Arch Neurosci. 2024 April; 11(2):e144345. https://doi.org/10.5812/ans-144345.

Published online 2024 March 18. **Research Article**

Prevalence and Outcome of COVID-19 Among Parkinson's Disease: A Report from Iran

Saeed Vaheb [1], Omid Mirmosayyeb [1, 2], Mahdi Barzegar [1, 2], Mina Rezaei [1], Mahshad Afsharzadeh [1], Roozbeh Bathaie [1], Alireza Afshari-Safavi [3], Ahmad Chitsaz [1, 2] and Vahid Shaygannejad [1, 2, *]

[1] Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran
[2] Department of Neurology, School of Medicine, Isfahan University of Medical Sciences, Isfahan, Iran
[3] Department of Biostatistics and Epidemiology, Faculty of Health, North Khorasan University of Medical Sciences, Bojnurd, Iran

[*] *Corresponding author*: Isfahan Neurosciences Research Center, Isfahan University of Medical Sciences, Isfahan, Iran. Email: v.shaygannejad@gmail.com

Received 2023 December 24; **Revised** 2024 February 05; **Accepted** 2024 February 12.

Abstract

Background: Parkinson's disease (PD) is a widely prevalent neurodegenerative disorder in the central nervous system, predominantly affecting older adults and frequently coexisting with other health conditions. The heightened vulnerability of individuals with chronic diseases and advanced age to adverse outcomes during the COVID-19 pandemic suggests an increased risk of COVID-19 infection in PD patients.

Objectives: This cross-sectional study, conducted from July to September 2021, aimed to evaluate the impact of COVID-19 on PD patients by examining infection rates, associated complications, and outcomes.

Methods: We utilized hospital records to reach out to 567 PD patients during the designated timeframe. If a patient had passed away, their families were contacted to ascertain whether COVID-19 was a contributing factor.

Results: Among the 558 PD patients who participated, 25.4% were tested for COVID-19, with 42.2% of those tested returning positive results. Significantly, 34.4% of the positive cases required oxygen therapy, 32.8% were admitted to the hospital, and 9.8% needed intensive care unit (ICU) admission. The prevalence of COVID-19 among the families of the patients was 29.8%, with 13.7% requiring hospitalization and 4.2% resulting in death. Common complications included worsening of movement issues (21.3%), weight loss (19.7%), and urinary problems (14.8%). Early-onset Parkinson's was associated with a decreased risk of COVID-19 (OR: 0.976, 95% CI: 0.953 - 0.999, P = 0.037), whereas the use of Levodopa was linked to an increased risk of infection (OR: 3.672, 95% CI: 1.095 - 12.31, P = 0.037).

Conclusions: This study underscores the changing clinical manifestations of PD during the COVID-19 pandemic. Further research is crucial to clarify the complex interaction between COVID-19 and Parkinson's disease.

Keywords: Parkinson's Disease, COVID-19, Movement Disorders

1. Background

The severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has been the cause of COVID-19 and has presented significant challenges since the early stages of the outbreak (1). Current evidence suggests that older adults and individuals with underlying comorbidities, such as cardiovascular disease, diabetes, chronic lung diseases, and neurological disorders, may be more prone to severe outcomes from COVID-19 (2-4).

Parkinson's disease (PD), a prevalent neurodegenerative disorder of the central nervous system, is more commonly diagnosed in older adults and is often accompanied by other comorbid conditions (5). Given that COVID-19 tends to result in more adverse outcomes among patients with chronic diseases and in the elderly, there is a concern that PD patients may face a higher risk of contracting COVID-19 (6). Recent research indicates that COVID-19 may independently trigger the onset of Parkinson's disease, highlighting the critical importance of exploring the interaction between COVID-19 and Parkinson's disease (7, 8).

As the coronavirus pandemic persists, an increasing body of observational studies has been documenting the clinical characteristics and outcomes of COVID-19 in PD patients. Yet, a definitive consensus on the effects of COVID-19 infection on individuals with Parkinson's disease

remains elusive.

2. Objectives

This study was undertaken to investigate the prevalence, clinical features, and outcomes of COVID-19 among Iranian patients with PD.

