






REVIEW

The impact of Parkinson's disease on manifestations and outcomes of Covid-19 patients: A systematic review and meta-analysis

Amr Ehab El-Qushayri¹  | Sherief Ghozy²  | Abdullah Reda³  |
Ahmed Mostafa Ahmed Kamel⁴  | Alzhraa Salah Abbas¹  | Adam A. Dmytriw⁵ 

¹Faculty of Medicine, Minia University, Minia, Egypt

²Faculty of Medicine, Mansoura University, Mansoura, Egypt

³Faculty of Medicine, Al-Azhar University, Cairo, Egypt

⁴Faculty of Pharmacy, Minia University, Minia, Egypt

⁵Neuroradiology and Neurointervention Service, Brigham and Women's Hospital, Boston, Massachusetts, USA

Correspondence

Sherief Ghozy, MD Faculty of Medicine, Mansoura University, Mansoura, Egypt.
Email: sherief_ghozy@yahoo.com

Summary

Parkinson's disease (PD) patients who contracted Coronavirus disease 2019 (Covid-19) had a decline in motor functions; nevertheless, there is limited evidence on whether PD patients have a higher risk for contracting Covid-19 or have worse outcomes. This is the first systematic review and meta-analysis to review the impact of PD on the prognosis of Covid-19 patients. We performed a systematic search through seven electronic databases under the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) guidelines. The R software version 4.0.2 was used to calculate pooled sample sizes and their associated confidence intervals (95%CI). Finally, we included 13 papers in this study. The pooled prevalence rate of Covid-19 was 2.12% (95%CI: 0.75–5.98). Fever, cough, fatigue and anorexia were the most common symptoms with a rate of 72.72% (95% CI: 57.3 - 92.29), 66.99% (95% CI: 49.08–91.42), 61.58% (95% CI: 46.69–81.21) and 52.55% (95% CI: 35.09–78.68), respectively. The pooled rates were 39.89% (95% CI: 27.09–58.73) for hospitalisation, 4.7% (95% CI: 1.56–14.16) for ICU admission and 25.1% (95%CI: 16.37–38.49) for mortality. On further comparison of hospitalisation and mortality rates among Covid-19 patients with and without PD, there were no significant differences. In conclusion, the prevalence and prognosis of Covid-19 patients seem comparable in patients with PD and those without it. The increased hospitalisation and mortality may be attributed to old age and co-morbidities.

KEYWORDS

Covid-19, mortality, length of stay, Parkinson's disease, SARS-CoV-2, MLS

Abbreviations: CI, 95% confidence interval; Covid-19, Coronavirus disease 2019; DDC, Dopa Decarboxylase; HEV67, Haemagglutinating encephalomyelitis virus 67; HCoV-OC43, Human coronavirus OC43; ICU, Intensive care unit; MD, Mean difference; MERS-COV, Middle East respiratory syndrome-related coronavirus; NIH, National Institutes of Health; OR, Odds ratio; PD, Parkinson's disease; PRISMA, Preferred Reporting Items for Systematic Review and Meta-analyses statement; SARS-CoV, Severe acute respiratory syndrome coronavirus.

Amr Ehab El-Qushayri and Sherief Ghozy equally contributed to the work.

1 | INTRODUCTION

Coronavirus disease 2019 (Covid-19) is one of the beta coronaviruses (β CoVs), which has a well-documented propensity of neuro-invasion, including severe acute respiratory syndrome coronavirus (SARS-CoV),¹ Middle East respiratory syndrome-related coronavirus (MERS-COV),² human coronavirus 229E,³ human coronavirus OC43 (HCoV-OC43).^{4,5} In some earlier studies, SARS-CoV particles were found in the brain of SARS patients,⁶⁻⁸ which was also experimentally produced through intranasal injection of SARS-CoV⁵ or MERS-COV,² passing through the olfactory nerves.⁵ Although the exact route of SARS-CoV or MERS-COV reaching the brain is unknown, non-neurological routes are not probable since no viral particles were detected in non-neuronal cells of infected brain regions.⁶⁻⁸ Viral invasion of the terminal nerves followed by trans-synaptic transfer to the central nervous system is well-documented for haemagglutinating encephalomyelitis virus 67 (HEV67)⁹⁻¹² and avian bronchitis virus,^{13,14} which are members of the corona family.^{5,15} Noteworthy, the HEV67 shares over 91% homology with HCoV-OC43.^{16,17} Taken together, SARS-CoV-2 mostly has the same neuroinvasive propensity documented in other CoVs.

In general, Covid-19 neurological manifestations were evident in many patients since the very beginning of this pandemic, ranging from mild headache, nausea, vomiting, and up to generalised seizure and altered consciousness.¹⁸⁻²³ Less frequent, yet important, manifestations include seizures, strokes of multiple etiologies, and Guillain-Barre syndrome.^{20-22,24,25} The possible neuroinvasive mechanism may help explain the respiratory failure in COVID-19 patients; the median time from the first symptom to respiratory deterioration (5-8 days) is enough for viral particles to infiltrate the brain and disrupt medullary neurons.^{5,10}

The Covid-19-related case fatality is higher among vulnerable groups such as older age groups and those with co-morbidities.²⁶⁻²⁸ Individuals with Parkinson's disease (PD) show multiple patterns of vulnerability, being advanced in age, mostly have age-related chronic conditions, and related polypharmacy burden.²⁹ The current literature shows that PD patients who contracted Covid-19 had a decline in motor functions and stress-induced psychiatric problems (e.g., anxiety and mood changes)³⁰⁻³⁴; however, whether PD patients have a higher risk for contracting Covid-19 or have worse outcomes is still debatable.³⁵⁻³⁹ This is the first systematic review and meta-analysis to review the impact of PD on the prognosis of Covid-19 patients.

2 | METHODS

2.1 | Search strategy and study selection

We performed a systemic search through the electronic databases from the commencement and till 12th March 2021 under the recommendations of the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA) guidelines.⁴⁰ The

search went through seven databases including System for Information on Grey Literature in Europe, Google Scholar, Web of Science, PubMed, Scopus, The New York Academy of Medicine, and Virtual Health Library, under the search term ([Parkinson] AND [Covid-19 OR COVID 19 OR novel coronavirus]). To ensure not missing any paper, a manual search was conducted after the systemic one using various methods, all relevant papers in PubMed and Google Scholar were checked, we searched into the references of papers included from the systemic search, and we also used relevant Mesh terms and keywords to check for missing papers.^{41,42} Duplication between database results was removed using EndNote X8 software. Four authors independently reviewed search results from the title and the abstract considering our inclusion and exclusion criteria in a preformed excel sheet, all original papers reporting patients with PD and Covid-19 were included. We made no restrictions for the language, country, study design, age, sex, or ethnicity of patients. Reviews, animal studies, papers with overlapping data, incomplete data or not reliable for extraction, case reports, case series less than five patients and papers including the same patients in a previously included paper were all excluded. We performed another phase of full-text screening to get the final included studies and identify papers eligible for the analysis. A study was included when all the reviewers agreed to include it; whenever contradiction was found, a discussion was held to resolve the conflict using a senior reviewer if needed.

