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RESEARCH ARTICLE

Disease progression in Parkinson's disease patients with subjective cognitive complaint

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Abstract

Objective: Little is known about the disease progression of Parkinson's disease patients with subjective cognitive complaint (PD-SCC). This longitudinal cohort study aims to compare the progression of clinical features and quality of life (QoL) in PD patients with normal cognition (NC), SCC, and mild cognitive impairment (MCI). **Methods**: A total of 383 PD patients were enrolled, including 189 PD-NC patients, 59 PD-SCC patients, and 135 PD-MCI patients, with 1–7 years of follow-up. Linear mixed models were applied to evaluate longitudinal changes in motor symptoms, nonmotor features (cognitive impairment, depression, and excessive daytime sleepiness), and QoL in PD. **Results**: At baseline, PD-SCC patients had lower Beck Depression Inventory (BDI) scores and Parkinson's Disease Questionnaire-39 (PDQ-39) scores than PD-NC patients (all $p < 0.05$). Longitudinal analyses revealed that the PD-SCC group exhibited faster progression in terms of BDI scores ($p = 0.042$) and PDQ-39 scores ($p = 0.035$) than the PD-NC group. The PD-MCI group exhibited faster progression rates in the Epworth Sleepiness Scale scores ($p = 0.001$) and PDQ-39 scores ($p = 0.005$) than the PD-NC group. In addition, the PD-SCC group exhibited a greater reduction in attention (Trail Making Test Part A, $p = 0.047$) and executive function (Stroop Color-Word Test, $p = 0.037$) than the PD-NC group. **Interpretation**: PD-SCC patients exhibited faster deterioration of depression and QoL than PD-NC patients, and SCC may be an indicator of initial attention and executive function decline in PD. Our findings provided a more accurate prognosis in PD-SCC patients.

Introduction

Cognitive impairment, including mild cognitive impairment (MCI) and dementia, is common in Parkinson's disease (PD).[1] MCI was considered an intermediate level on the continuum between normal cognition and dementia, which showed high conversion rates to PD with dementia (PDD) (19%–62% at up to 5 years of follow-up[2,3]). Recently, prior to MCI, some studies indicated subjective cognitive complaint (SCC) as a sensitive indicator of initial cognitive decline in PD.[4,5]

In 2014, an international working group of researchers and clinicians proposed a common framework for SCC research within the context of Alzheimer's disease (AD) research.[6] These criteria include two major features of SCC: a self-experienced cognitive decline compared with a previously normal cognitive status; and normal performance on standardized cognitive tests used to classify MCI after

adjusting for age, sex, and education. Frank Jessen et al. pointed out broader applied settings of these SCC criteria in healthcare research.[7] As there were no proposed SCC criteria for PD, we believe that the same SCC criteria can also be useful in our study. This retrospective study inspects SCC by asking patients whether they feel cognitive decline and testing on a school of neuropsychological assessments.

The prevalence of SCC in nondemented PD patients is estimated to be between 16.3% and 38.8%.[8–11] Several studies have been performed on the association between SCC and objective cognitive impairment or subsequent cognitive decline in PD patients. A 2-year follow-up study reported no significant changes in neuropsychological assessments between nondemented patients with and without SCC. However, the other four long-term longitudinal studies validated the higher conversion of nondemented patients with SCC to PD-MCI or PDD during the 2- to 7.5-year follow-up.[4,5,8,12]

These longitudinal studies mentioned above mainly focused on depicting cognitive trajectories in PD-SCC.[5] To our knowledge, little is known about the complete picture of the disease progression of PD-SCC, and its relationship with PD-MCI. Here, we analyzed the longitudinal changes in the progression of motor and nonmotor symptoms and quality of life (QoL) among PD patients in PD-NC, PD-SCC, and PD-MCI.

Materials and Methods

Participants

We enrolled 383 consecutive Chinese Han population patients from the Department of Neurology, Huashan Hospital, Fudan University, from January 2010 to January 2020 (detailed workflow is shown in Fig. S1). PD diagnosis for each patient was determined by two senior investigators of movement disorders according to the UK Brain Bank criteria.[13] Patients were excluded from the analysis if they (a) had a diagnosis of dementia at baseline by current clinical diagnostic criteria of the Movement Disorder Society (MDS) Task Force 2007[14,15]; (b) had undergone deep brain stimulation; (c) had a major psychiatric disorder; (d) had a stroke or head injury by history; or (e) had previous genetic testing related to PD. These patients were followed up annually in the same month ($\pm$2 weeks) as in the previous year in our institution if available. This study was approved by the Human Studies Institutional Review Board, Huashan Hospital, Fudan University. All participants provided written informed consent.

