






ORIGINAL ARTICLE

Risk of SARS-CoV-2 infection, hospitalization, and death for COVID-19 in people with Parkinson disease or parkinsonism over a 15-month period: A cohort study

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Abstract

Background and purpose: The patterns of long-term risk of SARS-CoV-2 infection, hospitalization for COVID-19, and related death are uncertain in people with Parkinson disease (PD) or parkinsonism (PS). The aim of the study was to quantify these risks compared to a control population cohort, during the period March 2020–May 2021, in Bologna, Northern Italy.

Methods: ParkLink Bologna cohort (759 PD, 192 PS) and controls (9226) anonymously matched (ratio = 1:10) for sex, age, district, and comorbidity were included. Data were analysed in the whole period and in the two different pandemic waves (March–May 2020 and October 2020–May 2021).

Results: Adjusted hazard ratio of SARS-CoV-2 infection was 1.3 (95% confidence interval [CI] = 1.04–1.7) in PD and 1.9 (95% CI = 1.3–2.8) in PS compared to the controls. The trend was detected in both the pandemic waves. Adjusted hazard ratio of hospitalization for COVID-19 was 1.1 (95% CI = 0.8–1.7) in PD and 1.8 (95% CI = 0.97–3.1) in PS. A higher risk of hospital admission was detected in PS only in the first wave. The 30-day mortality risk after hospitalization was higher ($p = 0.048$) in PS (58%) than in PD (19%) and controls (26%).

Conclusions: Compared with controls, after adjustment for key covariates, people with PD and PS showed a higher risk of SARS-CoV-2 infection throughout the first 15 months of the pandemic. COVID-19 hospitalization risk was increased only in people with PS and only during the first wave. This group of patients was burdened by a very high risk of death after infection and hospitalization.

KEYWORDS

cohort studies, COVID-19, frail elderly, Parkinson disease, parkinsonism

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INTRODUCTION

The COVID-19 pandemic has been globally striking most countries since early 2020 [1]. Italy has been among the five most affected countries in Europe, with approximately 4,300,000 cases of SARS-CoV-2 infection and approximately 127,000 deceased patients by the end of June 2021. The Emilia-Romagna region, Northern Italy, similarly to the rest of the country, was hit by two main waves (from March to May 2020, and from October 2020 to May 2021). In the province of Bologna, the regional capital city, 5021 cases and 590 deaths with COVID-19 were recorded by the end of May 2020, and 93,378 cases with 2619 deaths by the end of June 2021.

Whether patients with Parkinson disease (PD) are at higher risk of SARS-CoV-2 infection is still not well established [2]. In hospitalized subjects, after COVID-19 infection, the presence of a neurodegenerative disease increases the risk of an unfavourable short-term outcome [3, 4]. People with PD often show a significant clinical worsening [5, 6] however, controversial data are reported about the risk of hospitalization [5, 7] or death [6–10]. These discrepancies are probably due to methodological issues (different study design, source of data, definitions, etc.) and differences in contextual factors (population at risk, pandemic wave, health care system response measures). By means of a population-based historical cohort study [11], we found that, during the first pandemic wave, patients with PD did not have a different risk for COVID-19 hospitalization than a matched control population. Conversely, being affected by parkinsonism (PS) showed a threefold risk.

The present study was aimed to assess (i) the risk of SARS-CoV-2 infection (detected by real time polymerase chain reaction [PCR] test), (ii) the risk of hospital admission for COVID-19, and (iii) the 30-day mortality risk after a positive SARS-CoV-2 test or hospitalization, in a population-based cohort of people with PD or PS (ParkLink Bologna cohort [11]) compared to a matched population cohort. The period of observation was 15 months from the pandemic onset. Stratified analyses of the two main pandemic waves (March–May 2020, October 2020–May 2021) were also performed.

METHODS

The STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [12] and the RECORD (The REporting of studies Conducted using Observational Routinely-collected health Data) guidelines [13] were followed.

Study design

A historical cohort design was applied.

Setting and study population

On 31 December 2019, the local health trust (LHT) of Bologna, Northern Italy, had a population of 752,104 adults. At the beginning of the pandemic, the area included nine general hospitals, three academic hospitals, and 11 private clinics operating within the Italian National Health Service, for a total of approximately 4400 beds, of which approximately 120 were in intensive care. In response to the first wave, hospital facilities underwent major reorganization; since mid-March 2020, eight COVID-19 hospitals/wards have been created, with a total of approximately 400 beds for symptomatic patients and approximately 150 intensive care unit beds. Dedicated diagnostic protocols for suspected COVID-19 patients to be applied at every emergency department (ED) access were implemented. Dedicated COVID-19 wards were progressively dismantled during June–September 2020 but, since October 2020, at the start of the second wave, new organizational measures were put in place in response to infection and hospitalization rates, and trends have been continuously monitored.

SARS-CoV-2 testing strategies varied over the study period, as new evidence on virus transmission emerged and as organizational difficulties and laboratory shortage problems were solved. During the first wave, access to testing was limited and targeted mainly subjects with COVID-19-related symptoms and subjects at the end of quarantine of case contacts. Gradually, the use of tests became more widespread, and it was extended also for screening purpose among some work categories (e.g., health care and school workers). As of October 2020, tests have been available not only in public health structures but also in private facilities. Throughout the study period, only real time PCR-based tests of nasopharyngeal and/or oropharyngeal swabs were used for case confirmation.

This study is based on the ParkLink Bologna project (<https://ambo.ausl.bologna.it/metro/som/istituto-scienze-neurologiche-bologna/ricerca/i-progetti/parklink-bologna>), an ongoing record linkage system started in 2015, including consecutive prevalent and incident cases of PD or PS, living in the area of the LHT of Bologna. For the purpose of the present study, we included people with PD or PS and people anonymously matched from the general population (control cohort), alive on 1 March 2020. The data cutoff for ParkLink Bologna recruitment was 30 September 2020. Thirty neurologists operating in the area, including three hospital-based movement disorders outpatient services and several public and private outpatient services, voluntarily joined the project. Diagnosis of PD or PS is defined prospectively by the recruiting neurologist during usual clinical practice. Neurologists applied Gelb diagnostic criteria [14] for PD and other international criteria for prespecified types of PS [15–17]. The latter and other rare neurological causes affecting basal ganglia or unspecified PS are recorded in the system and labeled as PS altogether. Training on the application of more recent international diagnostic criteria is ongoing [18, 19]. People with drug-induced PS were excluded. The following data were recorded in an electronic case report form, linked to other administrative databases: unique

anonymous identification code, date of birth, diagnosis, year of onset, motor symptoms at onset (tremor or bradykinesia), side of onset (unilateral or bilateral), and Hoehn and Yahr score. For all clinical data, the coverage was 100%, except for motor symptoms at onset (tremor/bradykinesia), which had 14% missing data.

