



COVID-19 and Parkinson's disease: a systematic review and meta-analysis

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Abstract

This meta-analysis aimed to determine the prevalence, symptoms, and outcomes of COVID-19 in the elderly with Parkinson's disease (PD) by searching in the international databases of PubMed, Scopus, Web of Sciences, and EMBASE using the keywords of "COVID-19" and "Parkinson's." All articles related to Parkinson's disease and COVID-19 from January 2019 to October 20, 2021 were reviewed. The STATA software was used for analysis. A total of 20 articles were selected for data extraction in this meta-analysis, of which ten were cross-sectional studies (to determine the prevalence), five case-control studies, and five cohort studies (to examine the association). The results of the meta-analysis showed the prevalence of COVID-19 in patients with PD was 1.06% (95% CI 1.03–1.1%; $P=0.02$), and the prevalence of their hospitalization due to COVID-19 was 0.98% (95% CI: 0.95–1.02%; $P=0.00$). Also, the prevalence of depression and anxiety during the pandemic in this group was 46% (95% CI 29–64%; $P=0.00$) and 43% (95% CI: 24–63%; $P=0.00$), respectively. The prevalence of tremor and sleep problems were higher than those of other symptoms in the studied population. According to the results, there was no significant difference in the risk of COVID-19 infection between Parkinson's patients and healthy people. In other words, the risk of COVID-19 infection was equal in both groups (RR = 1.00 (CI 95% 0.77–1.30%; $P=0.15$)). The results showed mortality and hospitalization rates of the elderly with Parkinson's disease were not significantly different from those of the general population during the COVID-19 pandemic. Also, the symptoms of Parkinson's disease and mental disorders increased during the COVID-19 pandemic. So, designing and developing more specific studies, like cohort studies, with large sample size is required for assessing these associations.

Keywords COVID-19 · Parkinson's disease · Systematic review · Meta-analysis

Introduction

COVID-19 spread in most countries so rapidly that the World Health Organization (WHO) declared a pandemic on March 11, 2020 [1–4]. The pandemic has had a profound

effect on all human life aspects, including people's physical and mental health around the world [5, 6]. The risk of COVID-19 and its mortality is higher among vulnerable populations, such as the elderly with chronic diseases, especially neurological ones [7]. However, the pandemic and the subsequent emergency situation forced officials to focus on controlling and adhering to the care associated with this virus while ignoring the priority of caring for those with chronic and neurological diseases [8]. On the other hand, the outcomes of this disease increased in older people living with neurological diseases, one of the most prominent of which is Parkinson's disease [6]. Parkinson's disease (PD) is one of the most common neurological diseases prevalent in the elderly. In addition to motor symptoms, such as bradykinesia, rigidity, and tremor caused by degeneration and the destruction of dopaminergic nigrostriatal neurons, non-motor symptoms, such as depression, anxiety, and sleep disorders, to advanced stages are also common in the early [8, 9]. Therefore, changes and social conditions during the

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pandemic may have affected the motor and non-motor symptoms experienced by PD patients and negatively affected their life quality [6, 9, 10]. To date, few clinical studies have been performed on patients with PD, infected by COVID-19 [4]. Therefore, there is currently insufficient evidence to suggest PD itself increases the risk of COVID-19 or COVID-19 exacerbates PD symptoms. Contradictory results have been reported from studies with small sample sizes of PD patients with COVID-19 [2].

However, studies have shown the COVID-19 pandemic has directly and indirectly affected patients with PD worldwide in various ways [6, 11]. First, although the risk of developing PD does not increase in the general population [3], individuals infected with SARS-CoV-2 are more likely to have worsening symptoms [12]. It is not yet clear whether patients with Parkinson's and those receiving advanced treatment are likely to be at greater risk of COVID-19 death [13]. Second, the conditions of caring for PD patients have changed [14]: surgical treatments have been delayed [15], and access to outpatient clinics has been limited to prevent the spread of COVID-19 [16]. Regular physical evaluation and adjustment of medications in non-emergency situations have also become more difficult. Third, the social, economic, and medical outcomes have led to profound lifestyle changes in patients with PD, including decreased overall physical activities, inability to attend exercise classes, and increased levels of mental distress.

In PD, these lifestyle changes are referred to the "hidden sorrows" of COVID-19 [17] because they may indirectly worsen symptoms. Physical activities help reduce PD motor symptoms [18]. Also, staying at home is especially psychologically harmful to this population. Mental distress worsens a variety of motor symptoms and also causes or exacerbates neuropsychiatric symptoms, such as anxiety and depression [6].

The study aimed to systematically review and meta-analyze the status of patients with PD during the COVID-19 pandemic. The first goal of this meta-analysis was to determine the prevalence of COVID-19 in patients with Parkinson's disease. Subsequently, the occurrence of symptoms and outcomes associated with COVID-19 was determined in these patients. Finally, the effect of COVID-19 and its conditions was determined on the symptoms of PD, like physical activities, sleep complications, and mental disorders.

Methods

The study protocol has previously been registered in PROSPERO with the code CRD42021282398. The present study was a systematic review and meta-analysis designed and conducted with the PECOT structure. P means the study population, patients with Parkinson's disease, E means

exposure to COVID-19, C means the comparison group, including all people with Parkinson's who did not have COVID-19, and O means the study outcome, the prevalence of COVID-19, depression and anxiety, physical activities, Parkinson's symptoms, and sleep disorders in patients with Parkinson's disease during the pandemic. This meta-analysis is the most comprehensive one associated with COVID-19 in patients with Parkinson's disease, which has considered all possible outcomes reported in the early studies.