Clinical and neuropsychological assessments

Clinical and neuropsychological assessments were performed at Huashan Hospital. Dosages of PD medications were standardized to the total levodopa equivalent daily dosage (LEDD).[16] The modified Hoehn and Yahr scale and the Unified Parkinson's Disease Rating Scale motor (UPDRS-III) score examination were conducted during the off-medication state, which was defined as the withdrawal of anti-PD medications for at least 12 h. The self-reported Beck Depression Inventory (BDI)[17] was performed to evaluate depression. The Epworth Sleepiness Scale (ESS)[18] was used to evaluate excessive daytime sleepiness. The Mini Mental State Examination (MMSE)[19] was performed to assess global cognitive function, and a full set of neuropsychological tests for five specific cognitive domains were performed as previously described.[20,21] The routinely used Parkinson's Disease Questionnaire (PDQ-39) was conducted to determine QoL and included eight subscales.[22]

Cognitive classifications

SCC was diagnosed if there was no evidence of cognitive impairment on standard tests and the patient's answer to the following single question is "yes" as previously recommended: "Over the past week have you had problems remembering things, following conversations, paying attention, thinking clearly, or finding your way around the house or in town?".[3,23–25]

MCI was determined according to the recommendations of the MDS Task Force 2012 by Level 2.[26] Impairment (>1.5 SD below the normative mean) on at least two neuropsychological tests within the same cognitive domain or across different domains was required. PD patients who failed to fulfill the criteria for MCI and in absence of SCC were defined as normal cognition (NC).

Data analysis

In the case of quantitative data, differences among three groups were compared by one-way analysis of variance (ANOVA) with Bonferroni post hoc test for normally distributed variables and Kruskal–Wallis test for nonnormally distributed variables. Categorical variables were analyzed using the chi-square test or Fisher's exact test.

To compare the longitudinal changes of the different symptoms, linear mixed models (LMM) were applied with the NC group as the reference category against which the SCC and MCI groups were compared. The models were fit using maximum likelihood estimation, and time from baseline was used as the time scale. LMM accounts for the correlation between repeated measurements, so a participant-specific random effect was considered. Fixed effects in the mixed effects model include cognitive group status, follow-up time, and interaction between cognitive group status and follow-up time along

with appropriate covariates. The analysis was adjusted for baseline age, sex, and disease duration at baseline. In addition, years of education was included in the analysis of cognitive impairment. Visual inspection of the distribution of residuals was used to assess the assumption of normality. Data were analyzed using Stata (version 15). Statistically significant differences were defined as $p < 0.05$.

Results

Clinical characteristics at baseline

We enrolled 383 PD patients in total, including 189 PD-NC patients, 59 PD-SCC patients, and 135 PD-MCI patients. The average follow-up times were 3.19 years in the PD-NC group, 2.97 years in the PD-SCC group, and 2.39 years in the PD-MCI group. Table 1 summarized patients' demographic and general clinical features at baseline, and a detailed observation of cognition performance at initial was reported in Table 2.

Compared to the PD-NC group, the PD-SCC group had higher BDI scores and worse performance in memory tests (AVLT-delay recall and AVLT-T). Compared to the PD-MCI group, the PD-SCC group was significantly younger at diagnosis, had a greater number of years of education, and had a higher H&Y stage. In addition, the PD-SCC group performed better in all neuropsychological tests than the PD-MCI group.

QoL, which was measured by the PDQ-39, was more impaired in the PD-SCC and PD-MCI groups (both $p < 0.001$). For the PDQ-39 subscales, both the PD-SCC and PD-MCI groups exhibited significantly higher subscores, except for the stigma and social support aspects, than the PD-NC group (Fig. S2).

Longitudinal progression of motor and nonmotor symptoms

Linear mixed models, adjusting for baseline age, sex, and disease duration at baseline, were used to analyze the difference in the UPDRS-III score, ESS scores, and BDI scores in longitudinal progression among the PD-NC, PD-SCC, and PD-MCI groups (Table 3). The rates of change in UPDRS-III scores per year among the three groups did not reach statistical significance ($p > 0.05$) (Fig. 1A). Relative to PD-NC patients, PD-SCC patients had faster BDI score increases (estimate = 0.90 [0.03 to 1.76], $p = 0.042$) (Fig. 1B). PD-MCI patients exhibited a more rapid increase in ESS scores than PD-NC patients (estimate = 0.57 [0.24 to 0.90], $p = 0.001$) (Fig. 1C).

