

Research Report

Impact of the COVID-19 Pandemic on the Quality of Life of Patients with Parkinson's Disease and Their Caregivers: A Single-Center Survey in Tochigi Prefecture

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Abstract.

Background: The coronavirus disease 2019 (COVID-19) pandemic has negatively affected the mental health of the general population.

Objective: We investigated the determinants of quality of life (QOL) in Parkinson's disease (PD) patients during the COVID-19 pandemic.

Methods: Impacts of lifestyle changes due to the COVID-19 pandemic on 100 patients with PD and their caregivers/spouses were assessed. The Hospital Anxiety and Depression Scale was used to assess anxiety and depression. The physical component summary (PCS) and mental component summary (MCS) scores of the short form (SF)-8 were used to evaluate health-related QOL.

Results: Regarding health-related QOL, physical function, role physical, general health, vitality and the PCS score were significantly worse in PD patients than in caregivers. Worsening of PD-related symptoms, increased stress, and decreased physical activity were observed in 29.0%, 37.0% and 44.0% of PD patients, respectively. Sixteen patients (16.0%) experienced problems with hospital access, but none reported medication shortages. Strong concerns about COVID-19 were reported by 47.0% of caregivers and 50.0% of PD patients. In PD patients, increased gait disturbance and rigidity, disease severity, smoking, the levodopa equivalent dose and decreased body weight predicted a worse PCS score; anxiety, depression, female sex, stress and long disease duration predicted a worse MCS score. In caregivers, age and smoking contributed to a worse PCS score; depression, stress and worsening patient mood contributed to a worse MCS score.

Conclusion: We report the negative impacts of the COVID-19 pandemic on health-related QOL and its determinants in PD patients and their caregivers.

Keywords: Caregivers, COVID-19, Parkinson's disease, quality of life, SARS-CoV-2

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INTRODUCTION

The novel coronavirus called severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which causes coronavirus disease 2019 (COVID-19), was first reported in Wuhan, China, in December 2019 [1] and is responsible for a global pandemic. A nationwide lockdown in Italy during the COVID-19 pandemic reportedly negatively impacted mental health, anxiety and sleep [2]. In Japan, a state of emergency was declared on April 7, 2020, in seven prefectures, including Tokyo and Kanagawa; on April 16 until May 31, the state of emergency was expanded throughout Japan to prevent the spread of SARS-CoV-2. People were asked to refrain from leaving their homes. Even after the declaration of the state of emergency was lifted, the government instructed the public to continue avoiding 1) closed spaces with poor ventilation, 2) crowded places with many people nearby, and 3) close-contact settings such as close-range conversations, resulting in significant changes in lifestyles and social situations.

Parkinson's disease (PD) is a movement disorder characterized by core motor features, namely, bradykinesia plus rigidity and/or resting tremor, that are caused by the degeneration of nigrostriatal dopaminergic neurons. In addition to dopaminergic dysfunction, other neurotransmitter deficits are common in PD and contribute to various highly prevalent nonmotor features, such as sleep disorders, anxiety, depression, autonomic dysfunction, cognitive impairment, and olfactory impairment [3]. It has been reported that a strong earthquake in Kumamoto Prefecture in Japan resulted in clinical worsening of neuropsychiatric symptoms, such as fear, anxiety, insomnia, and fatigue, and motor symptoms in 335 PD patients who lived in the region [4].

Moreover, a community-based case-control study investigating the direct effect of COVID-19 on PD found that compared with PD patients without COVID-19, PD patients with COVID-19 experienced clinical deterioration of motor and nonmotor symptoms, including cognitive impairment, fatigue and urinary symptoms [5]. Prasad et al. [6] also reported that 11% of 100 patients with PD in India had worsening motor or nonmotor symptoms during the COVID-19 pandemic but that only 4% had problems with medical consultations or medication supplies. In contrast, 46 (28%) of 162 PD patients in Italy experienced an acute exacerbation of clinical symptoms (50% experienced worsening of their motor symptoms), 52% of whom required a change in medication

[7]. In a report from Iran, 81.2% of 137 patients with PD had symptoms of anxiety after the COVID-19 outbreak, with 25.5% experiencing severe symptoms, and symptoms of anxiety were significantly more common in PD patients than in their caregivers (57.9% with anxiety and 4.2% with severe symptoms) [8]. Overall, increased psychological distress during the COVID-19 pandemic may also worsen motor symptoms [9] and various nonmotor symptoms, such as cognitive function [10], anxiety, depression [9] and pain [11], among PD patients. Indeed, in an online-based study including 5,429 patients with PD, 43% and 52% reported worsened motor and nonmotor symptoms, respectively [12].