Search strategy and screening

All articles published in international databases were searched to extract studies which examined PD during the COVID-19 pandemic. The search was conducted in these databases without any language or time restrictions. Search strategies included the following keywords: "COVID 19," "COVID-19 Virus Disease," "2019-nCoV Infections," "2019 Novel Coronavirus Disease," "Coronavirus Disease 2019," "SARS Coronavirus 2 Infection," "SARS-CoV-2 Infection," "SARS-CoV-2 Infections," "COVID-19 Virus," "Wuhan Coronavirus," "SARS Coronavirus 2," "Severe Acute Respiratory Syndrome Coronavirus 2," "Parkinson," "Idiopathic Parkinson's Disease," "Lewy Body Parkinson's Disease," "Parkinson's Disease," "Primary Parkinsonism," and "Secondary Parkinson's Disease," all of which have been compiled from Mesh. The search databases included (Medline) PubMed, Scopus, Web of Sciences, and EMBASE, and its timeline was from January 2019 to October 20, 2021. The duplicate studies were removed using the title of the published articles, their authors, and year of publication using Endnote software, version 9. Then, the remaining articles were reviewed and evaluated based on their titles, abstracts, and full texts considering the inclusion criteria. Two study authors independently (MA, PM) screened articles based on their titles, abstracts, and full texts, and disagreements were resolved by a third one (YM). After screening, the final selection of articles was made by evaluating the full text of the selected ones.

Study selection

The search strategy in international databases was independently performed by the two researchers (MA and PM), and the disagreements were resolved by the third person (YM).

Inclusion and exclusion criteria

This study aimed to determine the prevalence of COVID-19 infection and its symptoms in elderly patients with PD and the association between PD and COVID-19. Therefore, both descriptive observational studies (cross-sectional ones) and analytical observational studies (case or cohort ones) were

examined. The prevalence of PD symptoms and those of COVID-19 in Parkinson's patients should have been reported in these studies. Review studies, case reports, case series, clinical trials, other interventional studies, and letters to the editor were excluded from the present research (Table 1).

Data extraction

After three stages of evaluation based on the title, abstract, and full text, the selected articles were retrieved for detailed analysis. The data were collected using a checklist containing the authors' names, country, publication year, study type, study population, sample size, data source, duration of Parkinson's disease, age, number of patients with COVID-19, rates of hospitalization and mortality due to COVID-19, evaluation of depression and anxiety, physical activities, COVID-19 symptoms (fever, cough, weakness, respiratory problems and shortness of breath, dysuria, decreased sense of smell, decreased sense of taste, fatigue, headache, myalgia, diarrhea, nausea, and vomiting), and PD symptoms (tremor, dyskinesia, bradykinesia, rigidity, gait, freezing of gait, balance problems, cognitive impairment, sleep problems, and daytime sleepiness) (Table 2).

Qualitative evaluation of articles

Two of the study authors (MA, MA) conducted a qualitative evaluation of the studies on the basis of the Newcastle–Ottawa Quality Assessment Scale (NOS) checklist. This checklist was designed to evaluate the quality of observational studies. This tool examines each research with six items in three groups of selecting study samples, comparing and analyzing study groups, and measuring and analyzing the desired outcome. Each of these items is given a score of one if observed in the studies, and the maximum score for each study is nine points. In case of disagreements in the score assigned to the published articles, the discussion method and a third researcher were used [19].

Statistical analysis

The Metaprop command was used to calculate the cumulative prevalence with a 95% confidence interval. First, the total sample volume was extracted from the initial studies. Then, the sample volumes with the desired outcomes were identified in the initial studies and analyzed by the Metaprop command.

Because the prevalence of COVID-19 was very low in patients with Parkinson's disease, it was decided to combine the indexes in the case–control and cohort studies and report them in the form of the relative risk (RR) indicating the rate of risk of the preferred outcomes in people with Parkinson's.

To investigate the association using the cumulative RR with a 95% confidence interval, the methane command was used considering the logarithm and standard deviation of the logarithm of the RR. The heterogeneity between the studies was assessed using I² and Q Cochrane tests. Also, Egger test was used to assess publication bias. The statistical analysis was performed using STATA 16.0, and the *P* value < 0.05 was considered.

Results

Qualitative results

Based on the search strategy, 522 studies were obtained from the PubMed, Scopus, Web of Sciences, and EMBASE databases, of which 135 were excluded due to duplication, and 390 remained. After reviewing the title and full text of the articles, 20 studies remained for analysis, of which ten were cross-sectional studies [5, 6, 8–11, 20–23], five case–control studies [2, 3, 12, 24, 25], and five cohort studies [4, 7, 26–28] (Table 2), and all were from 2020 to 2021 (Fig. 1).

The quality assessment checklist (NOS checklist) of the observational studies showed 50% of the scores were

Table 1 The eligibility criteria

Eligibility criteria	
Association	Prevalence
The study population was patients with Parkinson's disease (with Covid-19 or not)	The study population was patients with Parkinson's disease (with Covid-19 or not)
The exposure in these studies was Covid-19	The intended outcomes in studies were evaluation of the Parkinson's symptoms such as tremor, physical activity, sleep disorders, and mental disorders
The comparison group included people with Parkinson's who did not have Covid-19	The intended type of studies was analytical or descriptive cross sectional
The intended outcomes were the risk of complications associated with Covid-19 and its symptoms (Covid-19, hospitalization, and death and symptoms, including fever, cough, respiratory difficulties, diarrhea, smell reduction, taste reduction, muscle pain/ joint pain, nausea/vomiting, and fatigue)	