2.2 | Data extraction

We developed a data extraction form using Microsoft Excel-based on the type of data in our included papers. The extraction sheet consisted of three domains. The first one included study ID, study design, sample size, age, male prevalence, and method of Covid-19 diagnosis. The second part included our outcomes of interest (prevalence of Covid-19 in PD, the prevalence of mortality, hospitalisation, intensive care unit (ICU) admission, length of hospital stay, manifestations, and comorbidities in PD patients with Covid-19). The third part included the quality rating of the included studies. Three authors independently extracted the data from included papers using the formed excel sheet. Another fourth author was added to recheck the extracted data. A discussion was held to solve any disputations. Upon reaching the final extracted data, we made another phase of checking to ensure the validity of the data.

2.3 | Quality assessment

We used the National Institutes of Health (NIH) tool for the methodological quality assessment of included studies.⁴³ Three independent reviewers evaluated each study using a pre-formed 14 question assessment sheet for the cohort and cross-sectional studies, 12 questions for the case-control studies and nine question assessment sheet for the case series studies. The final decision

was based upon a discussion between the reviewers. Depending on the answers to the questions a score was given for each study. Regarding cohort and cross-sectional studies, an 11 to 14 score was considered to have a good quality, a 6 to 10 score was considered to have a fair quality, and below 6 scores were considered to have a low quality. Meanwhile, in case series studies good quality was adopted when the score was 7–9 points, fair quality and poor quality were considered if the score was 3–6 and 0–3 points, in order. For case-control studies, the scores for good, fair and poor quality was reported when the points fall in the range of 10–12, 7–9 and 0–6, respectively.

2.4 | Statistical analysis

We used R software version 4.0.2 to perform the meta-analysis whenever available. Event rate and the corresponding 95% confidence interval (CI) were used to analyse categorical data. Meanwhile, the pooled mean difference (MD) and the corresponding 95% CI was

used to analyse continuous data. The odds ratio (OR) with 95% CI was used to analyse categorical outcomes when outcomes of two compared groups were presented in more than one study. A significant difference was considered when the p value was <0.05 . Heterogeneity between studies was evaluated using the I-squared and Q-test, significant heterogeneity was considered when the p -value exceeds 0.1.⁴⁴ We used a fixed-effect model under Mantel-Haenszel methods when there was no evidence for heterogeneity; otherwise, a random effect model was used to pool the data.⁴⁵ We performed publication bias according to the method of Egger and colleagues if the outcomes were presented in more than 10 studies.^{46,47}

3 | RESULTS

3.1 | Study characteristics

We exported 910 records into endnote after performing the systematic search, of those 89 records were considered as duplicates.

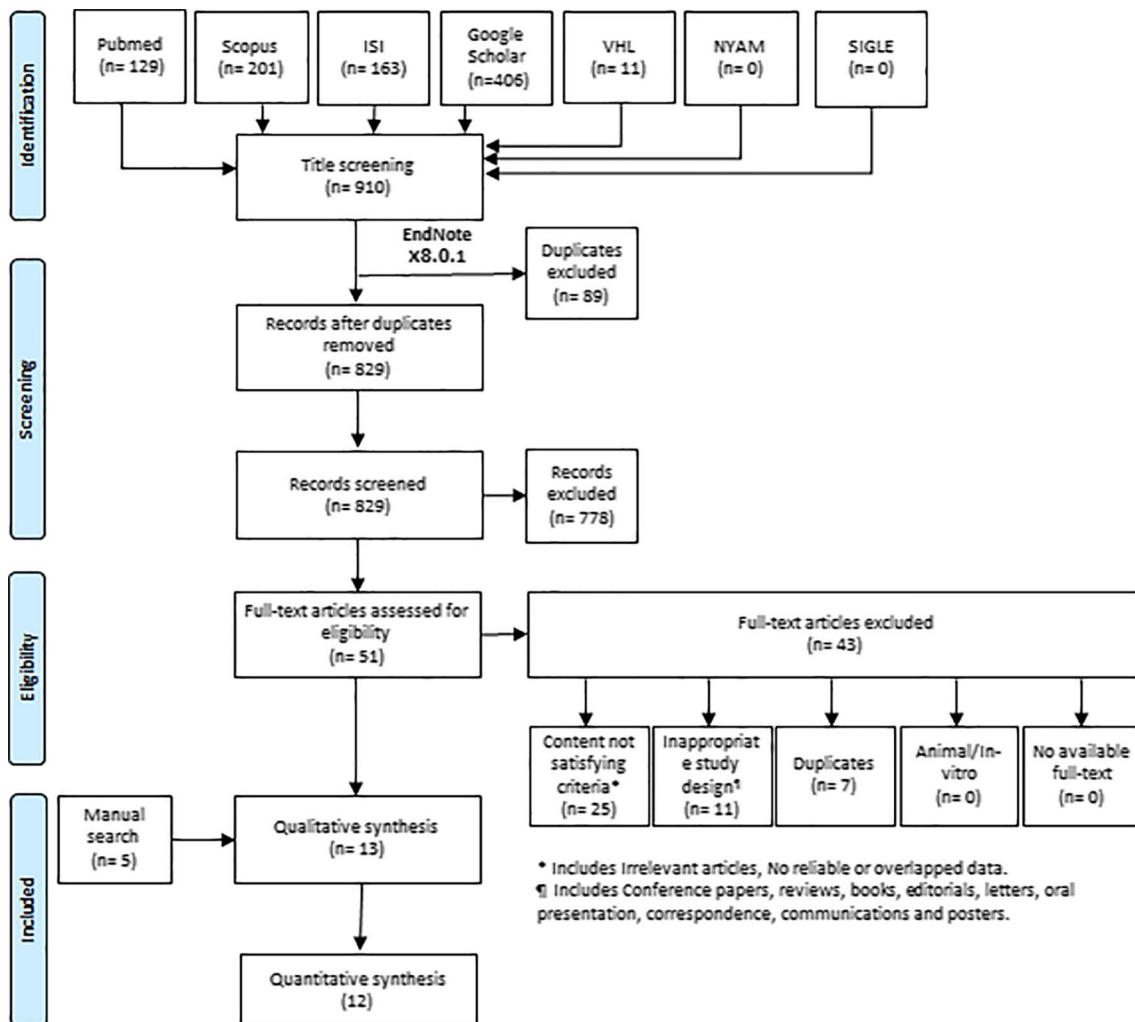


FIGURE 1 Preferred reporting items for systematic review and meta-analyses statement flow diagram of qualitative study selection process

We scanned 829 records for a title and abstract screening followed by a full-text screening of 51 eligible full texts. Finally, we included eight papers from the systematic search in addition to five papers obtained by the manual search making a total of 13 papers⁴⁸⁻⁶⁰ (Figure 1). One paper was excluded due to the inclusion of duplicate patients,⁶¹ and another one reported combined outcomes of PD patients combined with parkinsonism patients.⁶²

Regarding study design, there were five retrospective cohorts, three case-controls, two cross-sectionals, two case series, and one prospective cohort (Table 1). We included 8649 PD patients and 88710 control subjects. Covid-19 diagnosis was reported in only six papers. One paper was categorised as poor quality while the

rest of the papers were categorised as fair quality (Table S1, S2 and S3).

