

# Effects of COVID-19 on Outpatient Visitation of Japanese Parkinson's Disease and Parkinsonism Patients Receiving Rehabilitation

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## Abstract

**Background:** Rehabilitation is effective for preventing progression of Parkinson's disease (PD) and parkinsonism, but access to services during the COVID-19 pandemic was difficult. The Japanese already practice high levels of social distancing and personal restraint and are keenly aware of dangers related to infectious disease. We therefore presume that many patients discontinued rehabilitation due to behavioral restraint. **Objectives:** We investigated whether PD patients and parkinsonism patients attending outpatient rehabilitation facilities in Japan initiated rehabilitation interruptions and their associated reasons before and during the COVID-19 pandemic. **Methods:** Subjects were PD and parkinsonism patients attending a neurology clinic outpatient rehabilitation department in Japan before and during the first year of the COVID-19 pandemic (February 1, 2019, to January 31, 2021). Patients lost to follow-up were investigated as to how long they attended rehabilitation until interruption. We classified factors causing rehabilitation interruption into COVID-19-related factors, disease factors and social reasons. **Results:** Among 259 subjects (125 men, 134 women, mean age:  $76.6 \pm 8.5$  years), 133 patients (51.4%) initiated interruption of rehabilitation therapy. Cumulative incidence of interruption events was significantly higher during than before the COVID-19 pandemic ( $p < 0.001$ ). COVID-19-related factors dramatically increased as a reason for interruption after the pandemic started, but disease-related and social factors gradually increased thereafter. Incidences of disease-related and social factors before and during the COVID-19 pandemic

were not different. **Conclusions:** Cumulative incidence of interruption events increased in Japanese PD and parkinsonian patients attending an outpatient rehabilitation facility during the COVID-19 pandemic, primarily due to COVID-19-related factors. Patients and their families need education and guidance to facilitate continuous rehabilitation.

## Keywords

Parkinson's Disease, Parkinsonism, COVID-19, Rehabilitation, Outpatients

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## 1. Introduction

Parkinson's disease (PD) and parkinsonism are neurodegenerative disorders that present with motor and non-motor symptoms [1]. Studies in recent years have shown that high-intensity rehabilitation is effective at preventing disease progression and improving physical function in patients with neurodegenerative disorders [2] [3] [4], and treatment guidelines from various countries recommend maintaining a high level of exercise and activity for rehabilitation [5] [6] [7]. Furthermore, according to systematic reviews and meta-analyses, continuous rehabilitation effectively decreases both motor symptoms and anti-PD drug dosages [8]. We also provide continuous rehabilitation for PD patients as an outpatient service, and in our experience, patients are able to maintain physical function over the long term [9]. However, as the SARS-CoV-2 infection (COVID-19: Coronavirus disease 2019) spread, lockdown and control measures were globally implemented, and maintaining a high level of exercise or activity under these conditions became challenging.

When thinking back to the first COVID-19 infections in Japan, we can remember that the first COVID-19 patient was confirmed on January 15, 2020. We also started dealing with the COVID-19-positive ship passengers from the Diamond Princess from February 2020, and the number of newly infected individuals within Japan increased [10]. As COVID-19 infections spread within Japan, concerns and psychological anxiety regarding these infections increased, and fewer people participated in everyday activities [11]. A characteristic feature of the Japanese is their high level of awareness of their social responsibility, and many people wore masks even before the COVID-19 pandemic to prevent the spread of respiratory infections in winter [12]. The national habits and culture also naturally facilitate social distancing. A survey was conducted using the 25 items of the Societal Influences Survey Questionnaire as a means to detect the social effects of the COVID-19 pandemic among Asian populations. The results showed that Japanese individuals were more likely to adhere to social distancing and personal restraint than individuals from other countries [13]. This suggests that the Japanese exhibited a higher level of awareness of infectious disease crisis management, further limiting contact with others during the COVID-19 pandemic. This led to concerns that motor function in PD and parkinsonism pa-

tients would worsen due to rehabilitation interruptions.

