applied sciences

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Clinical and Functional Evolution in Subjects with Parkinson's Disease during SARS-CoV-2 Pandemic

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Abstract: The COVID-19 pandemic has been a stress test for the population, especially for people with chronic disorders such as Parkinson's disease (PD). In addition to public health restrictions that contrast with PD management recommendations, there were deep changes in health care delivery. This retrospective study evaluates the impact of COVID-19 on the clinical and functional evolution of a cohort of 221 PD patients consecutively referred to the Movement Disorders Center between 2018 and 2021. We analyzed the trend in motor and non-motor symptoms and functional status across years based on the Unified Parkinson's Disease Rating Scale (UPDRS) and Non-Motor Symptom Scale (NMSS). We also compared the number of emerging complications, neurologic visits, and rehabilitation sessions per subject per year. In 2020, all primary endpoint measures worsened compared to 2019, without age, disease duration, or greater neurologic impairment explaining this outcome. Concurrently, the percentage of patients receiving neurologic visits or rehabilitation sessions reduced by 53% and 58%, respectively. The subgroup analysis of 167 subjects revealed that those who received at least one cycle of rehabilitation sessions in 2020 maintained their independence level. These findings lead to emphasizing the importance of regular monitoring and rehabilitation delivery in people with chronic neurological disorders.

Keywords: COVID-19; healthcare; rehabilitation; Parkinson's disease; disability; SARS-CoV-2; movement disorders; neurodegenerative disease

Citation: Capecci, M.; Baldini, N.; Campignoli, F.; Lombardo, L.P.; Andrenelli, E.; Ceravolo, M.G. Clinical and Functional Evolution in Subjects with Parkinson's Disease during SARS-CoV-2 Pandemic. *Appl. Sci.* **2023**, *13*, 1126. https://doi.org/10.3390/app13021126

Academic Editors: Marianna Semprini and Fabio La Foresta

Received: 25 February 2022
Revised: 19 July 2022
Accepted: 11 January 2023
Published: 14 January 2023

1. Introduction

More than 400,000,000 cumulative cases and more than 5,500,000 cumulative deaths are the figures of the COVID-19 pandemic in February 2022 [1]. Italy is one of the most affected countries, where a strict lockdown was imposed from 9 March to 3 May in 2020, followed by the second period of hard restrictions from October 2020 to April 2021. During the whole period of interest of our study (March 2020–December 2021), there were 147,936 COVID-19 diagnoses in the Marche region (namely in the population from which the patients with PD are referred to the Movement Disorder Center), with a cumulative incidence rate of 9853.16/100,000 inhabitants [2]. The COVID-19 pandemic has been a stress test for the world population, especially for the healthcare systems that could not help but reduce providing diagnostic, therapeutic, and rehabilitation services to individuals with emerging or chronic conditions [3–6]. The impact of these changes has been particularly felt by people with disabilities, like patients with Parkinson's disease (PD), leading to physical and psychological consequences on mental health [7–9]. Due to the pandemic and associated restrictions, they have faced severe and specific challenges. It is worth considering that the restrictions to routine life obliged individuals to adapt quickly to the new situation, which requires well-preserved dopamine functioning [10]. Many PD patients experienced worsening motor and non-motor symptoms, perhaps due to changes in medical care, daily activities, social support, or physical activity [11]. Anxiety, chronic stress, and depression increased, whereas the opportunities to perform regular physical

activity and access to physiotherapy, advanced therapies, and functional surgery were dramatically reduced [12,13]. People with chronic diseases and disabilities benefit from regular follow-up visits to strengthen their empowerment, screen for the risks of emerging illness, and prescribe drug and rehabilitation treatment as needed. During the first lockdown, follow-up face-to-face visits were suspended or drastically reduced, as were physiotherapy and any rehabilitation intervention [14]. According to a survey conducted in Italy between April and May 2020, around 80% of PD patients interrupted physiotherapy treatments, and up to 60% reported worsening symptoms [15]. The negative impact of the COVID-19 pandemic has also been felt by PD caregivers, who experienced a worsening of their stress level in around 50% of the cases [16].

This study evaluates the clinical and functional evolution of a cohort of PD patients undergoing a standard assessment at an acknowledged Movement Disorders Center, in Italy, over four years, from 2018 to 2021. The research hypothesis is that the reduced access to healthcare services and the interference with the standardized disease management approach worsened this frail population's clinical and functional status during the pandemic.

2. Materials and Methods

2.1. Study Design and Population

In this retrospective, monocentric cohort study, we included patients with PD who were consecutively referred to the Center for Diagnosis and Treatment of Movement Disorders based in a university hospital in Italy.

To the scope of the present study, we considered data collected during the follow-up visits performed in 15 June through 15 December of 2018, 2019, 2020, and 2021. With the selection of this 6-month period, we aimed at ensuring the same time interval between subsequent assessments, while avoiding the overlap with Christmas holidays when outpatient visits are suspended. Specifically, the second part of each year was selected in order to avoid the months of 2020 (March 9th through May 3rd) when outpatients activities were suspended due to the general lockdown.

We searched the clinical records of all subjects with a confirmed PD diagnosis according to the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's disease [17], excluding those that were referred to the Center after 2018 or had stopped clinical monitoring before 2021. We obtained written consent to use anonymized data for research purposes from each participant.

2.2. Model of Care Applied at the Movement Disorder Center

According to the standard model of care adopted at the Movement Disorder Center, outpatients with PD undergo regular neurological and functional assessment, conducted by the same physician, every six months, to evaluate disability progression, check for emerging clinical problems, and prescribe medical and rehabilitation treatment, as needed. At each visit, the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [18] and Non-Motor Symptom Scale (NMSS) [19] are scored. In addition, the checklist of emerging complications, rehabilitation treatment delivery (yes/no, number of sessions), and hospitalizations (yes/no, admission diagnosis) is also filled; finally, the Levodopa Equivalent Daily Dose (LEDD) [20] and the body mass index are recorded.