The COVID-19 pandemic has impacted the management of patients with neurological disorders. In general, replacing outpatient care with telemedicine, postponing surgery, including deep brain stimulation, and avoiding nonemergency hospitalizations have been recommended for patients with PD and other movement disorders during the COVID-19 pandemic [13]. Therefore, telemedicine has rapidly expanded to provide appropriate medical care [14]. Telemedicine has been introduced in Japan, and it has been particularly promoted for patients who are at risk of severe COVID-19, such as elderly patients and those with underlying diseases. In a study evaluating the clinical profiles of 10 PD patients infected with SARS-CoV-2, older age and a longer duration of PD were associated with increased mortality (40%), with a 50% mortality rate in those receiving advanced-stage treatment, such as deep brain stimulation and continuous levodopa infusion [15].

Thus, changes in social conditions during the COVID-19 pandemic may have affected the motor and nonmotor symptoms experienced by PD patients, negatively affecting their quality of life (QOL). However, determinants of the QOL of patients with PD during the COVID-19 pandemic have not been thoroughly studied. Accordingly, we aimed to investigate changes in motor symptoms, cognition, mood, sleep and stress as well as determinants of QOL in PD patients and their spouses/caregivers during the COVID-19 outbreak in Japan in a single-center setting.

METHODS

We performed a cross-sectional survey between June and December 2020 to assess the impact of changes in social behaviors and lifestyles during

135 the COVID-19 pandemic on patients with PD at
136 Dokkyo Medical University Hospital, Tochigi, Japan.
137 Tochigi Prefecture has a population of 2 million and
138 is located in the northern part of Kanto region, which
139 includes the capital of Japan, Tokyo. The institutional
140 review boards of Dokkyo Medical University Hos-
141 pital approved this study. All participants provided
142 written informed consent to participate in the study.

143 One hundred consecutive patients with PD and
144 their spouses/caregivers from our outpatient clinic
145 in the Department of Neurology were included in
146 this study. A diagnosis of PD was made by neu-
147 rologists according to well-established criteria [16].
148 Drug-induced parkinsonism, vascular parkinsonian
149 syndrome and atypical parkinsonian syndrome, such
150 as progressive supranuclear palsy and multiple sys-
151 tem atrophy, were carefully ruled out by clinical
152 examination and brain imaging. The exclusion crite-
153 ria were as follows: under 20 years of age; dementia,
154 defined as cognitive dysfunction interfering with
155 activities of daily living; and a diagnosis of or treat-
156 ment for COVID-19. Disease severity was rated
157 according to the Hoehn and Yahr (HY) stage. The
158 levodopa equivalent dose was calculated based on the
159 conversion factors in a recently published proposal
160 [17].

161 The participants were asked about changes in
162 stress, physical activity, and body weight after mid-
163 April 2020, when a nationwide state of emergency
164 was issued and people were requested to refrain from
165 leaving their homes. The patient global impression
166 of change (PGIC) scale, in which individuals self-
167 rate on a scale from 1 “very much improved” to 7
168 “very much worse”, was applied to PD patients to
169 assess motor symptoms (tremor, rigidity, bradykine-
170 sia, gait, and postural stability), sleep, and mood after
171 the start of the COVID-19 pandemic, with reference
172 to their condition prior to that time. Additionally,
173 the caregivers/spouses of the PD patients were asked
174 about the changes in the patients’ symptoms that they
175 observed.