3.2 | Prevalence of Covid19 among patients with PD

Four studies reported the prevalence of Covid-19 in a total of 6878 PD patients. The pooled prevalence rate of Covid-19 was 2.12% (95% CI: 0.75-5.98); nevertheless, heterogeneity was significant among the pooled studies ($I^2 = 95\%$; $p < 0.001$) with prevalence rates ranging from 0.94% to 8.51% (Figure 2).

TABLE 1 Characteristics of the included studies

Study ID	Study design	Compared group	Sample size	Age (mean [SD])	Male prevalence	COVID-19 diagnosis	Quality assessment
Kobylecki/2020/UK	Prospective cohort	P/C	13/27	78.3 (9.5)/79.8 (8.5)	8/15	NR	Poor
Zhang/2021/USA	Retrospective cohort	P/C	694/78,355	79/50 ^a	417/35024	NR	Fair
Zahi/2021/China	Retrospective cohort	P/C	10/286	70/66 ^a	3/147	Guidelines outlined in the diagnosis and treatment protocol for novel coronavirus (2019-nCoV) disease (trial version 7) compiled by the Chinese National Health Commission.	Fair
Vignatelli/2021/Italy	Retrospective cohort	P/C	696/8590	75/76	409/5000	(ICD-9-CM)	Fair
Garcia/2020/Spain	Cross-sectional	P	568	63.5 (12.5)	267	NR	Fair
Sainz-Amo/2020/Spain	Case-control	P	211	74.1 (9.5)	124	Centres for Disease Control and Prevention (2020) Coronavirus disease 2019 (COVID-19).	Fair
Fasano/2020/Italy	Retrospective cohort	P	117	71.4 (10.8)	74	Real-time PCR assay or when symptoms were compatible with COVID-19 and the patient has been in contact with a PCR-confirmed case	Fair
Del Prete/2020/Italy	Case-control	P	740	NR	NR	NR	Fair
Cilia/2020/Italy	Case-control	P	141	NR	NR	World Health Organization criteria on March 20, 2020	Fair
Buccafusca/2021/Italy	Retrospective cohort	P	12	NR	6	Rhinopharyngeal swab	Fair
Brown/2020/USA	Cross-sectional	P/C	5429/1452	68/60	2800/313	NR	Fair
Artusi/2020/Italy	Case series	P	8	63-80 ^b	5	NR	Fair
Antonini/2020/UK	Case series	P	10	78.3	6	NR	Fair

Abbreviations: P, Parkinson; C, control; NR, not reported.

^amedian.

^brange.

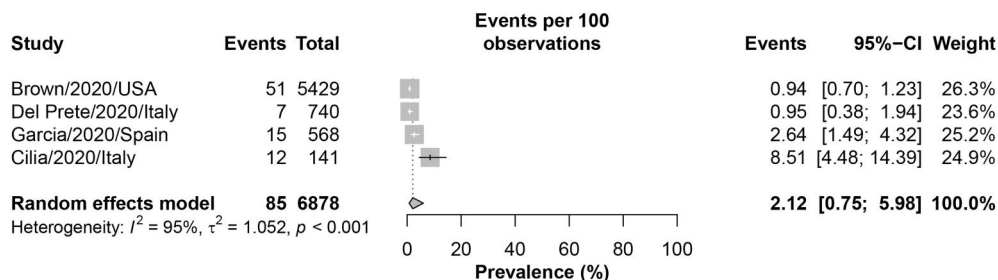


FIGURE 2 Prevalence of COVID-19 in Parkinson's disease patients (represented by the pooled event rate and the corresponding 95% CI)

To investigate the presence of possible co-founders to the investigated prevalence rates, the rates of different comorbidities among PD patients were compared in SARS-CoV-2 positive and SARS-CoV-2 negative patients. The results showed significantly higher rates of diabetes mellitus (OR: 2.12, 95% CI: 1.06–4.23; $p = 0.033$) and immunocompromise (OR: 2.06, 95% CI: 1.08–3.94; $p = 0.029$), with no heterogeneity in both analyses ($I^2 = 0\%$). However, no significant differences were noticed in the rates of hypertension, obesity, dementia, chronic pulmonary disease, malignancy, or cardiomyopathy (Figure 3).

3.3 | Covid-19 manifestations among patients with PD

Fever, cough, fatigue and anorexia were found to be the most common symptoms with a rate of 72.72% (95% CI: 57.3–92.29), 66.99% (95% CI: 49.08–91.42), 61.58% (95% CI: 46.69–81.21) and 52.55% (95% CI: 35.09–78.68), respectively. Heterogeneity was only found among cough ($I^2 = 79\%$; $p < 0.001$), fever ($I^2 = 73\%$; $p < 0.001$), and diarrhoea ($I^2 = 64\%$; $p < 0.064$) analyses (Figure 4a). On the further comparison of PD patients with Covid-19 to the Covid-19 patients without PD, there was no significant difference in cough (OR: 0.93, 95% CI: 0.01–98.09; $p = 0.977$) or fever (OR: 0.54, 95% CI: 0.22–1.32; $p = 0.177$) rates. There was a significant heterogeneity in the cough comparison ($I^2 = 86\%$; $p = 0.008$), while the fever analysis did not show the same ($I^2 = 0\%$; $p = 0.819$) (Figure 4b).

3.4 | Patient outcomes

Hospitalisation was reported in eight studies (263 patients) with a pooled rate of 39.89% (95% CI: 27.09–58.73); nevertheless, there was a significant heterogeneity among the pooled studies ($I^2 = 81\%$; $p < 0.001$) (Figure 5a). Moreover, the length of hospital stay was comparable in PD patients with Covid-19 and Covid-19 patients without PD (MD: 2.69, 95%CI: –6.99–12.37; $p = 0.586$), with no heterogeneity observed ($I^2 = 0\%$; $p = 0.396$) (Figure 5b). In the same context, the pooled rate of ICU admission was 4.7% (95% CI: 1.56–14.16) with no present heterogeneity ($I^2 = 0\%$; $p = 0.655$) (Figure 5a).

The mortality rates among PD patients with Covid-19 were reported in 11 studies with a total of 928 patients. The pooled

mortality rate was found to be 25.1% (95% CI: 16.37–38.49), with significant heterogeneity among the included studies ($I^2 = 77\%$; $p < 0.001$) (Figure 5a). The Egger's regression test showed no risk bias in the mortality analysis ($p = 0.972$). On further comparison of mortality rates among Covid-19 patients with PD and those with Covid-19 without PD, there were no significant differences among the two groups (OR: 1.42, 95% CI: 0.26; 7.70; $p = 0.687$). However, there was significant heterogeneity among the included studies ($I^2 = 82\%$; $p = 0.003$) (Figure 5c).

