This suggests shared nondopaminergic pathogenic mechanisms and potentially enables the prediction of early development of postural instability.

**Keywords** Depression; Freezing of gait; Parkinson's disease; Postural instability.

Parkinson's disease (PD) is a common neurodegenerative disorder characterized by cardinal motor symptoms, including resting tremor, bradykinesia, rigidity, and postural instability.[1,2] Although the clinical diagnosis relies primarily on motor symptoms, PD is also well known for many nonmotor symptoms. These include depression, anxiety, dementia, hallucinations, delirium, sleep disturbances, and autonomic dysfunction.[3] Depression, one of the common nonmotor symptoms of PD, causes impairment of the patient's quality of life (QoL) but is often overlooked.[4,5] The pathogenic mechanisms of depression in PD are still unclear; however, they may be related to dopaminergic and nondopaminergic dysfunction.[6,7] It may precede the clinical diagnosis of PD with an overlap of other symptoms, including hyposmia, sleep disturbance, reduced appetite, constipation, fatigue, and psychomotor retardation.[5] Depression is reported to have correlations with other clinical features of PD, including a longer duration of illness, a younger onset of PD, frequent falls, poor motor compensation, and therapy complications.[5,8]

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Among the motor symptoms of PD, postural instability and gait disturbance (PIGD) are the main causes of the decreased QoL of patients, and they are associated with the severity and prognosis of the disease.[9,10] Postural instability can be reflected by the Hoehn and Yahr scale (H-Y) screening tool as stages 3−5, which could be disabling motor symptoms in mid- or late-stage PD.[11,12] Freezing of gait (FOG), defined as a brief episodic absence of effective step generation despite having the intention to walk, is one of the main causes of gait disturbance and increases the risk of falls, which results in QoL impairment in patients with PD.[13,14] However, in PD, the time of occurrence of these symptoms is heterogeneous, with some patients showing rapid progression and early onset of postural instability and FOG, whereas others show a relatively stable course of disease progression without these balance problems or gait difficulties over time.[15] Although several clinical characteristics have been suggested to be associated with prognosis and mortality in PD patients, the predictive factors in patients with early-stage PD are still unclear.[3-5,8,9,14]

Based on previous studies that have found that the pathophysiology of postural instability and FOG is associated with the non-dopaminergic system beyond the nigrostriatal system,[16,17] we investigated the association of depression with the progression of these axial motor symptoms in drug-naïve patients with early-stage PD. We compared these associations with the association of depression with motor complications, including levodopa-induced dyskinesia and wearing-off, which are known to be mainly related to the nigrostriatal dopaminergic systems.[2,18]

## MATERIALS & METHODS

### Study subjects

This retrospective study enrolled patients who were diagnosed with PD by movement disorder experts at the Asan Medical Center, Seoul, Korea, from November 2011 to November 2018. All patients were initially diagnosed with PD according to the clinical diagnostic criteria of the UK PD Society Brain Bank and had no prior histories of exposure to antiparkinsonian drugs.[19] All subjects underwent initial baseline assessments for depression and cognitive function with the Korean version of the Geriatric Depression Scale (GDS) and the Seoul Neuropsychological Screening Battery (SNSB).[20,21]

The study exclusion criteria included the following: 1) patients with a long duration of cardinal motor symptoms (> 3 years) prior to the diagnosis of PD; 2) patients who underwent assessment for depression and cognitive function more than 6 months after the diagnosis of PD; 3) patients with Parkinson's disease dementia (PDD) based on the Movement Disorder Society diagnostic criteria for PDD;[22] 4) patients with histories of major depression or exposure to antidepressant drugs prior to a PD diagnosis; 5) patients with H-Y stage 3 or higher and FOG at the time of the PD diagnosis; and 6) patients whose motor severities at the time of diagnosis of PD were not evaluated properly.

The Institutional Review Board of Asan Medical Center approved this study (no. 2021-1670). The board waived the need for prior informed consent from the participants because this research was a solely retrospective observational study. All procedures performed in studies involving human participants were conducted in accordance with the ethical standards of the institutional and/or national research committee and with the 1975 Helsinki declaration and its later amendments or comparable ethical standards.

### Clinical assessments

#### Baseline characteristics

The baseline patient demographic characteristics collected included the following: sex, age at the onset of PD, age at the diagnosis of PD, and duration of the disease before the diagnosis of PD. Age at the onset of PD was defined as the age at which the patient first showed any cardinal motor symptoms of PD. These data were based on the history obtained from the patients and their caregivers. The age at the diagnosis of PD was defined as the age at which the patients were diagnosed with PD in our clinic, and the duration of their disease at the time of their diagnosis with PD was calculated as the time interval between the patient's age at the onset of PD symptoms and their age at the time of the diagnosis with PD.

Baseline motor characteristics of PD included the initial chief complaint, motor score, and H-Y stage of each patient at the first visit to our clinic. The initial chief complaint, which caused the patient to be disabled and visit the clinic, was assessed from the medical chart review. All patients visited the clinic due to one or more cardinal motor symptoms of PD. If the patient visited due to tremor, the initial chief complaint was classified as tremor, and if the patient visited due to cardinal motor symptoms other than tremor, it was classified as akinetic-rigid or PIGD.[23] The initial motor score is the sum of the Unified Parkinson's Disease Rating Scale (UPDRS) Part 3 motor Item 20 (tremor at rest: jaw, upper and lower extremities, 0−20), 21 (action or postural tremor: upper extremities, 0−8), 22 (rigidity: upper and lower extremities, 0−16), 23 (finger taps: upper extremities, 0−8), and 26 (leg agility: lower extremities, 0−8), which has a range from 0 to 60 points. In our institution, at the first visits to our clinic, tremor, rigidity, and bradykinesia were recorded as UPDRS motor subscores, and axial symptoms, including postural instability, were recorded as the H-Y stage. These initial motor scores and H-Y stages were assessed through neurological examination by move-

ment disorder experts during periods when the patient met the criteria of a drug-naïve state.

### Assessment of depression and cognitive function

This study analyzed each patient using the Korean version of the GDS score for an assessment of depression. The Korean version of the GDS is a self-report questionnaire for evaluating the severity of depression that consists of 30 questions and has a cut-off score of 18 points.[20] Based on this threshold, we classified patients with a score of 18 or more as the patient group with depression and those with scores less than 18 points as the patient group without depression.