Table 2 Characteristics of participants and mental disorders

Authors (Years) (R) Country	Type of study	Study population	Sample size	Data sources	Age (male)	Duration of Disease	Number of COVID-19	Admission to hospital (COVID-19)	Mortality Causes (EF; 95% CI)	Depression (COVID-19)	Anxiety (COVID-19)	NOS score
Birgul Balci (2021) [23] Turkish	Case control	PD Non-PD	Patients = 45 Healthy = 43	Questionnaire screening	Patients = 67 (66%) Healthy = 66 (55.8%)	8 years	0	NR	NR	NR	NR	7
Elisa Montanaro (2021) [24] Italy	Case control	PD Non-PD	All Patients = 100 Caregivers = 60	Electronic database of the movement disorder Center of the University Hospital of Turin	All patients = 62.4 ± 9.0 (38–78) Male = 60 Caregivers = 62.1 ± 9.2 (43–83) Male = 21	All Patients = 13.4 ± 4.6 (6–31)	Execution of nasopharyngeal swab (from February 2020 to TO) n = 1	NR	NR	T = 0 All patients = 35% T = 1 All patients = 34.1%	T = 0 All patients = 39% T = 1 All patients = 30.6%	7
Luca Vignatelli (2020) [7] Italy	Historical cohort design	PD Non-PD	Parkinson's disease = 696 Parkinsonism = 184 Control cohort = 8590	Italian health system	Control cohort = 76 (58.2) Parkinson's disease = 75 (58.8) Parkinsonism = 80.5 (57.1)	-	PD: 4 (3 men) PS = 6 (3 men) control cohort = 64 (44 men)	Number of hospital admission for COVID-19 control cohort = 25 Parkinson's disease = 4 Parkinsonism = 6	NR	NR	NR	8
Maria Bucafusa (2020) [25] Italy	Cohort	Patients with COVID and Parkinson's	Patients with COVID and Parkinson's = 12	Hospital	73 (50%)	22 years	12 (100%)	Days of hospitalization – average = 30.7	NR	NR	NR	6
Raphael Scherbaum (2020) [11] Germany	Cross-sectional non-PD study	PD Non-PD	5,210,432 numbers PD = 65,127 Non-PD = 5,176,177	Hospital	NR	NR	30,872 Non-PD = 30,179 PD = 693	Non-PD = 6241 20.7% PD = 245 35.4%	NR	NR	NR	7

Table 2 (continued)

Authors (Years) (R) Country	Type of study	Study population	Sample size	Data sources	Age (male)	Duration of Disease	Number of COVID-19	Admission to hospital (COVID-19)	Mortality (COVID-19)	Mortality Causes (EF; 95% CI)	Depression (COVID-19)	Anxiety (COVID-19)	NOS score
Mehri Salari (2020) [19] Iran	Cross-sectional, case-control survey	Parkinson's disease (PD) and non-PD control	500 PD=137 Caregivers=95 Control=442	NR	PD=55 (34.3) Control=43 (25.3)	<5 32.8 5-10 35.8 >10 31.4	PD=1.5% Control=4.5	NR	NR	NR	NR	PD % No anxiety = 18.2 Mild = 26.3 Moderate = 29.9 Severe = 25.5 CONTROL No anxiety = 56.3 Mild = 28.3 Moderate = 10.6 Severe = 4.8 PD = 183 25%	7
Eleonora Del Prete (2020) [2] Italy	Case-controlled survey	Parkinson's disease (PD)	21 PD non-COVID=14 PD=733	NR	75	PD non-COVID=8.93 PD COVID-19=9.29	PD COVID-19=19=7	NR	NR	NR	NR	NR	8

Table 2 (continued)

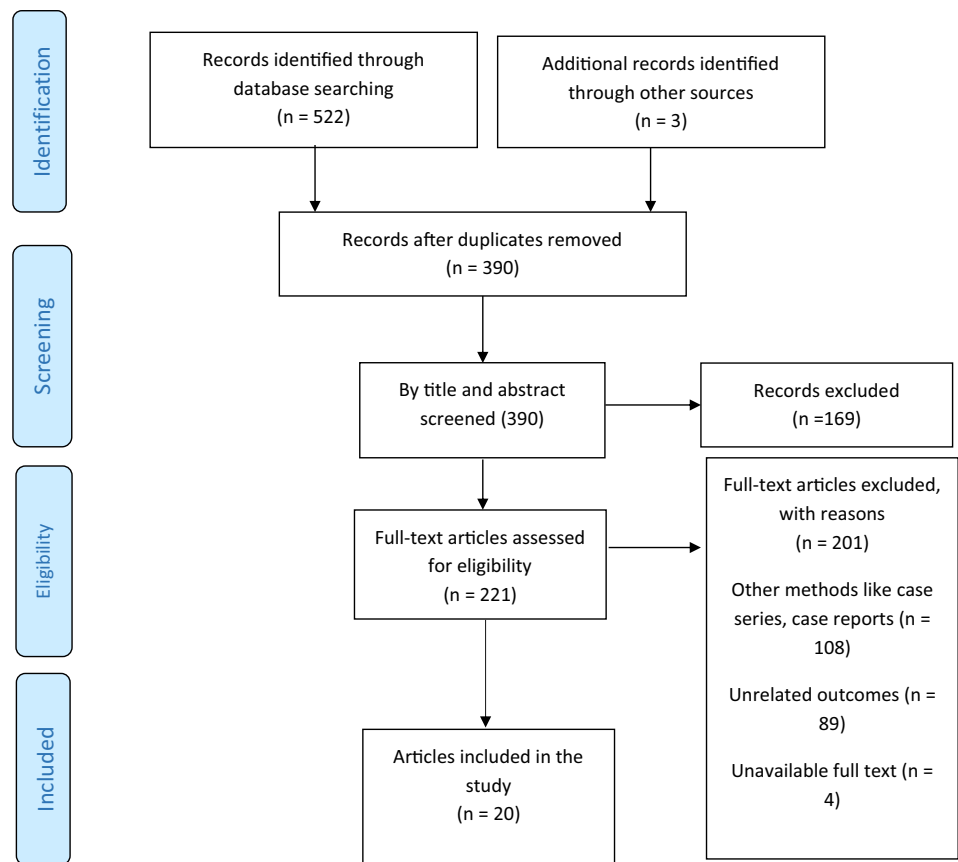
Authors (Years) (R) Country	Type of study	Study population	Sample size	Data sources	Age (male)	Duration of Disease	Number of COVID-19	Admission to hospital (COVID-19)	Mortality (COVID-19)	Mortality Causes (EF; 95% CI)	Depression (COVID-19)	Anxiety (COVID-19)	NOS score
Fukiko Kitani-Morii (2020) [8] Japan	Cross-sectional study	PD patients and their family members	71 PD patients and 32 controls	NR	<70 = 25 (35.2) 70–79 = 33 (46.4) >80 = 13 (18.3)	<5 = 22 (56.4) >5 = 17 (43.5)	NR	NR	NR	Total Normal = 32 (46.3) Mild = 20 (28.9) Moderate = 9 (13.0) Severe = 8 (11.5) PD = 14 (36.8) Normal = 9 (23.6) Mild = 8 (21.0) Severe = 7 (18.4) CONTROL = 18 (58.0) Mild = 11 (0.35) Moderate = 1 (3.2) Severe = 1 (3.2)	Total Normal = 35 (49.2) Mild = 20 (28.1) Moderate = 10 (14.0) Severe = 6 (8.4) PD = 9 (13.0) Normal = 18 (46.1) Mild = 9 (23.0) Moderate = 7 (17.9) Severe = 5 (12.8) CONTROL = 14 (36.8) Normal = 9 (23.6) Mild = 11 (34.3) Moderate = 3 (9.3) Severe = 1 (3.1)	8	
Francesco Cavallieri (2020) [10] Italy	Cross-sectional online survey	PD Caregivers	103 PD = 67 Caregivers = 36	online survey	(Men = 61.17%) 41–50 = 3 51–60 = 16 61–70 = 54 71–80 = 22 >80 = 8	<2 = 11 2–5 = 28 >5 = 64	NR	NR	NR	NR	NR	NR	6