176 We used the short form (SF)-8 Japanese version
177 to assess health-related QOL during the COVID-
178 19 pandemic [18]. The SF-8 has 8 subscales to
179 measure physical functioning, role physical, general
180 health, vitality, social functioning, role emotional and
181 mental health. Two summary scores, the physical
182 component summary (PCS) and mental component
183 summary (MCS) scores, were also calculated from
184 the weighted sums of the relevant subscale scores.
185 Subscale and summary scores range from 0 to
186 100, with higher values indicating better QOL. The

187 Hospital Anxiety and Depression Scale (HADS) was
188 applied to evaluate anxiety and depression [19]; it
189 consists of 14 subitems, with 7 for anxiety and 7 for
190 depression, and the scores range from 0 to 21 for
191 each subscale [20]. The HADS has been validated
192 and shown to be useful for application in PD patients,
193 and scores of > 10 indicate the presence of anxiety or
194 depression [21]. We also collected information on the
195 impact of COVID-19 on hospital visits and interest
196 in and concern about COVID-19.

197 *Statistical analysis*

198 To compare results between PD patients and their
199 caregivers/spouses, the Mann-Whitney U test or Stu-
200 dent’s *t* test was used for continuous variables;
201 chi-square tests were employed for the categorical
202 variables, as appropriate. Stepwise linear regression
203 analyses were performed to determine the health-
204 related QOL (MCS and PCS scores on the SF-8) of
205 the PD patients and their caregivers/spouses. Missing
206 values of independent variables were determined by
207 multiple imputation. Results across 10 imputed data
208 sets were combined. Two-tailed *p* values < 0.05 were
209 considered to be statistically significant. Because of
210 the exploratory nature of our study, we did not per-
211 form adjustments of multiplicity for multiple tests.
212 IBM SPSS Statistics v26.0 (IBM SPSS, Tokyo,
213 Japan) was used for the statistical analyses.

214 **RESULTS**

215 Table 1 shows the demographics and clinical char-
216 acteristics of PD patients and their caregivers. PD
217 patients were older and had a lower proportion of
218 smokers than caregivers. The mean evaluation period
219 after the end of the state of emergency was 2.6 ± 1.7
220 months for both groups. Overall, the proportions
221 of individuals with anxiety and depression did not
222 differ between the groups. However, PD patients
223 had a significantly higher rate of comorbidities than
224 caregivers (63.0% vs. 42.0%, $p=0.003$), though no
225 significant difference in the comorbidity rate between
226 PD patients and caregivers was found, except that
227 diabetes mellitus was more prevalent in the former
228 than the latter (10.0% vs 3.0%, $p=0.045$) (Sup-
229 plementary Table 1). Regarding health-related QOL
230 as measured by the SF-8, physical function, role
231 physical, general health, vitality and PCS scores
232 were significantly lower in PD patients than in care-
233 givers. The PGIC scale scores showed the same
234 worsening trends reported by patients and caregivers.