3. Methods

3.1. Study Design and Population

This cross-sectional study was conducted at Alzahra and Kashani hospitals, which are affiliated with Isfahan University of Medical Sciences in Isfahan, Iran, from July to September 2021. These hospitals serve the largest population of PD patients in Isfahan and the neighboring regions. All patients who had been diagnosed with PD by a neurologist and were registered at these hospitals were eligible for inclusion in the study.

3.2. Data Collection

Participants in the study were individuals with a confirmed diagnosis of Parkinson's disease by specialist neurologists in accordance with the established inclusion criteria. Contact was made via the telephone numbers provided or through their immediate family members. Cases, where there was no response, unwillingness to participate, or incorrect contact information, were noted as non-participation.

Patients were requested to respond to a structured three-part checklist over the phone. Part 1 collected demographic data such as age, gender, marital status, weight, and height. Part 2 inquired about disease specifics, including smoking habits, duration of illness, comorbid conditions, and medication use. Part 3 involved questions about the presence of COVID-19 symptoms (e.g., fever, cough, shortness of breath, fatigue, muscle pain, dizziness, and weakness) and diagnoses among their family members. Further, patients were asked if they had experienced COVID-19 symptoms in recent months, undergone COVID-19 testing, been hospitalized for COVID-19, or suffered any post-COVID-19 complications. In the event of a patient's death, family members were contacted to determine whether COVID-19 was a contributing cause.

3.3. Ethics

The bioethics committee of Isfahan University of Medical Sciences granted approval for this study (IR.MUI.MED.REC.1400.113). Informed consent was obtained from all participating patients. For interviews conducted by telephone, verbal consent was secured before the commencement of the checklist inquiries.

3.4. Statistical Analysis

Descriptive data are presented as mean (standard deviation) for continuous variables and as frequency (percentage) for categorical variables. A logistic regression model was used to assess the impact of demographics (age, sex, marital status, BMI, smoking, and blood group) and clinical characteristics (age at onset, disease duration, medication use, comorbidities, and the use of vitamin D, aspirin, and either Ibuprofen or Gelofen) on COVID-19 outcomes. Initially, a univariate model identified the influence of each independent variable on COVID-19 infection. Subsequently, risk factors associated with the univariate analysis were incorporated into a multivariate model. A backward selection process was then employed to identify the most significant factors related to COVID-19 in the final multivariate model. The outcomes of the logistic regression analyses are reported as odds ratios (OR), 95% confidence intervals (CI), and P-values. A significance level was established at 0.05 (2-tailed). All statistical analyses were conducted using IBM SPSS Statistics (version 18; IBM Corporation, Armonk, NY, USA).

4. Results

4.1. Demographic Characteristics

Of the 567 PD patients contacted, 558 responded and participated in the study. The average age was 65.14 (± 12.26) years, with a majority being male (62.6%). The mean age at onset and disease duration were 58.46 (± 13.04) years and 6.71 (± 5.20) years, respectively. Levodopa (78.3%) and Amantadine (54.8%) were the most frequently used medications. Hypertension (HTN), cardiovascular disease (CVD), and diabetes mellitus (DM) were the most prevalent comorbidities, affecting 36.8%, 21%, and 20.6% of the patients, respectively. The demographic and clinical characteristics of the patients are summarized in Table 1.

4.2. History of COVID-19 Among Patients' Family Members

The prevalence of COVID-19 among patients' families was 29.8%; of these, 13.7% were hospitalized, and 4.2% died (Table 2).

4.3. History of COVID-19 Among Patients

Out of 144 (25.4%) patients who were tested for COVID-19, 61 (42.2%) had positive test results. Among patients with a positive test, 21 (34.4%) required oxygen therapy, 20 (32.8%) were hospitalized, and 6 (9.8%) were admitted to the intensive care unit (ICU) (Table 3).