The control cohort included a random sample of anonymous people matched with the ParkLink cohort (ratio = 1:10) for age, sex, district of residence, and comorbidity according to Charlson Comorbidity Index. Subjects who used drugs for PD (levodopa, dopaminergic agents, monoamine oxidase-B inhibitors) for at least 180 consecutive days during 2019 were considered to be affected by PD or PS and excluded.

Data sources

As the Italian health system is universal, any access to public or private health facilities is routinely recorded, and data are stored by the Bologna LHT, therefore the coverage of health care provision is 100%. The Institute of Neurological Sciences of Bologna is in charge of the ParkLink Bologna project and has access to several health databases (outpatient tests and visits, ED admissions, hospital discharge, drug prescription, mortality). The Charlson Comorbidity Index was calculated according to the adapted method for International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) [20]. Information about SARS-CoV-2 infection cases were retrieved from the Infectious Disease Surveillance database, a regional electronic archive of laboratory-confirmed cases, regularly updated by the Public Health Department of the LHT. Hospital admissions for COVID-19 were captured using an algorithm of the Emilia-Romagna region based on the ICD-9-CM codes (28 October 2020, document available upon request).

Outcomes

From 1 March 2020 to 31 May 2021, the following outcomes were investigated: (i) SARS-CoV-2 infection rate, (ii) hospital admission rate for COVID-19, and (iii) overall 30-day mortality risk calculated in the group of people with a positive swab and in the group of hospitalized people.

Statistical analysis

In the descriptive analysis, the characteristics of the cohorts are presented as mean and SD or median and interquartile range (IQR) for the continuous variables and with absolute (n) and relative (%) frequency for categorical variables. Chi-squared test, followed by post hoc Bonferroni correction, and Kruskal–Wallis test, followed by post hoc Dunn test, were used to evaluate the univariate association between conditions (PD/PS/controls) and categorical or continuous variables, respectively. SARS-CoV-2 infection rate and hospital

admission rate for COVID-19 were calculated using 1 March 2020 as time at entry, and the date of positive swab/hospital admission or 31 May 2021 as time at endpoint. Additionally, separate subanalyses were performed for first and second waves (March–May 2020 and October 2020–May 2021). We calculated the infection rate and hospital admission rate, for each period and for each cohort, using the following equation: $\text{rate} = \text{cases in the period} / \text{person-years at risk in the period} \times 100$ (constant). These rates represent the absolute risk of infection and hospital admission in time.

We used univariate and multivariate Cox regression models to estimate the hazard ratio (HR) with 95% confidence interval (CI) associating SARS-CoV-2 positivity or COVID-19 hospitalization to the presence of PD/PS. Results of the univariate analysis are presented as Kaplan–Meier curves. In the multivariate models, we included sex, age, Charlson Comorbidity Index, and district of residence as covariates. The proportional hazards assumption was tested ($p > 0.05$) using Schoenfeld residuals.

For the calculation of the risk of hospital admission for COVID-19 after SARS-CoV-2 infection, the time to entry was the date of a positive swab. For the calculation of the overall 30-day mortality risk, the time to entry was the date of a positive swab or hospital admission. Multivariate logistic regression models, adjusted for confounding variables, were used to evaluate the 30-day mortality risk and the hospital admission risk after a positive swab. These analyses were carried out only for the entire study period.

Data linkage and statistical analyses were conducted using Stata SE version 14.2 [21].

RESULTS

The ParkLink cohort included 758 subjects with PD (mean age = 74.8 years) and 192 with PS (mean age = 80.4 years), followed up for 881 and 204 person-years, respectively. The control cohort included 9,222 subjects (75.8 years, 10,981 person-years), after the exclusion of 27 subjects on treatment with drugs for PD. Demographic and clinical characteristics data are summarized by groups in Table 1. People with PS were older, with higher Hoehn and Yahr scale score and with more frequent comorbidities than people with PD (Table 1, Table 2, Table S1).

Risk of SARS-CoV-2 infection

The overall number of people infected was 736: 68 among PD subjects (38 males), 24 among PS subjects (14 males), and 644 in the control cohort (380 males; Figure 1). The infection rate in the total period was 7.7 per 100 person-years in PD, 11.8 in PS, and 5.9 in controls. Kaplan–Meier curves showed a progressive higher risk of infection for PD and PS groups compared to the control group during the overall time frame (Figure 2a). The crude HR of infection was 1.3 (95% CI = 1.03–1.7, $p = 0.027$) for PD and 2.1 (95% CI = 1.4–3.1, $p < 0.001$) for PS compared to the control cohort. Univariate analysis

TABLE 1 Demographic and clinical features of the control cohort and ParkLink cohort (including subjects with Parkinson disease and Parkinsonism) on 1 March 2020