Table 1
Clinical background, demographics and symptoms associated with COVID-19

	CG (n = 100)	PD (n = 100)	p ^a
Age, y	65.5 ± 12.0	72.2 ± 9.1	< 0.001
Sex (M/F)	47/53	45/55	0.777
Smoking, n (%)			0.007
Never	67 (67.0)	74 (74.0)	
Past	21 (21.0)	25 (25.0)	
Current	12 (12.0)	1 (1.0)	
Alcohol intake, n (%)			0.434
Never	50 (50.0)	59 (59.0)	
< 1 day/week	21 (21.0)	23 (23.0)	
1–2 days/week	11 (11.0)	8 (8.0)	
3–5 days/week	7 (7.0)	3 (3.0)	
6–7 days/week	11 (11.0)	7 (7.0)	
Caffeine, n (%)	92 (92.0)	90 (90.0)	0.621
Caffeine, cups/day	2.7 ± 1.8	2.3 ± 1.6	0.098
Evaluation period after the end of the state of emergency (days)	79.1 ± 54.3	79.1 ± 54.3	–
Onset age of PD (y)	–	66.4 ± 9.6	–
Disease duration ^b (y)	–	5.8 ± 4.4	–
Hoehn and Yahr stage	–	2.5 ± 0.9	–
LED, mean (median) ± SD, mg/day	–	479.8 (400.0) ± 308.0	–
Comorbidities ^b , n (%)	42 (42.0)	63 (63.0)	0.003
Anxiety, n (%)	6 (6.0)	6 (6.0)	1.000
Depression, n (%)	17 (17.0)	20 (20.0)	0.585
Health-related QOL (SF-8)			
Physical function	48.3 ± 6.3	43.9 ± 7.5	< 0.001
Role physical	48.4 ± 6.7	44.3 ± 8.4	< 0.001
Bodily pain	47.8 ± 8.7	45.3 ± 9.8	0.055
General health	50.2 ± 6.9	46.7 ± 7.2	0.001
Vitality	50.7 ± 5.9	47.0 ± 6.1	< 0.001
Social functioning	44.6 ± 9.0	44.5 ± 8.5	0.949
Role emotional	47.2 ± 7.6	46.5 ± 7.7	0.490
Mental health	48.9 ± 6.7	48.6 ± 6.7	0.804
Physical composite summary	47.7 ± 7.0	42.6 ± 7.2	< 0.001
Mental composite summary	47.1 ± 7.2	48.0 ± 6.9	0.349

COVID-19, coronavirus disease 2019; CG, caregivers; PD, Parkinson's disease; LED, levodopa equivalent dose; QOL (SF-8), quality of life (short form-8 version). ^aUsing the chi-square test or Student's t test, values in bold indicate significant differences. ^bComorbidities included hypertension, diabetes mellitus, dyslipidemia, stroke, heart disease, respiratory disease, thyroid disease, liver disease, gastrointestinal disease, spine/joint diseases, and others.

235 Approximately 30–40% of patients and caregivers
 236 reported worsening tremor, rigidity, gait, postural sta-
 237 bility, cognition, mood and sleep but not bradykinesia
 238 (Fig. 1). These changes in PD-related symptoms,
 239 stress, and physical activity showed trends similar
 240 to those reported by the two groups. Body weight
 241 increased by a smaller percentage in patients than
 242 in caregivers (Table 2). Moreover, worsening of PD-
 243 related symptoms, increased stress, and decreased
 244 physical activity were observed in 29.0%, 37.0%
 245 and 44.0% of PD patients, respectively. Strong con-
 246 cerns about or interest in COVID-19 were reported
 247 by 47.0% and 69.0% of caregivers and 50.0% and
 248 60.0% of PD patients, respectively. Although 16
 249 patients (16.0%) experienced problems with hospital
 250 access, none reported medication shortages. Online
 251 medical care was used by 9.0%. More than 80%

of the participants wore a mask, but daily mask
 usage (hours) was significantly shorter in the patient
 group than in the caregiver group. Regarding deter-
 minants of physical (PCS) and mental (MCS) aspects
 of health-related QOL in PD patients, stepwise lin-
 ear regression analysis identified that increased gait
 disturbance and rigidity, HY stage, smoking, LED
 and decreased body weight predicted worse PCS
 scores; anxiety, female sex, stress, longer disease
 duration and depression predicted worse MCS scores
 (Table 3). In caregivers, age and smoking con-
 tributed to worse PCS scores, whereas depression,
 stress and worsening of patients' mood contributed
 to worse MCS (Table 4). The results of stepwise lin-
 ear regression analysis of the subscales of the SF-8
 (health-related QOL) are shown in Supplementary
 Tables 2 and 3. Overall, anxiety, depression, stress,