Controlling for baseline age, sex, disease duration at baseline, and years of education, LMM examined longitudinal changes in cognitive function among the three groups (Fig. 2 and Table 4). Relative to PD-NC patients, PD-MCI patients exhibited a more rapid decrease in MMSE scores (estimate = −0.47[−0.71 to −0.23], $p < 0.001$), whereas PD-SCC patients had a slightly but

Table 1. Demographic and general clinical features at baseline.

Variables	PD-NC (n = 189)	PD-SCC (n = 59)	PD-MCI (n = 135)	p-value	Post hoc significance
Average follow-up years	3.19 (0.14)	2.97 (0.23)	2.39 (0.15)	/	/
Age (years)	54.96 (10.34)	55.51 (11.00)	61.49 (8.56)	<0.001	[N < M***] [S < M***]
Sex (female)	68 (35.4%)	19 (33.9%)	64 (47.6%)	0.070	/
Education (years)	12.69 (3.25)	11.62 (2.97)	9.74 (4.22)	<0.001	[N < M***] [S < M**]
Disease duration (years)	5.71 (4.46)	6.02 (4.13)	7.82 (5.60)	<0.001	[N < M***]
Age at onset (years)	49.42 (11.42)	49.29 (11.65)	53.76 (9.10)	<0.001	[N < M***] [S < M***]
UPDRS-III score (Med-Off)	24.54 (9.42)	26.28 (9.65)	30.71 (11.68)	<0.001	[N < M***]
Hoehn and Yahr stage (IQR)	2 (2–2)	2 (2–2.5)	2 (2–3)	<0.001	[N < M***] [S < M*]
PDQ-39 score	21.43 (14.73)	34.05 (22.63)	38.21 (23.06)	<0.001	[N < M***] [N < S***]
ESS score	4.91 (2.86)	6.07 (4.55)	6.19 (4.23)	0.103	/
BDI score	9.01 (7.19)	13.64 (9.04)	14.37 (8.53)	<0.001	[N < M***] [N < S***]
LEDD (mg/day)	360.14 (198.87)	379.49 (267.80)	412.72 (214.95)	0.055	/

Data are mean (SD) or n (%). p values correspond to three-group comparison.

Abbreviations: ESS, Epworth Sleepiness Scale; BDI, Beck Depression Inventory; LEDD, levodopa equivalent daily dosage; N, the PD-NC group; IQR, interquartile range; M, the PD-MCI group; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; PDQ-39, the Parkinson's Disease Questionnaire-39; PD-SCC, Parkinson's disease with subjective cognitive complaint; S, the PD-SCC group; UPDRS, Unified Parkinson's Disease Rating Scale.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

Table 2. Cognition performance at baseline.

Variables	PD-NC (n = 189)	PD-SCC (n = 59)	PD-MCI (n = 135)	p-value	Post hoc significance
MMSE score	28.84 (1.07)	28.42 (1.25)	27.51 (1.86)	<0.001	[N > M***] [S > M***]
Attention and working memory					
SDMT	46.35 (11.82)	43.51 (14.69)	29.46 (13.45)	<0.001	[N > M***] [S > M***]
TMT-A (s)	50.95 (16.07)	53.51 (19.73)	77.54 (30.09)	<0.001	[N < M***] [S < M***]
Executive function					
CWT-C time (s)	70.80 (18.14)	78.41 (27.76)	91.54 (34.91)	<0.001	[N < M***] [S < M**]
CWT-C right	47.56 (2.70)	47.41 (3.18)	44.86 (4.61)	<0.001	[N > M***] [S > M***]
TMT-B (s)	123.04 (41.78)	137.57 (58.54)	184.74 (65.36)	<0.001	[N < M***] [S < M***]
Language					
BNT	24.91 (2.80)	24.68 (3.32)	21.66 (4.12)	<0.001	[N > M***] [S > M***]
AFT	17.44 (4.47)	17.12 (5.20)	13.87 (4.29)	<0.001	[N > M***] [S > M***]
Memory					
AVLT-delay recall	6.53 (2.16)	5.44 (2.63)	3.98 (2.21)	<0.001	[N > M***] [S > M***] [N > S**]
AVLT-T	32.43 (10.67)	28.10 (9.55)	22.78 (8.68)	<0.001	[N > M***] [S > M**] [N > S*]
CFT-delay recall	18.77 (6.37)	17.14 (5.38)	11.63 (5.91)	<0.001	[N > M***] [S > M***]
Visuospatial function					
CFT	33.03 (3.01)	33.16 (2.26)	28.90 (6.69)	<0.001	[N > M***] [S > M***]
CDT	21.99 (5.30)	20.58 (6.16)	18.24 (6.54)	<0.001	[N > M***] [S > M*]