Demographic	Control cohort	Parkinson disease	Parkinsonism	<i>p</i>
<i>n</i>	9222	758	192	–
Mean age, years (SD, range)	75.8 (9.4, 40–97)	74.8 (9.5, 40–95)	80.4 (6.9, 55–97)	<0.001 ^a
Age distribution, <i>n</i> (%)				<0.001 ^a
40–49 years	140 (1.5)	14 (1.8)	0 (0)	
50–59 years	429 (4.7)	42 (5.5)	1 (0.5)	
60–69 years	1487 (16.1)	140 (18.5)	13 (6.8)	
70–79 years	3554 (38.5)	303 (40.0)	62 (32.3)	
80–89 years	3320 (36.0)	244 (32.2)	100 (52.1)	
≥90 years	292 (3.2)	15 (2.0)	16 (8.3)	
Sex, <i>n</i> (%)				0.836
Male	5341 (57.9)	446 (58.8)	109 (56.8)	
Female	3881 (42.1)	312 (41.2)	83 (43.2)	
District, <i>n</i> (%)				0.678
Bologna	4129 (44.8)	335 (44.2)	87 (45.3)	
Reno	1098 (11.9)	93 (12.3)	20 (10.4)	
Pianura Est	1657 (18.0)	131 (17.3)	42 (21.9)	
Pianura Ovest	1022 (11.1)	86 (11.4)	21 (11.0)	
Appennino	640 (6.9)	59 (7.8)	6 (3.1)	
San Lazzaro	676 (7.3)	54 (7.1)	16 (8.3)	
Charlson Comorbidity Index, <i>n</i> (%)				<0.001 ^a
0	7310 (79.3)	618 (81.6)	125 (65.1)	
1	930 (10.1)	66 (8.7)	30 (15.6)	
2	696 (7.5)	51 (6.7)	22 (11.5)	
≥3	286 (3.1)	23 (3.0)	15 (7.8)	
Comorbidities, <i>n</i> (%)				
Myocardial infarction	178 (1.9)	12 (1.6)	3 (1.6)	0.752
Congestive heart failure	453 (4.9)	40 (5.3)	20 (10.4)	0.002 ^a
Peripheral vascular disease	127 (1.4)	5 (0.7)	1 (0.5)	0.155
Cerebrovascular disease	392 (4.3)	18 (2.4)	21 (10.9)	<0.001 ^a
Dementia	158 (1.7)	30 (4.0)	22 (11.5)	<0.001 ^a
Chronic pulmonary disease	263 (2.9)	11 (1.5)	10 (5.2)	0.010 ^a
Peptic ulcer disease	27 (0.3)	3 (0.4)	2 (1.0)	0.171
Liver disease	33 (0.4)	1 (0.1)	0 (0.0)	0.421
Diabetes	320 (3.5)	22 (2.9)	17 (8.9)	<0.001 ^a
Renal disease	141 (1.5)	14 (1.9)	5 (2.6)	0.406
Any malignancy	498 (5.4)	37 (4.9)	8 (4.2)	0.636

^aStatistically significant.

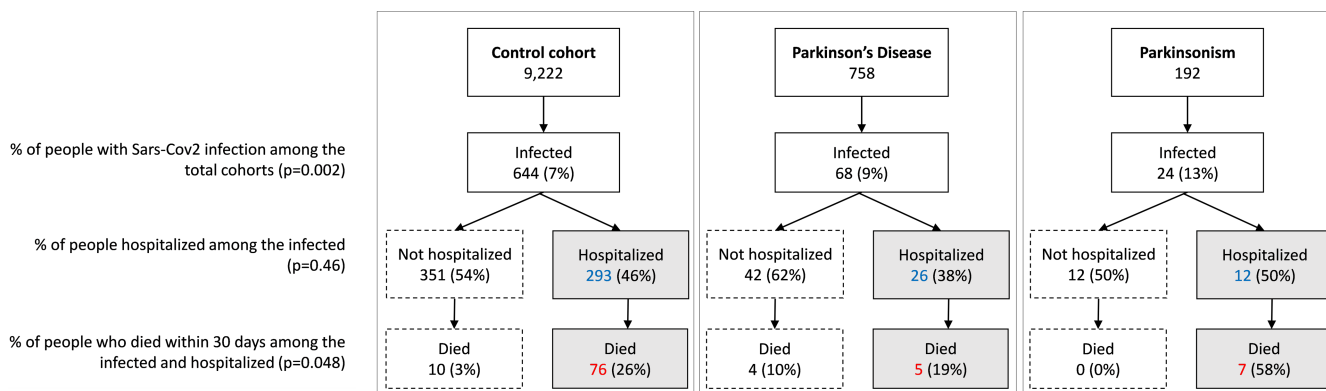
found the following factors associated with infection (Table 3): age, Charlson Comorbidity Index, district of residence, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, diabetes, and renal disease. After adjustment (Table 3), HR of infection was 1.3 (95% CI = 1.04–1.7, *p* = 0.020) in PD and 1.9 (95% CI = 1.3–2.8, *p* = 0.002) in PS compared to the control cohort. Considering only the ParkLink cohort, the Hoehn and Yahr scale score was associated with infection (HR = 1.3, 95% CI = 1.1–1.6, *p* = 0.003).

During the first pandemic wave, the number of people included in the analysis was 10,172 (758 PD, 192 PS, 9222 controls). The number with a positive swab was 89 (10 PD, 7 PS, 72 controls). The Kaplan–Meier curves showed a higher risk of infection in PS compared to the control group (Figure 3a). The infection rate in the first wave was 5.4 per 100 person-years in PD, 15.3 in PS, and 3.2 in controls. The adjusted HR of infection was 1.8 (95% CI = 0.94–3.5, *p* = 0.078) for PD and 3.6 (95% CI = 1.6–7.9, *p* = 0.001) for PS compared to the control cohort.

TABLE 2 Specific clinical features of the ParkLink cohort subgroups Parkinson disease and Parkinsonism) on 1 March 2020

Demographic	Parkinson disease	Parkinsonism	<i>p</i>
<i>n</i>	758	192	
Clinical features at onset, <i>n</i> (%)			
Unilateral	623 (82.2)	71 (37.0)	<0.001 ^a
Bilateral	135 (17.8)	121 (63.0)	
Tremor [yes]	483 (63.7)	77 (40.1)	<0.001 ^a
Bradykinesia [yes]	525 (69.3)	156 (81.3)	0.004 ^a
Probability level of PD, <i>n</i> (%)			
Possible	242 (32.0)		
Probable	516 (68.0)		
Etiology in parkinsonism, <i>n</i> (%)			
Vascular parkinsonism		99 (51.6)	
Progressive supranuclear palsy		16 (8.3)	
Multiple system atrophy		10 (5.2)	
Other/undetermined		67 (34.9)	
Hoehn and Yahr scale at latest observation			
Median (IQR)	2.5 (2–3)	3 (2.5–4)	<0.001 ^a
Score 4–5, <i>n</i> (%)	132 (17.4)	73 (38.0)	<0.001 ^a
Therapy, <i>n</i> (%)			
No therapy	87 (11.5)	44 (22.9)	<0.001 ^a
Levodopa only	456 (60.2)	117 (60.8)	
Dopaminergic or inhibitors of MAO-B only	23 (3.0)	3 (1.6)	
Any combination of drugs	192 (25.3)	28 (14.7)	

Abbreviations: IQR, interquartile range; MAO-B, monoamine oxidase type B.