Thus, the purpose of this study was to investigate whether PD and parkinsonism patients initiated interruptions of periodic outpatient rehabilitation visits before and during the COVID-19 pandemic and, if so, the reasons for doing so.

## 2. Methods

### 2.1. Subjects

Our subjects were PD and parkinsonism patients attending an outpatient department of rehabilitation at a specialized neurology clinic in Japan's Kanagawa prefecture during the period from February 1, 2019, to January 31, 2021. There are two different health insurance systems in Japan that pay out rehabilitation benefits. The first is for treatment and is known as "medical insurance", whereas the second is for non-medical care and is known as "long-term care insurance". Rehabilitation that is provided on an outpatient basis is covered by medical insurance, and it is not possible to make use of rehabilitation services covered by both rehabilitation and long-term care insurance simultaneously.

We defined the COVID-19 pandemic period as the one-year period from February 1, 2020, when we started to treat COVID-19-positive passengers from the Diamond Princess to January 31, 2021. We defined the non-pandemic period as the one year prior to this, *i.e.*, February 1, 2019 to January 31, 2020. PD was defined as a definitive diagnosis meeting the diagnostic criteria in the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease [14], whereas parkinsonism was defined as a definitive diagnosis of progressive supranuclear palsy (PSP), multiple system atrophy (MSA) or corticobasal syndrome (CBS), which are all parkinsonian neurological disorders, based on the information from the Japan Intractable Disease Information Center [15].

### 2.2. Items Assessed

The subjects extracted were followed up for a maximum period of 24 months, and the endpoint was defined as two or more consecutive interruptions of periodic rehabilitation caused by a specific reason. We determined each subject's age, sex, diagnosis, morbidity and periodic rehabilitation frequency at the start of the follow-up period. At the end of the follow-up period, we investigated the duration and frequency of rehabilitation until interruption, whether rehabilitation was resumed and time until resumption. PD disease severity was also determined using the Hoehn and Yahr (H-Y) scale. Factors leading to rehabilitation interruption were divided into three categories: COVID-19-related factors, such as the patients themselves being infected, or concerns regarding transmission of the infection to close personal contacts such as rehabilitation personnel; disease-related factors, such as admission or other measures to treat diseases other than COVID-19, such as stroke, pneumonia, malignant tumors, urinary tract infections or worsening parkinsonism; and social factors, such as relocation, difficulty accessing healthcare services or switching from rehabilitation paid

for by medical insurance to that paid for by long-term care insurance. Each assessment item was enquired about during the medical history or measured over time during routine treatment, and data were obtained from an electronic medical records system.

We used the opt-out method to assure patients that their clinical evaluation data would not be used during the clinical study if they so desired. This study was approved by the Japan Primary Care Association institutional review board (approval number: 2021-003).

### 2.3. Statistical Analysis

Rehabilitation interruption was treated as an event during the time analysis, which entailed the creation of a cumulative onset curve, and the rehabilitation interruption factors during the entire observation period, the pandemic period and the non-pandemic period were subjected to univariate and multivariate Cox regression analysis using rehabilitation interruption as an independent variable. The cumulative incidence of interruption events during the non-pandemic and COVID-19 pandemic periods were compared and subjected to Gray's test. We divided the subjects into four groups, *i.e.*, one group for each of the rehabilitation interruption factors during the COVID-19 pandemic period, and one group with no interruption factors, and then compared patient attributes in these groups using the Kruskal Wallis test. If the Kruskal Wallis test showed a significant difference in any of the items, then multiple comparison was performed using the Dann-Bonferroni method. The statistical software SPSS version 27 (IBM SPSS Statistics for Windows; IBM Corp, Armonk, NY) was used for analysis and to create graphs, and EZR was used to calculate the sample size [16]. The data for each item were tested using the Shapiro-Wilk test to determine if they followed a normal probability distribution, and the level of significance for the difference between each group was set to less than 5%. The numerical data are shown as the mean  $\pm$  standard deviation or as a median value.