Table 2 (continued)

Authors (Years) (R) Country	Type of study	Study population	Sample size	Data sources	Age (male)	Duration of Disease	Number of COVID-19	Admission to hospital (COVID-19)	Mortality (COVID-19)	Mortality Causes (EF, 95% CI)	Depression (COVID-19)	Anxiety (COVID-19)	NOS score
Hei Otmani (2020) [26] Moroccan	Prospective cohort	PD patients	50	via the Internet	60.4 (48%)	NR	0	NR	NR	NR	At the beginning = 14 (28%) After 6 weeks = 17 (34%) Depression Improved = 5 Worsening = 12	At the beginning = 14 After 6 weeks = 15 (30%) Anxiety Improved = 4 Worsening = 8	8
Yun Xia (2020) [37] China	A quantitative study Cross-sectional and	PD patients healthy controls	288 PD patients = 119 healthy controls = 169	Questionnaire based interview investigation	61.18 ± 8.77 years PD = (51.3%) male	6.84 ± 4.60 years	NR	NR	NR	NR	HADS-depression ≥ 8 PD = 27 Control = 27	HADS-anxiety ≥ 8 PD = 25 Control = 29	6
Anouk van der Heide (2020) [6] Netherlands	Longitudinal observational cross-sectional study	PD patients	PD = 498 Responders (n = 358) non-responders (n = 140)	sent an online survey to the Personalized Parkinson Project (PPP) cohort	Responders = 62.8 Non-responders = 61.5% male = 63.3 (55.7%) male	Responders = 3.9 (1.8) Non-responders = 4.3 (2.0)	NR	NR	NR	NR	Worsened = 31.6% No change = 62.7% Improved = 5.8%	NR	9
Niraj Kumar (2020) [21] India	Cross-sectional study	PD patients	832 35.4% reported sleep disturbances = 295 New-onset/worsening of sleep disturbances (NOWS) was reported by 23.9% subjects = 199	Questionnaire	Nearly 84% patients were aged 50 years or older	NR	NR	NR	NR	NR	New-onset/worsening of sleep disturbances (n = 199) = 56.3% Parkinson's disease subjects who never had sleep disturbances (n = 537) = 35.7%	New-onset/worsening of sleep disturbances (n = 199) = 60% Parkinson's disease subjects who never had sleep disturbances (n = 537) = 39.1%	8
Keisuke Suzuki (2020) [38] Japan	Cross-sectional survey	PD Caregivers	200 PD = 100 Caregivers = 100	NR	CG = 65.5 ± 12.0 PD = 72.2 ± 9.1	5.8 ± 4.4 YEARS	NR	NR	NR	NR	CG = 17 (17.0) PD = 20 (20.0)	CG = 6 (6.0) PD = 6 (6.0)	8

Table 2 (continued)

Authors (Years) (R) Country	Type of study	Study population	Sample size	Data sources	Age (male)	Duration of Disease	Number of COVID-19	Admission to hospital (COVID-19)	Mortality (COVID-19)	Depression (COVID-19)	Anxiety (COVID-19)	NOS score
Heng Zhai (2020) [4] China	Retrospective, cohort and observational study	1-PD+COVID 2-COVID	296 1–10 2–286	Hospital	66 years (50.68%)	NR	296	ALL=13.00 (7.00–18.75) PD+COVID=12.00 (5.25–24.50) COVID + non-COVID + Non-PD =13.00 (7.00–18.00)	ALL=119 (40.20%) PD+COVID =3(30.00%) Non-PD =116 (40.56%)	NR	NR	7
Joomee Song(2020) [27] e United Kingdom	Cohort	PD patients	100	NR	70 Male (54%)	6	NR	NR	NR	5 (5)	NR	8
Eithan G Brown (2020) [22] USA	Cross sectional	PD non-PD	PD=5429 Non-PD=1452	NR	PD+COVID=65(47) PD=68(52) Non-PD+COVID=57(8) Non-PD=61(22)	NR	PD=51 Non-PD=26	PD=5 (9.8%) Non-PD=2 (7.7%)	NR	NR	NR	8
Cilia (2020) [12] Italy	Case control	PD+COVID PD	PD+COVID=12 PD=36	NR	PD+COVID=65.5(41.7) PD=66.3(41.7)	Case=6.3 Control=6.1	Confirmed COVID-19 Case=6 Control=0	N (%) Case=1 (8.3)	0	NR	NR	6
Fasano (2020) [3] Italy	Case control	PD+COVID Non-PD	Case=1381 Control=1207	NR	Case+COVID=70.5(52.4) Case non-COVID=73(57.2)	Case+COVID=9.9 Case non-COVID=9.1	Case=105 (32 confirmed and 73 probable cases) Control=95	N (%) Case=18(17.1) Control=25(27.2)	N (%) Case=6(5.7) Control=7(7.6)	NR	NR	8
Diego Santos-Garcia (2020) [5] Spain	Cross sectional	PD+COVID PD	568 PD+COVID=15 PD=553	NR	63.5 (47)	8.6	15	NR	NR	PD+COVID=57.1% PD=65.6% Total=65.4%	PD+COVID=60% PD=65.5% Total=65.6	6

Fig. 1 The flowchart of search strategy and syntax

between 6 and 8 and the other 50% were between 8 and 10, indicating most of these studies had a good quality (Table 2).