The MDS-UPDRS [18] is a revision of the UPDRS originally developed in the 1980s. It is designed to evaluate various aspects of Parkinson's disease, including Non-motor (UPDRS Part I: score range 0–52) and Motor Experiences of Daily Living (UPDRS Part II; score range 0–52), Motor Examination (UPDRS Part III; score range 0–128), and Motor Complications (UPDRS Part IV; score range 0–24), characterizing the extent and burden of disease across various populations. It has been validated in different languages, Italian included. The full assessment takes around 30 min.

The NMSS [19] is a 30-item rater-based scale to assess a wide range of non-motor symptoms in patients with PD. The NMSS measures the severity and frequency of non-

motor symptoms across nine dimensions (score range: 0–360) and can be used for patients at all stages of PD. Its administration takes around 10 min.

2.3. Data Analysis

The primary endpoints were changes in motor (UPDRS III score) and non-motor symptoms (NMSS score), and functional status (UPDRS II score) in 2020 (under the lockdown) when compared to the preceding (2018–2019) and subsequent years (2021).

Secondary endpoints were changes in UPDRS IV scores, LEDD, body mass index, requests for neurological counsels, rehabilitation sessions, hospitalizations, and emerging comorbidities with particular attention to SARS-CoV-2 infections.

We used descriptive statistics to outline the trend in UPDRS III, NMSS, and UPDRS II scores across the period of interest, representing the data as mean, Standard Deviation (SD), median, and interquartile range (IQR). The same procedure was applied to UPDRS IV, LEDD, body mass index, number of neurological visits, rehabilitation sessions, and hospitalizations. Incident SARS-CoV-2 infections and related outcomes (i.e., mortality, need for hospitalization) were described as percentages of the total subjects assessed/year. In order to cope with the high inter-individual variability of the outcome mesures, we computed the percentage change of each variable of interest over one year with respect to the previous years' value; namely, the UPDRS II change over 2019/2018 was computed as: (2019 UPDRS II score–2018 UPDRS II score)/2018 UPDRS II score) $\times$ 100.

As the higher the UPDRS or NMSS scores the worse the impairment, positive changes indicate worsened patients' conditions.

Comparative statistics used the Wilcoxon signed-rank test to ascertain differences between changes observed in 2019–2020, with respect to the previous and subsequent time periods.

The simple regression analysis was applied to check the relationship between the %changes observed in 2019–2020 in the primary outcome measures with several explanatory variables (e.g., age, BMI, disease duration, disease severity in terms of NMSS score and UPDRS subscores). When appropriate, a multiple regression analysis was applied.

Based on the application of Bonferroni correction for multiple comparisons, statistical significance was set at a p-value of <0.001. We used SAS StatView 5.0 for data analysis.

3. Results

A total of 466 patients received at least one visit over the whole period of interest (15 June 2018, through 15 December 2021). Of them, 24 subjects did not meet the diagnosis criterion (they suffered from atypical parkinsonism), and 185 patients were excluded because they were referred to the center for the first time after 1 January 2019 (namely, 88 in 2019, 26 in 2020, and 71 in 2021), so no information was available about the trend in their clinical and functional status before the pandemic. Finally, out of 257 subjects with complete records from 2018 through 2021, 36 did not show up in the period of interest (15 June–15 December) of 2020 for fear of attending the hospital. Therefore, the analysis focused on the remaining 221. They were 116 men and 105 women, with a mean age of 72.5 ($\pm$8.9 SD) years [range 51–91] and a disease duration of 14.6 ($\pm$7.6 SD) years [range 4–37].

3.1. Primary Endpoints

Table 1 presents the results of the descriptive and comparative statistics of primary endpoint measures across the period of interest. Overall, the mean values of UPDRS-II (15.02 $\pm$ 8.0) and UPDRS-III (22.63 $\pm$ 13.1) recorded in 2018 are representative of a varied population of patients with mild to moderate motor impairment and reduced independence in ADL, though generally preserved walking ability. The disabling impact of non-motor symtoms (NMSS score = 65.89 $\pm$ 34.6 in 2018) is mild to moderate as well. The analysis of changes of primary outcome measures in the 2018–2019 time period showed high inter-individual variability in the trends of UPDRS-II, UPDRS-III, and NMSS scores with mean values of 0.3% ($\pm$33.0), $-$3.8% ($\pm$39.3), and $-$11.5% ($\pm$32.4), respectively. Even if the large

variability of motor and non-motor symptom progression was confirmed in subsequent years, the matched comparison of % changes observed in 2019–2020, with those recorded in 2018–2019 in the same subjects, showed a statistically significant trend towards increasing for all primary outcome measures. On average, UPDRS-II, UPDRS-III, and NMSS scores increased by 22% (±55.3), 28.8% (±64.2), and 12.5 (±8.1), respectively, at the end of 2020 compared to the year before. In the 2020–2021 period, UPDRS-II, UPDRS-III, and NMSS increased by 12.0% (±58.3), 0.01% (±0.4), and 12.5% (±49.5), respectively. When compared to the changes observed in the previous year, only the UPDRS-III trend was significantly different from the trend observed before.

Table 1. Clinical and functional status scores collected on 221 patients with PD from 2018 to 2021. Main outcome changes at the end of each period of interest are described as a percentage of the change compared to the starting value. Statistically significant comparisons are indicated in bold.