The results for cognitive functioning based on the SNSB were also collected as the baseline data for cognitive characteristics. The SNSB is a standardized neuropsychological test battery used in Korea and it includes the assessment of five major cognitive domains: attention, frontal/executive, language, memory, and visuospatial domains.[21] The result for each domain was considered to indicate impairment if the score of the domain was more than 1.0 standard deviation (SD) below the mean of the validated norms for that domain.[21]

### Assessment of the outcome variables

We defined the following four outcome variables to evaluate the effect of depression on PD patients in this study: the progression to H-Y stage 3, the occurrence of FOG, levodopa-induced dyskinesia, and wearing-off. After the diagnosis of PD, the patients visited our clinic every 3−6 months, and the four outcome variables were routinely assessed at every visit based on the protocol of our clinic. H-Y stage and the presence of FOG were assessed through neurological examination during the medication 'on' state of the patients. The presence of levodopa-induced dyskinesia or wearing-off was assessed through the patient's history obtained from the patients and their caregivers or observation at the clinic. These data were documented in the patient's electronic medical record. During the follow-up period, we documented any occurrences of these four symptoms and obtained the time when they occurred and additionally obtained the H-Y stage and levodopa equivalent daily dose (LEDD) of each patient at the last visit within the period. The LEDD of each patient at the time of occurrence of the four outcome variables, if they occurred, was also obtained. LEDD was obtained as a variable for adjustment in the analyses of the study, and the method of calculating the LEDD was based on a previous report.[24]

### Statistical analysis

The clinical characteristics of the PD patient subgroups with and without depression were compared using Student's *t*-test, the Mann−Whitney U test, the chi-squared test, or Fisher's exact test according to the variable type. Kaplan−Meier survival curves were applied for each outcome variable to compare the disease progression between the depressed and nondepressed groups and to visualize the differences. The significance of the differences in the Kaplan−Meier survival curves was verified with log-rank tests.

The effect of each variable, including depression, sex, age at onset of PD, duration of PD, initial chief complaint, initial motor score and H-Y stage, cognitive functions, and LEDD (at the time of occurrence of each outcome variable or at the last visit of the patients without an occurrence of the outcome variable), on the four outcome variables was measured with three-step Cox proportional hazard regression analyses for each outcome variable. First, univariate Cox proportional hazard regression analyses for each independent variable with an unadjusted hazard ratio (HR) were performed. Thereafter, multivariate Cox proportional hazard regression analyses for each independent variable after adjusting for all other variables were performed. Finally, we conducted multivariate Cox proportional hazard regression analyses after selecting and adjusting the associated variables with $p$ values < 0.2 in the previous steps. Additionally, we repeated these steps using initial motor subscores for bradykinesia (summation of UPDRS Part 3 motor Item 23 and 26 scores), rigidity (summation of UPDRS Part 3 motor Item 22 scores), and tremor (summation of UPDRS Part 3 motor Item 20 and 21 scores) as variables instead of the initial motor scores in the analyses of the four outcome variables and using daily levodopa dose as a variable instead of LEDD in the analyses for levodopa-induced dyskinesia and wearing-off.

Statistical significance for the $p$ value was set to less than 0.05, and all statistical analyses were performed using SPSS version 21.0 (IBM Corp., Armonk, NY, USA).

## RESULTS

### Clinical characteristics

The study participants' clinical characteristics are documented in Table 1. A total of 95 PD patients (25 depressed and 70 nondepressed patients) who met the criteria of this study were enrolled and had a mean follow-up period of 53.40 ± 16.79 (range, 13−98) months. The participant's mean age at onset of PD symptoms was 66.62 ± 8.65 years, and the mean age at diagnosis was 67.53 ± 8.50 years. The mean duration of disease before diagnosis was 9.96 ± 7.62 months. SNSB data were unavailable for eight patients (4 in each group).

The GDS score was 22.48 ± 2.86 points in the depressed group and 9.16 ± 4.74 points in the nondepressed group ($p$ < 0.001). Among the clinical characteristics at baseline, the initial motor

**Table 1.** The clinical characteristics of the patients

| | Total (*n* = 95) | Depressed (*n* = 25) | Non-depressed (*n* = 70) | *p*-value |
|---|---|---|---|---|
| GDS | 12.66 ± 7.30 | 22.48 ± 2.86 | 9.16 ± 4.74 | < 0.001 |
| Female sex (%) | 62.1 | 72.0 | 58.6 | 0.235 |
| Age at onset of PD (yr) | 66.62 ± 8.65 (42–85) | 66.12 ± 9.18 (49–83) | 66.80 ± 8.51 (42–85) | 0.738 |
| Age at diagnosis of PD (yr) | 67.53 ± 8.50 (44–85) | 67.12 ± 9.14 (51–85) | 67.67 ± 8.32 (44–85) | 0.782 |
| Duration of PD (mon) | 9.96 ± 7.62 (0–36) | 10.36 ± 7.14 (2–28) | 9.81 ± 7.83 (0–36) | 0.760 |
| Duration of follow-up (mon) | 53.40 ± 16.79 (13–98) | 52.56 ± 21.11 (18–94) | 53.70 ± 15.12 (13–98) | 0.805 |
| Initial chief complaint (%) | | | | 0.278 |
| Akinetic-rigid or PIGD | 54.7 | 64.0 | 51.4 | |
| Tremor | 45.3 | 36.0 | 48.6 | |
| Initial H-Y stage | 1.83 ± 0.48 | 1.94 ± 0.46 | 1.79 ± 0.49 | 0.171 |
| Initial motor score | 12.46 ± 5.21 | 14.16 ± 4.88 | 11.81 ± 5.22 | 0.052 |
| Bradykinesia | 6.05 ± 2.77 | 7.28 ± 2.69 | 5.61 ± 2.69 | 0.009 |
| Rigidity | 4.44 ± 2.52 | 5.04 ± 2.57 | 4.23 ± 2.48 | 0.168 |
| Tremor | 1.93 ± 2.19 | 1.84 ± 1.75 | 1.96 ± 2.34 | 0.809 |
| Cognitive impairment (%)* | | | | |
| Attention | 10.3 | 9.5 | 10.6 | > 0.999 |
| Language | 9.2 | 9.5 | 9.1 | > 0.999 |
| Visuospatial | 17.4 | 15.0 | 18.2 | > 0.999 |
| Memory | 26.4 | 38.1 | 22.7 | 0.164 |
| Frontal and executive | 20.9 | 23.8 | 20.0 | 0.761 |
| LEDD at the last visit (mg) | 567.13 ± 270.18 | 651.40 ± 286.61 | 537.04 ± 259.59 | 0.069 |
| Daily levodopa dose at the last visit (mg) | 489.74 ± 208.80 | 550.00 ± 184.56 | 468.21 ± 213.92 | 0.093 |
| H-Y stage at the last visit | 2.69 ± 0.58 | 3.00 ± 0.50 | 2.58 ± 0.57 | 0.001 |

The values shown are means ± standard deviation with or without the range, unless otherwise indicated. *8 missing data: 4 each in both groups. GDS, Geriatric Depression Scale; PD, Parkinson's disease; PIGD, postural instability and gait disturbance; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose.

scores showed a slightly different trend between the depressed and nondepressed PD groups (14.16 ± 4.88 and 11.81 ± 5.22, respectively; $p = 0.052$), with higher motor subscores for bradykinesia in the depressed PD group than in the nondepressed PD group (7.28 ± 2.69 and 5.61 ± 2.69, respectively; $p = 0.009$). The other characteristics at baseline were not significantly different between the two groups. At the last visits during the period, LEDD showed a different trend in the two groups; however, it did not achieve statistical significance (651.40 ± 286.61 and 537.04 ± 259.59, respectively; $p = 0.069$). The H-Y stages at the last visits were significantly different between the two groups (3.00 ± 0.50 and 2.58 ± 0.57, respectively; $p = 0.001$).