Table 1. Demographic and Clinical Characteristics of Patients [a]

Variables	Values
Age	65.14 ± 12.26
Sex	
Male	355 (62.6)
Female	212 (37.4)
Marital status	
Single	53 (9.3)
Married	514 (90.7)
BMI	26.02 ± 4.33
Smoking	
Yes	46 (8.1)
No	520 (91.9)
Age at onset	58.46 ± 13.04
Disease duration	6.71 ± 5.20
Who takes care of you	
Myself	285 (50.4)
Nurse	13 (2.3)
My family	268 (47.3)
Drug	
Levodopa	445 (78.3)
Amantadine	311 (54.8)
Pramipexole	177 (31.2)
Biperiden	40 (7)
Selegiline	12 (2.1)
Trihexyphenidyl	92 (16.2)
Vitamin D supplement	
Yes	327 (58)
No	237 (42)
Comorbidity	
CVD	119 (21)
DM	117 (20.6)
Asthma	14 (2.5)
Lung	44 (7.7)
HTN	209 (36.8)
Cancer	9 (1.6)
Stroke	46 (8.1)
Kidney	58 (10.2)
Liver	13 (2.3)
No comorbidity	233 (100)
Aspirin	
Yes	194 (34.3)
No	371 (65.7)
Ibuprofen or Gelofen	
Yes	142 (25.1)
No	424 (74.9)

[a] Values are presented as mean ± SD or No. (%).

4.4. Post COVID-19 Complications

Table 4 displays the post-COVID-19 complications. Accordingly, exacerbation of movement problems (21.3%), weight loss (19.7%), and urinary problems (14.8%) were the most common complications. However, 69% of patients did not report any complications.

4.5. The Relation Between COVID-19 and Patient Characteristics

In the univariate logistic regression model (Table 5), blood group, age at onset, Levodopa, history of HTN, and history of Ibuprofen or Gelofen use have shown a significant association with COVID-19. Patients with blood group B had 3.5 times higher odds of COVID-19 compared to patients with blood group O. Every one-unit increase in the age at onset decreased the odds of being COVID-19 positive by 2% (OR = 0.980; 95% CI: [0.961 - 0.999]). The chance of COVID-19 was 2.2 times greater (OR = 2.289; 95% CI: [1.014 - 5.166]) for patients taking Levodopa than for patients receiving other treatments. Patients with a history of HTN had a lower risk of COVID-19 (OR = 0.879; 95% CI: [0.779 - 0.994]) than those without. Patients who had a history of Ibuprofen or Gelofen use were 2 times more likely to have COVID-19 compared with those who did not use this drug (OR = 2.022; 95% CI: [1.155 - 3.537]).

In the final multivariate logistic regression model (Table 5), blood group (OR = 3.417; 95% CI: [1.455 - 8.025]), age at onset (OR = 0.976; 95% CI: [0.953 - 0.999]), and Levodopa (OR = 3.672; 95% CI: [1.095 - 12.31]) were associated with COVID-19.

5. Discussion

COVID-19 has been associated with complications in patients with underlying diseases since the beginning of the pandemic, and numerous studies have been published focusing on the effects of COVID-19 on Parkinson's disease (PD) (9). Previous studies have suggested a poorer outcome in patients with PD after contracting COVID-19 compared to the general population (10). We conducted this study to evaluate the prevalence of COVID-19 in PD patients and explore possible associations between COVID-19 and clinical features of PD.

There are conflicting results regarding the prevalence of COVID-19 among PD patients compared to the general population. Del Prete et al. reported a higher prevalence of COVID-19 among PD patients in Tuscany, Italy, compared to the general population (11). However, other studies have reported lower or similar prevalence rates (12, 13). A recent study conducted on 647 Iranian patients showed a lower prevalence of COVID-19 compared to an age-matched control group. The prevalence of COVID-19

Table 2. Prevalence of COVID-19 Infection Among Patients' Families and the Outcomes

	Overall	Sex		Age	
		Male	Female	≤ 65	> 65
History of COVID-19 in family					
Yes	168 (29.8)	110 (31.3)	58 (27.4)	81 (31.3)	87 (28.6)
No	396 (70.2)	242 (68.8)	154 (72.6)	178 (68.7)	217 (71.4)
When did she/he get the disease					
Last week	10 (6)	6 (5.5)	4 (6.9)	6 (7.4)	4 (4.6)
Two weeks ago	18 (10.7)	14 (12.7)	4 (6.9)	13 (16)	5 (5.7)
Last month	34 (20.2)	17 (15.5)	17 (29.3)	16 (19.8)	18 (20.7)
More than a month ago	106 (63.1)	73 (66.4)	33 (56.9)	46 (56.8)	60 (69)
Covid-19 outcome					
Hospitalized	23 (13.7)	14 (12.7)	9 (15.5)	8 (9.9)	15 (17.2)
Dead	7 (4.2)	5 (4.5)	2 (3.4)	3 (3.7)	4 (4.6)
Quarantined	138 (82.1)	91 (82.7)	47 (81)	70 (86.4)	68 (78.2)
ICU	19 (11.1)	110 (31.3)	58 (27.4)	81 (31.3)	87 (28.6)
No	149 (88.7)	242 (68.8)	154 (72.6)	178 (68.7)	217 (71.4)

[a] Values are presented as No. (%).