Parameter	2018	2019	2020	2021	%Change (2018–2019)/2018	%Change (2019–2020)/2019	%Change (2020–2021)/2020	Wilcoxon Rank Test (2018–2019 vs. 2019–2020) Z; Tied P	Wilcoxon Rank Test (2019–2020 vs. 2020–2021) Z; Tied P
UPDRS II Mean ± SD [median; IQR]	15.02 ± 8.0 [14; 12]	14.10 ± 8.4 [13; 11.3]	15.47 ± 8.6 [14; 13]	16.13 ± 8.1 [15; 11.3]	0.3 ± 33.0 [0; 26.4]	22 ± 55.3 [10.0; 36.6]	12.0 ± 58.3 [0; 31.8]	**−3.4; p = 0.0007**	−2.3; p = 0.01
UPDRS III Mean (SD) [median; IQR]	22.63 ± 13.1 [20; 17.5]	20.68 ± 12.7 [18; 17]	23.52 ± 13.7 [21; 19]	23.26 ± 13.3 [22; 18]	−3.8 ± 39.3 [4.7; 39.9]	28.8 ± 64.2 [14.3; 50.9]	0.01 ± 0.4 [0; 0.39]	**−3.9; p = 0.0001**	**−5.8; p = 0.0001**
NMSS Mean (SD) [median; IQR]	65.89 ± 34.6 [62.5; 44]	55.95 ± 31.1 [50; 42.8]	60.42 ± 35.7 [52.5; 46]	58.69 ± 34.3 [53.5; 50.5]	−11.5 ± 32.4 [−13.0; 38.1]	12.5 ± 8.1 [2.3; 51.1]	12.5 ± 49.5 [4.7; 55.7]	**−3.2; p = 0.001**	−0.67; p = 0.49

Legend: IQR: Interquartile Range; NMSS = Non-Motor Symptoms Scale; SD: Standard Deviation; UPDRS = Unified Parkinson's Disease Rating Scale.

We run a simple regression analysis to look for any correlation between demographic and clinical variables and the progression of primary outcome measures in 2019–2020. Table 2 details the results, showing that only the baseline values of the different measures at the start of 2019 explained the change. Most importantly, it showed that the lower the starting values, the higher the changes in the following year.

Table 2. Results of the simple regression analysis matching different independent variables with %changes observed in 2019–2020 in the primary outcome measures. Statistically significant correlations are in bold.

	Dependent Variable		
Independent Variable (2019 Values)	**UPDRS II % Change 2019–2020**	**UPDRS III % Change 2019–2020**	**NMSS % Change 2019–2020**
Age	Coeff. 0.569; R2:0.008 p = 0.21	Coeff. 0.361; R2:0.002 p = 0.50	Coeff. −0.543; R2:0.010 p = 0.17
Disease duration	Coeff.− 0.347; R2:0.002 p = 0.49	Coeff. −1.36; R2:0.027 p = 0.02	Coeff. −0.261; R2:0.002 p = 0.55
BMI	Coeff. −0.558; R2:0.002 p = 0.54	Coeff. −0.731; R2:0.003 p = 0.48	Coeff. 0.139; R2:0.0001 p = 0.86
UPDRS II	Coeff. **−2.42; R2:0.113 p = 0.0001**	Coeff.−1.24; R2:0.023 p = 0.03	Coeff. −0.109; R2:0.0001 p = 0.80
UPDRS III	Coeff. −0.509; R2:0.013 p = 0.10	**Coeff. −1.84; R2:0.128 p = 0.0001**	Coeff. 0.204; R2:0.003 p = 0.46
NMSS	Coeff. −0.218; R2:0.014 p = 0.09	Coeff. −0.084; R2:0.002 p = 0.58	Coeff. −0.477; R2:0.090 **p = 0.0001**

Legend: BMI = Body Mass Index; Coeff = coefficient; NMSS = Non-Motor Symptoms Scale; UPDRS = Unified Parkinson's Disease Rating Scale; val: value.

Age, disease duration, and BMI were not correlated to the trends observed in 2018–2019 and 2020–2021 in the primary outcome measures. When we matched the % changes in UPDRS II, UPDRS III, and NMSS observed in 2018–2019 with their starting values,

we found no significant relationship. On the other side, significant correlations were observed between the % changes in UPDRS II and UPDRS III observed in 2020–2021 with their starting values, and, more precisely, the lower the starting values, the greater their worsening during the subsequent year (Table 3).

Table 3. Results of the simple regression analysis matching %changes observed in 2018–2019 and 2020–2021 in the primary outcome measures with their starting values. Statistically significant correlations are in bold.

	Dependent Variable					
Independent Variable	**UPDRS II % Change 2018–2019**	**UPDRS III % Change 2018–2019**	**NMSS % Change 2018–2019**	**UPDRS II % Change 2020–2021**	**UPDRS III % Change 2020–2021**	**NMSS % Change 2020–2021**
UPDRS II 2018	Coeff. −0.759; R2: 0.032 ***p* = 0.01**	Coeff. −0.055; R2: 0.0001 $p = 0.88$	Coeff. 0.088; R2: 0.0001 $p = 0.78$			
UPDRS III 2018	Coeff. −0.013; R2: 0.0001 $p = 0.94$	Coeff. −0.342; R2: 0.013 $p = 0.13$	Coeff. 0.136; R2: 0.003 $p = 0.49$			
NMSS 2018	Coeff. −0.072; R2: 0.006 $p = 0.32$	Coeff. −0.069; R2: 0.004 $p = 0.42$	Coeff. −0.119; R2: 0.016 $p = 0.10$			
UPDRS II 2020				**Coeff. −2.51; R2: 0.131 *p* = 0.0001**	Coeff. −0.007; R2: 0.023 ***p* = 0.04**	Coeff. −0.439; R2: 0.005 $p = 0.38$
UPDRS III 2020				Coeff. −0.573; R2: 0.017 $p = 0.08$	Coeff. −0.007; R2: 0.064 ***p* = 0.0007**	Coeff. −0.279; R2: 0.005 $p = 0.37$
NMSS 2020				Coeff. −0.427; R2: 0.056 ***p* = 0.002**	Coeff. −0.002; R2: 0.017 $p = 0.08$	Coeff. −0.394; R2: 0.054 ***p* = 0.003**

Legend: Coeff = coefficient; NMSS = Non-Motor Symptoms Scale; UPDRS = Unified Parkinson's Disease Rating Scale; val: value.

3.2. Secondary Endpoints

Table 4 presents the results of the descriptive and comparative statistics of secondary endpoint measures across the period of interest. No statistically significant changes were observed in any measure.

Table 4. Values of the secondary outcome measures (BMI, UPDRS IV, and LevoDopa Equivalent Daily Doses (LEDDs)) in the period of interest. Comparisons between measures taken in two consecutive years are presented. No statistically significant changes were observed over time.