## Progression to Hoehn and Yahr stage 3

During the follow-up period, 49 of 95 patients (51.6%) showed progression to H-Y stage 3 (17 of 25; 68.0% in the depressed group, 32 of 70; 45.7% in the nondepressed group). Figure 1 shows Kaplan–Meier curves for survival under H-Y stage 3, illustrating a more prominent progression to H-Y stage 3 in the depressed group than in the nondepressed group (log-rank $p = 0.025$). In Table 2, multivariate Cox proportional hazard analysis after adjusting for associated variables showed that depression (HR = 2.55; 95% confidence interval [CI] = 1.32–4.93; $p = 0.005$), higher age at onset (HR = 1.05; 95% CI = 1.01–1.10; $p = 0.007$), and frontal and executive dysfunction (HR = 2.09; 95% CI = 1.02–4.31; $p = 0.045$) were associated with the progression to H-Y stage 3. Initial H-Y stage showed a significant association in univariate Cox proportional hazard analysis (HR = 2.60; 95% CI = 1.24–5.44; $p = 0.011$); however, it only showed a trend toward an association without achieving statistical significance in multivariate analysis after adjusting for associated variables (HR = 2.22; 95% CI = 0.90–5.47; $p = 0.084$). The initial chief complaint for tremor showed a negative association (HR = 0.43; 95% CI, 0.22–0.82; $p = 0.010$). Analyses using initial motor subscores as variables instead of initial motor scores are presented in Supplementary Table 1 (in the online-only Data Supplement), and the effect of depression was not different from the analyses using initial motor scores as a variable.

## Occurrence of freezing of gait

FOG developed in 5 (5.3%) out of the 95 patients (4 of 25; 16.0% in the depressed group, 1 of 70; 1.4% in the nondepressed group). Figure 1 shows the Kaplan–Meier curves for FOG-free patient survival, illustrating more prominent occurrences of FOG

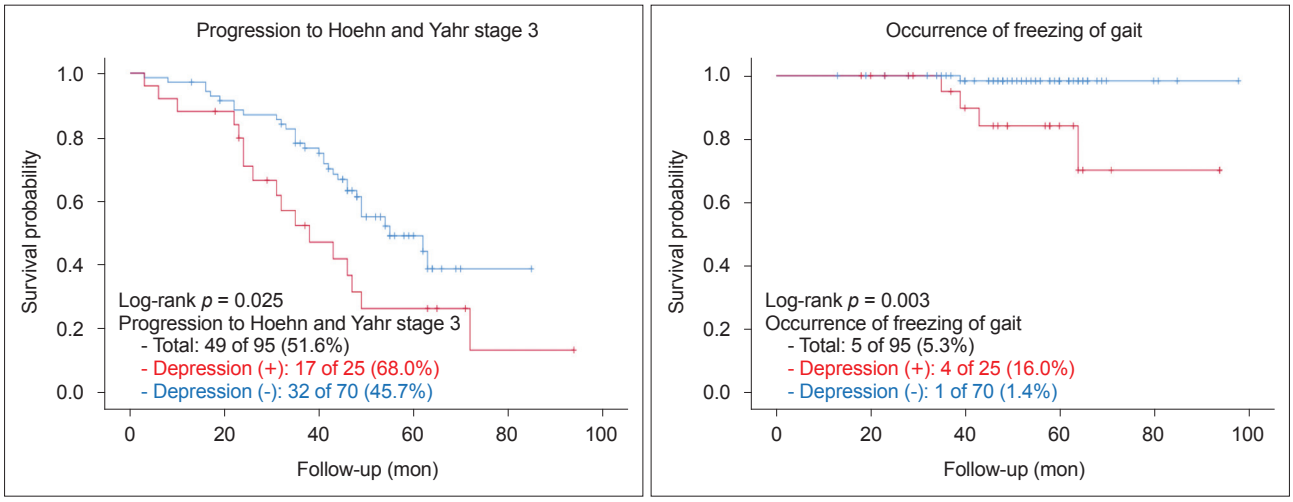


**Figure 1.** Kaplan–Meier survival curves for the progression to Hoehn and Yahr stage 3 and the occurrence of freezing of gait among patients with Parkinson's disease.

**Table 2.** The associations of the clinical characteristics with the progression to Hoehn and Yahr stage 3

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.95 (1.07–3.54) | 0.029 | 2.41 (1.23–4.72) | 0.011 | 2.55 (1.32–4.93) | 0.005 |
| Female sex | 0.82 (0.46–1.45) | 0.489 | 0.83 (0.37–1.86) | 0.647 | - | - |
| Age at onset of PD | 1.06 (1.02–1.10) | 0.002 | 1.05 (1.01–1.10) | 0.008 | 1.05 (1.01–1.10) | 0.007 |
| Duration of PD | 0.98 (0.94–1.02) | 0.321 | 0.99 (0.94–1.04) | 0.547 | - | - |
| Initial chief complaint - tremor | 0.52 (0.29–0.93) | 0.028 | 0.41 (0.21–0.79) | 0.008 | 0.43 (0.22–0.82) | 0.010 |
| Initial H-Y stage | 2.60 (1.24–5.44) | 0.011 | 2.22 (0.90–5.48) | 0.085 | 2.22 (0.90–5.47) | 0.084 |
| Initial motor scores | 1.06 (1.01–1.12) | 0.034 | 1.01 (0.93–1.10) | 0.830 | 1.02 (0.94–1.11) | 0.601 |
| Cognitive impairment | | | | | | |
| Attention | 2.20 (0.92–5.25) | 0.077 | 2.16 (0.75–6.24) | 0.154 | 1.82 (0.73–4.58) | 0.200 |
| Language | 1.62 (0.64–4.13) | 0.313 | 1.36 (0.46–4.01) | 0.578 | - | - |
| Visuospatial | 1.34 (0.62–2.90) | 0.462 | 0.91 (0.32–2.57) | 0.863 | - | - |
| Memory | 1.82 (0.96–3.45) | 0.065 | 1.48 (0.59–3.70) | 0.399 | 1.30 (0.58–2.91) | 0.530 |
| Frontal and executive | 2.23 (1.11–4.48) | 0.025 | 2.14 (1.03–4.42) | 0.040 | 2.09 (1.02–4.31) | 0.045 |
| LEDD | 1.001 (0.999–1.002) | 0.351 | 1.001 (0.999–1.003) | 0.357 | - | - |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

in the depressed PD group than in the nondepressed PD group (log-rank $p = 0.003$). In Table 3, univariate Cox proportional hazard analysis revealed that patients with depression (HR = 12.70; 95% CI = 1.42−113.89; $p = 0.023$) and higher LEDD (HR = 1.003; 95% CI = 1.000−1.006; $p = 0.024$) might have associations with the occurrence of FOG; however, multivariate analyses found no significant associated factors. Analyses using initial motor subscores as variables instead of the initial motor scores are presented in Supplementary Table 2 (in the online-only Data Supplement), and the results are not significantly different.