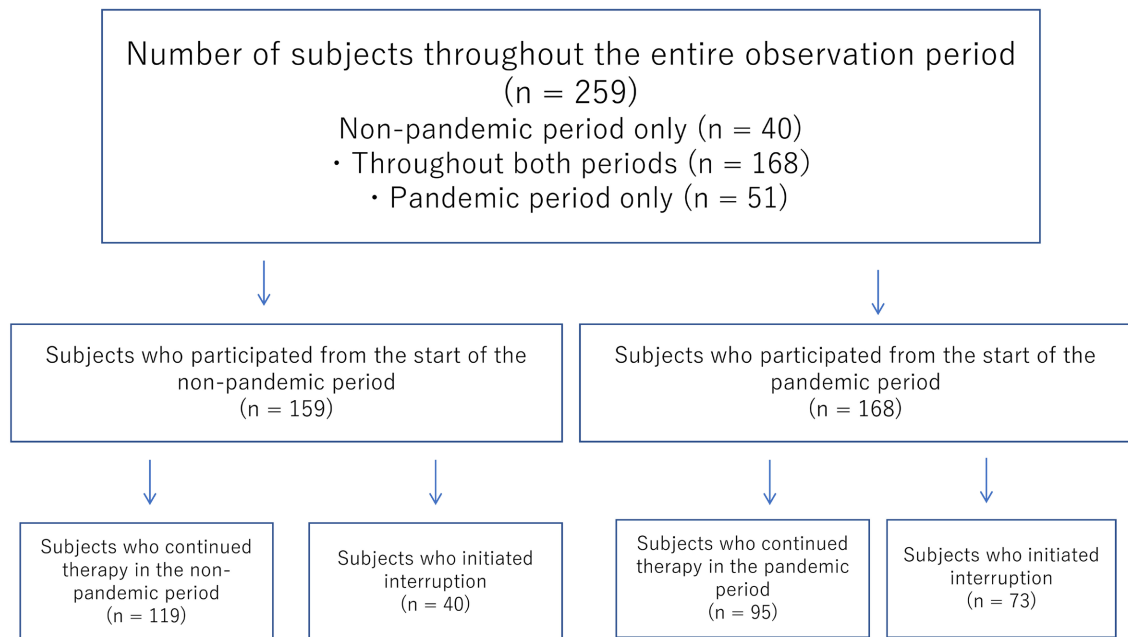
## 3. Results

During the period from February 1, 2019, to January 31, 2021, we studied 259 PD and parkinsonism patients (125 men, 134 women, mean age:  $76.6 \pm 8.5$  years) (**Figure 1**). There were 40 subjects who only attended outpatient rehabilitation during the non-pandemic period, 51 who only attended during the pandemic period, and 168 subjects who attended throughout both periods. In total, 159, 168 and 127 subjects were scheduled to attend outpatient rehabilitation visits during the non-pandemic, pandemic and combined periods, respectively. The median observation period was 54 weeks (0 - 105 weeks), and 133 subjects (51.4%) initiated rehabilitation interruption.