Data are mean (SD) or n (%). p values correspond to three-group comparison.

Abbreviations: AFT, Animal Fluency Test; AVLT, Auditory Verbal Learning Test; BNT, Boston Naming Test; CDT, Clock Drawing Test; N, the PD-NC group; CFT, the Rey-Osterrieth Complex Figure Test; CWT, Stroop Color-Word Test; M, the PD-MCI group; MMSE, Mini Mental State Examination; PD-MCI, Parkinson's disease with mild cognitive impairment; PD-NC, Parkinson's disease with normal cognition; PD-SCC, Parkinson's disease with subjective cognitive complaint; S, the PD-SCC group; SDMT, Symbol Digit Modality Test; TMT, Trail Making Test.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

Table 3. Estimates for change in UPDRS-III score, ESS score, BDI score, and PDQ-39 score compared to the PD-NC group.

	PD-SCC			PD-MCI		
Variables	Estimate (β)	95% CI	p Value	Estimate (β)	95% CI	p Value
UPDRS-III score (Med-Off)[1]	0.14	−1.38 to 1.65	0.860	0.17	−1.04 to 1.37	0.786
PDQ-39[1]	2.22	0.16 to 4.28	0.035*	2.43	0.75 to 4.10	0.005**
ESS score[2]	0.03	−0.36 to 0.42	0.897	0.57	0.24 to 0.90	0.001**
BDI score[2]	0.90	0.03 to 1.76	0.042*	0.67	−0.07 to 1.41	0.075

Abbreviations: PD-NC, Parkinson's disease with normal cognition; PD-SCC, Parkinson's disease with subjective cognitive complaint; PD-MCI, Parkinson's disease with mild cognitive impairment; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, the Parkinson's Disease Questionnaire-39; ESS, Epworth Sleepiness Scale; BDI, Beck Depression Inventory.

[1]Linear mixed models analysis with PD-NC group as reference category. The analyses were corrected for gender, age, and disease duration at baseline.

[2]Linear mixed models analysis with PD-NC group as reference category. The analyses were corrected for gender, years of education, age, and disease duration at baseline.

*$p < 0.05$.

**$p < 0.01$.

statistically insignificantly faster decline in MMSE scores (Fig. 2A). In the further analysis of cognitive domains, the PD-SCC group exhibited a faster decline in attention and working memory (TMT-A completion time, estimate = 6.85 [0.082 to 13.62], $p = 0.047$) (Fig. 2C) and executive function (CWT-C right scores, estimate = −0.52 [−1.00 to −0.031], $p = 0.037$) (Fig. 2E) than the PD-NC group. The PD-MCI group exhibited a faster decline in attention and working memory (SDMT scores, estimate = −1.59[−2.97 to −0.21], $p = 0.024$; TMT-A scores, estimate = 10.34[4.58 to 16.10], $p < 0.001$) (Fig. 2B and C), executive function (CWT-C completion time,