## Occurrence of levodopa-induced dyskinesia

Levodopa-induced dyskinesia developed in 15 of 95 (15.8%) PD patients (4 of 25; 16.0% in the depressed group, 11 of 70; 15.7% in the nondepressed group). The Kaplan−Meier curves for levodopa-induced dyskinesia showed no significant differences between the depressed and nondepressed groups (log-rank $p = 0.903$) (Figure 2). In Table 4, multivariate Cox proportional hazard analysis after adjusting for associated variables showed that female sex (HR = 10.40; 95% CI = 1.25−86.77; $p = 0.030$), higher initial motor scores (HR = 1.17; 95% CI = 1.01−1.36; $p = 0.043$), and visuospatial dysfunction (HR = 3.86; 95% CI = 1.09−13.65; $p = 0.036$) were associated with the occurrence of levodopa-induced dyskinesia. Analyses using initial motor subscores or daily levodopa dose as variables instead of initial motor scores or LEDD are presented in Supplementary Tables 3 (initial motor subscores) and 4 (daily levodopa dose) (in the online-only Data Supplement), and the results are not significantly different.

**Table 3.** The associations of the clinical characteristics with the occurrence of freezing of gait

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 12.70 (1.42–113.89) | 0.023 | ∞* (0.00–∞*) | 0.727 | ∞* (0.00–∞*) | 0.948 |
| Female sex | 0.35 (0.06–2.11) | 0.250 | 0.09 (0.00–∞*) | 0.976 | | |
| Age at onset of PD | 0.95 (0.86–1.05) | 0.334 | 0.95 (0.004–246.32) | 0.984 | | |
| Duration of PD | 1.03 (0.92–1.15) | 0.606 | 0.70 (0.00–∞*) | 0.929 | | |
| Initial chief complaint – tremor | 0.02 (0.00–19.93) | 0.251 | 0.25 (0.00–∞*) | 0.984 | | |
| Initial H-Y stage | 7.48 (0.34–166.87) | 0.204 | ∞* (0.00–∞*) | 0.888 | | |
| Initial motor scores | 1.02 (0.86–1.20) | 0.849 | 0.37 (0.00–∞*) | 0.917 | | |
| Cognitive impairment | | | | | | |
| Attention | 5.48 (0.49–60.52) | 0.165 | 2.31 (0.00–∞*) | 0.992 | 8.91 (0.41–192.46) | 0.163 |
| Language | 0.04 (0.00–∞*) | 0.748 | 0.002 (0.00–∞*) | 0.969 | | |
| Visuospatial | 3.41 (0.31–37.65) | 0.316 | ∞* (0.00–∞*) | 0.897 | | |
| Memory | 1.83 (0.17–20.16) | 0.623 | 0.000 (0.00–∞*) | 0.928 | | |
| Frontal and executive | 2.58 (0.23–28.47) | 0.440 | ∞* (0.00–∞*) | 0.943 | | |
| LEDD | 1.003 (1.000–1.006) | 0.024 | 1.02 (0.77–1.34) | 0.916 | 1.004 (0.999–1.009) | 0.105 |

*> 1,000 without statistical significance. PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

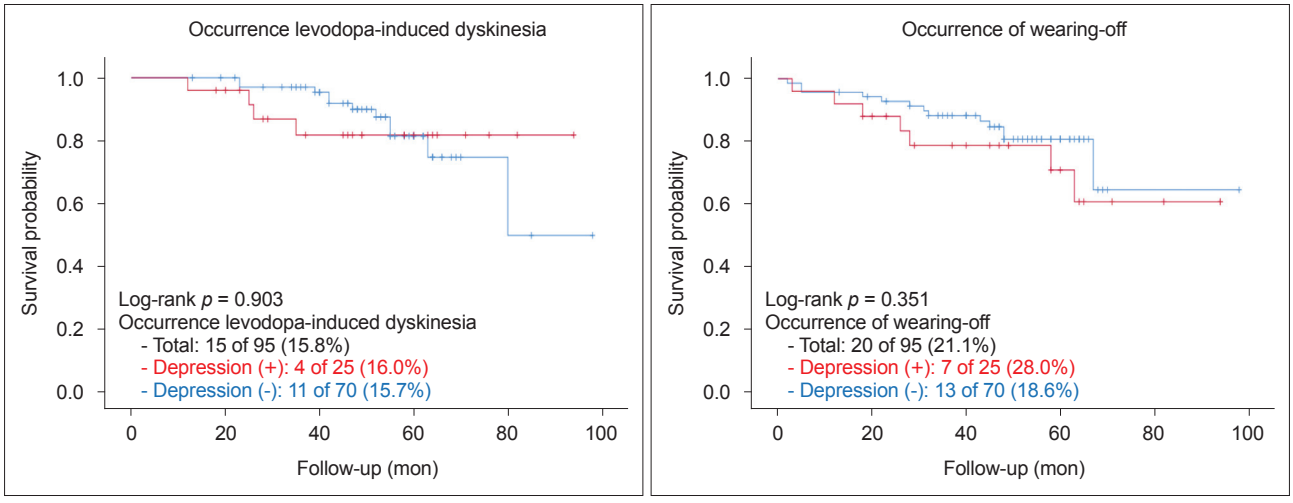


**Figure 2.** Kaplan–Meier survival curves for the occurrence of levodopa-induced dyskinesia and wearing-off among patients with Parkinson's disease.

## Occurrence of wearing-off

Wearing-off developed in 20 of 95 (21.1%) PD patients (7 of 25; 28.0% in the depressed group, 13 of 70; 18.6% in the nondepressed group). The Kaplan−Meier curves for wearing-off showed no difference between the depressed and nondepressed groups (log-rank $p = 0.351$) (Figure 2). In Table 5, only higher age at onset showed a negative association with the occurrence of wearing-off in multivariate Cox proportional hazard analysis after adjusting for associated variables (HR = 0.95; 95% CI = 0.90−1.00; $p = 0.040$). Analyses using initial motor subscores or daily levodopa dose as variables instead of initial motor scores or LEDD are presented in Supplementary Tables 5 (initial motor subscores) and 6 (daily levodopa dose) (in the online-only Data Supplement). When using initial motor subscores, motor subscores for bradykinesia (HR = 1.38; 95% CI = 1.11−1.71; $p = 0.004$) and rigidity (HR = 0.60; 95% CI = 0.45−0.81; $p = 0.001$) were associated with the occurrence of wearing-off (Supplementary Table 5 in the online-only Data Supplement). The results in the analysis using the daily levodopa dose as a variable (Supplementary Table 6 in the online-only Data Supplement) were not significantly different from those in the analysis using LEDD (Table 5).