Depression in PD patients was examined in nine studies [5, 6, 8, 9, 21, 22, 25, 27, 28], of which two [25, 27] were performed before and during the pandemic and seven [5, 6, 8, 9, 21, 22, 27, 28] during the pandemic. The results of the two comparative studies showed the depression frequency in patients with PD increased during the COVID-19 pandemic compared to before the pandemic (32.6% vs. 34%) [25, 27]. In cross-sectional studies [5, 6, 8, 9, 21, 22] which determined the depression frequency in PD patients during the COVID-19 pandemic, the results showed a high frequency of depression (with an average above 20%) in these patients. The prevalence of depression among Parkinson's patients during the pandemic was evaluated in six reference studies.

Nine studies [2, 5, 8, 9, 20–22, 25, 27] examined and compared anxiety in PD patients before and during the pandemic, of which two studies [25, 27] checked the level before and during the pandemic and seven [2, 5, 8, 9, 20–22] during the pandemic. The results of the two comparative studies for anxiety levels before and during the pandemic showed a reduction in anxiety in patients with PD during the COVID-19 pandemic (36.6% vs. 30%) [25, 27]. However, cross-sectional studies [5, 8, 9, 20–22] showed a high prevalence of anxiety in these patients during the pandemic.

Sleep disorders were investigated in the selected articles in two categories of sleep problems and daytime sleepiness. Sleep problems were studied in nine articles [2, 6, 8, 9, 20–22, 24, 28], three of which [24] examined the changes after the occurrence of COVID-19 infection. In the first study [24], this symptom became more severe in 25.9% of patients over 65 years old and 11% of those under 65 years old. In the second study [6], the sleep-related symptoms became more severe in 27% of the study population, and in the third study [9], 41% of patients were affected. In a study [21], the average sleep time rose to 1.39 during the pandemic. Another study [28] found the sleep rate was reduced in 5% of people with PD. Daytime sleepiness was studied in one article [24] which found it became more severe in 25.9% of patients over 65 years old and 5.6% of ones under 65 years old. Finally, sleep disorders became more severe in the population with Parkinson's disease in the post-pandemic period.

Quantitative results

Prevalence of COVID-19 and its associated outcomes in patients with Parkinson's disease

The COVID-19 prevalence in Parkinson's patients during the pandemic was evaluated in four studies [5, 11, 20, 23].

Table 3 Meta-analysis of the prevalence of COVID-19, mental disorders, Parkinson's symptoms in patients with Parkinson's disease

Categories	Outcomes	No. study (SS)	No. of patients	Pooled prevalence	Heterogeneity assessment		
					I ²	p value	Test Q
Outcomes of covid-19	Covid-19	4 (71,261)	761	1.06% (1.03–1.1%)	70.36%	0.02	10.12
	Admission to Hospital	3 (71,124)	703	0.98% (0.91–1.7%)	98.05%	0.00	102.70
Mental Disorder	Depression	6 (2156)	1104	46% (29–64%)	98.33%	0.00	299.13
	Anxiety	6 (1795)	864	43% (24–63%)	98.37%	0.00	307.53
Parkinson's symptoms	The physical activity	5 (1352)	768	57% (45–67%)	92.96%	0.00	56.83
	Tremor	4 (1998)	976	68% (35–94%)	99.54%	0.00	649.51
	Dyskinesia	3 (1898)	866	50% (21–79%)	99.45%	0.00	362.97
	Rigidity	2 (598)	458	79% (76–83%)	0.00	0.00	51.80
	Gait impairments	2 (932)	377	43% (40–46%)	0.00	0.00	41.26
	Freezing of gait	2 (1330)	555	42% (39–44%)	0.00	0.00	49.73
	Sleep problems	6 (1725)	898	72% (45–92%)	99.08%	0.00	545.45

The sample size of patients with Parkinson's disease was 71,261 people in 4 studies, of whom 761 were infected with COVID-19. The prevalence of COVID-19 in patients with PD was 1.06% (CI 95% 1.03–1.1%; $P=0.02$) with a heterogeneity rate of 70.36% after combining these studies (Table 3). The results of Egger test showed the publication bias occurred (B: 0.34, SE: 0.05, $P<0.001$).

The hospitalization prevalence in Parkinson's patients during the pandemic was evaluated in three studies [5, 11, 23], in which the sample size of patients with Parkinson's disease was 71,124 people, of whom 703 were hospitalized due to COVID-19. After combining these studies, the hospitalization prevalence in patients with Parkinson's disease was equal to 0.98% (CI 95% 0.95–1.02%; $P=0.00$) with a heterogeneity rate of 98.05% (Table 3). The results of Egger test showed the publication bias occurred (B 0.22, SE 0.03, $P<0.001$).