Table 3. Prevalence of COVID-19 Symptoms

	Overall	Sex		Age	
		Male	Female	≤ 65	> 65
Symptoms in the past month					
Fever	45 (7.9)	18 (5.1)	27 (12.7)	21 (8)	24 (7.9)
Fatigue	97 (17.1)	53 (14.9)	44 (20.8)	48 (18.4)	49 (16.1)
Pain	110 (19.4)	60 (16.9)	50 (23.6)	51 (19.5)	59 (19.3)
Shortness of breath	43 (7.6)	18 (5.1)	25 (11.8)	21 (8)	22 (7.2)
Diarrhea	20 (3.5)	11 (3.1)	9 (4.2)	10 (3.8)	10 (3.3)
Nausea	19 (3.3)	5 (1.4)	14 (6.6)	11 (4.2)	8 (2.6)
Headache	66 (11.6)	33 (9.3)	33 (15.6)	36 (13.8)	30 (9.8)
Imbalance	111 (19.5)	69 (19.4)	42 (19.8)	46 (17.6)	64 (21)
Taste disorder	19 (3.3)	10 (2.8)	9 (4.2)	11 (4.2)	8 (2.6)
Smell disorder	27 (4.8)	15 (4.2)	12 (5.7)	18 (6.9)	9 (3)
Result of COVID-19 test					
Positive	61 (42.4)	37 (43)	23 (40.4)	37 (56.9)	23 (29.9)
Negative	83 (57.6)	49 (57)	34 (59.6)	28 (43.1)	54 (70.1)
Need to receive oxygen therapy					
Yes	21 (34.4)	11 (29.7)	9 (39.1)	10 (27)	10 (43.5)
No	40 (65.6)	26 (70.3)	14 (60.9)	27 (73)	13 (56.5)
Need to be hospitalized					
Yes	20 (32.8)	13 (35.1)	6 (26.1)	9 (24.3)	10 (43.5)
No	41 (67.2)	24 (64.9)	17 (73.9)	28 (75.7)	13 (56.5)
ICU					
Yes	6 (9.8)	3 (8.1)	2 (8.7)	4 (10.8)	1 (4.3)
No	55 (90.2)	34 (91.9)	21 (91.3)	33 (89.2)	22 (95.7)

[a] Values are presented as No. (%).

Table 4. Post-COVID Complications

Post COVID Complications	No. (%)
Loss of consciousness	5 (8.2)
Sexual dysfunction	4 (6.6)
Exacerbation of imbalance	8 (13.1)
Exacerbation of movement problems	13 (21.3)
Thrombosis	2 (3.3)
Hair loss	5 (8.2)
Weight loss	12 (19.7)
Weight gain	1 (1.6)
Urinary problems	9 (14.8)
Skin problems	5 (8.2)
Gastrointestinal problems	6 (9.8)
Other	2 (3.3)
No problem	42 (68.9)

was 11.28% among patients with PD, while it was 15.39% in the age-matched control group (14). The prevalence of COVID-19 among PD patients was 10.7% in our study, which is consistent with these findings. Khoshnood et al. conducted a systematic review and meta-analysis, estimating a 5% prevalence of COVID-19 in PD patients. The hospitalization rate was 49%, with a mortality rate of 12%. However, the study's high heterogeneity emphasized the necessity for comprehensive studies with larger sample sizes (15). These inconsistent results could be attributed to different methodologies, patient ethnicities, lockdown situations, and variations in healthcare systems. PD patients might exercise extra caution due to their underlying disease and adhere strictly to social distancing and isolation protocols, potentially resulting in the lower prevalence of COVID-19 reported in some studies (16). Factors such as limited access to diagnostic tests and healthcare in impoverished countries, combined with inadequate disease transmission control due to social and economic reasons, can introduce heterogeneity into the results. This diversity makes it challenging to draw overarching conclusions on this matter.