^aStatistically significant.**FIGURE 1** Flow chart reporting the occurrence of the three outcomes (SARS-CoV-2 infection, COVID-19 hospitalization, 30-day death) in the control cohort and ParkLink cohort (subdivided as people with Parkinson disease and parkinsonism), during the whole period of observation (1 March 2020 to 31 May 2021). The null hypothesis of the *p*-values is the equality of percentage between the three groups [Colour figure can be viewed at [wileyonlinelibrary.com](https://onlinelibrary.wiley.com)]

In the second pandemic wave, the number of people included in the analysis was 9830 (719 PD, 170 PS, and 8941 controls). The number with a positive swab was 634 (57 PD, 17 PS, 560 controls). The Kaplan–Meier curves show a higher risk of infection in PS compared to the control group (Figure 3b). The infection rate was 12.6 per 100 person-years in PD, 17.0 in PS, and 9.8 in controls. The adjusted HR of infection was 1.3 (95% CI = 0.99–1.7, *p* = 0.064) for PD and 1.6 (95% CI = 0.99–2.6, *p* = 0.054) for PS compared to the control cohort.

Risk of hospital admission for COVID-19

Hospital admissions for COVID-19 totaled 331: 26 among subjects with PD (19 males), 12 among subjects with PS (9 males), and 293 in the control cohort (193 males). The hospital admission rate in the whole period was 3.0 per 100 person-years in PD, 5.9 in PS, and 2.7 in controls. Kaplan–Meier curves show a progressively higher risk of hospitalization for PS compared to the PD group and the

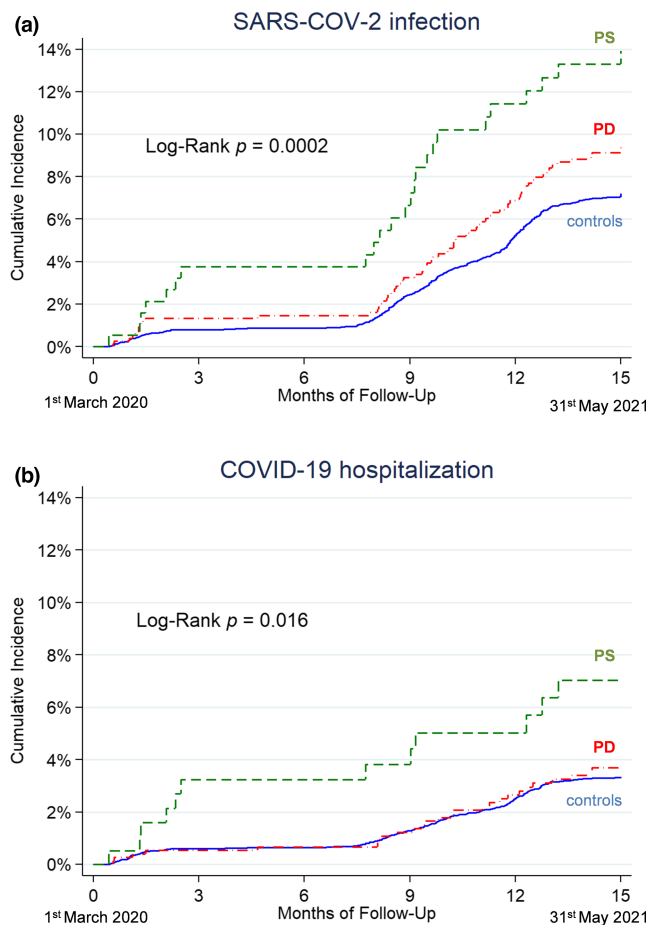


FIGURE 2 Kaplan-Meier curves reporting the SARS-CoV-2 infection rate (a) and COVID-19 hospitalization rate (b) in the group of people with Parkinson disease (PD; red dashed-dotted line), people with parkinsonism (PS; green dashed line), and the control cohort (blue solid line), during the whole period of observation (1 March 2020 to 31 May 2021) [Colour figure can be viewed at wileyonlinelibrary.com]

control group (Figure 2b). The crude HR compared to the control cohort was 1.1 (95% CI = 0.7–1.7, $p = 0.607$) for PD and 2.3 (95% CI = 1.3–4.0, $p = 0.006$) for PS. Univariate analysis found the following factors to be associated with hospital admission (Table 4): age, sex, Charlson Comorbidity Index, congestive heart failure, cerebrovascular disease, dementia, chronic pulmonary disease, diabetes, and renal disease. After adjustment (Table 4), HR was 1.1 (95% CI = 0.8–1.7, $p = 0.497$) in PD and 1.8 (95% CI = 0.97–3.1, $p = 0.059$) in PS. Considering only the ParkLink cohort, the Hoehn and Yahr scale score was not associated with hospital admission (HR = 1.2, 95% CI = 0.9–1.6, $p = 0.145$).

In the first pandemic wave, the number of people hospitalized was 66 (4 PD, 6 PS, 56 control cohort). The Kaplan-Meier curves show a higher risk of PS compared to the control group (Figure 3c). The hospitalization rate was 2.1 per 100 person-years in PD, 13.1 in PS, and 2.5 in controls. The adjusted HR of hospitalization was 0.9 (95% CI = 0.3–2.5, $p = 0.88$) for PD and 3.9 (95% CI = 1.7–9.2, $p = 0.002$) for PS compared to the control cohort.