Parameter	**2018**	**2019**	**2020**	**2021**	**Wilcoxon Rank Test (2018 vs. 2019) Z; Tied P**	**Wilcoxon Rank Test (2019 vs. 2020) Z; Tied P**	**Wilcoxon Rank Test (2020 vs. 2021) Z; Tied P**
BMI Mean ± SD [median; IQR]	26.3 ± 4.9 [25.7; 5.5]	25.9 ± 4.5 [25.4; 4.9]	25.8 ± 4.8 [25.0; 5.5]	25.9 ± 5.3 [25.5; 5.5]	−2.4 $p = 0.01$	−0.76 $p = 0.44$	−1.58 $p = 0.11$
UPDRS IV Mean ± SD [median; IQR]	3.30 ± 3.2 [3; 5]	2.63 ± 2.8 [2; 4]	3.06 ± 3.0 [3; 5]	2.93 ± 3.1 [2; 5]	−1.8 $p = 0.06$	−2.5 $p = 0.009$	−0.4 $p = 0.67$
LEDD Mean ± SD [median; IQR]	689.7 ± 374.7 [650; 464.3]	701.9 ± 436.4 [606.5; 411.0]	668.1 ± 383.4 [562, 471.5]	661.7 ± 414.0 [560; 472.7]	0.34 $p = 0.73$	1.5 $p = 0.12$	0.0 $p > 0.99$

Legend: BMI = Body Mass Index; UPDRS = Unified Parkinson's Disease Rating Scale; LEDD = Levodopa Equivalent Daily Dose.

In 2020, we observed a 53% decrease in the number of neurologic counsels per subject. In addition, the rate of subjects receiving at least one rehabilitation cycle per year dropped from 87% (in 2018 and 2019) to 29% in 2020 (Chi-square = 20; $p < 0.0001$), rising again to 42% in 2021.

Looking for factors explaining the variance of UPDRS II % change in 2019–2020, we considered patients who received rehabilitation in 2020. The U-Mann–Whitney was applied for this post-hoc comparison between a group of 64 patients who had undergone at least one cycle of rehabilitation sessions (mean UPDRS II change 2019–2020: 0.7% ± 26.4 [median −2.6; IQR 27.8] and the remaining 157 who had not received any training (mean UPDRS II change 2019–2020: 24.7% ± 57.5 [median 11.1; IQR 39.3]. The comparison by the U-Mann–Whitney test did not show any significant difference though, just a trend towards a different disability progression in the two subgroups ($Z = -1.9$; $p = 0.04$).

Eleven patients with PD (5% of the study sample) developed a SARS-CoV-2 infection in the period of interest. Four subjects died: of them, three were in the advanced stage of disease with comorbidities (diabetes mellitus, cerebral vasculopathy, blood hypertension), and one was in a moderate stage without comorbidity. Among the seven survivors, two suffered from bilateral interstitial pneumonia and were hospitalized and recovered completely, while five subjects suffered from a mild infection without the need for hospitalization. The survivors did not show a significant worsening in either UPDRS or NMSS scores compared to the premorbid condition.

4. Discussion

The longitudinal observation of a cohort of patients with PD from 2018 to 2021 allowed us to have a comprehensive view of what happened in recent years. 2020 was the most critical year because we were taken aback by the spreading of the COVID-19 pandemic and suffered the strictest and most challenging lockdown measures. 2021 combined the long-term response to the pandemic with the resumption of follow-up visits and face-to-face rehabilitation sessions, the implementation of remote technology solutions, and, eventually, the introduction of the most important prevention tool, i.e., the vaccines against the SARS-CoV-2 virus. Data from 2018 and 2019 presented the health status of patients with PD immediately before the pandemic and offered a reference point for the interpretation of disability progression across the whole period of interest.

The current understanding of evolving disability in PD shows some limitations linked to the limited number of studies, [21–28], the frequent cross-sectional designs that overestimate the actual rate of progression, [21] and/or different and limited measures of disability. However, authors largely agree that the growth curve, or change over time, for MDS-UPDRS is curvilinear [21,28] and that there is little to no change in motor and functional status through 12 months [21,27] Ellis et al. [21] showed that the adjusted linear effect at 18 months is 1.79 (95% CI 0.99, 2.59) and at 24 months is 2.48 (95% CI 1.16, 3.79), a 2.5 point increase at 2 years. Schrag et al. [29] showed that the mean deterioration of motor and disability scores ranges from 2.4 to 7.4% of the maximum possible score per year, and standard deviations indicated the considerable variability of progression rates between individuals. The progression of motor scores decreases with follow-up over 4 years and significantly declines in more advanced disease stages. The deterioration of disability scores does not differ between disease stages; this may reflect the increasing rate of non-motor symptoms or disease complications, which contribute to increasing disability in addition to motor impairment alone in more advanced disease. Alves et al. [23] found a mean annual decline in the UPDRS motor score of 3.2%, and the UPDRS Activity of Daily Living (ADL) score changed similarly, by 3.6% per year. Many authors demontrated that age, age at onset, disease duration, mild cognitive impairment at baseline, severe rigidity or bradykinesia, prominent gait problem at the onset, and nonmotor symptoms (i.e., rapid eye movement, sleep behavior disorder, mild cognitive impairment and orthostatic hypotension) are strong and independent predictors of greater impairment and rapid evolution in motor function and disability [23,30]

Our sample, followed retrospectively for 4 years, lies outside the range of progression identified in the literature, which characterizes the motor and functional evolution of individuals with PD. In particular, the mean progression in UPDRS II and III scores over the 2019–2020 period identifies a singular anomaly. In contrast, the evolution described

in the previous period (i.e., 2018–2019) followed the reference pattern, while that of the 2020–2021 biennium tends to go back toward expected values. The standard deviations are large in relation to the variability of the enrolled sample. However, the median shows that the motor, non-motor, and functional evolution described in our study does not relate to a normal evolution of PD history but seems to be influenced by external and novel factors.