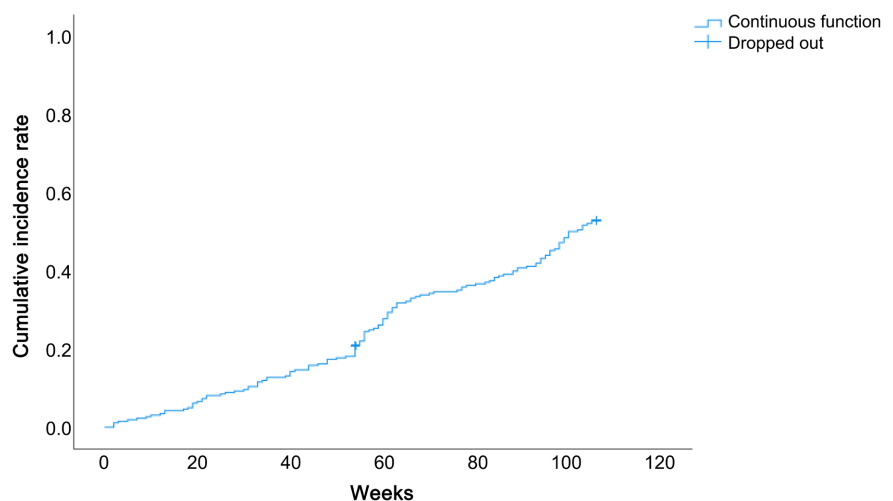
**Figure 2** shows the cumulative incidence of interruption events throughout the entire observation period. Interruptions occurred in 109 subjects with PD, 17 subjects with PSP, five subjects with MSA and two subjects with CBS (**Table 1**).

Meanwhile, the interruption rates for each underlying disorder of PD, PSP, MSA and CBS were 49.5%, 58.6%, 71.4% and 66.7%, respectively. The median period until interruption among the 133 subjects was 39 weeks (0 - 104 weeks), whereas 29 subjects (21.8%) subsequently restarted rehabilitation after interruption.

A Cox regression analysis was run to determine the relationship between interruption events throughout the entire observation period and both patient attributes and COVID-19-related factors (**Table 2**). Interruption events were significantly related to COVID-19-related factors in both the univariate and multivariate analyses ( $p = 0.001$ ), but age, disease duration and sex were not found to be significant factors.



**Figure 1.** Subject inclusion flowchart.



**Figure 2.** Trends in the cumulative incidence of interruption events throughout the entire observation period.

**Table 1.** Patients characteristics.

	Study patients (n = 259)
Age, yrs, mean $\pm$ SD	76.6 $\pm$ 8.5
Sex ratio (male/female)	125:134
Disease duration, yrs	6.2 $\pm$ 5.1
Observation period, wks, median (range)	54 (0 - 105)
<b>Underlying disease</b>	
PD (n)	220 (84.9%)
H-Y stage, mean $\pm$ SD	3.1 $\pm$ 1.0
PSP, n (%)	29 (11.2%)
MSA, n (%)	7 (2.7%)
CBS, n (%)	3 (1.2%)
<b>Subjects who interrupted, n (%)</b>	
PD, n (%)	109/220 (49.5%)
PSP, n (%)	17/29 (58.6%)
MSA, n (%)	5/7 (71.4%)
CBS, n (%)	2/3 (66.7%)
<b>Period until interruption, wks (range)</b>	39 (0 - 104)
<b>Subjects who restarted</b>	
PD, n (%)	26/109 (23.9%)
PSP, n (%)	1/17 (5.9%)
MSA, n (%)	0/5 (0%)
CBS, n (%)	2/2 (100%)
<b>Period until restart, wks, median (range)s</b>	10 (2 - 40)

Abbreviations: PD, Parkinson's disease; H-Y, Hoehn and Yahr scale; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; CBS, corticobasal degeneration.

**Table 2.** Factors related to interruption events across both periods.

	Univariate			Multivariate		
	HR	p Value	95% CI	HR	p Value	95% CI
Age (yrs)	1.02	0.08	0.998 - 1.043	1.02	0.11	0.996 - 1.039
Disease duration (yrs)	1.01	0.39	0.982 - 1.048	1.01	0.78	0.972 - 1.039
Sex	1.11	0.55	0.790 - 1.562	1.03	0.89	0.720 - 1.458
COVID-19-related factors	2.55	<0.001	1.689 - 3.853	2.49	<0.001	1.641 - 3.775

Abbreviation: HR, hazard ratio.