In our study, the most common comorbidities were hypertension (HTN), cardiovascular disease (CVD), and diabetes mellitus (DM). Patients with HTN were at a lower risk of COVID-19 compared to those without HTN. Moreover, PD patients are often elderly, and older individuals tend to have poorer outcomes with COVID-19 (10). This result does not necessarily imply a positive correlation between HTN and COVID-19. Instead, it may be attributed to the higher prevalence of hypertension in the elderly. Given that negative outcomes of COVID-19 are less pronounced in this age group, fewer consequences were observed. However, in younger individuals, the coexistence of Parkinson's and hypertension could potentially exacerbate the infection's progression and spread, considering the adverse effects of hypertension and the poor prognosis associated with COVID-19 in such patients (17, 18).

While this study didn't reveal a notable association between DM and COVID-19 infection in multivariate analysis, the overall impact on infection and its spread in patients with both Parkinson's and DM was more severe than in those with Parkinson's alone. Furthermore, the likelihood of superinfection in Parkinson's patients with DM exceeded that in those without DM, contributing to the compounded negative consequences of COVID-19 in the diabetic group and showcasing a potential synergistic effect with Parkinson's and COVID-19 (18, 19).

In our study, among the 61 patients who were COVID-19 positive, 34.4% required oxygen therapy, 32.8% were hospitalized, and 9.8% were admitted to the ICU. Previous studies suggest that PD patients are often hospitalized due to the severity of COVID-19, but the rate of hospitalization in these patients is not higher compared to the normal population (20). Similarly, Salari et al. reported that the hospitalization rate in PD patients was even lower than in the normal population (14).

Regarding post-COVID-19 complications, the majority of the patients (69%) in our study did not experience any complications. However, 21.3% reported motor problems, 19.71% reported weight loss, and 14.8% complained about urinary problems. Some studies have stated that there is no significant association between COVID-19 and motor symptom deterioration (11). On the other hand, other studies have reported that more than half of the patients experienced worsening motor symptoms (13). Anxiety, isolation, prolonged inactivity, and sudden discontinuation of anti-Parkinson drugs are among the possible causes that trigger the motor symptoms of patients.

There was a significant association between blood types and the risk of COVID-19 in our study. Patients with blood type B were 3.5 times more likely to test positive for COVID-19 compared to those with blood type O. Previous studies show a slightly increased prevalence of COVID-19 in non-O blood types in the normal population (13). However, the association between blood types and the risk of COVID-19 was not evaluated previously.

Our study showed that the risk of COVID-19 in patients taking Levodopa was 2.2 times greater than in those taking other treatments, such as Amantadine (14). Amantadine is hypothetically proposed as a beneficial drug for COVID-19 due to its antiviral properties. However, there is not

Table 5. Univariate and Multivariate Logistic Regression Models

Characteristics	Univariate		Multivariate	
	OR (95% CI)	P-Value	OR (95% CI)	P-Value
Age	0.981 (0.958 - 1.005)	0.120		
Sex (Ref = Female)	0.956 (0.551 - 1.658)	0.873		
Marital status (Ref = Married)	0.148 (0.020 - 1.093)	0.061		
BMI	1.048 (0.988 - 1.113)	0.120		
Smoking (Ref = No)	0.567 (0.170 - 1.886)	0.355		
Age at onset	0.980 (0.961 - 0.999)	0.041	0.976 (0.953 - 0.999)	0.037
Disease duration	1.036 (0.989 - 1.084)	0.133		
Levodopa (Ref = No)	2.289 (1.014 - 5.166)	0.046	3.672 (1.095 - 12.31)	0.035
Amantadine (Ref = No)	1.190 (0.906 - 1.564)	0.212		
Peramipexole (Ref = No)	1.175 (0.980 - 1.409)	0.082		
Biperiden (Ref = No)	0.669 (0.405 - 1.103)	0.115		
Selegiline (Ref = No)	0.944 (0.625 - 1.427)	0.786		
Trehexyphenidyl (Ref = No)	0.955 (0.839 - 1.088)	0.490		
Vitamin D (Ref = No)	1.469 (0.833 - 2.591)	0.184		
CVD (Ref = No)	0.625 (0.298 - 1.307)	0.212		
DM (Ref = No)	0.912 (0.647 - 1.286)	0.600		
Asthma (Ref = No)	0.859 (0.433 - 1.702)	0.663		
Lung (Ref = No)	1.017 (0.798 - 1.297)	0.889		
HTN (Ref = No)	0.879 (0.779 - 0.994)	0.039	0.884 (0.754 - 1.036)	0.127
Cancer (Ref = No)	1.006 (0.710 - 1.427)	0.971		
Stroke (Ref = No)	1.093 (0.973 - 1.228)	0.134		
Kidney (Ref = No)	1.062 (0.965 - 1.169)	0.219		
Liver (Ref = No)	1.048 (0.884 - 1.243)	0.587		
Aspirin (Ref = No)	1.214 (0.699 - 2.109)	0.491		
Ibuprofen or Gelofen (Ref = No)	2.022 (1.155 - 3.537)	0.014	1.422 (0.699 - 2.891)	0.331