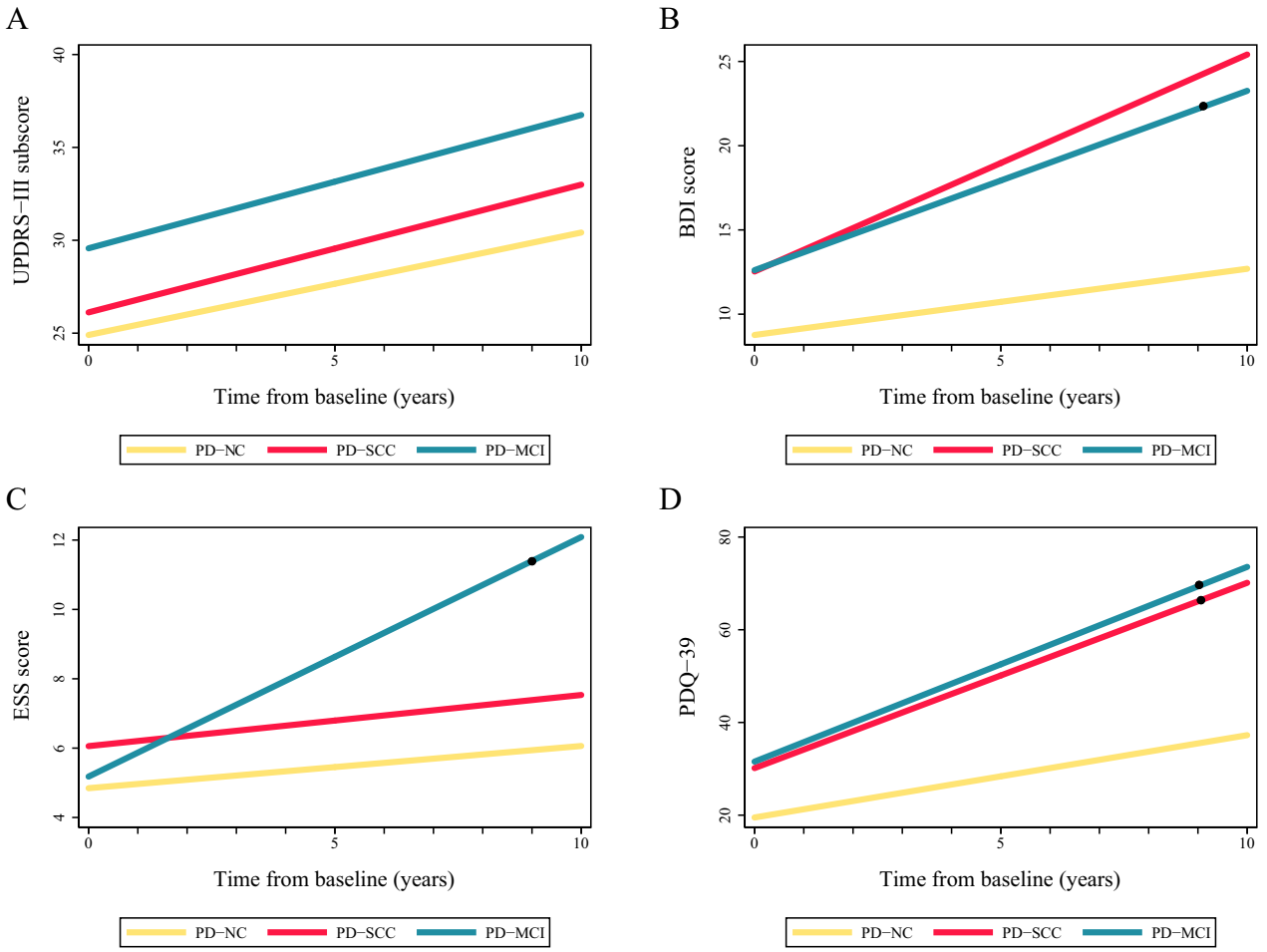

Figure 1. Longitudinal trajectories of UPDRS-III score, ESS score, BDI score, and PDQ-39 score by cognitive group. Linear mixed models (LMM) indicate that UPDRS-III scores trajectories over time are similar across diagnostic groups (A) but the PD-SCC group had faster BDI scores increase (B) while the PD-MCI group had faster increase in ESS scores (C). Both the PD-SCC and the PD-MCI group had faster PDQ-39 scores increase by LMM (D). The black solid circle indicates the longitudinal trajectories that are significantly different from the PD-NC group (the reference group) ($p < 0.05$). Abbreviations: NC, Parkinson's disease with normal cognition; SCC, Parkinson's disease with subjective cognitive complaint; MCI, Parkinson's disease with mild cognitive impairment; UPDRS, Unified Parkinson's Disease Rating Scale; PDQ-39, the Parkinson's Disease Questionnaire-39; ESS, Epworth Sleepiness Scale. BDI, Beck Depression Inventory.

estimate = 4.18[1.35 to 7.01], $p = 0.004$) (Fig. 2E), and visuospatial function (CFT scores, estimate = 4.18[1.35 to 7.01], $p = 0.004$) (Fig. 2F) than the PD-NC group. The rates of change in all the neuropsychological tests did not significantly differ between the PD-SCC and PD-MCI groups.