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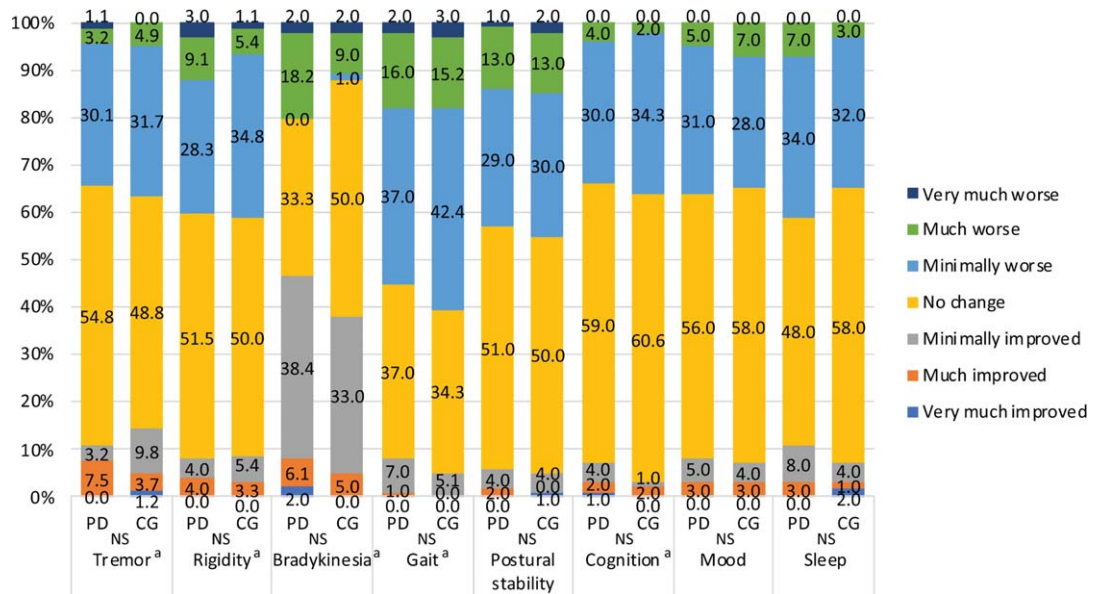


Fig. 1. PGIC scales for tremor, rigidity, bradykinesia, gait, postural stability, cognition, mood and sleep in PD patients and caregivers. *The caregivers assessed the patients' symptoms. PGIC, patient's global impression of change; NS, not significant; PD, Parkinson's disease; CG, caregivers. ^aMissing values for tremor (CG = 18, PD = 7), rigidity (CG = 8, PD = 1), bradykinesia (PD = 1), gait (CG = 1), and cognition (CG = 1) were excluded.

and disease severity, as reflected by the HY stage, had negative effects on the subscales in patients with PD. In caregivers, depression and anxiety had negative effects on the subscales. Alcohol consumption had a positive effect on physical function and caffeine intake had a positive effect on bodily pain in the PD patient group.

DISCUSSION

We found that several subscale scores on the SF-8 and physical aspects of health-related QOL (PCS) were significantly more impaired in PD patients than in caregivers. The MCS and PCS scores in our study were significantly lower than the national standard value (50 ± 10) and comparable to those of Japanese PD patients in nonemergency situations [22]. We also determined key predictors of health-related QOL in patients and caregivers by stepwise linear regression analysis. In our study, a significant number of patients reported worsening of PD-related symptoms, increased stress and decreased physical activity during the COVID-19 pandemic, in agreement with previous studies from other countries [9–12]. Kitani-Morii et al. [23] reported that in 71 Japanese PD patients, anxiety and depression were associated with motor experiences of daily living (MDS-UPDRS

II) during the COVID-19 pandemic. Additionally, a study including 38 PD patients and 20 controls showed that during the COVID-19 pandemic, PD patients had more stress, depression, and anxiety, less physical activity, and worse QOL than controls [24].

Increased stress levels during the COVID-19 pandemic are likely to worsen motor symptoms, and reduced physical activity may worsen anxiety, insomnia and constipation [9]. Furthermore, a study evaluating social distancing due to the COVID-19 pandemic found that PD patients who reported being lonely experienced 55% more severe symptoms over time, and loneliness correlated with decreased QOL [25]. Xia et al. [26] investigated the impact of the COVID-19 pandemic on sleep in patients with PD, with 68.9% reporting sleep disturbances, as assessed by the Pittsburgh Sleep Quality Index, which was independently associated with the exacerbation of PD symptoms and anxiety. In contrast, changes in sleep status were not a key determinant for health-related QOL in our study; we used the PGIC scale to assess changes in sleep status, which may not have been sufficiently sensitive to detect such changes.