Prevalence of anxiety and depression in patients with Parkinson's disease during the COVID-19 pandemic

The depression prevalence in patients with Parkinson's disease during the pandemic was investigated in 6 studies with a sample size of 2156 patients, of whom 1104 had depression. The lowest prevalence was related to the study of Suzuki et al. [9] with 20% (CI 95% 13–29%), and the highest rate to the study of Van der Heide [6] with 72% (CI 95% 68–76%). The depression prevalence after combining these studies was 46% (CI 95% 29–64%; $P=0.00$) with heterogeneity of 98.33% (Table 3). The results of Egger test showed the publication bias occurred (B 0.69, SE 0.12, $P<0.001$). The anxiety prevalence in Patients with Parkinson's disease during the pandemic was evaluated in 6 studies with a sample size of 1,795 people, of whom 864 suffered from anxiety [5, 8, 9, 20–22]. The lowest prevalence was related to the study of Xia et al. [21] with 21% (CI 95% 14–29%), and the

highest rate to the study of Salari et al. [20] with 81% (CI 95% 73–87%). The anxiety prevalence in patients with PD was 43% (CI 95% 24–63%; $P=0.00$) with the heterogeneity of 98.37% after combining these studies (Table 3). The results of Egger test showed the publication bias occurred (B 1.09, SE 0.88, $P<0.001$).

The anxiety prevalence in Parkinson's patients was different in Asia and Europe. Of course, only one study was conducted in Europe, but in Asia, five studies were published in this regard. After combining the studies conducted in Asia, the prevalence was 38% (95% CI 16–63%; $P=0.00$) while it was 65% in Europe (95% CI 61–69%). Also, depression was higher in the Europe continent (Prevalence: 68%; % 95 CI 66–71%).

Physical activities in Parkinson's patients during the Covid-19 pandemic

The prevalence of physical activities in Parkinson's patients during the pandemic period was investigated in five studies [5, 6, 9, 10, 21]. The study of Suzuki et al. [9] had the lowest prevalence with 44% (CI 95% 34–54%), and the highest was related to the study of Xia et al. [21] with 73% (CI 95% 64–81%). Finally, the prevalence of physical activities in patients with PD was 57% (CI 95% 45–67%; $P=0.00$) with the heterogeneity of 92.96% after combining these studies (Table 3). The results of Egger test showed the publication bias occurred (B 0.33, SE 0.05, $P<0.001$).

Prevalence of symptoms in Parkinson's patients during the COVID-19 pandemic

Four studies [5, 6, 9, 22] investigated the tremor prevalence in Parkinson's patients during the pandemic. The tremor prevalence in patients with Parkinson's disease during the pandemic was evaluated in four studies with a sample size

of 1,998 patients, of whom 976 had tremors. The lowest rate was related to the study of Kumar et al. [22] with 21% (CI 95% 19–24%), and the highest to the study of Suzuki et al. [9] with 100% (CI 95% 96–100%). The tremor prevalence was 68% (CI 95% 35–94%; $P=0.00$) with the heterogeneity of 99.54% (I²) after combining these studies (Table 3). The results of Egger test showed the publication bias occurred (B 0.11, SE 0.01, $P<0.001$). The results of the meta-analysis also showed the prevalence of dyskinesia, rigidity, gait, and freezing of gait were equal to 50% (CI 95% 21–79; $P=0.00$), 79% (CI 95% 76–83; $P=0.00$), 43% (CI 95% 40–46; $P=0.00$), and 42% (CI 95% 39–44; $P=0.00$), respectively (Table 3). The results of subgroup analyses based on the different continents showed the tremor prevalence in European patients was higher than its prevalence in those living in Asia (Table 3).

Sleep disorders in patients with Parkinson's before and during the incidence of the COVID-19 pandemic

The prevalence of sleep problems in patients with Parkinson's disease during the COVID-19 pandemic was evaluated in 6 studies with a sample size of 1,725 people, of whom 898 had sleep disorders. The prevalence of sleep problems in Parkinson's patients during the pandemic period was 72% (CI 95% 45–92%; $P=0.00$) with a rate of heterogeneity of 99.08% after combining these studies (Table 3). The results of Egger test showed the publication bias occurred (B 1.33, SE 0.92, $P<0.001$).

The association of Parkinson's disease with the occurrence of COVID-19 and its related outcomes

The association of COVID-19 with PD during the pandemic was studied in four [3, 4, 7, 25] articles. The lowest RR was related to the study of Montanaro et al. [25] with 0.20 (CI 95% 0.01–4.92), and the highest RR to the study of Vignatelli et al. [7] with 1.53 (CI 95% 0.78–2.99). The reported RR was 1.00 (CI 95% 0.77–1.30; $P=0.15$) with a heterogeneity rate of 43.49% after combining these studies (Table 4). Also, the results after combining the studies [3, 4, 7] showed a reduction in the hospitalization rate of those with PD (RR 0.90; CI 95% 0.57, 1.41; $P=0.04$; I square 43.49%) due to not seeking care for fear of COVID-19 infection (Table 4 and Fig. 2). The results of Egger test showed the publication bias not occurred (B: 2.33, SE: 1.00, $P=0.44$).

The association of mortality and PD during the pandemic was examined, and the results of the meta-analysis showed the risk of mortality caused by COVID-19 in patients with Parkinson's disease was 0.96 (CI 95% 0.50–1.87; $P=0.49$) with the heterogeneity of 0% [3, 4, 7] (Table 4 and Fig. 2). The results of Egger test showed the publication bias not occurred (B 1.09, SE 0.77, $P=0.20$).

The results of the meta-analysis showed the risk of fever, cough, respiratory problems, diarrhea, a loss of sense of smell, and a decreased sense of taste caused by COVID-19 in patients with Parkinson's were equal to 0.92 (CI 95% 0.67–1.27; $P=0.75$), 1.04 (CI 95% 0.73–1.48; $P=0.25$), 0.63 (CI 95% 0.38–1.07; $P=0.76$), 1.01 (CI 95% 0.62–1.67; $P=0.44$), 0.79 (CI 95% 0.41–1.54; $P=0.21$), and 0.97 (CI 95% 0.50–1.87; $P=0.32$), respectively (Table 4).