Longitudinal change in QoL

After adjusting for age, sex, and disease duration at baseline, LMM revealed a faster PDQ-39 score increase in PD-SCC patients (estimate = 2.22 [0.16 to 4.28], $p = 0.035$) and PD-MCI patients (estimate = 2.43 [0.75 to 4.10], $p = 0.005$) compared with PD-NC patients (Table 3) (Fig. 1D). In further analysis of eight subscales, the PD-SCC group had faster increase in emotional well-being and stigma subscales (estimate = 0.55 [0.10 to 0.99], $p = 0.016$ and estimate = 0.60 [0.26 to 0.93], $p = 0.001$, respectively) than the PD-NC group. The PD-MCI group had faster increase in the cognition and communication subscales (estimate = 0.41 [0.15 to 0.67], $p = 0.002$ and estimate = 0.27 [0.03 to 0.50], $p = 0.030$, respectively) than the PD-NC group (Table S1).

Discussion

To our knowledge, this is the first longitudinal follow-up study to assess the progression of clinical features and

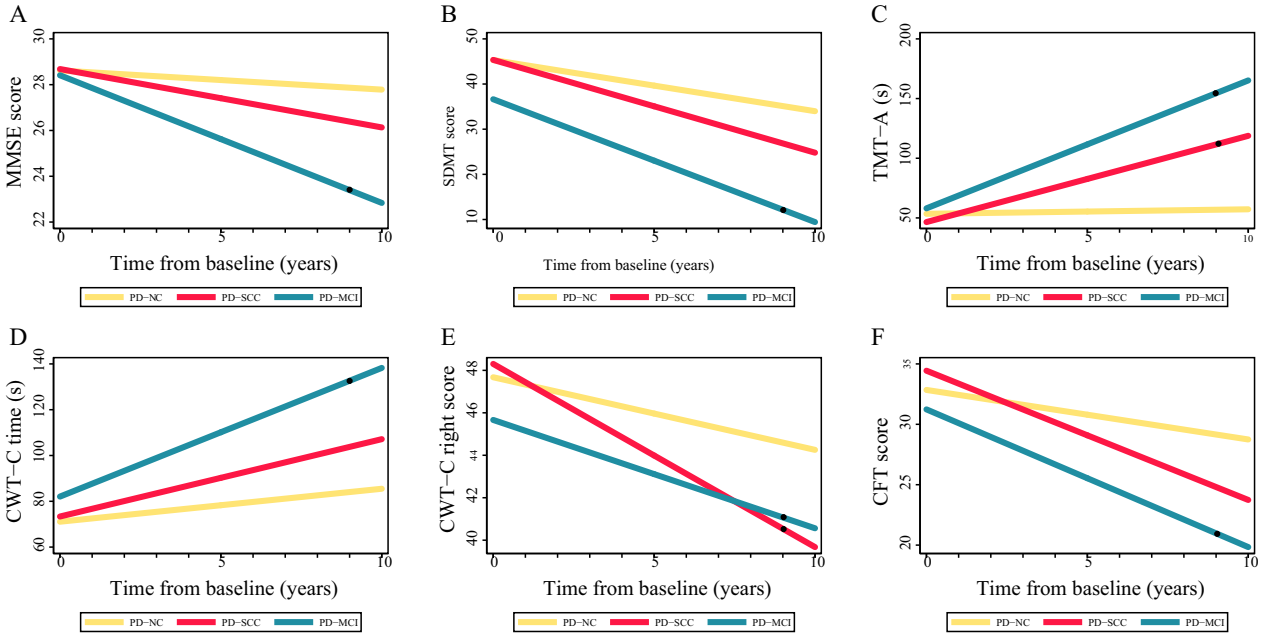

Figure 2. Longitudinal trajectories of neuropsychological scores in the PD-NC, PD-SCC, and PD-MCI groups. Linear mixed models show PD-MCI patients had faster decrease in MMSE scores while PD-SCC patients had slightly but statistically insignificant faster decline in MMSE scores (A). In addition, (B–F) show the neuropsychological tests which have different trajectories over time across diagnostic groups. The black solid circle indicates the longitudinal trajectories that are significantly different from the PD-NC group (the reference group) ($p < 0.05$). Abbreviations: NC, Parkinson's disease with normal cognition; SCC, Parkinson's disease with subjective cognitive complaint; MCI, Parkinson's disease with mild cognitive impairment; MMSE, Mini Mental State Examination; SDMT, Symbol Digit Modality Test; TMT, Trail Making Test; CWT, Stroop Color-Word Test; CFT, the Rey-Osterrieth Complex Figure Test.