In our study, disease severity, disease duration, gait impairment, rigidity, anxiety, depression and stress were related to the worsening of health-related QOL. According to Fan et al. [27], motor impairment was the most crucial determinant of QOL in PD patients

Table 2
Changes in symptoms and conditions related to COVID-19

	CG (n = 100)	PD (n = 100)	<i>p</i> ^a
PD-related symptoms, n (%) ^c			0.938
Improved	5 (5.0)	4 (4.0)	
Unchanged	67 (67.0)	67 (67.0)	
Worsened	28 (28.0)	29 (29.0)	
Stress, n (%)			0.192
Decreased	0 (0.0)	1 (1.0)	
Unchanged	52 (52.0)	62 (62.0)	
Increased	48 (48.0)	37 (37.0)	
Physical activity, n (%)			0.218
Decreased	34 (34.0)	44 (44.0)	
Unchanged	63 (63.0)	51 (51.0)	
Increased	3 (3.0)	5 (5.0)	
Body weight, n (%)			0.035
Decreased	14 (14.0)	22 (22.0)	
Unchanged	68 (68.0)	71 (71.0)	
Increased	18 (18.0)	7 (7.0)	
Interest in COVID-19, n (%)			0.493
Not at all	0 (0.0)	0 (0.0)	
Very little	1 (1.0)	3 (3.0)	
Little	9 (9.0)	12 (12.0)	
Moderate	21 (21.0)	25 (25.0)	
Strong	69 (69.0)	60 (60.0)	
Concerns about COVID-19, n (%)			0.770
Not at all	3 (3.0)	1 (1.0)	
Very little	3 (3.0)	5 (5.0)	
Little	22 (22.0)	19 (19.0)	
Moderate	23 (25.0)	25 (25.0)	
Strong	47 (47.0)	50 (50.0)	
Problems with seeing a doctor, n (%)	–	16 (16.0)	–
Shortage of medications, n (%)	–	0 (0.0)	–
Received online medical care, n (%)	–	9 (9.0)	–
Wore masks, n (%)	92 (92.0)	83 (83.0)	0.054
Mask usage ^b (hours/day)	4.2 ± 3.4	2.7 ± 3.1	0.001

COVID-19, coronavirus disease 2019; CG, caregivers; PD, Parkinson's disease ^aUsing the chi-square test or Student's *t* test, values in bold indicate significant differences. ^bUsing the Mann-Whitney U test after the exclusion of missing values for mask usage in hours per day (CG = 9). ^cThe caregivers assessed the patients' symptoms.

without cognitive impairment, whereas depression was the key determinant for QOL in PD patients with cognitive impairment. A systematic review of health-related QOL in PD patients identified depression, disease severity and disease disability as determinants [28]. The motor symptoms that most often contribute to QOL include gait impairments, as observed in our study. We also found that female sex was related to worsening of the mental aspects of health-related QOL. Sex differences in motor and several nonmotor features in PD have been explored, and female patients with PD have been found to be more likely to experience anxiety, nervousness, sadness, fatigue and

constipation [29–31]. In our study sample, women were more susceptible than men to worsening of the mental aspects of QOL with regard to anxiety and stress during the COVID-19 pandemic.

In addition to stress and depression, the worsening of patients' mood as perceived by caregivers was a determinant of the mental aspects of the health-related QOL of caregivers, suggesting that caregivers were deeply involved in supporting the patients when their motor symptoms deteriorated. Our findings may support a previous study reporting that a greater caregiver burden is associated with a longer disease duration and more motor complications in PD patients [32]. In contrast, the presence of caregivers is associated with higher QOL of PD patients, despite worse cognitive and motor function than those without caregivers [33], indicating the important influence of caregivers on patient outcomes and QOL. We further observed a high rate of agreement between the two groups with regard to changes in patients' symptoms on the PCIG scale during the COVID-19 pandemic, which suggested a high degree of attentiveness on the part of the caregivers. PD patients require multidisciplinary and integrated outpatient care, and receiving that care can improve their health-related QOL [34].