Discussion

The prevalence of PD symptoms during the pandemic, among which sleep problems, rigidity, and tremor were more prevalent, was examined in this study. Home quarantine, travel ban, and decrease in physical activities during the pandemic were among the factors contributing to the increase in sleep disorders in patients with PD [29]. In addition, insomnia has been exacerbated in this population during the pandemic due to the fact that PD patients are primarily elderly with various underlying diseases and take numerous drugs [30]. Anxiety and depression caused by the pandemic are other factors affecting the increase in insomnia in patients with PD [29, 31]. Studies of Xia et al. [20] and Kitani-Morii et al. [8] found sleep disorders increased during the COVID-19 pandemic and were associated with depression and anxiety in patients with inadequate access to medical services.

Studies showed physical activities were associated with reducing stress levels, so reduced physical activities during this period became one of the factors increasing stress levels in people [6]. In Parkinson's patients, the amount of experienced stress was related to their physical symptoms, and the increase in anxiety and depression in this period was grounds for increasing their physical symptoms [6, 32–34]. Suzuki et al. [9] and Balci et al. [23] in their studies found physical disorders, such as rigidity and tremor, sleep disorders, depression, and anxiety increased because of COVID-19 conditions.

In this study, the association between the symptoms and outcomes of COVID-19 and PD was investigated in addition to their prevalence. The results of this meta-analysis showed there was no significant association between COVID-19 and the hospitalization rate of patients with PD and without PD. Parkinson's patients were less likely to visit hospitals and medical centers during the pandemic for Parkinson's-related care because of fear for COVID-19 infection, which may be the reason for decreased hospitalization rates of this population.

Also, the rate of mortality caused by COVID-19 did not show a significant association with Parkinson's disease. In PD patients, most of the variables, such as age and duration of COVID-19, seemed to be insignificantly different from

Table 4 Meta-analysis of RR of outcomes and symptoms of COVID-19 in patients with Parkinson's disease

Categories	Outcomes	No. of study	Sample size PD	Sample size non-PD		No. of covid-19				Pooled RR	Heterogeneity assessment	
				a	b	c	d	I2	p value		Test Q	
Outcomes of covid-19	Covid-19	4 (12,514)	2371	10,143	125	447	2246	9696	1.00 (0.77–1.30)	43.49%	0.15	5.31
	Admission to Hospital	3 (12,354)	2271	10,083	38	357	2233	9708	0.9 (0.57–1.41)	68.22%	0.04	6.30
	Mortality	3 (12,345)	2271	10,083	13	148	2253	9935	0.96 (0.50–1.87)	0.00	0.49	1.42
Symptoms of Covid-19	Fever	3 (3044)	1491	1553	89	320	1402	1233	0.92 (0.67–1.27)	0.00	0.75	0.56
	Cough	3 (3044)	1491	1553	80	246	1411	1307	1.04 (0.73–1.48)	28.83%	0.25	2.93
	Respiratory difficulties	3 (3044)	1491	1553	26	165	1465	1388	0.63 (0.38–1.07)	0.00	0.76	0.55
	Diarrhea	3 (3044)	1491	1553	36	68	1455	1485	1.01 (0.62–1.67)	0.00	0.44	1.34
	Smell reduction	2 (2748)	1481	1267	17	19	1464	1248	0.79 (0.41–1.54)	37.23%	0.21	1.61
	Taste reduction	2 (2748)	1481	1267	19	17	1462	1250	0.97 (0.50–1.87)	0.00	0.32	0.98
	Muscle/Joint	2 (2884)	1391	1493	38	97	1353	1396	1.06 (0.55–1.68)	0.00	0.67	0.18
Nausea/vomiting	2 (2884)	1391	1493	29	44	1362	1449	1.23 (0.70–2.14)	0.00	0.99	0.00	
Fatigue	2 (2884)	1391	1493	47	185	1344	1308	1.20 (0.77–1.88)	0.00	0.44	0.59	