4 | DISCUSSION

In this meta-analysis, we investigated whether PD has a significant impact on the severity and prognosis of Covid-19 infections. Our pooled analysis of the relevant studies showed that the hospitalisation rate for PD patients with Covid-19 infections was 39.89%, while the total mortality rate was 25.1%. Our estimated mortality rate is much higher than the previously reported rates for PD patients from the general population.⁶³ Akbar et al.⁶⁴ conducted a long-term follow-up investigation in the United States to find that among hospitalised patients, the mortality rate for PD was 17%, which was also smaller than the rate for the non-PD included population (22%) over 32 years. A previous systematic review by Macleod et al.⁶⁵ reported that among 88 studies, the estimated mortality ratio ranged between 0.9 and 3.8%, with this ratio reportedly increasing over time. On the other hand, a previous meta-analysis by Xu et al.⁶⁶ reported that PD increased the risk of all-cause mortality for patients suffering from the disease by 2.2 fold higher than the general population. Moreover, another meta-analysis reported that infections were the commonest cause for hospitalisation for PD patients.⁶⁷

For Covid-19 infections to occur, SARS-CoV-2 must attach to its receptors within human cells, namely angiotensin-converting enzyme 2 (ACE2) receptors, which can be extensively found within the epithelial cells of the respiratory tract. Moreover, the same receptors were also observed within dopaminergic neuronal cells,⁶⁸ which might explain the potential association between Covid-19 infections and neurological disorders. Recent studies have also described the potential role that angiotensin might have in PD by induction of neurodegeneration through some pro-oxidative and pro-inflammatory actions.⁶⁹ A previous investigation by Nataf et al.⁷⁰ also reported that ACE2 and Dopa Decarboxylase (DDC) probably

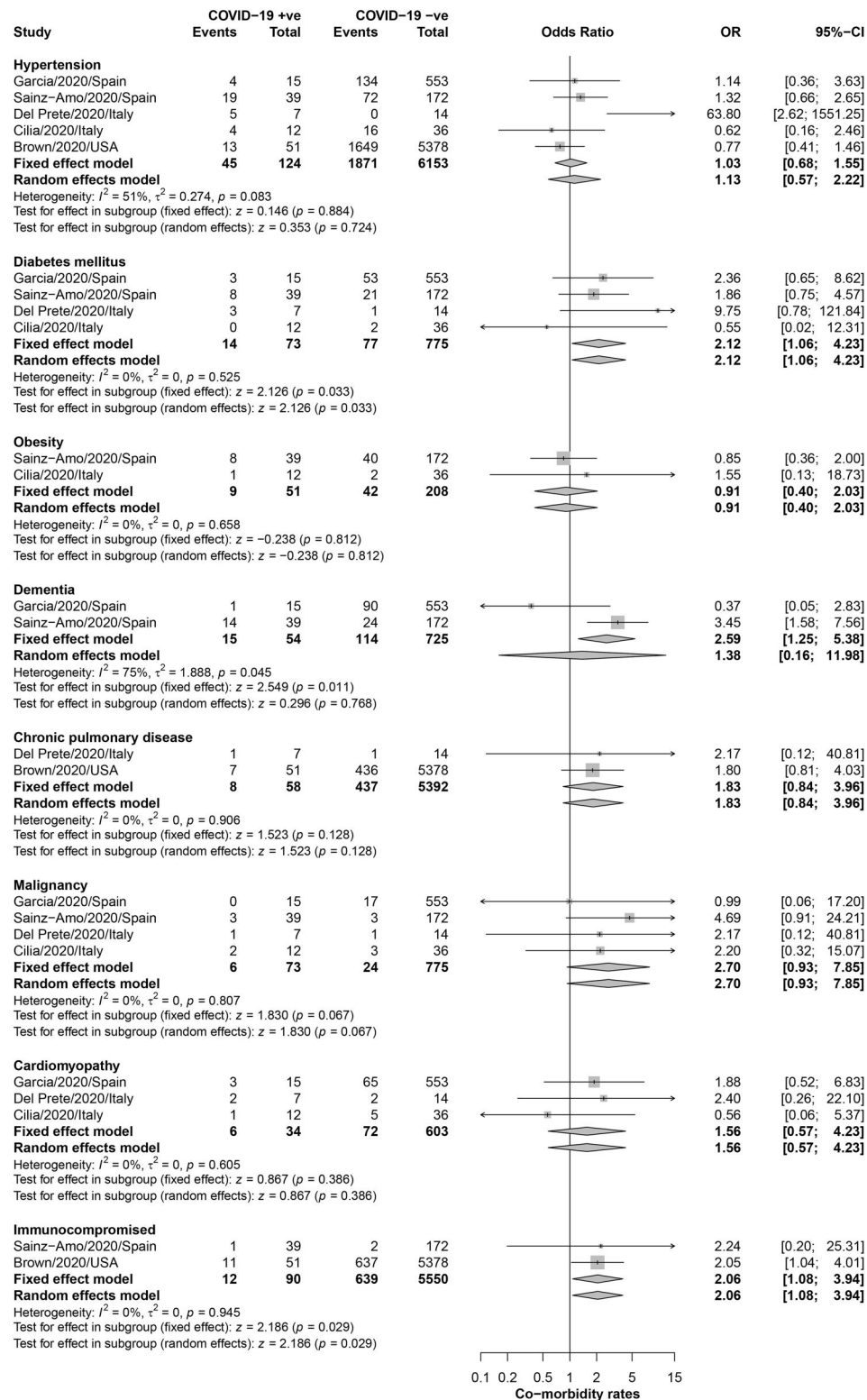
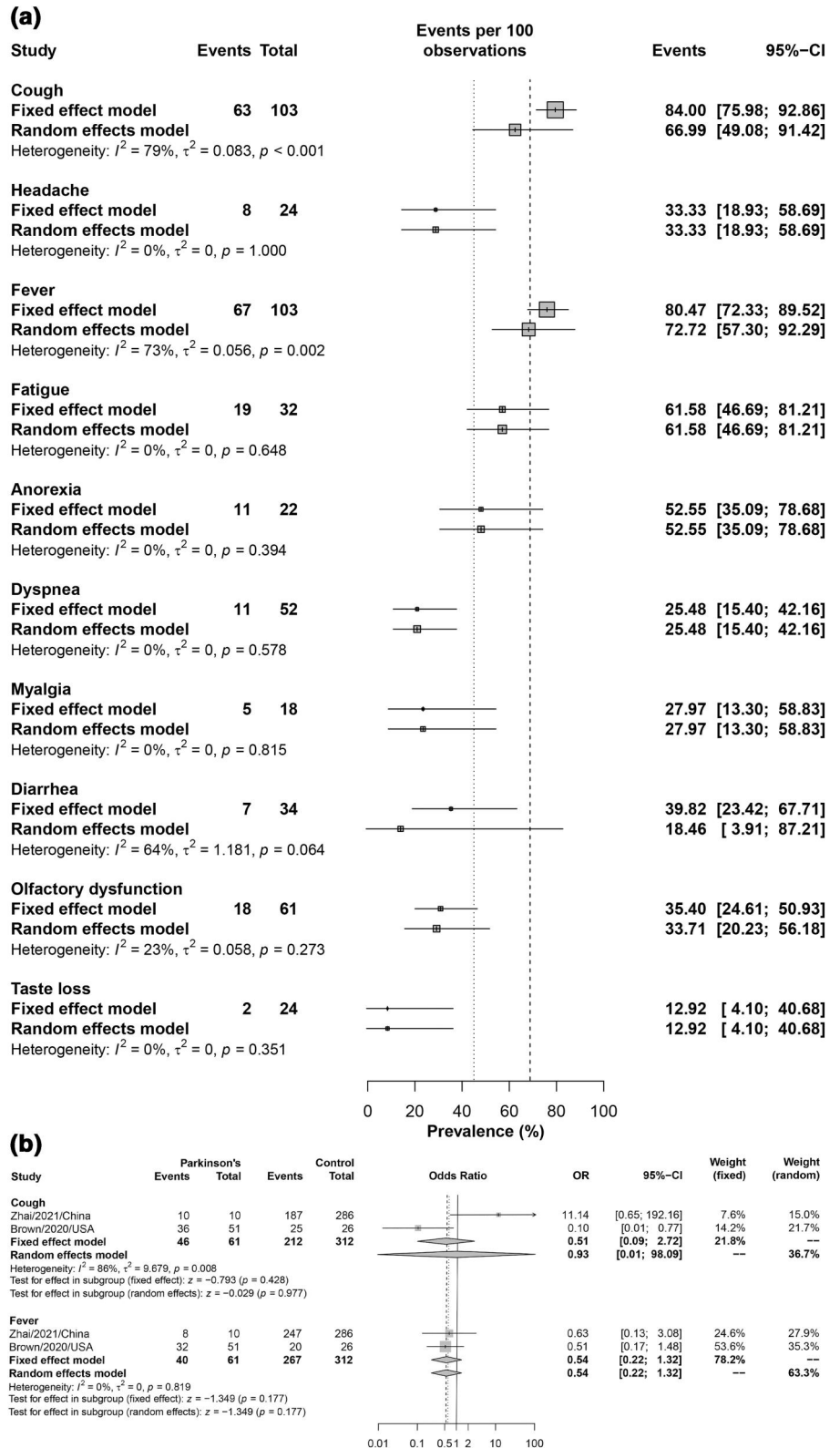