The duration of mask use was significantly shorter in the patient group than in the caregiver group, even though there was no difference in the mask use rate. This may reflect the effects of patients' symptoms, such as hypophonia and excessive drooling, which can complicate the prolonged use of masks. Moreover, the increased mask duration among caregivers might be due to their responsibilities, such as shopping, and the ability to go out in a limited capacity into the community compared to PD patients, who may have been more confined to home. In a survey of PD patients during the COVID-19 epidemic, 100% maintained social distancing, whereas only 37% wore masks [6].

Virtual visits facilitated by online applications for PD patients are reported to have high feasibility and satisfaction levels [35], and telemedicine approaches should improve care for patients with PD [36]. In an email survey of 1,342 PD patients in the USA, 63.5% received telehealth services [37]; conversely, only a few patients (9.3%) in our study received online medical care. In Japan, telemedicine has been included in universal insurance systems since 2018, but reimbursement for telemedicine by insurance is not sufficient. Nonetheless, a global survey on telemedicine utilization for movement disorders

Table 3
Stepwise linear regression analysis of physical and mental component summary scores of health-related QOL in patients with PD

Variables	Partial regression coefficient	SE	95% CI	<i>p</i> ^a
<i>Physical component summary</i>				
HY stage	-2.256	0.724	-3.675 to -0.837	0.002
LED	-3.965	1.228	-6.372 to -1.567	0.001
Smoking	-3.004	1.282	-5.516 to -0.492	0.019
Body weight	2.827	1.119	0.636 to 5.018	0.011
Gait	-1.809	0.721	-3.222 to -0.396	0.012
Rigidity	-2.167	0.738	-3.615 to -0.720	0.003
<i>Mental component summary</i>				
Sex	-4.671	1.145	-6.915 to -2.427	<0.001
Disease duration	-0.327	0.132	-0.585 to -0.069	0.013
Anxiety	-8.111	2.433	-12.880 to -3.342	0.001
Depression	-4.130	1.404	-6.883 to -1.378	0.003
Stress	-3.323	1.166	-5.608 to -1.039	0.004

QOL, quality of life; PD, Parkinson's disease; SE, standard error; HY, Hoehn and Yahr; LED, levodopa equivalent dose, PGIC, patient's global impression of change; COVID-19, coronavirus disease 2019. ^aUsing the results from the combined 10 data sets after the application of multiple imputation. Independent variables included in the analysis were age, sex (M=0, F=1), smoking, alcohol, caffeine, disease duration, onset age of PD (years), evaluation period after the end of the state of emergency (days), comorbidity (no=0, yes=1), HY stage, LED (<400 mg/day=0, ≥400 mg/day=1), anxiety (no=0, yes=1), depression (no=0, yes=1), PGIC scale score (1 to 7) for tremor, bradykinesia, rigidity, gait, mood, sleep, cognition, changes in stress (decreased=0, unchanged=1, increased=2), physical activity (decreased=0, unchanged=1, increased=2), body weight (decreased=0, unchanged=1, increased=2), PD-related symptoms (improved=0, unchanged=1, worsened=2), use of online medical care (no=0, yes=1), mask usage (hours/day), and interest and concern about COVID-19 (5-point scale).

Table 4
Stepwise linear regression analysis of physical and mental component summary scores of health-related QOL in caregivers

Variables	Partial regression coefficient	SE	95% CI	<i>p</i> ^a
<i>Physical component summary</i>				
Age	-0.179	0.055	-0.286 to -0.072	0.001
Smoking	-2.278	0.937	-4.114 to -0.440	0.015
<i>Mental component summary</i>				
Depression	-5.750	1.697	-9.076 to -2.424	0.001
Mood*	-2.065	0.833	-3.697 to -0.432	0.013
Stress	-3.773	1.292	-6.306 to -1.240	0.004