**Table 4.** The associations of the clinical characteristics with the occurrence of levodopa-induced dyskinesia

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.07 (0.34–3.41) | 0.903 | 1.69 (0.31–9.10) | 0.542 | | |
| Female sex | 3.67 (0.83–16.32) | 0.088 | 6.39 (0.82–50.06) | 0.077 | 10.40 (1.25–86.77) | 0.030 |
| Age at onset of PD | 0.98 (0.93–1.04) | 0.544 | 0.97 (0.88–1.06) | 0.478 | | |
| Duration of PD | 1.02 (0.96–1.09) | 0.532 | 0.97 (0.87–1.07) | 0.515 | | |
| Initial chief complaint – tremor | 0.75 (0.26–2.14) | 0.590 | 1.19 (0.26–5.40) | 0.825 | | |
| Initial H-Y stage | 9.99 (1.60–62.46) | 0.014 | 7.14 (0.92–55.51) | 0.060 | 3.27 (0.52–20.61) | 0.207 |
| Initial motor scores | 1.14 (1.03–1.26) | 0.014 | 1.04 (0.86–1.25) | 0.708 | 1.17 (1.01–1.36) | 0.043 |
| Cognitive impairment | | | | | | |
| Attention | 2.74 (0.58–12.92) | 0.203 | 0.57 (0.05–6.21) | 0.645 | | |
| Language | 1.82 (0.40–8.39) | 0.440 | 1.09 (0.13–9.50) | 0.936 | | |
| Visuospatial | 3.74 (1.09–12.84) | 0.036 | 10.80 (1.07–108.64) | 0.043 | 3.86 (1.09–13.65) | 0.036 |
| Memory | 1.17 (0.32–4.32) | 0.818 | 0.95 (0.01–1.72) | 0.111 | 0.54 (0.11–2.51) | 0.428 |
| Frontal and executive | 1.07 (0.23–4.98) | 0.933 | 5.32 (0.31–91.49) | 0.250 | | |
| LEDD | 1.000 (0.999–1.002) | 0.691 | 1.002 (0.998–1.005) | 0.437 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

**Table 5.** The associations of the clinical characteristics with the occurrence of wearing-off

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.55 (0.61–3.91) | 0.356 | 2.53 (0.95–6.74) | 0.063 | 1.64 (0.61–4.41) | 0.325 |
| Female sex | 0.79 (0.32–1.94) | 0.600 | 1.07 (0.33–3.41) | 0.914 | | |
| Age at onset of PD | 0.94 (0.90–0.99) | 0.024 | 0.97 (0.91–1.03) | 0.343 | 0.95 (0.90–1.00) | 0.040 |
| Duration of PD | 1.04 (0.98–1.09) | 0.182 | 1.00 (0.92–1.08) | 0.973 | 1.03 (0.98–1.09) | 0.234 |
| Initial chief complaint – tremor | 0.40 (0.15–1.04) | 0.061 | 0.38 (0.13–1.12) | 0.079 | 0.44 (0.17–1.16) | 0.098 |
| Initial H-Y stage | 0.97 (0.37–2.54) | 0.952 | 1.37 (0.37–5.04) | 0.639 | | |
| Initial motor scores | 0.96 (0.88–1.05) | 0.344 | 0.90 (0.78–1.04) | 0.155 | 0.94 (0.85–1.03) | 0.175 |
| Cognitive impairment | | | | | | |
| Attention | 1.51 (0.34–6.70) | 0.591 | 1.50 (0.25–9.12) | 0.663 | | |
| Language | 0.66 (0.09–5.01) | 0.687 | 0.48 (0.05–4.63) | 0.525 | | |
| Visuospatial | 1.34 (0.38–4.74) | 0.647 | 2.52 (0.48–13.20) | 0.273 | | |
| Memory | 0.98 (0.32–3.01) | 0.968 | 0.55 (0.11–2.68) | 0.461 | | |
| Frontal and executive | 0.61 (0.14–2.70) | 0.514 | 1.13 (0.14–9.07) | 0.906 | | |
| LEDD | 1.000 (0.998–1.002) | 0.760 | 1.001 (0.998–1.004) | 0.519 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

## DISCUSSION

In this study, depression among drug-naïve, early-stage PD patients was found to be independently associated with the earlier occurrence of postural instability. Although depression was not an independent factor associated with FOG, the data suggested that the incidence of FOG was higher in depressed PD patients in our study. The occurrence of levodopa-induced dyskinesia and wearing-off did not differ between depressed and nondepressed PD patients. These findings suggest that there are shared nondopaminergic pathogenic mechanisms between depression and PIGD symptoms of PD.

Previous research has found that depression associated with PD is related to the loss of serotonergic and noradrenergic neurons associated with the regulation of mood and reward systems. This includes the locus coeruleus, mesolimbic and mesocortical regions, and dorsal raphe.[6,7,25] Dysfunctions of the prefrontal cortex and alterations in the limbic network are also known to cause depression in PD patients.[26,27] For postural instability and FOG, the anatomical basis is less clear and is relatively complex.[17] Postural instability is related to the dysfunction of many nondopaminergic systems, as well as the dopaminergic nigrostriatal system, which includes brain regions associated with cognitive, sensory, and motor functions.[11,28,29] Additionally, neurotransmit-

ters, including norepinephrine, serotonin, and acetylcholine, are also related to the mechanism of postural instability, especially cell loss in the locus coeruleus.[30] In FOG, which frequently responds poorly to dopaminergic medication, a disconnection between the basal ganglia, the prefrontal cortex, and frontoparietal association areas is suggested to play a critical role.[2,31] Moreover, one recent study showed that limbic circuitry dysfunction was associated with FOG, suggesting that the fronto-striato-limbic pathways might be implicated in falls and FOG in PD patients.[16,17]

Based on this study's findings, it can be suggested that a possible shared nondopaminergic pathogenic mechanism exists between depression and PIGD-related axial symptoms in areas such as the locus coeruleus, prefrontal cortex, and limbic system, and that this might be the cause of the association of depression with this study's observed axial symptoms. In levodopa-induced dyskinesia and wearing-off, degeneration of the nigrostriatal dopaminergic systems with striato-cortical sensorimotor pathways is the most important mechanism, rather than the limbic system and other nondopaminergic systems, and the nonassociation of depression and these motor complications in the current findings reinforces the potential for a shared nondopaminergic pathogenic mechanism between depression and PIGD symptoms.[2,18]

At baseline, the depressed group presented more severe motor scores than the nondepressed group, and although the statistical significance was not satisfied, LEDDs at the last visits were also higher in the depressed group. However, although depression is already known to be associated with poor motor compensation and baseline motor severity is a known risk factor for motor progression,[8,32] depression was an independent risk factor for early postural instability presenting as H-Y stage 3 after adjusting for these motor severity-associated factors. In our multivariate analysis, initial motor scores did not achieve statistical significance; however, it should be considered that our motor score consisted of only a part of the UPDRS motor score with a relatively small range of scores. In particular, the initial motor scores used in the present study have a lower proportion of bradykinesia scores with a range of 0−16 compared to the rigidity (0−16) and tremor (0−28) scores, while the whole UPDRS motor score has a higher proportion of bradykinesia scores with a range of 0−36 compared to the rigidity (0−20) and tremor (0−28) scores. This might distort the effect of initial motor severity on the occurrence of outcome motor symptoms in our study.

Therefore, we conducted additional analyses using separate subscores for bradykinesia, rigidity, and tremor to compensate for these limitations. In this additional analysis, bradykinesia severity was associated with the progression to H-Y stage 3, and depression was another independent prognostic factor for rapid progression. Therefore, baseline motor severity should not be excluded from the prognostic factors of PD. However, rigidity severity was negatively associated in the additional analysis, and this confusing result suggests that the distorted effect of motor scores on the progression of H-Y stage is due to the incomplete UPDRS motor score. To establish depression as a prognostic factor for postural instability, completely independent of motor severity, additional prospective studies including the full UPDRS motor score at baseline are warranted. Although it did not reach statistical significance with $p = 0.084$, higher initial H-Y stages showed a trend toward a more rapid progression of H-Y stage in this study.