FIGURE 3 Comparison of comorbidities in Parkinson's disease (PD) patients with COVID-19 and PD patients without Covid-19 (represented by the pooled odds ratio and the corresponding 95% CI)

co-regulate within non-neuronal cells, knowing that DDC and ACE2 have been found to have a statistically significant genetic co-expression. The role of coronavirus infections in inducing neurodegeneration in PD might also be another explanation for a potential

association between Covid-19 and PD as it has been previously reported that antibodies against previous coronaviruses were observed within the cerebrospinal fluid of the infected patients with PD more frequently than other neurological diseases.⁷¹ However, due to the

FIGURE 4 Manifestations of COVID-19 in Parkinson's disease (PD) patients. (a): Prevalence of manifestations (represented by the pooled event rate and the corresponding 95% confidence interval [CI]); (b): Comparison of the manifestations in PD patients with COVID-19 to COVID-19 without PD (represented by the pooled OR and the corresponding 95% CI)



lack of solid specific evidence about these theories, we believe that the severity and mortality of Covid-19 patients are attributable to other causes than PD, as our findings indicated.

Other potential and reasonable explanations for the severity of PD cases with Covid-19 infections might include the old age of these

patients, who are usually over 60 years old, and the potential presence of age-related co-morbidities, which have been previously reported to significantly affect the prognosis of Covid-19 infections.^{29,72} Therefore, we suggest that these factors as reasonable justifications of the estimated relatively high hospitalisation and

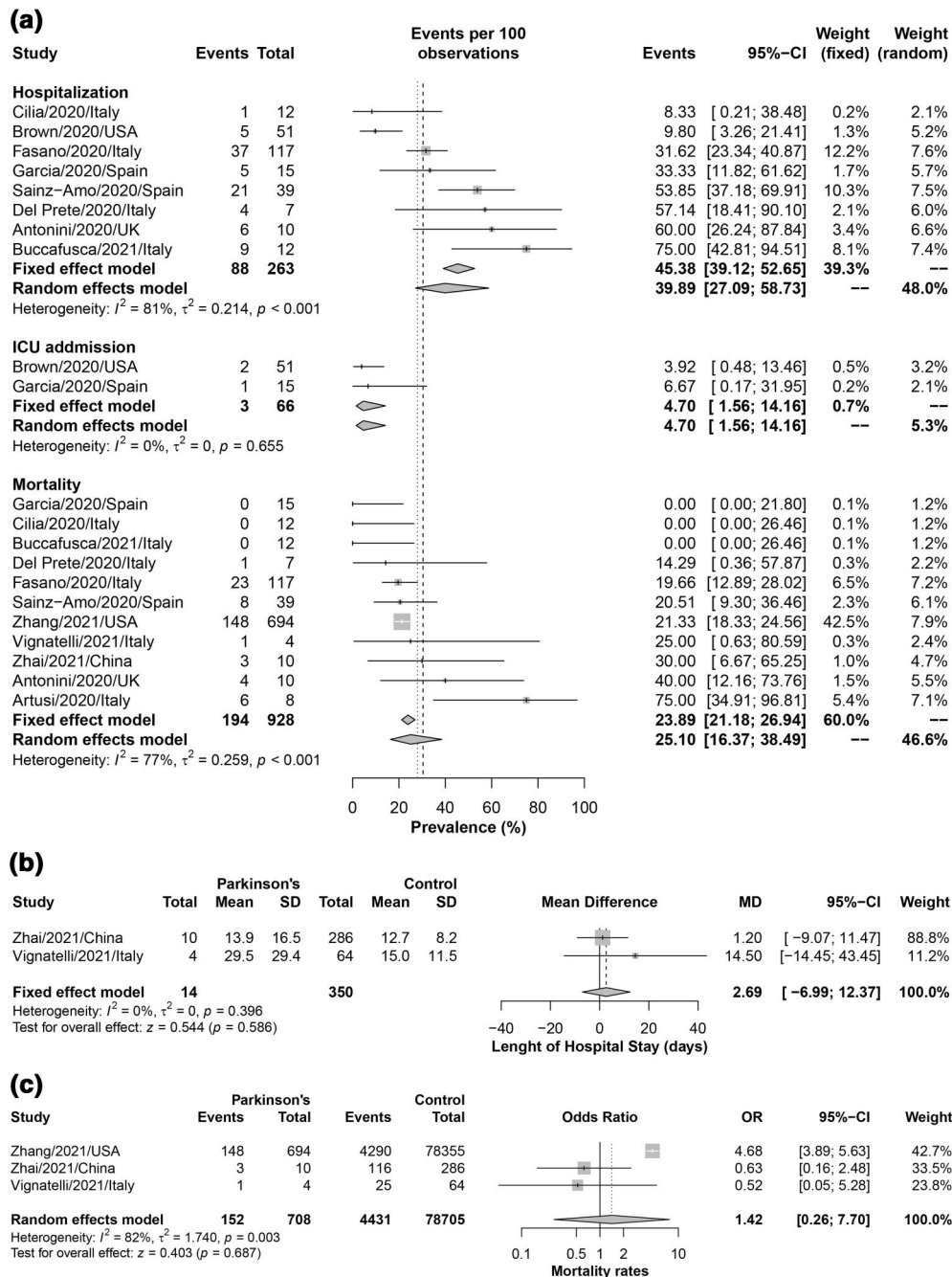


FIGURE 5 Outcomes of COVID-19 in Parkinson's disease (PD) patients. (a): Prevalence of patients' outcomes (represented by the pooled event rate and the corresponding 95% confidence interval [CI]); (b): Comparison of COVID-19 patients with PD to COVID-19 patients without PD in terms of length of hospital stay (represented by the pooled mean difference and the corresponding 95% CI); (c): Difference between COVID-19 patients with PD and COVID-19 patients without PD in terms of mortality (represented by the pooled OR and the corresponding 95% CI)

mortality rates in our cohort. Although many studies have reported that old age is a significant risk factor for Covid-19 infections and severity among PD patients,^{35,59,73-75} Fasano et al.³⁶ contraindicated this by showing that Covid-19 infections were more frequent with younger PD patients in a larger population-based investigation.