QOL, quality of life; SE, standard error; PGIC, patient's global impression of change; PD, Parkinson's disease; COVID-19, coronavirus disease 2019. ^aUsing the results from the combined 10 data sets after the application of multiple imputation. Independent variables included in the analysis were age, sex, smoking, alcohol, caffeine, evaluation period after the end of the state of emergency (days), comorbidity (no=0, yes=1), anxiety (no=0, yes=1), depression (no=0, yes=1), PGIC scale scores (1 to 7) for tremor*, bradykinesia*, rigidity*, gait*, cognition*, mood* and sleep*, changes in stress (decreased=0, unchanged=1, increased=2), physical activity (decreased=0, unchanged=1, increased=2), body weight (decreased=0, unchanged=1, increased=2), PD-related symptoms* (improved=0, unchanged=1, worsened=2), mask usage (hours/day), and interest in and concern about COVID-19 (5-point scale). *The patients' symptoms assessed by the caregivers.

387 showed that after the onset of the COVID-19 pan-
388 demic, the use of telemedicine was increased in
389 selected regions in Japan [38]. Access to telemedicine
390 depends on ease of availability and varies between
391 countries and regions; however, data regarding how
392 many patients were offered online medical care in

this study were not available. Furthermore, medica-
tion supply issues may arise during the COVID-19
pandemic [13]. In our study, 16% of the PD patients
reported difficulty in accessing medical facilities.
This may be because our university hospital is
located in a rural area, where transportation is not

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399 as convenient as it is in urban areas, and few patients
400 received alternative treatment options, such as online
401 treatment (9.3%); regardless, none experienced a
402 medication shortage. In contrast, Guo et al. [39]
403 reported that two-thirds of PD patients had problems
404 receiving medical advice, resulting in a decrease in
405 their QOL.

406 Our study has several limitations. First, this is a
407 single-center study, and although our region, Tochigi
408 Prefecture, is located in the Kanto region, which
409 includes Tokyo, it is not a representative metropolitan
410 area of Japan. We included caregivers instead of
411 healthy controls in this study, as we sought to ascertain
412 the relationship between caregivers' QOL and
413 PD patient symptoms as perceived by caregivers who
414 are closely involved with these patients. We, however,
415 did not include other family members or home care
416 assistance. Consecutive patients with PD and their
417 caregivers who agreed to participate in the study at
418 our outpatient clinic were included, but the possibility
419 of selection bias cannot be ruled out. In addition,
420 the retrospective nature of this questionnaire-based
421 study, which has no baseline data from the period
422 before the COVID-19 pandemic, may be affected by
423 cognitive impairment and mood, as detailed cognitive
424 tests were not performed and mild cognitive impairment
425 may have been present. Moreover, changes in
426 motor symptoms after the outbreak of COVID-19
427 were assessed with a questionnaire and not a clinical
428 examination by neurologists, which may result
429 in underestimation and overestimation. Additionally,
430 the nationwide state of emergency is not compulsory,
431 and it is based on the premise of voluntary
432 cooperation by the population. The difference in the
433 precautions taken and the degree of isolation and
434 patient care load might affect mood and caregiver
435 stress, though these aspects were not assessed in our
436 study. We also chose the SF-8 for QOL evaluation
437 instead of the SF-36 because of its shorter administration
438 time in an effort to recruit more patients
439 and caregivers in a limited time period during the
440 pandemic. Because we sought to assess the QOL
441 of patients and caregivers using the same instrument
442 (SF-8), no other PD-specific QOL rating scales,
443 such as the PD Questionnaire-8 or -39, were applied.
444 Finally, the study period of our study was limited to
445 six months, but the impact of recall bias on changes
446 in symptoms should be considered, even though we
447 adjusted for the evaluation period after the COVID-19
448 pandemic in the statistical analysis.

449 In conclusion, our study reveals the negative
450 impact of the COVID-19 pandemic on health-related

451 QOL and its determinants in PD patients and their
452 caregivers. The findings of this study may have
453 important implications for the understanding and
454 future management of changes in clinical symptoms
455 of PD patients and their caregivers during the
456 COVID-19 pandemic.

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468 CONFLICT OF INTEREST

469 There are no conflicts of interest to report.

470 SUPPLEMENTARY MATERIAL

471 The supplementary material is available in the
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