enough clinical data to support this hypothesis (21).

Neuropathologically, there is insufficient evidence supporting the entry of the SARS-CoV-2 virus into neurons and neuroglia. Despite the potential facilitation of virus entry by increasing angiotensin-converting enzyme 2 (ACE2) expression, no study has demonstrated elevated ACE2 levels in neurons during COVID-19 infection. This diminishes the likelihood of a direct connection between SARS-CoV-2 and the destruction of the Substantia nigra pathway to the corpus striatum (10). Some studies propose that the progression of Parkinson's may be influenced by the increased inflammation induced by the presence of SARS-CoV-2 (22, 23).

In summary, it is clear that, like many other chronic diseases, the clinical features of PD change during the course of COVID-19 infection. Although many studies have been published to evaluate the clinical characteristics of PD in different populations, there is still no consensus on the results and various reasons contributing to that. Among all the current studies, our study had the most similarity to the study by Salari et al. since they were both carried out in Iran and they shared a similar methodology (14). Additionally, our study proposed some new features, such as the association between blood type, Levodopa, and age at onset with COVID-19, that need to be further investigated. Given this study's limitation in examining the long-term complications of COVID-19 in patients, it is advisable to undertake cohort studies with extended follow-up periods to provide a more comprehensive understanding.

5.1. Study Limitations

This study encountered several limitations. Firstly, the memory status of Parkinson's patients posed a challenge, as the aging population might experience recall bias, impacting the accuracy of recorded events related to COVID-19 infection. Despite efforts to verify information through interviews with key individuals, the complete elimination of recall bias remained unattainable. Additionally, the study faced limitations

due to incomplete checklist responses from elderly patients. The inability to manage confounding factors in diagnosing and treating COVID-19 in Parkinson's patients. Cost constraints and limited healthcare access might have led to the potential underrepresentation of cases. Moreover, the study's cross-sectional design hindered the exploration of long-term complications arising from COVID-19 infection in Parkinson's patients.

Footnotes

Authors' Contribution: Conceptualization: OM, SV, VSh, Ach. Data curation: OM, AAS, SV, MR. Formal analysis: OM, AAS, SV, MR. Funding acquisition: Not applicable. Investigation: MA, RB. Methodology: SV, MB, MA, RB. Project administration: OM, MB, VSh. Supervision: VSh, Ach. Validation: OM, AAS, VSh. Visualization: AAS. Writing – original draft: SV. Writing – review & editing: OM, MB, MA, RB.

Conflict of Interests: The authors declared they have no conflict of interest.

Data Availability: The dataset presented in the study is available on request from the corresponding author during submission or after publication.

Ethical Approval: IR.MUI.MED.REC.1400.113.

Funding/Support: This study did not receive any funding from universities and industrial companies, and all costs for the implementation of the study and publishing were borne by the corresponding author.