Being diabetic and immunocompromised can also significantly increase the risk of catching Covid-19 infections in PD patients. Many infections are common among patients with these disorders

which might be attributable to the potential breakdown in the immunological response in these patients,^{76,77} which might facilitate and increase the severity of Covid-19. Diabetes was previously marked as the second commonest co-morbidity among patients with Covid-19 infections. In the same context, hypertension and cardiovascular diseases were marked as the first and third most prevalent comorbidities,⁷² however, none of these two had a significant association with the infection in our population.

Our findings might be limited by some factors. For instance, adjustment for age and other baseline demographics were not approached in this study. As previously discussed with age, Willis et al.⁷⁸ also reported the significance of race and sex in predicting the survival of PD patients. Moreover, when investigating the association between PD and Covid-19 and the effect of any underlying comorbidity, other factors as the history of drug administration should also be studied for proper adjustment and validation. The period and place where each study was conducted should also be considered when estimating the prevalence and severity of the disease due to the difference in the Covid-19 timeline, which might be a major contributor to the risk of catching the infection and developing a severe disease for patients within one burdened healthcare system over another. Accordingly, further investigations from different healthcare systems and with better adjustment of the study parameters are further encouraged for validation. Finally, although some included studies reported that the prevalence of Covid-19 and mortality rates in their PD population was higher than the corresponding rates for the general population,^{35,59,73-75} we could not conduct a proper comparison between our estimated rates and the currently reported Covid-19 statistics due to the absence of the global representativeness of the data from the included studies, which makes it hard to compare.

5 | CONCLUSION

PD patients with Covid-19 infections have relatively high mortality and hospital admission rates. However, the impact of PD on these outcomes is not statistically significant. Being diabetic and immunocompromised, among other co-morbidities, were significant predictors for catching Covid-19 infections in our PD population. Further worldwide studies are encouraged for further validation of the current evidence.

ACKNOWLEDGMENT

None.

CONFLICT OF INTEREST

None.

AUTHOR CONTRIBUTIONS

Amr Ehab El-Qushayri and Sherief Ghozy were responsible for the idea and the study design. All authors extracted the data. Sherief Ghozy performed the analysis. All authors shared in the manuscript writing, formatting and approval of final version.

DATA AVAILABILITY STATEMENT

Data can be requested from the corresponding author upon reasonable request.

ORCID

Amr Ehab El-Qushayri  <https://orcid.org/0000-0002-0967-797X>

Sherief Ghozy  <https://orcid.org/0000-0001-5629-3023>

Abdullah Reda  <https://orcid.org/0000-0002-2180-0029>

Ahmed Mostafa Ahmed Kamel  <https://orcid.org/0000-0003-3494-9188>

Alzhraa Salah Abbas  <https://orcid.org/0000-0003-3975-1496>

Adam A. Dmytriv  <https://orcid.org/0000-0003-0131-5699>

REFERENCES

- Glass WG, Subbarao K, Murphy B, Murphy PM. Mechanisms of host defense following severe acute respiratory syndrome-coronavirus (SARS-CoV) pulmonary infection of mice. *J Immunol.* 2004;173:4030-4039. <https://doi.org/10.4049/jimmunol.173.6.4030>
- Li K, Wohlford-Lenane C, Perlman S, et al. Middle East respiratory syndrome coronavirus causes multiple organ damage and lethal disease in mice transgenic for human dipeptidyl peptidase 4. *J Infect Dis.* 2016;213:712-722. <https://doi.org/10.1093/infdis/jiv499>
- Talbot PJ, Ekandé S, Cashman NR, Mounir S, Stewart JN. Neurotropism of human coronavirus 229E. *Adv Exp Med Biol.* 1993;342:339-346. https://doi.org/10.1007/978-1-4615-2996-5_52
- Dubé M, Le Coupance A, Wong AHM, Rini JM, Desforges M, Talbot PJ. Axonal transport enables neuron-to-neuron propagation of human coronavirus OC43. *J Virol.* 2018;92. <https://doi.org/10.1128/jvi.00404-18>
- Li Y-C, Bai W-Z, Hashikawa T. The neuroinvasive potential of SARS-CoV2 may play a role in the respiratory failure of COVID-19 patients. *J Med Virol.* 2020;92:552-555. <https://doi.org/10.1002/jmv.25728>
- Ding Y, He L, Zhang Q, et al. Organ distribution of severe acute respiratory syndrome (SARS) associated coronavirus (SARS-CoV) in SARS patients: implications for pathogenesis and virus transmission pathways. *J Pathol.* 2004;203:622-630. <https://doi.org/10.1002/path.1560>
- Gu J, Gong E, Zhang B, et al. Multiple organ infection and the pathogenesis of SARS. *J Exp Med.* 2005;202:415-424. <https://doi.org/10.1084/jem.20050828>
- Xu J, Zhong S, Liu J, et al. Detection of severe acute respiratory syndrome coronavirus in the brain: potential role of the chemokine mig in pathogenesis. *Clin Infect Dis.* 2005;41:1089-1096. <https://doi.org/10.1086/444461>
- Li YC, Bai WZ, Hirano N, Hayashida T, Hashikawa T. Coronavirus infection of rat dorsal root ganglia: ultrastructural characterization of viral replication, transfer, and the early response of satellite cells. *Virus Res.* 2012;163:628-635. <https://doi.org/10.1016/j.virusres.2011.12.021>
- Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *Jama.* 2020;323:1061-1069.
- Mengeling WL, Boothe AD, Ritchie AE. Characteristics of a coronavirus (strain 67N) of pigs. *Am J Vet Res.* 1972;33:297-308.
- Andries K, Pensaert MB. Immunofluorescence studies on the pathogenesis of hemagglutinating encephalomyelitis virus infection in pigs after oronasal inoculation. *Am J Vet Res.* 1980;41:1372-1378.
- Matsuda K, Park CH, Sunden Y, et al. The vagus nerve is one route of transneuronal invasion for intranasally inoculated influenza A virus in mice. *Vet Pathol.* 2004;41:101-107. <https://doi.org/10.1354/vp.41-2-101>
- Chasey D, Alexander DJ. Morphogenesis of avian infectious bronchitis virus in primary chick kidney cells. *Arch Virol.* 1976;52:101-111. <https://doi.org/10.1007/bf01317869>
- Li YC, Bai WZ, Hirano N, et al. Neurotropic virus tracing suggests a membranous-coating-mediated mechanism for transsynaptic communication. *J Comp Neurol.* 2013;521:203-212. <https://doi.org/10.1002/cne.23171>