In the second pandemic wave, the number of people hospitalized was 258 (21 PD, 6 PS, 231 control cohort). The Kaplan-Meier curve did not show differences between the three groups (Figure 3d). The hospitalization rate was 4.7 per 100 person-years in PD, 6.0 per 100 person-years in PS, and 4.1 per 100 person-years in controls. The adjusted HR of hospitalization was 1.2 (95% CI = 0.8–1.8, $p = 0.47$) for PD and 1.2 (0.5–2.6, $p = 0.73$) for PS compared to the control cohort.

Length of hospital stay

The overall median length of hospital stay was 11 days (IQR = 6–19, range = 1–109) in controls, 14 days in PD (IQR = 10–28, range = 2–55), and 9.5 days in PS (IQR = 6–17.5, range = 4–63), without statistical difference among groups ($p = 0.084$). Median length of hospital stay among living patients was 13 days (IQR = 7–19, range = 1–109) in controls, 16 days in PD (IQR = 10–28, range = 5–46), and 17 days in PS (IQR = 10–24, range = 10–24), without statistical difference among groups ($p = 0.21$).

Hospital admission for COVID-19 after SARS-CoV-2 infection

The percentage of hospital admission after SARS-CoV-2 infection was 45% without significant differences between the three groups ($p = 0.46$): 38% among PD subjects, 50% among PS subjects, and 46% in the control cohort (Figure 1).

Thirty-day mortality risk

Overall, 102 out of 736 infected subjects and 88 out of 331 hospitalized patients died within 30 days after positive swab or hospitalization (Figure 1). Among controls, 86 (13.3%) died after a median of 12 days from infection (IQR = 7–19, range = 1–30), and 76 (25.9%) after a median of 11 days from hospital admission (IQR = 5–17, range = 1–28). Among PD, nine (13.2%) died after a median of 9 days from positive swab (IQR = 2–12, range = 1–27), and five (19.2%) after a median of 11 days from hospital admission (IQR = 6–15, range = 2–27). Among PS, seven (29.2%) died after a median of 6 days from a positive swab (IQR = 6–11, range = 5–16), and seven (58.3%) after a median of 6 days from hospital admission (IQR = 6–11, range = 5–15).

Adjusted odds ratio (OR) for death after positive swab was 1.4 (95% CI = 0.6–3.0, $p = 0.408$) in PD and 2.3 (95% CI = 0.9–6.1, $p = 0.095$) in PS, compared to controls. Adjusted OR for death after hospital admission was 0.9 (95% CI = 0.3–2.8, $p = 0.889$) in PD and 4.8 (95% CI = 1.3–17.9, $p = 0.020$) in PS, compared to controls (Table 5). The seven dead people with PS had the following diagnosis: four vascular parkinsonism (all men, age range = 75–91), one progressive supranuclear palsy (80-year-old man), one multiple system atrophy (77-year-old woman), one undetermined PS (65-year-old man).

TABLE 3 Risk of Sars-Cov2 infection in the three cohorts ($n = 10,172$: control, 9222; Parkinson disease, 758; parkinsonism, 192): Univariate and multivariate Cox regression models

Demographic	Sars-Cov2 infection, <i>n</i>	HR (95% CI)	<i>p</i>	Adjusted HR (95% CI)	<i>p</i>
Control	644	Ref.		Ref.	
Parkinson disease	68	1.3 (1.03–1.7)	0.027 ^a	1.3 (1.04–1.7)	0.020 ^a
Parkinsonism	24	2.1 (1.4–3.1)	<0.001 ^a	1.9 (1.3–2.8)	0.002 ^a
Age, years, mean = 76.3, SD = 9.6	–	1.01 (1.001–1.02)	0.027 ^a	1.01 (0.99–1.6)	0.143
Sex, <i>n</i> (%)					
Male	432 (7.3)	Ref.		Ref.	
Female	304 (7.1)	0.96 (0.8–1.1)	0.583	0.98 (0.9–1.1)	0.795
District, <i>n</i> (%)					
Bologna	353 (7.8)	Ref.		Ref.	
Reno	88 (7.3)	0.9 (0.7–1.2)	0.578	1.0 (0.8–1.2)	0.680
Pianura Est	104 (5.7)	0.7 (0.6–0.9)	0.004 ^a	0.7 (0.6–0.9)	0.007 ^a
Pianura Ovest	80 (7.1)	0.9 (0.7–1.2)	0.499	0.9 (0.7–1.2)	0.595
Appennino	53 (7.5)	0.9 (0.7–1.3)	0.847	1.0 (0.8–1.4)	0.898
San Lazzaro	58 (7.8)	0.9 (0.8–1.3)	0.970	1.0 (0.8–1.4)	0.750
Charlson Comorbidity Index, <i>n</i> (%)					
0	530 (6.6)	Ref.		Ref.	
1	85 (8.3)	1.3 (1.1–1.7)	0.017 ^a	1.3 (0.99–1.6)	0.059
2	76 (9.9)	1.7 (1.3–2.1)	<0.001 ^a	1.6 (1.3–2.0)	<0.001 ^a
≥3	45 (13.9)	2.4 (1.8–3.3)	<0.001 ^a	2.3 (1.7–3.2)	<0.001 ^a
Comorbidities, <i>n</i> (%)					
Myocardial infarction	7 (3.6)	1.1 (0.7–1.8)	0.756		
Congestive heart failure	34 (6.6)	2.1 (1.6–2.7)	<0.001 ^a		
Peripheral vascular disease	2 (1.5)	0.6 (0.3–1.4)	0.252		
Cerebrovascular disease	24 (5.6)	1.5 (1.1–2.0)	0.014 ^a		
Dementia	25 (11.9)	3.9 (2.8–5.2)	<0.001 ^a		
Chronic pulmonary disease	23 (8.1)	1.7 (1.2–2.4)	0.003 ^a		
Peptic ulcer disease	3 (9.4)	1.3 (0.4–4.0)	0.678		
Liver disease	2 (5.9)	1.4 (0.5–4.5)	0.527		
Diabetes	26 (7.2)	1.9 (1.4–2.5)	<0.001 ^a		
Renal disease	12 (7.5)	2.5 (1.7–3.7)	<0.001 ^a		
Any malignancy	18 (3.3)	0.9 (0.6–1.3)	0.527		

Abbreviations: CI, confidence interval; HR, hazard ratio; Ref., reference.

^aStatistically significant.