In the literature, many studies focused on the self-perceived health status change reported by patients with PD during and after the outbreak of COVID-19 [31–33]. In this study, we used objective clinical and functional measures to establish the impact of restricted access to personalized care and the limitations to physical activity imposed by the lockdown on the health status of a cohort of PD patients referred to a Movement Disorder Center for regular monitoring.

In the second semester of 2020, PD-related symptoms and the independence in activity of daily living significantly worsened in the whole sample. Most patients showed a stable functional condition in the year immediately preceding the pandemic (as measured by the UPDRS II %score change in 2018–2019). Between 2019 and 2020, we found a trend towards worsening in UPDRS-II and UPDRS-III, which was not explained by age, disease duration, or severity. Most importantly, patients with lower functional impairment experienced a greater worsening in their functional condition. The trend towards worsening was confirmed in 2020–2021 for UPDRS-II even at a lower extent, though not for UPDRS-III, whose scores remained relatively stable. Also, non-motor symptoms showed a trend toward worsening in 2019–2020 that was maintained in the subsequent year.

Other surveys reported similar findings in different cohorts of patients with PD. In particular, Balci et al. described a worsening of motor and non-motor symptoms in 68.9% of sample subjects [34]. Santos-Garcia et al. reported a subjective worsening of parkinsonian symptoms in 65.7% of interviewed patients in Spain [33], whereas Del Prete et al. described such a negative outcome in 30% of their subjects, in Italy [35].

The results of the regression analysis lead us to hypothesize that the impact of the lockdown mostly affected subjects with milder disability at the time COVID-19 hit our country, i.e., those who most suffered from the mobility restrictions imposed by the lockdown. According to these findings, patients with PD exhibit psychological vulnerability and poor resilience to social isolation, irrespective of age and disease severity. Emotional and behavioral adaptation to stressful situations may be impaired in patients with PD due to different factors, like a high prevalence of depressive disorders [36], impaired modulation of autonomic nervous system [37], impaired interpretation of other emotions [38], and impaired selection of proper coping strategies [39]. Moreover, our survey demonstrated that the number of neurologic visits per subject per year was shortened by around 50% in 2020. In addition, the percentage of patients undergoing at least one rehabilitation cycle in a year dropped from 87% (on average in 2018–2019) to 29% in 2020. It is reasonable to argue that people used to performing regular motor training, as recommended in our care pathway, were most disadvantaged by being cut off from rehabilitation provision.

Our hypothesis is in line with the findings by other authors who pointed out the effects of physical activity changes in patients with PD during COVID-19 lockdown [15,32,40,41]. The reduced access to health care services could be related not only to a reduced supply but also to a reduced demand due to individuals' fear of contracting the virus when accessing the hospital [42] or to the difficulty in getting to the hospital because of the shortage of transport [43]. It has been reported that the longer the history of PD, the greater the difficulty and the fear of accessing hospitals or health facilities [44]. In addition, as the disease progresses, the grade of disability increases, just like the care needs. These data could explain the significant correlation between worsening functional status after the first year of the COVID-19 pandemic and disease duration and UPDRS II score, in line with Fasano et al. [45].

In our sample, the execution of at least one cycle of rehabilitation, including telerehabilitation, in 2020 was associated with a lower (though not significant) risk of worsening functional status. This finding leads to emphasizing the importance of physical activity and

supports the need for finding alternative tools to ensure a regular engagement of patients with PD in rehabilitation sessions, even remotely delivered. Physical activity, especially aerobic exercise, provides significant advantages for health [46], contributing to slowing down disease progression and, in some cases, improving clinical outcomes [47].

In our cohort, 5% of patients with PD developed a COVID-19 infection, confirmed by the molecular test. This proportion mirrors the data from two systematic reviews reporting a median infection prevalence ranging from 0.6% to 8.5% and 0.94% to 8.5%, respectively [48,49]. In line with the literature [44,45,48], we observed that the more advanced Parkinson's disease, the worse the infection outcome. Furthermore, comorbidities, such as diabetes, hypertension, and cerebral vasculopathy, were predictors of unfavorable outcomes in PD subjects developing COVID-19, thus confirming findings from other studies [35,45,48–51]. It is essential to highlight that a person in the advanced stage of PD is often elderly, with comorbidities and polypharmacy: three of the most important predictors of a negative outcome in the general population [52–54].

Finally, in those patients who survived COVID-19, we did not observe a significant worsening of UPDRS or NMSS scores.

Our analysis has intrinsic limitations of retrospective studies, particularly regarding data completeness, like more detailed information about the level of physical activity performed across years. Nonetheless, our standard assessment protocol applied during the outpatient visits has allowed us to collect a wide range of clinical and functional parameters covering all the domains affecting health status in patients with PD.

5. Conclusions

The restrictive measures imposed on the population during the COVID-19 pandemic have negatively impacted patients with PD, with a greater adverse effect on those with milder disease severity. The study shows that subjects with lower disability and motor impairment suffered from a more severe worsening of their functional condition; on the other hand, subjects who received at least one cycle of rehabilitation sessions in 2020 maintained their health status. This finding emphasizes the importance of regular clinical monitoring and rehabilitation delivery for people with chronic disabilities and supports the need to expand the access even to telerehabilitation to foster the empowerment of the greatest possible number of subjects.

Author Contributions: Conceptualization, M.C. and M.G.C.; methodology, M.C.; formal analysis, M.C.; investigation, N.B., F.C., L.P.L.; writing—original draft preparation, N.B., F.C., E.A.; writing—review and editing, M.C., E.A., M.G.C.; supervision M.C., M.G.C. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki.

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.