16. González JM, Gomez-Puertas P, Cavanagh D, Gorbalenya AE, Enjuanes L. A comparative sequence analysis to revise the current taxonomy of the family Coronaviridae. *Arch Virol.* 2003;148:2207-2235. <https://doi.org/10.1007/s00705-003-0162-1>
17. Li Z, He W, Lan Y, et al. The evidence of porcine hemagglutinating encephalomyelitis virus induced nonsuppurative encephalitis as the cause of death in piglets. *Peer J.* 2016;4:e2443. <https://doi.org/10.7717/peerj.2443>
18. Asadi-Pooya AA, Simani L. Central nervous system manifestations of COVID-19: a systematic review. *J Neurol Sci.* 2020;413:116832. <https://doi.org/10.1016/j.jns.2020.116832>
19. Mao L, Jin H, Wang M, et al. Neurologic manifestations of hospitalized patients with coronavirus disease 2019 in Wuhan, China. *JAMA Neurology.* 2020;77:683. <https://doi.org/10.1001/jamaneurol.2020.1127>
20. Khandelwal P, Al-Mufti F, Tiwari A, et al. Incidence, characteristics and outcomes of large vessel stroke in COVID-19 cohort: an international multicenter study. *Neurosurgery.* 2021;89:E35-E41. <https://doi.org/10.1093/neuros/nyab111>
21. Sheikh AB, Chourasia PK, Javed N, et al. Association of Guillain-Barre syndrome with COVID-19 infection: an updated systematic review. *J Neuroimmunol.* 2021;355:577577. <https://doi.org/10.1016/j.jneuroim.2021.577577>
22. Tiwari A, Berekashvili K, Vulkanov V, et al. Etiologic subtypes of ischemic stroke in SARS-CoV-2 patients in a cohort of New York city hospitals. *Front Neurol.* 2020;11:1004. <https://doi.org/10.3389/fneur.2020.01004>
23. Elgamasy S, Sakr EE, Kamel MG, et al. Epidemiologic features and clinical course of COVID-19: a retrospective analysis of 19 patients in Germany. *Future Virol.* 2021;16:191-199. <https://doi.org/10.2217/fvl-2020-0256>
24. Elgamasy S, Kamel MG, Ghozy S, Khalil A, Morra ME, Islam SMS. First case of focal epilepsy associated with SARS-coronavirus-2. *J Med Virol.* 2020;92:2238-2242. <https://doi.org/10.1002/jmv.26113>
25. Whittaker A, Anson M, Harky A. Neurological manifestations of COVID-19: a systematic review and current update. *Acta Neurol Scand.* 2020;142:14-22. <https://doi.org/10.1111/ane.13266>
26. Onder G, Rezza G, Brusaferro S. Case-fatality rate and characteristics of patients dying in relation to COVID-19 in Italy. *Jama.* 2020;323:1775-1776. <https://doi.org/10.1001/jama.2020.4683>
27. Palmieri L, Vanacore N, Donfrancesco C, et al. Clinical characteristics of hospitalized individuals dying with COVID-19 by age group in Italy. *J Gerontol A Biol Sci Med Sci.* 2020;75:1796-1800. <https://doi.org/10.1093/gerona/glaa146>
28. Clark A, Jit M, Warren-Gash C, et al. Global, regional, and national estimates of the population at increased risk of severe COVID-19 due to underlying health conditions in 2020: a modelling study. *Lancet Glob Health.* 2020;8:e1003-e1017. [https://doi.org/10.1016/S2214-109X\(20\)30264-3](https://doi.org/10.1016/S2214-109X(20)30264-3)
29. McLean G, Hindle JV, Guthrie B, Mercer SW. Co-morbidity and polypharmacy in Parkinson's disease: insights from a large Scottish primary care database. *BMC Neurol.* 2017;17:126. <https://doi.org/10.1186/s12883-017-0904-4>
30. Prasad S, Holla VV, Neeraja K, et al. Parkinson's disease and COVID-19: perceptions and implications in patients and caregivers. *Mov Disord.* 2020;35:912-914. <https://doi.org/10.1002/mds.28088>
31. Moro E, Fernandez HH. Adaptive neurology in COVID-19 times. *Parkinsonism Relat Disord.* 2020;75:124-125.
32. Salari M, Zali A, Ashrafi F, et al. Incidence of anxiety in Parkinson's disease during the coronavirus disease (COVID-19) pandemic. *Mov Disord.* 2020;35:1095-1096. <https://doi.org/10.1002/mds.28116>
33. Zipprich HM, Teschner U, Witte OW, Schöenberg A, Prell T. Knowledge, attitudes, practices, and burden during the COVID-19 pandemic in people with Parkinson's disease in Germany. *J Clin Med.* 2020;9:1643. <https://doi.org/10.3390/jcm9061643>
34. Schirinzi T, Cerroni R, Di Lazzaro G, et al. Self-reported needs of patients with Parkinson's disease during COVID-19 emergency in Italy. *Neurol Sci.* 2020;41:1373-1375. <https://doi.org/10.1007/s10072-020-04442-1>
35. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord.* 2020;35:905-908. <https://doi.org/10.1002/mds.28104>
36. Fasano A, Cereda E, Barichella M, et al. COVID-19 in Parkinson's disease patients living in lombardy, Italy. *Mov Disord.* 2020;35:1089-1093. <https://doi.org/10.1002/mds.28176>
37. Helmich RC, Bloem BR. The impact of the COVID-19 pandemic on Parkinson's disease: hidden sorrows and emerging opportunities. *J Park Dis.* 2020;10:351-354. <https://doi.org/10.3233/jpd-202038>
38. Papa SM, Brundin P, Fung VSC, et al. Impact of the COVID-19 pandemic on Parkinson's disease and movement disorders. *Mov Disord.* 2020;35:711-715. <https://doi.org/10.1002/mds.28067>
39. Spina Tensini F, Spina Tensini T, Franklin GL, Teive HAG. May Parkinson's disease be a protective factor against CNS involvement by SARS-CoV2? *Park Relat Disord.* 2020;77:20-20. <https://doi.org/10.1016/j.parkreldis.2020.06.012>
40. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *PLoS Med.* 2009;6:28. <https://doi.org/10.1371/journal.pmed.1000100>
41. Ghozy S, Tran L, Naveed S, et al. Association of breastfeeding status with risk of autism spectrum disorder: a systematic review, dose-response analysis and meta-analysis. *Asian J Psychiatr.* 2020;48:101916. <https://doi.org/10.1016/j.ajp.2019.101916>
42. Hashan MR, Ghozy S, El-Qushayri AE, Pial RH, Hossain MA, Al Kibria GM. Association of dengue disease severity and blood group: a systematic review and meta-analysis. *Rev Med Virol.* 2021;31:1-9. <https://doi.org/10.1002/rmv.2147>
43. Health Nlo. *Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies.* Available online at: <https://www.nhlbi.nih.gov/health-pro/guidelines/in-develop/cardiovascular-risk-reduction/tools/cohort> (Accessed put in date); 2014.
44. Higgins JPTGS. *Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0. The Cochrane Collaboration.* Available from www.handbook.cochrane.org; 2011.
45. Mantel N, Haenszel W. Statistical aspects of the analysis of data from retrospective studies of disease. *J Natl Cancer Inst.* 1959;22:719-748.
46. Peters JL, Sutton AJ, Jones DR, Abrams KR, Rushton L. Comparison of two methods to detect publication bias in meta-analysis. *J Am Med Assoc.* 2006;295:676-680. <https://doi.org/10.1001/jama.295.6.676>
47. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ Clin Res ed.* 1997;315:629-634.
48. Kobylecki C, Jones T, Lim CK, Miller C, Thomson AM. Phenomenology and outcomes of in-patients with Parkinson's disease during COVID-19 pandemic. *Mov Disord.* 2020;35:1295-1296.
49. Zhang Q, Schultz JL, Aldridge GM, Simmering JE, Narayanan NS. COVID-19 Case Fatality and Parkinson's Disease. *Mov Disorders.* 2020;35:1914-1915.
50. Zhai H, Lv Y, Xu Y, et al. Characteristic of Parkinson's disease with severe COVID-19: a study of 10 cases from Wuhan. *J Neural Transm.* 2021;128:37-48.
51. Vignatelli L, Zenesini C, Belotti LM, et al. Risk of hospitalization and death for COVID-19 in people with Parkinson's disease or Parkinsonism. *Mov Disord.* 2021;36:1-10.
52. Santos-García D, Oreiro M, Pérez P, et al. Impact of coronavirus disease 2019 pandemic on Parkinson's disease: a cross-sectional survey of 568 Spanish patients. *Mov Disord.* 2020;35:1712-1716.