**Figure 3** shows the cumulative incidence curve for interruption events during the non-pandemic and COVID-19 pandemic periods. When we compared the cumulative incidence of interruption events before and during the COVID-19 pandemic (Gray's test), there was a significant difference between the two periods ( $p < 0.001$ ). In terms of the disease breakdown, there were 36 (85.5%), 17

(10.7%), four (2.5%) and two (1.3%) subjects with PD, PSP, MSA and CBS, respectively, during the non-pandemic period and 144 (85.7%), 17 (10.1%), five (3.0%) and two (1.2%) subjects, respectively, during the pandemic period. Cox regression analysis was conducted to determine the relationship between interruption events during the pandemic period and both patient attributes and COVID-19-related factors (**Table 3**).

Interruption events were significantly related to COVID-19-related factors in both the univariate and multivariate analyses ( $p = 0.001$ ), but again, age, disease duration and sex were not found to be significant factors. The cumulative incidences of each of the interruption factors indicated that COVID-19-related factors increased precipitously immediately after the pandemic period started. Meanwhile, disease-related factors and social factors did not increase dramatically and instead, gradually increased during the observation period (**Figure 4**). There were also no differences in the incidence of disease-related and social factors before and during the COVID-19 pandemic. We compared the group without interruptions and the three groups with interruption factors in terms of patient attributes and found a significant difference in the ages of those in the group without interruptions and the group with disease-related factors (**Table 4**). Otherwise, there were no further significant differences between patient attributes in these groups.

**Table 3.** Factors related to interruption events only during the COVID-19 pandemic period.

	Univariate			Multivariate		
	HR	p Value	95% CI	HR	p Value	95% CI
Age (yrs)	1.02	0.19	0.990 - 1.051	1.01	0.58	0.984 - 1.030
Disease duration (yrs)	1.01	0.62	0.968 - 1.056	0.98	0.45	0.692 - 1.630
Sex	1.07	0.77	0.675 - 1.698	1.06	0.78	0.941 - 1.027
COVID-19-related factors	8.42	<0.001	5.078 - 13.954	5.85	<0.001	3.680 - 9.314

Abbreviation: HR, hazard ratio.

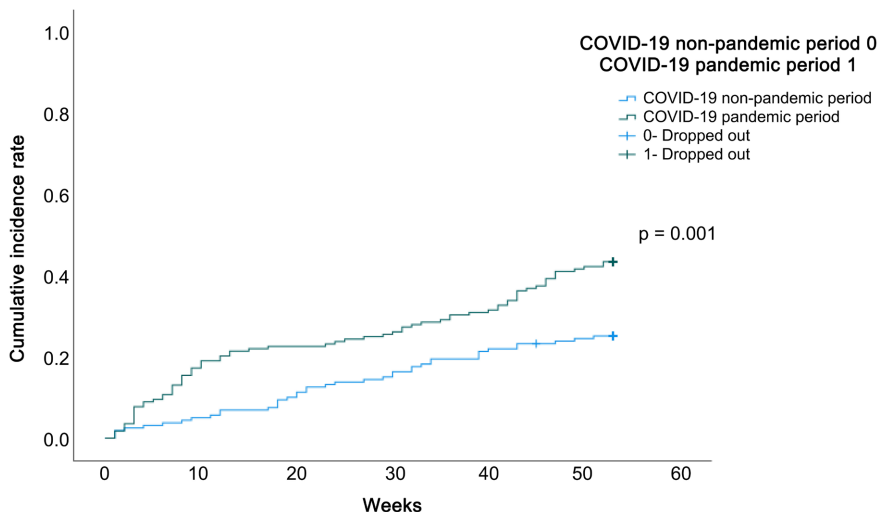
**Table 4.** Patient attributes related to interruption factors and continuation during the COVID-19 pandemic period.