Data Availability Statement: The data presented in this study are available on request from the corresponding author. The data are not publicly available due to privacy restrictions.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. WHO Coronavirus (COVID-19) Dashboard. Available online: https://covid19.who.int (accessed on 20 February 2022).
2. Ministero della Salute, Istituto Superiore di Sanità. Monitoraggio Fase 2 Report Settimanale Regione Marche. Available online: https://www.salute.gov.it/imgs/C_17_monitoraggi_95_9_fileRegionale.pdf (accessed on 20 February 2022).
3. Negrini, S.; Grabljevec, K.; Boldrini, P.; Kiekens, C.; Moslavac, S.; Zampolini, M.; Christodoulou, N. Up to 2.2 Million People Experiencing Disability Suffer Collateral Damage Each Day of COVID-19 Lockdown in Europe. *Eur. J. Phys. Rehabil. Med.* **2020**, *56*, 361–365. [CrossRef]

4. Fekadu, G.; Bekele, F.; Tolossa, T.; Fetensa, G.; Turi, E.; Getachew, M.; Abdisa, E.; Assefa, L.; Afeta, M.; Demisew, W.; et al. Impact of COVID-19 pandemic on chronic diseases care follow-up and current perspectives in low resource settings: A narrative review. *Int. J. Physiol. Pathophysiol. Pharmacol.* **2021**, *13*, 86–93.
5. Danhieux, K.; Buffel, V.; Pairon, A. The impact of COVID-19 on chronic care according to providers: A qualitative study among primary care practices in Belgium. *BMC Fam. Pract.* **2020**, *21*, 255. [CrossRef]
6. Brasso, C.; Bellino, S.; Blua, C.; Bozzatello, P.; Rocca, P. The Impact of SARS-CoV-2 Infection on Youth Mental Health: A Narrative Review. *Biomedicines* **2022**, *10*, 772. [CrossRef]
7. Tufail, M.; Wu, C. Psychological impact of COVID-19 pandemic on Parkinson's disease patients. *Heliyon* **2022**, *8*, e09604. [CrossRef] [PubMed]
8. Piano, C.; Bove, F.; Tufo, T.; Imbimbo, I.; Genovese, D.; Stefani, A.; Marano, M.; Peppe, A.; Brusa, L.; Cerroni, R.; et al. Effects of COVID-19 Lockdown on Movement Disorders Patients with Deep Brain Stimulation: A Multicenter Survey. *Front. Neurol.* **2020**, *11*, 616550. [CrossRef]
9. Immovilli, P.; Morelli, N.; Terracciano, C.; Rota, E.; Marchesi, E.; Vollaro, S.; De Mitri, P.; Zaino, D.; Bazzurri, V.; Guidetti, D. Multiple Sclerosis Treatment in the COVID-19 Era: A Risk-Benefit Approach. *Neurol. Int.* **2022**, *14*, 368–377. [CrossRef]
10. Helmich, R.C.; Aarts, E.; de Lange, F.P.; Bloem, B.R.; Toni, I. Increased Dependence of Action Selection on Recent Motor History in Parkinson's Disease. *J. Neurosci.* **2009**, *29*, 6105–6113. [CrossRef]
11. Brooks, S.K.; Weston, D.; Greenberg, N. Social and Psychological Impact of the COVID-19 Pandemic on People with Parkinson's Disease: A Scoping Review. *Public Health* **2021**, *199*, 77–86. [CrossRef] [PubMed]
12. Fasano, A.; Antonini, A.; Katzenschlager, R.; Krack, P.; Odin, P.; Evans, A.H.; Foltynie, T.; Volkmann, J.; Merello, M. Management of Advanced Therapies in Parkinson's Disease Patients in Times of Humanitarian Crisis: The COVID-19 Experience. *Mov. Disord. Clin. Pract.* **2020**, *7*, 361–372. [CrossRef] [PubMed]
13. Cartella, S.M.; Terranova, C.; Rizzo, V.; Quartarone, A.; Girlanda, P. COVID-19 and Parkinson's Disease: An Overview. *J. Neurol.* **2021**, *268*, 4415–4421. [CrossRef] [PubMed]
14. De Donno, A.; Acella, A.; Angrisani, C.; Gubinelli, G.; Musci, G.; Gravili, G.; Ciritella, C.; Santamato, A. Suspension of Care for Patients with Spasticity During COVID-19 Pandemic: Ethical and Medico-Legal Point of View Starting From an Italian Study. *Front. Med.* **2021**, *8*, 754456. [CrossRef] [PubMed]
15. Schirinzi, T.; Di Lazzaro, G.; Salimei, C.; Cerroni, R.; Liguori, C.; Scalise, S.; Alwardat, M.; Mercuri, N.B.; Pierantozzi, M.; Stefani, A.; et al. Physical Activity Changes and Correlate Effects in Patients with Parkinson's Disease during COVID-19 Lockdown. *Mov. Disord. Clin. Pract.* **2020**, *7*, 797–802. [CrossRef]
16. Oppo, V.; Serra, G.; Fenu, G.; Murgia, D.; Ricciardi, L.; Melis, M.; Morgante, F.; Cossu, G. Parkinson's Disease Symptoms Have a Distinct Impact on Caregivers' and Patients' Stress: A Study Assessing the Consequences of the COVID-19 Lockdown. *Mov. Disord. Clin. Pract.* **2020**, *7*, 865–867. [CrossRef]
17. Postuma, R.B.; Berg, D.; Stern, M.; Poewe, W.; Olanow, C.W.; Oertel, W.; Obeso, J.; Marek, K.; Litvan, I.; Lang, A.E.; et al. MDS Clinical Diagnostic Criteria for Parkinson's Disease. *Mov. Disord. Off. J. Mov. Disord. Soc.* **2015**, *30*, 1591–1601. [CrossRef]
18. Goetz, C.G.; Tilley, B.C.; Shaftman, S.R.; Stebbins, G.T.; Fahn, S.; Martinez-Martin, P.; Poewe, W.; Sampaio, C.; Stern, M.B.; Dodel, R.; et al. Movement Disorder Society-Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS): Scale Presentation and Clinimetric Testing Results. *Mov. Disord.* **2008**, *23*, 2129–2170. [CrossRef]
19. Van Wamelen, D.J.; Martinez-Martin, P.; Weintraub, D.; Schrag, A.; Antonini, A.; Falup-Pecurariu, C.; Odin, P.; Ray Chaudhuri, K.; International Parkinson and Movement Disorder Society Parkinson's Disease Non-Motor Study Group. The Non-Motor Symptoms Scale in Parkinson's Disease: Validation and Use. *Acta Neurol. Scand.* **2021**, *143*, 3–12. [CrossRef]
20. Tomlinson, C.L.; Stowe, R.; Patel, S.; Rick, C.; Gray, R.; Clarke, C.E. Systematic review of levodopa dose equivalency reporting in Parkinson's disease. *Mov. Disord.* **2010**, *25*, 2649–2653. [CrossRef]
21. Ellis, T.D.; Cavanaugh, J.T.; Earhart, G.M.; Ford, M.P.; Foreman, K.B.; Thackeray, A.; Thiese, M.S.; Dibble, L.E. Identifying clinical measures that most accurately reflect the progression of disability in Parkinson disease. *Parkinsonism Relat. Disord.* **2016**, *25*, 65–71. [CrossRef]
22. Shulman, L.M.; Gruber-Baldini, A.L.; Anderson, K.E.; Vaughan, C.G.; Reich, S.G.; Fishman, P.S.; Weiner, W.J. The evolution of disa-bility in Parkinson disease. *Mov. Disord.* **2008**, *23*, 790–796. [CrossRef] [PubMed]
23. Alves, G.; Wentzel-Larsen, T.; Aarsland, D.; Larsen, J.P. Progression of motor impairment and disability in Parkinson disease: A population-based study. *Neurology.* **2005**, *65*, 1436–1441. [CrossRef] [PubMed]
24. Poewe, W.; Seppi, K.; Tanner, C.M.; Halliday, G.M.; Brundin, P.; Volkmann, J.; Schrag, A.E.; Lang, A.E. Parkinson disease. *Nat. Re-Views Dis. Prim.* **2017**, *3*, 1–21. [CrossRef] [PubMed]
25. Jankovic, J.; Kapadia, A.S. Functional decline in Parkinson disease. *Arch. Neurol.* **2001**, *58*, 1611e1615. [CrossRef]
26. Marinus, J.; van der Heeden, J.F.; van Hilten, J.J. Calculating clinical progression rates in Parkinson's disease: Methods matter, Park. *Relat. Disord.* **2014**, *20*, 1263e1267. [CrossRef]
27. Bugalho, P.; Ladeira, F.; Barbosa, R.; Marto, J.P.; Borbinha, C.; da Conceição, L.; Salavisa, M.; Saraiva, M.; Meira, B.; Fernandes, M. Progression in Parkinson's Disease: Variation in Motor and Non-motor Symptoms Severity and Predictors of Decline in Cognition, Motor Function, Disability, and Health-Related Quality of Life as Assessed by Two Different Methods. *Mov Disord Clin. Pract.* **2021**, *8*, 885–895, Erratum in *Mov. Disord. Clin. Pract.* **2022**, *9*, 411. [CrossRef]