DISCUSSION

Covering the first 15-month period of the SARS-CoV-2 pandemic, we observed a higher risk of SARS-CoV-2 infection in PD and PS (HR = 1.3 and 1.9, respectively), compared to a matched control population. The trend of a higher relative risk was detected in both pandemic waves (March–May 2020 and October 2020–May 2021). On the other hand, the higher risk of hospitalization for COVID-19 was observed particularly during the first wave (HR = 3.9), only in people with PS, and not in the second wave. Finally, the 30-day mortality risk was utmost in people with PS after hospitalization (58%),

compared to people with PD and controls (19% and 26%, respectively). Similarly, the 30-day mortality risk after infection was higher in PS (29%) compared to PD and controls (13% in both groups).

A systematic review with meta-analysis of observational studies [22] reported that patients with neurological disorders in general have a doubled risk of COVID-19 susceptibility (positive laboratory results and diagnosis in conjunction with clinical presentation), approximately 40% higher risk of hospitalization, and approximately 50% higher risk of death for COVID-19. People with PD show a statistically nonsignificant trend of higher risk for susceptibility and hospitalization (OR = 1.89, 95% CI = 0.88–4.09, and OR = 1.37, 95%

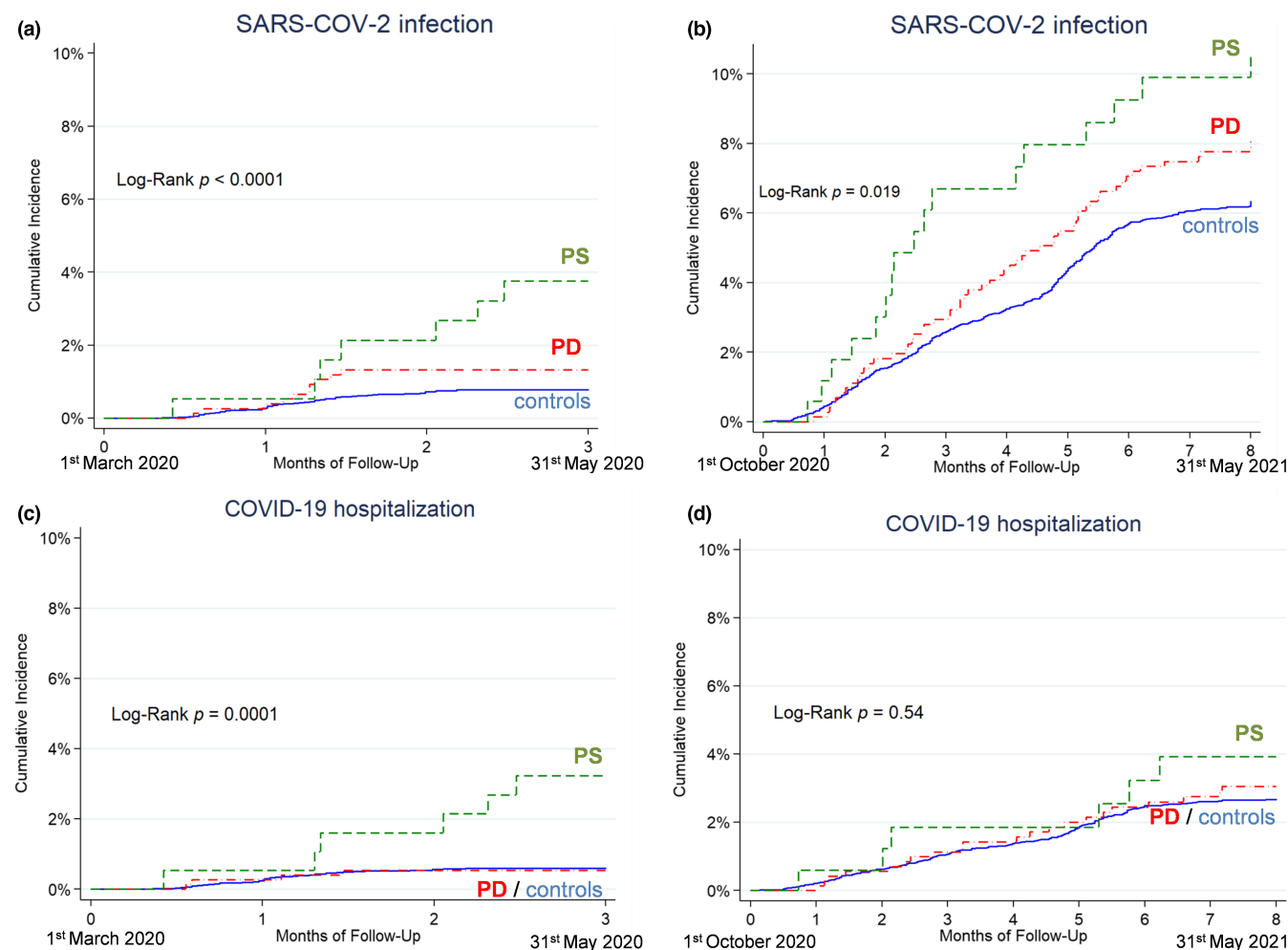


FIGURE 3 Kaplan-Meier curves reporting the SARS-CoV-2 infection rate (a, b) and COVID-19 hospitalization rate (c, d) in the group of people with Parkinson disease (PD; red dashed-dotted line), people with parkinsonism (PS; green dashed line), and the control cohort (blue solid line), during the first wave (1 March 2020 to 31 May 2020; a, c) and the second wave (1 October 2020 to 31 May 2021; b, d) [Colour figure can be viewed at wileyonlinelibrary.com]

CI = 0.78–2.42, respectively), and a higher risk of death (OR = 1.50, 95% CI = 1.06–2.10), although with a very high statistical heterogeneity among the studies included, and possible publication bias [22]. Available studies show heterogeneous design (case-controlled [23] vs. cross-sectional [24, 25] vs. cohort [11, 26–28]), case selection (movement disorder tertiary center [23] vs. patient association [24] vs. general population [11, 26, 28] vs. hospitalized [25] vs. biobank database [27]), definition of infection (self-reported [23, 24] vs. laboratory confirmed [11, 25–28]), definition of PD (clinical [11, 23, 27, 28] vs. self-reported [24] vs. diagnostic algorithm [25, 26]), and adjustment for confounders (not performed [23–25] vs. performed [11, 26–28]). Moreover, all but one [28] of the published studies refer only to the very first phase of pandemic in 2020.