	COVID-19 n = 28	Disease-related factors n = 32	Social factors n = 13	Continuous n = 95	Total n = 168	p Value
Age (yrs)	76.4 ± 10.5	<b>79.9 ± 6.6*</b>	74.8 ± 6.7	75.3 ± 7.9	76.3 ± 8.3	0.018
Sex (male: female)	11:17	14:18	8:5	46:49	79:89	0.58
Disease duration (yrs)	7.9 ± 6.1	6.7 ± 5.5	4.6 ± 3.8	6.4 ± 4.9	6.6 ± 5.3	0.21
H-Y, stage	3.4 ± 1.2	3.4 ± 0.8	3.1 ± 0.9	3.1 ± 0.9	3.2 ± 1.0	0.29

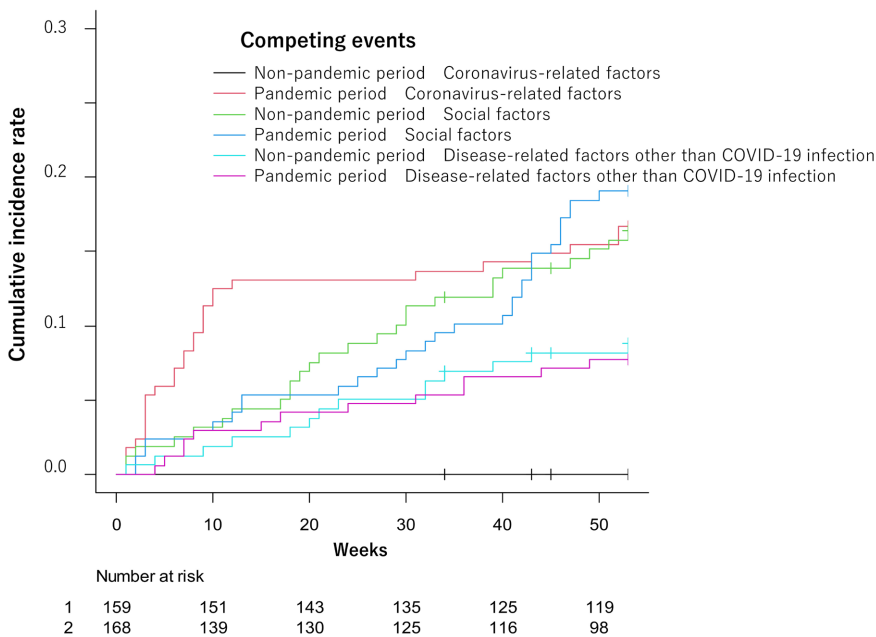
\* $p = 0.017$ . Bonferroni corrections in the continuous rehabilitation and disease-related factor groups. Abbreviations: H-Y, Hoehn and Yahr scale.

### 4. Discussion

During this study, we performed a retrospective investigation of factors affecting the ability of PD and parkinsonism patients to access outpatient rehabilitation during the two years covering the period before and during the COVID-19 pandemic while they were being managed by a specialized neurological outpatient clinic in a metropolitan region in Japan. This is the first report, to our knowledge, to have investigated the ability of Japanese PD and parkinsonism patients to attend periodic rehabilitation during the COVID-19 pandemic.



**Figure 3.** Cumulative incidence of interruption events during the non-pandemic and COVID-19 pandemic periods.



**Figure 4.** Cumulative incidence curves for each factor resulting in interruption during the non-pandemic and COVID-19 pandemic periods. Number at risk. 1, non-pandemic period; 2, COVID-19 pandemic period.



We found that the cumulative number of interruptions increased during the pandemic period when compared to the non-pandemic period and that COVID-19-related factors led to the outpatient rehabilitation interruptions.

#### **4.1. Incidence of Interruption Events and Interruption Factors throughout the Entire Two-Year Observation Period**