28. Post, B.; Muslimovic, D.; van Geloven, N.; Speelman, J.D.; Schmand, B.; de Haan, R.J.; CARPA-study group. Progression and prognostic factors of motor impairment, disability and quality of life in newly diagnosed Parkinson's disease. *Mov. Disord.* **2011**, *26*, 449–456. [CrossRef]
29. Schrag, A.; Dodel, R.; Spottke, A.; Bornschein, B.; Siebert, U.; Quinn, N.P. Rate of clinical progression in Parkinson's disease. A prospective study. *Mov. Disord.* **2007**, *22*, 938–945. [CrossRef] [PubMed]
30. Fereshtehnejad, S.M.; Zeighami, Y.; Dagher, A.; Postuma, R.B. Clinical criteria for subtyping Parkinson's disease: Biomarkers and longitudinal progression. *Brain* **2017**, *140*, 1959–1976. [CrossRef]
31. Leavy, B.; Hagströmer, M.; Conradsson, D.M.; Franzén, E. Physical Activity and Perceived Health in People With Parkinson Disease During the First Wave of COVID-19 Pandemic: A Cross-Sectional Study From Sweden. *J. Neurol. Phys. Ther. JNPT* **2021**, *45*, 266–272. [CrossRef]
32. Suzuki, K.; Numao, A.; Komagamine, T.; Haruyama, Y.; Kawasaki, A.; Funakoshi, K.; Fujita, H.; Suzuki, S.; Okamura, M.; Shiina, T.; et al. 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. *J. Park. Dis.* **2021**, *11*, 1047–1056. [CrossRef]
33. Santos-García, D.; Oreiro, M.; Pérez, P.; Fanjul, G.; Paz González, J.M.; Feal Painceiras, M.J.; Cores Bartolomé, C.; Valdés Aymerich, L.; García Sancho, C.; Castellanos Rodrigo, M.D.M. Impact of Coronavirus Disease 2019 Pandemic on Parkinson's Disease: A Cross-Sectional Survey of 568 Spanish Patients. *Mov. Disord. Off. J. Mov. Disord. Soc.* **2020**, *35*, 1712–1716. [CrossRef] [PubMed]
34. Balci, B.; Aktar, B.; Buran, S.; Tas, M.; Donmez Colakoglu, B. Impact of the COVID-19 Pandemic on Physical Activity, Anxiety, and Depression in Patients with Parkinson's Disease. *Int. J. Rehabil. Res. Int. Z. Rehabil. Rev. Int. Rech. Readaptation* **2021**, *44*, 173–176. [CrossRef] [PubMed]
35. Del Prete, E.; Francesconi, A.; Palermo, G.; Mazzucchi, S.; Frosini, D.; Morganti, R.; Coleschi, P.; Raglione, L.M.; Vanni, P.; Ramat, S.; et al. Prevalence and Impact of COVID-19 in Parkinson's Disease: Evidence from a Multi-Center Survey in Tuscany Region. *J. Neurol.* **2021**, *268*, 1179–1187. [CrossRef]
36. Cao, X.; Yang, F.; Zheng, J.; Wang, X.; Huang, Q. Aberrant Structure MRI in Parkinson's Disease and Comorbidity with Depression Based on Multinomial Tensor Regression Analysis. *J. Pers. Med.* **2022**, *12*, 89. [CrossRef] [PubMed]
37. Tanaka, M.; Spekker, E.; Szabó, Á.; Polyák, H.; Vécsei, L. Modelling the neurodevelopmental pathogenesis in neuropsychiatric disorders. Bioactive kynurenines and their analogues as neuroprotective agents-in celebration of 80th birthday of Professor Peter Riederer. *J. Neural. Transm.* **2022**, *129*, 627–642. [CrossRef]
38. Battaglia, S.; Fabius, J.H.; Moravkova, K.; Fracasso, A.; Borgomaneri, S. The Neurobiological Correlates of Gaze Perception in Healthy Individuals and Neurologic Patients. *Biomedicines* **2022**, *10*, 627. [CrossRef]
39. Haahr, A.; Groos, H.; Sørensen, D. Striving for normality' when coping with Parkinson's disease in everyday life: A metasynthesis. *Int J Nurs Stud.* **2021**, *118*, 103923. [CrossRef]
40. Fabbri, M.; Leung, C.; Baille, G.; Béreau, M.; Brefel Courbon, C.; Castelnovo, G.; Carriere, N.; Damier, P.; Defebvre, L.; Doe de Maindreville, A.; et al. A French Survey on the Lockdown Consequences of COVID-19 Pandemic in Parkinson's Disease. The ERCOPARK Study. *Parkinsonism Relat. Disord.* **2021**, *89*, 128–133. [CrossRef] [PubMed]