QoL in patients with NC, SCC, and MCI. Here, we revealed that PD-SCC patients exhibited faster progression in BDI scores and PDQ-39 scores than PD-NC patients. In addition, PD-SCC patients exhibited greater reductions in attention and executive function than the PD-NC group.

It has been reported that depression was independently associated with future development of cognitive impairment or dementia in PD.[27] We found higher BDI scores in the PD-SCC group than in the PD-NC group at baseline. Recent studies have validated the association between PD-SCC and depression,[28–30] and increased PD-SCC severity is associated with increasing depression scores.[11] However, the results might be attributed to the fact that PD patients with subthreshold depression tend to overestimate their cognitive deficits.[1,2,31] Furthermore, in our study, it is worth noting that PD-SCC patients, not PD-MCI patients, had significantly greater progression in depression than the NC group. This finding raises the question, whether the subjective complaints of cognitive loss were secondary to depression or depression is an intrinsic component of PD-SCC with specific neuropathologic changes in the brain. Some researchers in AD did not suggest considering depression as the cause of SCC, as it might co-occur with SCC or as a result of SCC itself.[7] An association between the activity of the right insular and the severity of depression has been found in PD-MCI.[32] However, depression-related brain structure in PD-SCC has not been reported and needs further study. Due to the faster progression in depression, caregivers, and physicians should pay more attention to depression in PD-SCC patients.

At baseline, PD-SCC patients performed similar cognitive function as PD-NC patients except for the memory subdomain. It has been reported that objective memory impairment has been a stronger predictor than dysfunction in other domains for the presence of SCC in PD.[33] Abnormalities in the angular gyrus[34,35] may contribute to memory decline in PD-SCC, which has a strong connection with the parahippocampal gyrus.[36] The longitudinal analysis of changes in cognitive performance showed that PD-SCC patients exhibited a more rapid decline in attention and executive function than the PD-NC group despite the fact that these two cognitive domains of the two groups were comparable at baseline. Attention and executive function are particularly reliant on fronto-subcortical circuits, which are the most commonly impaired domains in early cognitive dysfunction in PD. The findings of the present study suggest that the

Table 4. Estimates for change in neuropsychological scores compared to the PD-NC group.

	PD-SCC			PD-MCI		
Variables	Estimate (β)	95% CI	p Value	Estimate (β)	95% CI	p Value
MMSE	−0.17	−0.46 to 0.12	0.250	−0.47	−0.71 to −0.23	<0.001***
Attention and working memory						
SDMT	−0.92	−2.46 to 0.61	0.239	−1.59	−2.97 to −0.21	0.024*
TMT-A (s)	6.85	0.082 to 13.62	0.047*	10.34	4.58 to 16.10	<0.001***
Executive function						
CWT-C time (s)	1.94	−1.34 to 5.22	0.246	4.18	1.35 to 7.01	0.004**
CWT-C right	−0.52	−1.00 to −0.031	0.037*	−0.17	−0.60 to 0.26	0.444
TMT-B (s)	5.71	−3.60 to 15.01	0.229	6.56	−1.53 to 14.64	0.112
Language						
BNT	−0.01	−0.31 to 0.29	0.948	−0.05	−0.32 to 0.21	0.708
AFT	−0.29	−0.75 to 0.18	0.233	−0.35	−0.75 to 0.06	0.092
Memory						
AVLT-delay recall	−0.13	−0.39 to 0.14	0.361	−0.13	−0.36 to 0.11	0.290
AVLT-T	−0.93	−2.14 to 0.28	0.134	−0.59	−1.62 to 0.44	0.264
CFT-delay recall	−0.41	−1.02 to 0.20	0.186	−0.42	−0.95 to 0.11	0.123
Visuospatial function						
CFT	−0.66	−1.41 to 0.09	0.083	−0.73	−1.38 to −0.08	0.028*
CDT	−0.15	−0.91 to 0.62	0.704	−0.21	−0.90 to 0.48	0.544

Linear mixed models analysis with PD-NC group as reference category. The analyses were corrected for gender, years of education, age, and disease duration at baseline.