References

1. Papa SM, Brundin P, Fung VSC, Kang UJ, Burn DJ, Colosimo C, et al. Impact of the COVID-19 Pandemic on Parkinson's Disease and Movement Disorders. *Mov Disord*. 2020;**35**(5):711–5. [PubMed ID: 32250460]. [PubMed Central ID: PMC7996401]. https://doi.org/10.1002/mds.28067.
2. Del Sole F, Farcomeni A, Loffredo L, Carnevale R, Menichelli D, Vicario T, et al. Features of severe COVID-19: A systematic review and meta-analysis. *Eur J Clin Invest*. 2020;**50**(10). e13378. [PubMed ID: 32860457]. [PubMed Central ID: PMC7435565]. https://doi.org/10.1111/eci.13378.
3. Wang B, Li R, Lu Z, Huang Y. Does comorbidity increase the risk of patients with COVID-19: evidence from meta-analysis. *Aging (Albany NY)*. 2020;**12**(7):6049–57. [PubMed ID: 32267833]. [PubMed Central ID: PMC7185114]. https://doi.org/10.18632/aging.103000.
4. Barzegar M, Mirmosayyeb O, Gajarzadeh M, Afshari-Safavi A, Nehzat N, Vaheb S, et al. COVID-19 Among Patients With Multiple Sclerosis: A Systematic Review. *Neurol Neuroimmunol Neuroinflamm*. 2021;**8**(4). [PubMed ID: 34016734]. [PubMed Central ID: PMC8142838]. https://doi.org/10.1212/NXI.0000000000001001.
5. Poewe W, Seppi K, Tanner CM, Halliday GM, Brundin P, Volkmann J, et al. Parkinson disease. *Nat Rev Dis Primers*. 2017;**3**:17013. [PubMed ID: 28332488]. https://doi.org/10.1038/nrdp.2017.13.
6. Helmich RC, Bloem BR. The Impact of the COVID-19 Pandemic on Parkinson's Disease: Hidden Sorrows and Emerging Opportunities. *J Parkinsons Dis*. 2020;**10**(2):351–4. [PubMed ID: 32250324]. [PubMed Central ID: PMC7242824]. https://doi.org/10.3233/jpd-202038.
7. Huang P, Zhang LY, Tan YY, Chen SD. Links between COVID-19 and Parkinson's disease/Alzheimer's disease: reciprocal impacts, medical care strategies and underlying mechanisms. *Transl Neurodegener*. 2023;**12**(1):5. [PubMed ID: 36717892]. [PubMed Central ID: PMC9885419]. https://doi.org/10.1186/s40035-023-00337-1.
8. Wang AS, Perez JA, Gunzler SA. Frequency of Parkinson disease following COVID-19 infection: A two-year retrospective cohort study. *Parkinsonism Relat Disord*. 2023;**111**:105433. [PubMed ID: 37141688]. https://doi.org/10.1016/j.parkreldis.2023.105433.
9. Ellul MA, Benjamin L, Singh B, Lant S, Michael BD, Easton A, et al. Neurological associations of COVID-19. *Lancet Neurol*. 2020;**19**(9):767–83. [PubMed ID: 32622375]. [PubMed Central ID: PMC7332267]. https://doi.org/10.1016/S1474-4422(20)30221-0.
10. Sulzer D, Antonini A, Leta V, Nordvig A, Smeyne RJ, Goldman JE, et al. COVID-19 and possible links with Parkinson's disease and parkinsonism: from bench to bedside. *NPJ Parkinsons Dis*. 2020;**6**:18. [PubMed ID: 32885037]. [PubMed Central ID: PMC7441399]. https://doi.org/10.1038/s41531-020-00123-0.
11. Del Prete E, Francesconi A, Palermo G, Mazzucchi S, Frosini D, Morganti R, 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**(4):1179–87. [PubMed ID: 32880722]. [PubMed Central ID: PMC7471534]. https://doi.org/10.1007/s00415-020-10002-6.
12. Fasano A, Cereda E, Barichella M, Cassani E, Ferri V, Zecchinelli AL, et al. COVID-19 in Parkinson's Disease Patients Living in Lombardy, Italy. *Mov Disord*. 2020;**35**(7):1089–93. [PubMed ID: 32484584]. [PubMed Central ID: PMC7300944]. https://doi.org/10.1002/mds.28176.
13. Artusi CA, Romagnolo A, Imbalzano G, Marchet A, Zibetti M, Rizzone MG, et al. COVID-19 in Parkinson's disease: Report on prevalence and outcome. *Parkinsonism Relat Disord*. 2020;**80**:7–9. [PubMed ID: 32920322]. [PubMed Central ID: PMC7474816]. https://doi.org/10.1016/j.parkreldis.2020.09.008.
14. Salari M, Etemadifar M, Zali A, Aminzade Z, Navalpotro-Gomez I, Fateh ST. [Covid-19 in Parkinson's Disease treated by drugs or brain stimulation]. *Neurologia (Engl Ed)*. 2021. spa. [PubMed ID: 34366530]. [PubMed Central ID: PMC8326006]. https://doi.org/10.1016/j.nrl.2021.07.002.
15. Khoshnood RJ, Zali A, Tafreshinejad A, Ghajarzadeh M, Ebrahimi N, Safari S, et al. Parkinson's disease and COVID-19: a systematic review and meta-analysis. *Neurol Sci*. 2022;**43**(2):775–83. [PubMed ID: 34787753]. [PubMed Central ID: PMC8596358]. https://doi.org/10.1007/s10072-021-05756-4.
16. de Marcaida JA, Lahrmann J, Machado D, Bluth L, Dagostine M, Moro-de Casillas M, et al. Clinical Characteristics of Coronavirus Disease 2019 (COVID-19) among Patients at a Movement Disorders Center. *Geriatrics (Basel)*. 2020;**5**(3). [PubMed ID: 32962001]. [PubMed Central ID: PMC7555630]. https://doi.org/10.3390/geriatrics5030054.
17. Chambergo-Michilot D, Barros-Sevillano S, Rivera-Torrejon O, De la Cruz-Ku GA, Custodio N. Factors associated with COVID-19 in people with Parkinson's disease: a systematic review and meta-analysis. *Eur J Neurol*. 2021;**28**(10):3467–77. [PubMed ID: 33983673]. [PubMed Central ID: PMC8239569]. https://doi.org/10.1111/ene.14912.
18. El-Qushayri AE, Ghozy S, Reda A, Kamel AMA, Abbas AS, Dmytriw AA. The impact of Parkinson's disease on manifestations and outcomes of Covid-19 patients: A systematic review and meta-analysis. *Rev Med Virol*. 2022;**32**(2). e2278. [PubMed ID: 34260773]. [PubMed Central ID: PMC8420424]. https://doi.org/10.1002/rmv.2278.
19. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. *Diabetes Metab Res Rev*. 2020;**36**(7). e3319. [PubMed ID: 32233013]. [PubMed Central ID: PMC7228407]. https://doi.org/10.1002/dmrr.3319.