Additionally, frontal and executive dysfunction were identified as factors associated with postural instability in our study. Postural instability is known to be associated with cognitive impairment, and in particular, previous studies reported that postural instability in PD is related to impaired executive function and deterioration of frontal lobe function, which is consistent with the results of this study.[33] The initial chief complaint of tremor at baseline showed a negative correlation with the progression to H-Y stage 3, which suggests the possibility that patients with the tremor-dominant subtype of PD were more often included than those with an initial complaint for tremor.[23] However, assessing the risk of progression based on the presence of tremor requires caution, and due to the lack of the full UPDRS score in this study, tremor-dominant or PIGD subtypes were not distinguishable accurately.[23]

Unfortunately, despite the possible shared mechanisms between depression and FOG[2,31] and the more prominent occurrence of FOG in the depressed group in our study, we failed to demonstrate that depression is an independent risk factor for FOG or identify any factors associated with FOG. This might be because FOG occurred in only 5 patients, and thus, statistical power was clearly lacking. However, considering that 4 out of 5 patients who developed FOG belonged to the depressed group in our study and that depression preceded FOG in advanced PD patients in a previous study,[34] the association of depression and development of FOG in the early stage of PD deserves to be verified with a larger study.

Previous research has often reported on the observed association between depression and motor symptoms in PD. Depression was reported to be associated with poor motor compensation in PD in one study, and another study found that the prognostic factor of rapid progression in PD included mood impairment, such as depression and anxiety.[8,35] When examining PIGD symptoms, several previous studies have reported that depression is more common in patients with postural instability than in those without postural instability, but these studies only suggested a possible association of depression with postural instability and

did not specifically report or evaluate depression in PD patients as a predictor of postural instability in the future.[26,36] It is important to note that the timing of the occurrence of these axial symptoms reflects the progression and overall prognosis of the disease. Additionally, falls caused by postural instability and FOG increase the levels of disability, so predicting the occurrence of postural instability and FOG is important in practice.[10,36,37] The intent of this study was to determine whether depression identified in the early stages of PD, especially at the time of diagnosis, could predict an earlier occurrence of these axial motor symptoms. Since depression itself negatively affects the QoL of patients[4] and is also a predictor of postural instability in PD, it is of even more importance to emphasize that possible patient depression should be evaluated and should not be overlooked at the time of PD diagnosis.

In our study, levodopa-induced dyskinesia was associated with female sex, higher initial motor scores (subscore for bradykinesia, especially), and visuospatial dysfunction. Wearing-off was significantly negatively associated with a higher age at onset and showed a controversial relationship with bradykinesia and rigidity subscores, possibly due to the incomplete UPDRS motor scores. In previous studies, risk factors for these motor complications were reported to include younger age at onset, higher dose of levodopa, use of entacapone, lower weight, female sex, and severe motor symptoms at baseline.[38,39] Some of the previously known risk factors for these motor complications showed significant correlations in our study, but some showed negative results. This might be because our follow-up period was not long enough for motor complications to be observed (follow-up years < 5 years; 15 levodopa-induced dyskinesia and 20 wearing-off) and analyzed in detail. Furthermore, the nonassociations of LEDD or daily levodopa dose with these motor complications in this study might be due to the relatively low daily levodopa doses (489.74 ± 208.80 mg at the last visits) in most of our patients compared with other studies for motor complications, 39 which reported daily levodopa dose > 600 mg as a risk factor. We conducted additional analyses for motor complications using daily levodopa dose as a variable instead of LEDD (Supplementary Tables 4 and 6 in the online-only Data Supplement) based on these previous studies that reported a higher levodopa dose as a risk factor for motor complications.[38,39] The association of visuospatial dysfunction with levodopa-induced dyskinesia in our study lacks evidence, which is inconsistent with the result of one previous study that reported impairment of attention and executive function as a risk factor for levodopa-induced dyskinesia.[40] Additional research is needed with a longer observation period, including sufficient cases of the occurrence of motor complications.

This study has several limitations. First, it has a retrospective design in which the four motor outcomes were based on the clinician's accurate detection of the signs or symptoms, along with an accurate patient history data being obtained from the patients or their caregivers. The severity of the motor symptoms was evaluated only with partial items in the UPDRS motor scores, not the complete UPDRS scores. Although we partially compensated through the additional analysis using motor subscores for individual cardinal motor symptoms, the lower proportion of bradykinesia scores in the initial motor scores of our study compared to the proportion of bradykinesia scores in the complete UPDRS motor score limits the strength of our result that depression is an independent prognostic factor for postural instability, which was as described above. Furthermore, classification of the motor phenotype (tremor-dominant or PIGD subtype) could not be performed based on the UPDRS scores, so the motor phenotypes were replaced by the initial chief complaint. Second, the small size of the study population and the short duration of follow-up limit the strength of this study. An investigation with only 95 patients who visited a general tertiary hospital might cause some biases, and additionally, only 20 or fewer patients each developed FOG, levodopa-induced dyskinesia, and wearing-off. Therefore, the validities of the analyses for these three outcome variables are low, and in particular, the very large confidence intervals greater than 1,000 in these analyses support these facts. Third, this study did not include an evaluation of the effect of treatment for depression on the prognosis of the early-stage PD patients. A systematic prescription of antidepressants followed by GDS evaluations was not made in the study. Furthermore, new occurrence or remission of depression during the follow-up period was not reflected in our study. Fourth, progression of the H-Y stages in our study was slightly faster than generally reported for PD.[37] Although the patients were diagnosed with PD based on the criteria of the UK PD Society Brain Bank, the possibility of misdiagnosis of atypical parkinsonism as PD at baseline or overestimation of H-Y stages during the follow-up cannot be excluded.

In conclusion, the presence of depression can be a prognostic factor for an increased incidence of postural instability in drug-naïve patients with early-stage PD. These results suggest that depression and postural instability in PD share nondopaminergic mechanisms beyond the nigrostriatal dopaminergic system. Depression in PD patients should not be overlooked, as it may suggest a more rapid development of postural instability. Additionally, it is also necessary to study whether the treatment of depression in PD patients can improve their prognosis in terms of PIGD symptoms because this knowledge may help clinicians establish more effective treatment strategies beginning in earlier stages of PD.

## Supplementary Materials

The online-only Data Supplement is available with this article at https://doi.org/10.14802/jmd.22091.

## Conflicts of Interest

The authors have no financial conflicts of interest.

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## Author Contributions

Conceptualization: Yun Su Hwang. Data curation: Yun Su Hwang, Sangjin Lee. Formal analysis: Yun Su Hwang, Sungyang Jo, Seung Hyun Lee, Kye Won Park, Sangjin Lee. Funding acquisition: Sun Ju Chung. Investigation: Yun Su Hwang. Methodology: Yun Su Hwang. Project administration: Yun Su Hwang, Sun Ju Chung. Resources: Sun Ju Chung. Software: Yun Su Hwang. Supervision: Yun Su Hwang, Sun Ju Chung. Validation: Yun Su Hwang. Visualization: Sungyang Jo, Seung Hyun Lee, Kye Won Park. Writing—original draft: Yun Su Hwang. Writing—review & editing: Sun Ju Chung.