53. Sainz-Amo R, Baena-Álvarez B, Pareés I, et al. COVID-19 in Parkinson's disease: what holds the key? *J Neurol*. 2020;1-5.
54. Fasano A, Elia AE, Dallochio C, et al. Predictors of COVID-19 outcome in Parkinson's disease. *Park Relat Disord*. 2020;78:134-137.
55. Del Prete E, Francesconi A, Palermo G, et al. Prevalence and impact of COVID-19 in Parkinson's disease: evidence from a multi-center survey in Tuscany region. *J Neurol*. 2021;268:1179-1187.
56. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study. *Mov Disord*. 2020;35:1287-1292.
57. Buccafusca M, Micali C, Autunno M, Versace AG, Nunnari G, Musumeci O. Favourable course in a cohort of Parkinson's disease patients infected by SARS-CoV-2: a single-centre experience. *Neurol Sci*. 2021;42:811-816.
58. Brown EG, Chahine LM, Goldman SM, et al. The effect of the COVID-19 pandemic on people with Parkinson's disease. *J Parkinson's Dis*. 2020;10:1365-1377.
59. Artusi CA, Romagnolo A, Imbalzano G, et al. COVID-19 in Parkinson's disease: report on prevalence and outcome. *Park Relat Disord*. 2020;80:7-9.
60. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord*. 2020;35:905-908.
61. Fasano A, Cereda E, Barichella M, et al. COVID-19 in Parkinson's disease patients living in lombardy, Italy. *Mov Disord*. 2020;35:1089-1093.
62. Hanff A-M, Pauly C, Pauly L, et al. Unmet needs of people with Parkinson's Disease and their caregivers during COVID-19-related confinement: an explorative secondary data analysis. *Front neurology*. 2020;11:1910.
63. Bäckström D, Granäsén G, Domellöf ME, et al. Early predictors of mortality in Parkinsonism and Parkinson disease: a population-based study. *Neurology*. 2018;91:e2045-e2056. <https://doi.org/10.1212/WNL.0000000000006576>
64. Akbar U, Dham B, He Y, et al. Incidence and mortality trends of aspiration pneumonia in Parkinson's disease in the United States, 1979-2010. *Park Relat Disord*. 2015;21:1082-1086. <https://doi.org/10.1016/j.parkreldis.2015.06.020>
65. Macleod AD, Taylor KS, Counsell CE. Mortality in Parkinson's disease: a systematic review and meta-analysis. *Mov Disord*. 2014;29:1615-1622. <https://doi.org/10.1002/mds.25898>
66. Xu J, Gong DD, Man CF, Fan Y. Parkinson's disease and risk of mortality: meta-analysis and systematic review. *Acta Neurol Scand*. 2014;129:71-79. <https://doi.org/10.1111/ane.12201>
67. Okunoye O, Kojima G, Marston L, Walters K, Schrag A. Factors associated with hospitalisation among people with Parkinson's disease - a systematic review and meta-analysis. *Park Relat Disord*. 2020;71:66-72. <https://doi.org/10.1016/j.parkreldis.2020.02.018>
68. Rodriguez-Perez AI, Garrido-Gil P, Pedrosa MA, et al. Angiotensin type 2 receptors: role in aging and neuroinflammation in the substantia nigra. *Brain Behav Immun*. 2020;87:256-271. <https://doi.org/10.1016/j.bbi.2019.12.011>
69. Joglar B, Rodriguez-Pallares J, Rodriguez-Perez AI, Rey P, Guerra MJ, Labandeira-Garcia JL. The inflammatory response in the MPTP model of Parkinson's disease is mediated by brain angiotensin: relevance to progression of the disease. *J Neurochem*. 2009;109:656-669. <https://doi.org/10.1111/j.1471-4159.2009.05999.x>
70. Nataf S. An alteration of the dopamine synthetic pathway is possibly involved in the pathophysiology of COVID-19. *J Med Virol*. 2020;92:1743-1744. <https://doi.org/10.1002/jmv.25826>
71. Fazzini E, Fleming J, Fahn S. Cerebrospinal fluid antibodies to coronavirus in patients with Parkinson's disease. *Mov Disord*. 1992;7:153-158. <https://doi.org/10.1002/mds.870070210>
72. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-1062. [https://doi.org/10.1016/S0140-6736\(20\)30566-3](https://doi.org/10.1016/S0140-6736(20)30566-3)
73. Cilia R, Bonvegna S, Straccia G, et al. Effects of COVID-19 on Parkinson's disease clinical features: a community-based case-control study: COVID-19 effects on PD symptoms. *Mov Disord*. 2020;35:1287-1292. <https://doi.org/10.1002/mds.28170>
74. Del Prete E, Francesconi A, Palermo G, et al. Prevalence and impact of COVID-19 in Parkinson's disease: evidence from a multi-center survey in Tuscany region. *J Neurology*. 2021;268:1-9. <https://doi.org/10.1007/s00415-020-10002-6>
75. Antonini A, Leta V, Teo J, Chaudhuri KR. Outcome of Parkinson's disease patients affected by COVID-19. *Mov Disord official J Mov Disord Soc*. 2020;35:905-908. <https://doi.org/10.1002/mds.28104>
76. Casqueiro J, Casqueiro J, Alves C. Infections in patients with diabetes mellitus: a review of pathogenesis. *Indian J Endocrinol Metabol*. 2012;16(Suppl 1):S27-S36. <https://doi.org/10.4103/2230-8210.94253>
77. Puca E. Infections in immunocompromised patients from diabetes mellitus. *Int J Health Sci*. 2017;5:583-587.
78. Willis AW, Schootman M, Kung N, Evanoff BA, Perlmutter JS, Racette BA. Predictors of survival in patients with Parkinson disease. *Archives neurology*. 2012;69:601-607. <https://doi.org/10.1001/archneurol.2011.2370>

SUPPORTING INFORMATION

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

How to cite this article: 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. <https://doi.org/10.1002/rmv.2278>