20. Vignatelli L, Zenesini C, Belotti LMB, Baldin E, Bonavina G, Calandra-Buonaura G, et al. Risk of Hospitalization and Death for COVID-19 in People with Parkinson's Disease or Parkinsonism. *Mov Disord*. 2021;**36**(1):1–10. [PubMed ID: 33196119]. [PubMed Central ID: PMC7753472]. https://doi.org/10.1002/mds.28408.
21. Artusi CA, Romagnolo A, Ledda C, Zibetti M, Rizzone MG, Montanaro E, et al. COVID-19 and Parkinson's Disease: What Do We Know So Far? *J Parkinsons Dis*. 2021;**11**(2):445–54. [PubMed ID: 33749619]. [PubMed Central ID: PMC8150504]. https://doi.org/10.3233/JPD-202463.
22. Xu Y, Surface M, Chan AK, Halpern J, Vanegas-Arroyave N, Ford B, et al. COVID-19 manifestations in people with Parkinson's disease: a USA cohort. *J Neurol*. 2022;**269**(3):1107–13. [PubMed ID: 34482434]. [PubMed Central ID: PMC8418279]. https://doi.org/10.1007/s00415-021-10784-3.
23. Mysiris DS, Vavougios GD, Karamichali E, Papoutsopoulou S, Stavrou VT, Papayianni E, et al. Post-COVID-19 Parkinsonism and Parkinson's Disease Pathogenesis: The Exosomal Cargo Hypothesis. *Int J Mol Sci*. 2022;**23**(17). [PubMed ID: 36077138]. [PubMed Central ID: PMC9456372]. https://doi.org/10.3390/ijms23179739.