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**Supplementary Table 1.** The associations of the clinical characteristics with the progression to Hoehn and Yahr stage 3 (analyses adjusting initial motor subscores)

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.95 (1.07–3.54) | 0.029 | 2.48 (1.28–4.83) | 0.007 | 2.58 (1.34–4.97) | 0.004 |
| Female sex | 0.82 (0.46–1.45) | 0.489 | 0.79 (0.34–1.83) | 0.583 | | |
| Age at onset of PD | 1.06 (1.02–1.10) | 0.002 | 1.06 (1.02–1.11) | 0.003 | 1.06 (1.02–1.11) | 0.003 |
| Duration of PD | 0.98 (0.94–1.02) | 0.321 | 0.96 (0.91–1.01) | 0.128 | 0.97 (0.92–1.01) | 0.164 |
| Initial chief complaint - tremor | 0.52 (0.29–0.93) | 0.028 | 0.53 (0.26–1.09) | 0.083 | 0.55 (0.27–1.10) | 0.091 |
| Initial H-Y stage | 2.60 (1.24–5.44) | 0.011 | 1.15 (0.34–3.90) | 0.824 | 1.20 (0.37–3.87) | 0.765 |
| Initial motor subscores | | | | | | |
| Bradykinesia | 1.23 (1.11–1.37) | < 0.001 | 1.33 (1.12–1.58) | 0.001 | 1.34 (1.13–1.59) | 0.001 |
| Rigidity | 1.06 (0.95–1.18) | 0.332 | 0.83 (0.70–0.99) | 0.041 | 0.83 (0.70–0.99) | 0.033 |
| Tremor | 0.96 (0.84–1.10) | 0.557 | 1.10 (0.94–1.29) | 0.249 | | |
| Cognitive impairment | | | | | | |
| Attention | 2.20 (0.92–5.25) | 0.077 | 2.12 (0.68–6.59) | 0.196 | 1.55 (0.57–4.19) | 0.392 |
| Language | 1.62 (0.64–4.13) | 0.313 | 1.89 (0.59–6.05) | 0.280 | | |
| Visuospatial | 1.34 (0.62–2.90) | 0.462 | 0.58 (0.18–1.83) | 0.348 | | |
| Memory | 1.82 (0.96–3.45) | 0.065 | 1.53 (0.57–4.08) | 0.397 | 1.28 (0.54–3.08) | 0.578 |
| Frontal and executive | 2.23 (1.11–4.48) | 0.025 | 1.64 (0.56–4.83) | 0.368 | 1.64 (0.61–4.42) | 0.324 |
| LEDD | 1.001 (0.999–1.002) | 0.351 | 0.999 (0.997–1.001) | 0.542 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

**Supplementary Table 2.** The associations of the clinical characteristics with the occurrence of freezing of gait (analyses adjusting initial motor subscores)

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 12.70 (1.42–113.89) | 0.023 | ∞* (0.00–∞*) | 0.632 | ∞* (0.00–∞*) | 0.895 |
| Female sex | 0.35 (0.06–2.11) | 0.250 | 0.10 (0.00–∞*) | 0.926 | | |
| Age at onset of PD | 0.95 (0.86–1.05) | 0.334 | 0.94 (0.13–6.53) | 0.946 | | |
| Duration of PD | 1.03 (0.92–1.15) | 0.606 | 0.76 (0.05–10.83) | 0.841 | | |
| Initial chief complaint – tremor | 0.02 (0.00–19.93) | 0.251 | 0.22 (0.00–∞*) | 0.943 | | |
| Initial H-Y stage | 7.48 (0.34–166.87) | 0.204 | 48.90 (0.00–∞*) | 0.934 | | |
| Initial motor subscores | | | | | | |
| Bradykinesia | 1.27 (0.91–1.76) | 0.154 | 1.16 (0.00–∞*) | 0.988 | 0.82 (0.53–1.25) | 0.355 |
| Rigidity | 1.01 (0.71–1.44) | 0.967 | 0.28 (0.00–∞*) | 0.819 | | |
| Tremor | 0.61 (0.29–1.28) | 0.191 | 0.71 (0.00–∞*) | 0.963 | 0.000 (0.00–∞*) | 0.790 |
| Cognitive impairment | | | | | | |
| Attention | 5.48 (0.49–60.52) | 0.165 | 6.30 (0.00–∞*) | 0.953 | ∞* (0.00–∞*) | 0.812 |
| Language | 0.04 (0.00–∞*) | 0.748 | 0.02 (0.00–∞*) | 0.940 | | |
| Visuospatial | 3.41 (0.31–37.65) | 0.316 | ∞* (0.00–∞*) | 0.851 | | |
| Memory | 1.83 (0.17–20.16) | 0.623 | 0.003 (0.00–∞*) | 0.887 | | |
| Frontal and executive | 2.58 (0.23–28.47) | 0.440 | 283.56 (0.00–∞*) | 0.882 | | |
| LEDD | 1.003 (1.000–1.006) | 0.024 | 1.01 (0.84–1.21) | 0.932 | 1.000 (0.993–1.006) | 0.900 |

*> 1,000 without statistical significance. PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

**Supplementary Table 3.** The associations of the clinical characteristics with the occurrence of levodopa-induced dyskinesia (analyses adjusting initial motor subscores)

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.07 (0.34–3.41) | 0.903 | 1.89 (0.34–10.66) | 0.471 | | |
| Female sex | 3.67 (0.83–16.32) | 0.088 | 9.58 (1.16–79.00) | 0.036 | 15.11 (1.60–143.13) | 0.018 |
| Age at onset of PD | 0.98 (0.93–1.04) | 0.544 | 0.97 (0.88–1.07) | 0.563 | | |
| Duration of PD | 1.02 (0.96–1.09) | 0.532 | 0.98 (0.88–1.09) | 0.649 | | |
| Initial chief complaint – tremor | 0.75 (0.26–2.14) | 0.590 | 1.27 (0.23–6.89) | 0.785 | | |
| Initial H-Y stage | 9.99 (1.60–62.46) | 0.014 | 7.55 (0.35–161.86) | 0.196 | 1.94 (0.26–14.20) | 0.515 |
| Initial motor subscores | | | | | | |
| Bradykinesia | 1.37 (1.11–1.70) | 0.003 | 1.44 (1.08–1.92) | 0.012 | 1.46 (1.11–1.92) | 0.007 |
| Rigidity | 1.25 (1.00–1.55) | 0.047 | 0.80 (0.51–1.26) | 0.337 | 0.89 (0.62–1.27) | 0.515 |
| Tremor | 1.03 (0.83–1.28) | 0.762 | 1.13 (0.80–1.60) | 0.482 | | |
| Cognitive impairment | | | | | | |
| Attention | 2.74 (0.58–12.92) | 0.203 | 0.58 (0.05–7.49) | 0.680 | | |
| Language | 1.82 (0.40–8.39) | 0.440 | 1.38 (0.13–14.75) | 0.792 | | |
| Visuospatial | 3.74 (1.09–12.84) | 0.036 | 8.90 (0.81–97.89) | 0.074 | 4.14 (1.13–15.14) | 0.032 |
| Memory | 1.17 (0.32–4.32) | 0.818 | 0.11 (0.01–2.34) | 0.157 | 0.63 (0.13–3.04) | 0.565 |
| Frontal and executive | 1.07 (0.23–4.98) | 0.933 | 5.47 (0.22–136.47) | 0.301 | | |
| LEDD | 1.000 (0.999–1.002) | 0.691 | 1.000 (0.995–1.005) | 0.991 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