The higher risk of SARS-CoV-2 infection among people with PD and PS compared to controls could be explained by some intrinsic factors (such as coexisting cognitive impairment in patients at a later stage of disease) and contextual factors (such as need of assistance in strict vicinity and nursing home residency [29–31]), especially during the first wave, when protective measures were difficult to implement and Italian nursing homes registered record

morbidity and COVID-19-related mortality [32, 33]. Moreover, biological specific factors could be hypothesized, such as immune system dysregulation in people with PD [34–37]. On the other hand, the higher risk of hospitalization for COVID-19 in people with PS, compared to people with PD and controls, could be explained by more compromised respiratory functions [38, 39] in the context of relatively more rapid disease progression [40–44]. Patients with PS may more frequently need procedures (tracheostomy, percutaneous endoscopic gastrostomy, urinary catheterization, or supplementary nutrition and/or rehydration) burdened by a risk for complications and hospitalization.

People with PS were prone to an impressive twofold risk of 30-day mortality after positive swabs and almost fivefold risk after hospitalization, compared to PD patients and controls. To our knowledge, this finding—specifically for PS—has never been previously reported. Mortality risk after infection or hospital admission for COVID-19 is affected by many factors, such as case definition, case mix of patients, geographical context, and capacity of the health care system [45]. Globally, a pooled mortality of 17.6% has been found among hospitalized patients with COVID-19 [46], ranging from 12% to 25%

TABLE 4 Risk of hospital admission for COVID-19 in the three cohorts ($n = 10,172$: control, 9222; Parkinson disease, 758; parkinsonism, 192): Univariate and multivariate Cox regression models

Demographic	Hospital admission for COVID-19, <i>n</i>	HR (95% CI)	<i>p</i>	Adjusted HR (95% CI)	<i>p</i>
Control	293	Ref.		Ref.	
Parkinson disease	26	1 (0.7–1.7)	0.607	1.1 (0.8–1.7)	0.497
Parkinsonism	12	2.3 (1.3–4.0)	0.006 ^a	1.8 (0.97–3.1)	0.059
Age, years, mean = 77.8, SD = 8.5	–	1.03 (1.02–1.04)	<0.001 ^a	1.03 (1.01–1.04)	<0.001 ^a
Sex, <i>n</i> (%)					
Male	221 (3.8)	Ref.		Ref.	
Female	110 (2.6)	0.7 (0.5–0.9)	0.001 ^a	0.7 (0.5–0.9)	0.002 ^a
District, <i>n</i> (%)					
Bologna	150 (3.3)	Ref.		Ref.	
Reno	43 (3.6)	1.1 (0.8–1.5)	0.672	1.1 (0.8–1.5)	0.726
Pianura Est	61 (3.3)	1.0 (0.7–1.4)	0.985	1.0 (0.8–1.4)	0.814
Pianura Ovest	30 (2.7)	0.8 (0.5–1.2)	0.296	0.8 (0.5–1.2)	0.281
Appennino	20 (2.8)	0.9 (0.5–1.4)	0.535	0.9 (0.6–1.4)	0.655
San Lazzaro	27 (3.6)	1.1 (0.7–1.6)	0.680	1.2 (0.8–1.8)	0.443
Charlson Comorbidity Index, <i>n</i> (%)					
0	215 (2.7)	Ref.		Ref.	
1	47 (4.6)	1.8 (1.3–2.5)	<0.001 ^a	1.6 (1.2–2.2)	0.004 ^a
2	44 (5.7)	2.3 (1.7–3.2)	<0.001 ^a	2.1 (1.5–2.9)	<0.001 ^a
≥3	25 (7.7)	3.3 (2.2–5.0)	<0.001 ^a	2.9 (1.9–4.3)	<0.001 ^a
Comorbidities, <i>n</i> (%)					
Myocardial infarction	7 (3.6)	1.1 (0.5–2.4)	0.758		
Congestive heart failure	34 (6.6)	2.4 (1.7–3.4)	<0.001 ^a		
Peripheral vascular disease	2 (1.5)	0.5 (0.1–1.9)	0.277		
Cerebrovascular disease	24 (5.6)	1.9 (1.3–2.9)	0.003 ^a		
Dementia	25 (11.9)	4.9 (3.2–7.3)	<0.001 ^a		
Chronic pulmonary disease	23 (8.1)	2.7 (1.8–4.2)	<0.001 ^a		
Peptic ulcer disease	3 (9.4)	2.8 (0.9–8.9)	0.071		
Liver disease	2 (5.9)	2.1 (0.5–8.5)	0.288		
Diabetes	26 (7.2)	2.5 (1.7–3.7)	<0.001 ^a		
Renal disease	12 (7.5)	2.6 (1.5–4.7)	0.001 ^a		
Any malignancy	18 (3.1)	1.1 (0.7–1.7)	0.727		

Abbreviations: CI, confidence interval; HR, hazard ratio; Ref., reference.

^aStatistically significant.

in people with PD [7, 47]. These results are not far from estimates we found for PD (19%) and controls (26%) in our study.

The death risk in PS after hospitalization (58%) seems to be comparable or even higher than that reported for patients with dementia [48–52]. These two extremely vulnerable conditions possibly share the same risk factors for COVID-19 disease severity and death. In addition, it has been suggested that people with advanced neurodegenerative disorders may be less likely to receive all possible intensive medicine options, considering the limited expected success [3].