41. Knapik, A.; Szefler-Derela, J.; Wasiuk-Zowada, D.; Siuda, J.; Krzystanek, E.; Brzęk, A. Isolation Related to the COVID-19 Pandemic in People Suffering from Parkinson's Disease and Activity, Self-Assessment of Physical Fitness and the Level of Affective Disorders. *Healthcare* **2021**, *9*, 1562. [CrossRef]
42. Feeney, M.P.; Xu, Y.; Surface, M.; Shah, H.; Vanegas-Arroyave, N.; Chan, A.K.; Delaney, E.; Przedborski, S.; Beck, J.C.; Alcalay, R.N. The Impact of COVID-19 and Social Distancing on People with Parkinson's Disease: A Survey Study. *NPJ Park. Dis.* **2021**, *7*, 10. [CrossRef]
43. Kumar, N.; Gupta, R.; Kumar, H.; Mehta, S.; Rajan, R.; Kumar, D.; Kandadai, R.M.; Desai, S.; Wadia, P.; Basu, P.; et al. Impact of Home Confinement during COVID-19 Pandemic on Sleep Parameters in Parkinson's Disease. *Sleep Med.* **2021**, *77*, 15–22. [CrossRef] [PubMed]
44. Brown, E.G.; Chahine, L.M.; Goldman, S.M.; Korell, M.; Mann, E.; Kinel, D.R.; Arnedo, V.; Marek, K.L.; Tanner, C.M. The Effect of the COVID-19 Pandemic on People with Parkinson's Disease. *J. Park. Dis.* **2020**, *10*, 1365–1377. [CrossRef] [PubMed]
45. Fasano, A.; Elia, A.E.; Dallocchio, C.; Canesi, M.; Alimonti, D.; Sorbera, C.; Alonso-Canovas, A.; Pezzoli, G. Predictors of COVID-19 Outcome in Parkinson's Disease. *Parkinsonism Relat. Disord.* **2020**, *78*, 134–137. [CrossRef]
46. World Health Organization. *WHO Guidelines on Physical Activity and Sedentary Behaviour*; World Health Organization: Geneva, Switzerland, 2020.
47. Helmich, R.C.; Bloem, B.R. The Impact of the COVID-19 Pandemic on Parkinson's Disease: Hidden Sorrows and Emerging Opportunities. *J. Park. Dis.* **2020**, *10*, 351–354. [CrossRef] [PubMed]
48. Artusi, C.A.; Romagnolo, A.; Ledda, C.; Zibetti, M.; Rizzone, M.G.; Montanaro, E.; Bozzali, M.; Lopiano, L. COVID-19 and Parkinson's Disease: What Do We Know So Far? *J. Park. Dis.* **2021**, *11*, 445–454. [CrossRef]
49. El-Qushayri, A.E.; Ghozy, S.; Reda, A.; Kamel, A.M.A.; Abbas, A.S.; Dmytriw, A.A. The Impact of Parkinson's Disease on Manifestations and Outcomes of COVID-19 Patients: A Systematic Review and Meta-Analysis. *Rev. Med. Virol.* **2021**, *32*, e2278. [CrossRef]
50. Ahmad Malik, J.; Ahmed, S.; Shinde, M.; Hajjaj Saeid Al-Marmash, M.; Alghamdi, S.; Hussain, A.; Anwar, S. The Impact of COVID-19 on the Comorbidities: A Review of Recent Updates for Combating It. *Saudi J. Biol. Sci.* **2022**, *29*, 3586–3599. [CrossRef]

51. Nwabuobi, L.; Zhang, C.; Henchcliffe, C.; Shah, H.; Sarva, H.; Lee, A.; Kamel, H. Characteristics and Outcomes of Parkinson's Disease Individuals Hospitalized with COVID-19 in a New York City Hospital System. *Mov. Disord. Clin. Pract.* **2021**, *8*, 1100–1106. [CrossRef]
52. Huang, C.; Wang, Y.; Li, X.; Ren, L.; Zhao, J.; Hu, Y.; Zhang, L.; Fan, G.; Xu, J.; Gu, X.; et al. Clinical Features of Patients Infected with 2019 Novel Coronavirus in Wuhan, China. *Lancet* **2020**, *395*, 497–506. [CrossRef]
53. Onder, G.; Rezza, G.; Brusaferro, S. Case-Fatality Rate and Characteristics of Patients Dying in Relation to COVID-19 in Italy. *JAMA* **2020**, *323*, 1775–1776. [CrossRef]
54. Iloanusi, S.; Mgbere, O.; Essien, E.J. Polypharmacy among COVID-19 Patients: A Systematic Review. *J. Am. Pharm. Assoc. JAPhA* **2021**, *61*, e14–e25. [CrossRef] [PubMed]