**Supplementary Table 4.** The associations of the clinical characteristics with the occurrence of levodopa-induced dyskinesia (analyses adjusting daily levodopa dose)

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.07 (0.34–3.41) | 0.903 | 1.66 (0.31–8.86) | 0.551 | | |
| Female sex | 3.67 (0.83–16.32) | 0.088 | 6.39 (0.82–50.06) | 0.077 | 10.40 (1.25–86.77) | 0.030 |
| Age at onset of PD | 0.98 (0.93–1.04) | 0.544 | 0.97 (0.88–1.06) | 0.500 | | |
| Duration of PD | 1.02 (0.96–1.09) | 0.532 | 0.97 (0.87–1.08) | 0.551 | | |
| Initial chief complaint – tremor | 0.75 (0.26–2.14) | 0.590 | 1.08 (0.24–4.80) | 0.922 | | |
| Initial H-Y stage | 9.99 (1.60–62.46) | 0.014 | 7.14 (0.92–55.51) | 0.060 | 3.27 (0.52–20.61) | 0.207 |
| Initial motor scores | 1.14 (1.03–1.26) | 0.014 | 1.05 (0.87–1.26) | 0.642 | 1.17 (1.01–1.36) | 0.043 |
| Cognitive impairment | | | | | | |
| Attention | 2.74 (0.58–12.92) | 0.203 | 0.55 (0.05–5.83) | 0.617 | | |
| Language | 1.82 (0.40–8.39) | 0.440 | 1.20 (0.13–11.22) | 0.875 | | |
| Visuospatial | 3.74 (1.09–12.84) | 0.036 | 8.45 (0.98–73.03) | 0.052 | 3.86 (1.09–13.65) | 0.036 |
| Memory | 1.17 (0.32–4.32) | 0.818 | 0.11 (0.01–1.77) | 0.119 | 0.54 (0.11–2.51) | 0.428 |
| Frontal and executive | 1.07 (0.23–4.98) | 0.933 | 5.56 (0.32–98.10) | 0.241 | | |
| Daily levodopa dose | 1.000 (0.998–1.003) | 0.870 | 1.000 (0.996–1.005) | 0.885 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; HR, hazard ratio; CI, confidence interval.

**Supplementary Table 5.** The associations of the clinical characteristics with the occurrence of wearing-off (analyses adjusting initial motor subscores)

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.55 (0.61–3.91) | 0.356 | 3.04 (0.84–11.06) | 0.091 | 1.31 (0.49–3.53) | 0.594 |
| Female sex | 0.79 (0.32–1.94) | 0.600 | 1.03 (0.29–3.68) | 0.959 | | |
| Age at onset of PD | 0.94 (0.90–0.99) | 0.024 | 0.94 (0.88–0.99) | 0.030 | 0.92 (0.87–0.97) | 0.003 |
| Duration of PD | 1.04 (0.98–1.09) | 0.182 | 1.00 (0.92–1.08) | 0.962 | 1.02 (0.96–1.08) | 0.485 |
| Initial chief complaint – tremor | 0.40 (0.15–1.04) | 0.061 | 0.35 (0.11–1.11) | 0.074 | 0.45 (0.16–1.25) | 0.125 |
| Initial H-Y stage | 0.97 (0.37–2.54) | 0.952 | 1.26 (0.31–5.21) | 0.746 | | |
| Initial motor subscores | | | | | | |
| Bradykinesia | 1.04 (0.88–1.23) | 0.629 | 1.34 (1.06–1.70) | 0.015 | 1.38 (1.11–1.71) | 0.004 |
| Rigidity | 0.85 (0.70–1.02) | 0.080 | 0.59 (0.42–0.82) | 0.002 | 0.60 (0.45–0.81) | 0.001 |
| Tremor | 0.91 (0.72–1.15) | 0.431 | 1.06 (0.74–1.53) | 0.739 | | |
| Cognitive impairment | | | | | | |
| Attention | 1.51 (0.34–6.70) | 0.591 | 1.42 (0.17–11.56) | 0.744 | | |
| Language | 0.66 (0.09–5.01) | 0.687 | 1.10 (0.11–11.17) | 0.936 | | |
| Visuospatial | 1.34 (0.38–4.74) | 0.647 | 2.41 (0.45–12.83) | 0.304 | | |
| Memory | 0.98 (0.32–3.01) | 0.968 | 0.67 (0.10–4.28) | 0.669 | | |
| Frontal and executive | 0.61 (0.14–2.70) | 0.514 | 0.66 (0.05–9.14) | 0.758 | | |
| LEDD | 1.000 (0.998–1.002) | 0.760 | 0.999 (0.995–1.002) | 0.520 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; LEDD, levodopa equivalent daily dose; HR, hazard ratio; CI, confidence interval.

**Supplementary Table 6.** The associations of the clinical characteristics with the occurrence of wearing-off (analyses adjusting daily levodopa dose)

| | Univariate | | Multivariate (all variables) | | Multivariate (selected variables) | |
|---|---|---|---|---|---|---|
| | Unadjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value | Adjusted HR (95% CI) | *p*-value |
| Depression | 1.55 (0.61–3.91) | 0.356 | 2.53 (0.95–6.74) | 0.063 | 1.64 (0.61–4.41) | 0.325 |
| Female sex | 0.79 (0.32–1.94) | 0.600 | 1.02 (0.32–3.28) | 0.970 | | |
| Age at onset of PD | 0.94 (0.90–0.99) | 0.024 | 0.97 (0.91 -1.03) | 0.351 | 0.95 (0.90–1.00) | 0.040 |
| Duration of PD | 1.04 (0.98–1.09) | 0.182 | 1.00 (0.92–1.08) | 0.946 | 1.03 (0.98–1.09) | 0.234 |
| Initial chief complaint – tremor | 0.40 (0.15–1.04) | 0.061 | 0.38 (0.13–1.12) | 0.079 | 0.44 (0.17–1.16) | 0.098 |
| Initial H-Y stage | 0.97 (0.37–2.54) | 0.952 | 1.36 (0.36–5.18) | 0.651 | | |
| Initial motor scores | 0.96 (0.88–1.05) | 0.344 | 0.91 (0.79–1.05) | 0.197 | 0.94 (0.85–1.03) | 0.175 |
| Cognitive impairment | | | | | | |
| Attention | 1.51 (0.34–6.70) | 0.591 | 1.39 (0.23–8.45) | 0.724 | | |
| Language | 0.66 (0.09–5.01) | 0.687 | 0.54 (0.06–5.23) | 0.592 | | |
| Visuospatial | 1.34 (0.38–4.74) | 0.647 | 2.50 (0.48–13.13) | 0.278 | | |
| Memory | 0.98 (0.32–3.01) | 0.968 | 0.52 (0.11–2.56) | 0.424 | | |
| Frontal and executive | 0.61 (0.14–2.70) | 0.514 | 1.23 (0.15–9.75) | 0.848 | | |
| Daily levodopa dose | 0.999 (0.997–1.002) | 0.669 | 1.000 (0.997–1.004) | 0.825 | | |

PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; HR, hazard ratio; CI, confidence interval.