In our study, we observed an increase of the general infection rate between the first and the second wave. Such difference probably reflected the different testing strategies and swab availability between the two periods, rather than a real difference in the infection rate. Conversely, we found an inverse trend of hospitalization rate between the two waves; people with PS showed a decrease (from 13.1 to 6.0 per 100 person-years), whereas people with PD and controls had an increase (from 2.1 to 4.7 and from 2.5 to 4.1 per 100 person-years, respectively). This could be partly explained by a selection of the PS cohort over time; as they were older, with more

TABLE 5 Risk of death within 30 days after hospital admission for COVID-19 (*n* = 331: controls, 293; Parkinson disease, 26; parkinsonism, 12): Univariate and multivariate logistic regression models

Demographic	Death, <i>n</i>	OR (95% CI)	<i>p</i>	Adjusted OR (95% CI)	<i>p</i>
Control	76	Ref.		Ref.	
Parkinson disease	5	0.7 (0.2–1.9)	0.614	0.9 (0.3–2.8)	0.889
Parkinsonism	7	4.0 (1.2–13.0)	0.021 ^a	4.8 (1.3–17.9)	0.020 ^a
Age, years, mean = 81.4, SD = 6.2	–	1.09 (1.05–1.13)	<0.001 ^a	1.08 (1.04–1.12)	<0.001 ^a
Sex, <i>n</i> (%)					
Male	52 (23.5)	Ref.		Ref.	
Female	36 (32.7)	1.6 (0.95–2.6)	0.076	1.3 (0.8–2.3)	0.333
District, <i>n</i> (%)					
Bologna	46 (30.7)	Ref.		Ref.	
Reno	10 (23.3)	0.7 (0.3–1.5)	0.347	0.7 (0.3–1.7)	0.394
Pianura Est	15 (24.6)	0.7 (0.4–1.5)	0.378	0.8 (0.4–1.7)	0.589
Pianura Ovest	9 (30.0)	0.9 (0.4–2.3)	0.942	1.1 (0.4–2.8)	0.817
Appennino	6 (30.0)	0.9 (0.4–2.7)	0.952	1.2 (0.4–3.5)	0.785
San Lazzaro	2 (7.4)	0.2 (0.05–2.4)	0.024 ^a	0.2 (0.03–0.95)	0.044 ^a
Charlson Comorbidity Index, <i>n</i> (%)					
0	45 (20.9)	Ref.		Ref.	
1	17 (36.2)	2.1 (1.1–4.2)	0.028 ^a	1.6 (0.8–3.4)	0.189
2	15 (34.1)	2.0 (0.97–4.0)	0.062	1.7 (0.8–3.6)	0.186
≥3	11 (44.0)	3.0 (1.3–7.0)	0.013 ^a	2.6 (1.02–6.5)	0.044 ^a
Comorbidities, <i>n</i> (%)					
Myocardial infarction	2 (28.6)	1.1 (0.2–5.8)	0.904		
Congestive heart failure	13 (38.2)	1.8 (0.9–3.8)	0.108		
Peripheral vascular disease	1 (50.0)	2.8 (0.2–45.0)	0.471		
Cerebrovascular disease	12 (50.0)	3.0 (1.3–7.0)	0.010 ^a		
Dementia	14 (56.0)	4.0 (1.7–9.2)	0.001 ^a		
Chronic pulmonary disease	7 (30.4)	1.2 (0.5–3.1)	0.665		
Peptic ulcer disease	1 (33.3)	1.4 (0.1–15.5)	0.791		
Liver disease	2 (100)	n.a.	–		
Diabetes	11 (42.3)	2.2 (0.96–4.9)	0.064		
Renal disease	6 (50.0)	2.9 (0.9–9.2)	0.073		
Any malignancy	3 (16.7)	0.5 (0.2–1.9)	0.334		

Abbreviations: CI, confidence interval; HR, hazard ratio; n.a., not available; Ref., reference.

^aStatistically significant.

comorbidities, they suffered probably the greatest impact during the first wave (harvesting effect). Another reason for the smoothing of the risk in PS during the second wave could be the effective spreading of preventive infection measures in high-risk settings (e.g., hospitals and nursing homes).

The main strength of our study is the identification of people with PD and PS by means of a clinical diagnosis performed by a neurologist according to international criteria. The sample of 758 PD patients corresponds approximately to the 30% of the total PD population in the LHT of Bologna (assuming a PD prevalence of 300 per 100,000 [53]), with plausible representation of the entire spectrum of the disease, as the settings of source are mixed (district offices, hospitals,

private clinics). Moreover, we were able to analyse excess risks for both COVID-19 pandemic waves by comparing PD/PS population with a control population, obtained from administrative data, therefore avoiding the risk of recall bias. This study also has limitations. First, residual confounding could explain the observed risk to some extent; information regarding education or socioeconomic status was lacking, and the Charlson Comorbidity Index was a proxy for actual comorbidity status. Second, during the first wave, a positive swab as an outcome measure likely underestimated infection, and perhaps people with PD/PS were more likely to undergo swabbing because of factors related to the setting. However, the same trend was observed in the second wave, when this factor was less plausible.

By extending our preliminary observation on the first wave of COVID-19 [11], including two pandemic waves, we substantially enriched real world epidemiological data on risk factors and prognosis after SARS-CoV-2 among people with PD and PS. Our findings may inform health care policy decisions by suggesting that during global health emergencies these chronic neurological disorders are high-risk conditions and that particular attention should be paid to people with PS.

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CONFLICT OF INTEREST

All authors have completed the International Committee of Medical Journal Editors uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare no support from any organization for the submitted work, and no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years. L.V. has received honoraria for speaking from Lilly. G.C.-B. has received honoraria for speaking from AbbVie, Zambon, and Bial. P.G. has received honoraria for speaking from Chiesi.

DATA AVAILABILITY STATEMENT

The study data are available upon request.

DISSEMINATION TO PARTICIPANTS AND RELATED PATIENT AND PUBLIC COMMUNITIES

The size of the study population precludes direct dissemination to participants.

FINANCIAL DISCLOSURES

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years. LV has received honoraria for speaking from Lilly. GCB has received honoraria for speaking from AbbVie, Zambon, Bial. PG has received honoraria for speaking from Chiesi.

ETHICAL STATEMENT

The ethics committee of the Bologna local health trust (LHTB) approved the ParkLink Bologna project on 25 June 2015 (reference code: 15401). All patients included in the ParkLink cohort have given their written informed consent. The persons comprising the control cohort are anonymous. The approved protocol of the project defines as study population all the inhabitants of the geographical area covered by the LHTB.

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SUPPORTING INFORMATION

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

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