Abbreviations: PD-NC, Parkinson's disease with normal cognition; PD-SCC, Parkinson's disease with subjective cognitive complaint; PD-MCI, Parkinson's disease with mild cognitive impairment; MMSE, Mini Mental State Examination; SDMT, Symbol Digit Modality Test; TMT, Trail Making Test; CWT, Stroop Color-Word Test; BNT, Boston Naming Test; AFT, Animal Fluency Test; AVLT, Auditory Verbal Learning Test; CFT, the Rey-Osterrieth Complex Figure Test; CDT, Clock Drawing Test.

*$p < 0.05$.

**$p < 0.01$.

***$p < 0.001$.

diagnosis of PD-SCC may predict future declines in these cognitive domains.[8] Although a previous study reported the association of PD-SCC and visuospatial dysfunction, our study did not verify.[37] This inconsistency may due to the different tests and follow-up years between studies.

Additionally, the present study showed that the PD-SCC group performed better on the MMSE and all neuropsychological tests than the PD-MCI group at baseline. At follow-up, PD-SCC represented an intermediate state between normal cognition and MCI (PD-NC < PD-SCC < PD-MCI) in almost all cognitive domains. Several studies suggest that SCC is a risk factor for PD-MCI or PDD. PD-SCC patients are 8.4-fold more likely to develop PD-MCI within 2 years compared to those without SCC.[4] Another study showed that the conversion rate to MCI or dementia was increased 2.61-fold in PD patients with SCC than in those without SCC.[5] Taken together, PD-SCC might be a promising approach to recognizing high-risk individuals with cognitive decline prior to a diagnosis of PD-MCI.

It is vital to assess QoL in PD patients, and QoL is considered to be a crucial outcome indicator in PD. A recent study reported poorer cognition-specific functional abilities in PD-SCC patients using PDQA-15, whereas there was no significant difference in the ADCS-ADL scores.[5] In the current study, we used the PDQ-39, the most appropriate, thoroughly tested questionnaire specific to PD.[22] Our study showed that both PD-SCC and PD-MCI patients had worse QoL than PD-NC patients at baseline. This finding suggested that subtle impairment in daily functional abilities has already existed in PD patients with SCC. The longitudinal QoL changes varied across the groups, and the PD-SCC and PD-MCI groups exhibited reductions at faster rates than the PD-NC group. However, the most deteriorated subscales of the PDQ-39 in PD-SCC and PD-MCI were different. PD-SCC patients declined more quickly on the emotional and stigma subscales, whereas the PD-MCI group had more rapid progression on the cognition and communication subscales. This finding might indicate that the principal trouble that bothered PD-SCC patients was unpleasant subjective feelings, whereas objective declined cognition had a greater effect on the PD-MCI patients. Clinicians need to be aware of the relevance of these subscales and adequately address them over disease progression to maintain QoL.

Although some studies reported emerging and persistent daytime sleepiness was associated with higher incident cognitive decline risk compared with no daytime sleepiness, we only found this association in the PD-MCI group but not the PD-SCC group.[38–40]

However, several limitations in this study exist. First, the diagnostic criteria of PD-SCC lack consensus. The classification of PD-SCC in this study was based on a single question. In comparison to some previous studies examining only memory complaints, we assessed cognitive complaint more broadly, considering the pattern of early cognitive impairment in PD. Second, age and disease duration were not matched at baseline, which may bias the comparison among the three groups. Although we performed the longitudinal analysis using adjusted estimates, the effect of non-observed confounding factors could not be completely excluded. Third, our sample is homogenous without considering race differences. In addition, despite the relatively modest number of patients enrolled in this study, and the follow-up period was not sufficiently long. We will continue to followup these patients. A further limit might be related to the choice of MMSE for assessing global cognitive functioning. Although MMSE was considered an acceptable measure for PDD and PD-MCI diagnosis, future studies may benefit from additional measures, such as the Montreal Cognitive Assessment (MoCA).[15,41]

In conclusion, these results illustrated that PD patients with SCC have more rapid deterioration of depression, attention, and executive function and QoL than PD patients with normal cognition. Understanding disease progression in PD-SCC patients is of great prognostic significance. As a possible "pre-PD-MCI" stage, future studies are required to explore whether intervention in PD-SCC could delay or even prevent the objectively cognitive impairment.

Acknowledgments

None.

Conflict of Interest

None.

References

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Supporting Information

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

Figure S1. Flowchart of study participants.
Figure S2. Comparison of PDQ-39 subscales at baseline in PD-NC, PD-SCC and PD-MCI groups.
Table S1. Estimates for change in PDQ-39 subscales compared to the PD-NC group.