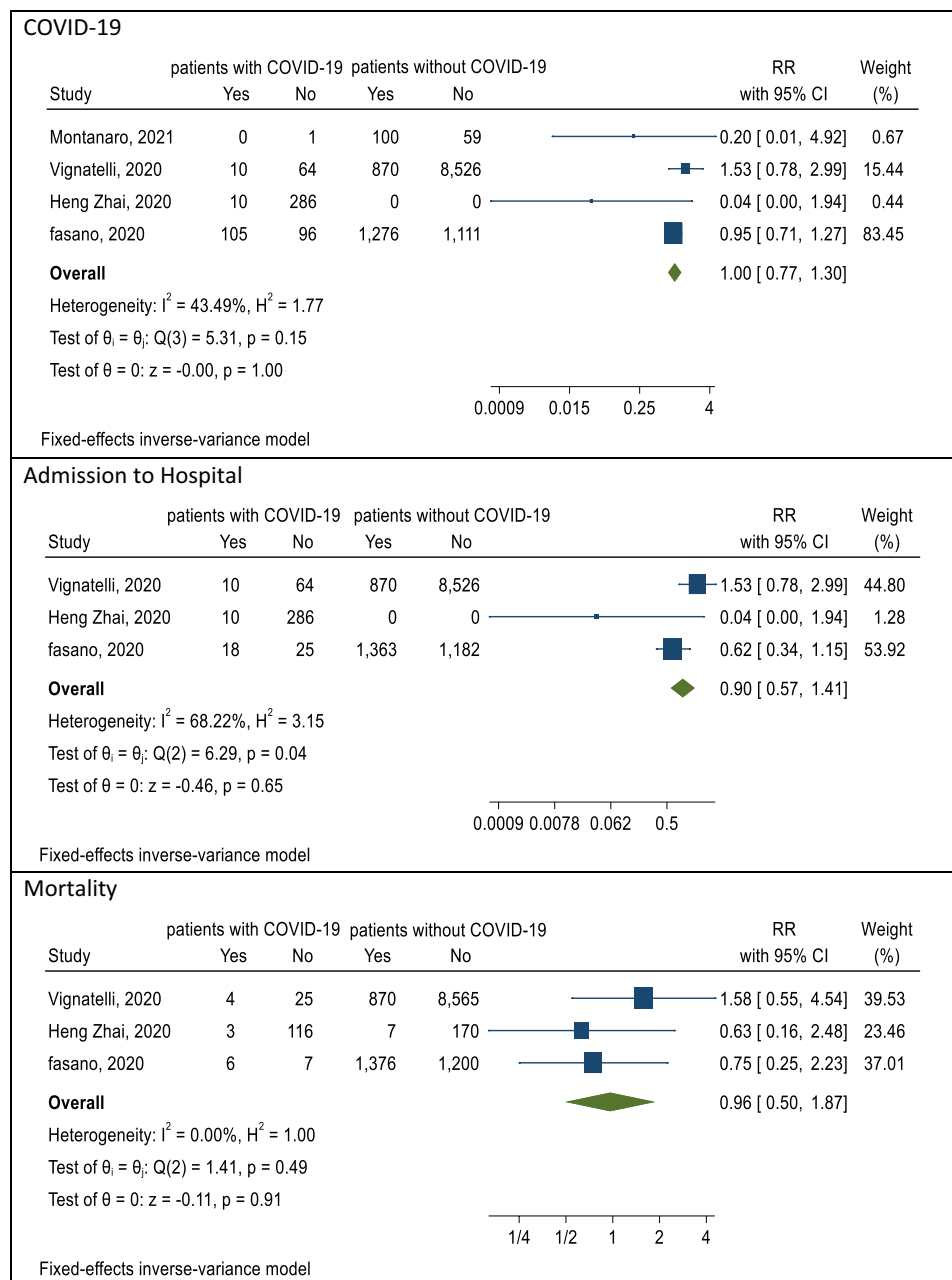
those of the general population [12, 35]. Zhai et al. [35] found no difference between patients with PD and healthy individuals in terms of COVID-19 infection and hospitalization. Their results are in line with the ones of this meta-analysis. Scherbaum et al. [11] found the incidence, hospitalization, and mortality caused by COVID-19 were associated with PD. A small number of studies also showed the duration of PD and the age of patients were not significantly related to the exacerbation of COVID-19 complications [12]. However, a number of other studies showed the duration of Parkinson's disease more than three years and older age were not factors affecting the exacerbation of COVID-19 symptoms and increase in its death rate [3]. Although there are conflicting results in the world, the present study rejects this association because of the higher sample size of our meta-analysis. It is not yet fully understood whether Parkinson's-related symptoms have an effect on the exacerbation of COVID-19 symptoms or the increase in the mortality rate. Therefore, cohort studies with larger sample sizes from many different countries are needed.

The meta-analysis results showed the symptom of fatigue due to COVID-19 was 1.20 times greater in patients with PD than ones without PD, which might be due to the fact that people with PD have been often elderly and have had a longer illness duration [13]. The results of studies conducted by Antonini et al. [13] and Zhai et al. [4] are consistent with those of this meta-analysis. So, fatigue was found to be one of the predominant COVID-19 symptoms in Parkinson's patients.

Parkinson's patients were highly affected by mental disorders during the COVID-19 pandemic. There was a high prevalence of anxiety and depression in these patients who have been more prone to these mental disorders due to old age, underlying diseases, taking Parkinson's drugs, quarantine conditions, and reduced contacts with family members [36, 37]. The results of this meta-analysis and those of Montanaro et al. [24] showed anxiety and distress increased due to the unavailability of care in medical centers and the discontinuation of drug treatments and sports activities. The results of another study performed by Santos-García et al. [5] showed a high prevalence of depression and anxiety, which were in line with the findings of this meta-analysis.

In this meta-analysis, the occurrence of selection bias in the sections of search strategy, screening, and data extraction has occurred less. Because in these sections, two researchers independently to perform these activities. But publication bias has occurred in this meta-analysis especially in the combination of cross-sectional studies to determine pooled prevalence. The occurrence of publication bias is expected in cross-sectional studies, but this bias is occurrence less in other effect sizes like risk ratio. Publication and selection biases have occurred in the present meta-analysis, but these biases have not affected the pooled effect sizes. The reason

Fig. 2 The pooled RR of association outcomes of covid-19 in Parkinson's patients



is that the number of sufficient studies and the sample size of these studies are also very high, so it can be said that the possibility of this bias and especially the occurrence of small study effect in connection with these biases in this meta-analysis is low.

Strengths

This study was the first meta-analysis in the world about Parkinson's disease during the COVID-19 pandemic. In this meta-analysis, most of the reviewed studies had appropriate populations. The examined studies were conducted in different parts of the world for estimating the prevalence

of COVID-19 infection. In this study, the heterogeneity was low, and in some cases, the studies were completely homogeneous.

Limitations

The number of studies in some subgroups, such as symptoms of Parkinson's disease and COVID-19, was low, making it difficult to obtain more accurate results. Also, in the report of the selected articles, confounding variables, such as age, sex, and the duration of Parkinson's disease, were discussed less, which prevented the use of many statistical methods, such as meta-regression and subgroup analysis.

Conclusion

The results of this study showed the rates of mortality and hospitalization were not significantly different between Parkinson's patients and the general population. However, the PD symptoms and mental disorders in patients with Parkinson's significantly increased during the COVID-19 pandemic. Therefore, some steps need to be taken to manage them. This study recommends the launch of applications and online services facilitating doctor visits, and monitoring patients' medications, as well as private and group counseling services, and exercise classes tailored to individual needs. Such suggestions could improve the care for Parkinson's patients during both pandemic periods, such as the COVID-19 pandemic and non-pandemic periods.

Author contributions YM: designed the study, determined the study concept, and was involved in data analysis and doing statistics; YM, MA, GM, PM, and MA: prepared the manuscript; YM and SR: edited the manuscript; SR: prepared the figures. All the authors read and approved the final manuscript.

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Data availability Data for analyses are available by the corresponding author on request.

Declarations

Conflicts of interest The authors declare that they have no conflict of interest. The authors have no relevant financial or non-financial interests to disclose.

Ethical approval This work was recorded in the Research Committee of Kurdistan University of Medical Sciences.

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