During the two-year period of observation in this study, 133/259 subjects (51.4%) did not attend periodic outpatient rehabilitation. Age, sex and disease duration were not found to be related to these interruptions. Rather, the factors that resulted in interruption were COVID-19-related, both throughout the entire observation period and specifically during the pandemic period. Yamamoto *et al.* investigated both the percentage of Japanese patients who took a break from rehabilitation covered by long-term care insurance and the factors that affected these breaks, such as age, sex, underlying disease and long-term care insurance, during the one-year period from April 2019 to March 2020 [17]. Their results showed that 81/132 patients (61.4%) took a break from rehabilitation, and while there were no differences in terms of age or sex between the group that took a break and the group that did not, the numbers of PD and parkinsonism patients were significantly higher in the former group. The present study also showed that age and sex were unrelated to rehabilitation interruptions. The fact that more than half of the patients interrupted rehabilitation was a similar finding to that in the previous study. However, the present study was conducted to investigate rehabilitation covered by medical insurance for the purpose of treatment, so we also included important disease-related factors, such as the onset of concomitant disorders and death. The factors in the previous study that cause patients to take a break included many conversions to long-term care insurance services.

#### **4.2. Cumulative Incidence of Interruption Events during the Non-Pandemic and COVID-19 Pandemic Periods**

The present study showed that COVID-19-related factors contributed to rehabilitation interruptions during the pandemic period. We found a significantly higher cumulative incidence of interruption events during the pandemic period than during the non-pandemic period, but there were no differences between these two periods in terms of the incidence of events due to disease-related and social factors. The subjects in this study were managed by an outpatient clinic in a metropolitan region within Japan. A state of emergency was first declared in this region on April 7, 2020, and continued until May 25. However, this declaration was not associated with legal restrictions of movement, and citizens were merely requested to exercise self-restraint. Furthermore, those who exercised self-restraint refused to visit medical facilities, and appropriate outpatient visits were recommended [18]. However, the results of the present study clarified the fact that COVID-19-related factors, and not self-restraint, decreased hospital attendance by the PD and parkinsonism patients. A previous study that investigated behavioral change during the COVID-19 pandemic in Japanese citizens

aged 20 to 60 years showed that chronic disease was a factor that increased social withdrawal during the pandemic period [19]. van der Heide *et al.* also investigated the relationship between increased psychological stress and physical activity in Dutch PD patients and what relationship existed between these factors and the severity of the motor and non-motor symptoms of PD [20]. Their results showed that increased psychological stress due to COVID-19 decreased physical activity in PD patients, which in turn was related to worsening of motor symptoms, such as rigidity and tremor, and non-motor symptoms, such as fatigue and pain. In other words, it appears that PD and parkinsonism patients tended to restrict their movements to include activities that should not be restricted, such as rehabilitation, as a result of COVID-19-related factors due to psychological anxiety regarding COVID-19. These restrictions in turn may worsen the symptoms of PD. Among the factors that led to rehabilitation interruption, disease-related and social factors occurred at the same frequency before and during the COVID-19 pandemic period, and these factors are difficult to prevent. However, COVID-19-related factors are preventable. Based on the appropriate infection control measures undertaken in Japan, it would be possible to continue rehabilitation even during the COVID-19 pandemic period. For this reason, it is particularly important to provide education and guidance to the patient themselves and their families that promote the continuation of rehabilitation to prevent the worsening of PD symptoms during pandemic periods.

There are some limitations in the present study. PD and parkinsonism patients from a single neurology clinic within a metropolitan area in Japan were included, and thus, selection bias cannot be ruled out. Different aspects with regard to outpatient clinics in different regions in Japan must also be considered. At present, only questionnaire surveys have been conducted [21] to determine the effects that changes in the life cycle of the pandemic period have on worsening of the disease state in PD and parkinsonism patients, and to the best of our knowledge, no reports have used data regarding the actual state of examination dynamics. As the present study did not clarify whether there was no association between the pandemic period itself and worsening of the disease state in these patients, this will need to be clarified by future studies.

## 5. Conclusion

In conclusion, the present study found that the cumulative incidence of rehabilitation interruption events increased during the COVID-19 pandemic period in Japan. The cumulative incidence of disease-related and social factors remained unchanged by the pandemic, but COVID-19-related factors (infection and concerns regarding infection and infecting close contacts) increased during the COVID-19 pandemic period, and this led to increased interruptions of periodic outpatient rehabilitation treatment.

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### Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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