Received: 10 May 2021 | Revised: 5 July 2021 | Accepted: 6 July 2021

DOI: 10.1002/rmv.2278

REVIEW

WILEY

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

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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 (βCoVs), which has a well-documented propensity of neuroinvasion, 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-CoV[5] 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.

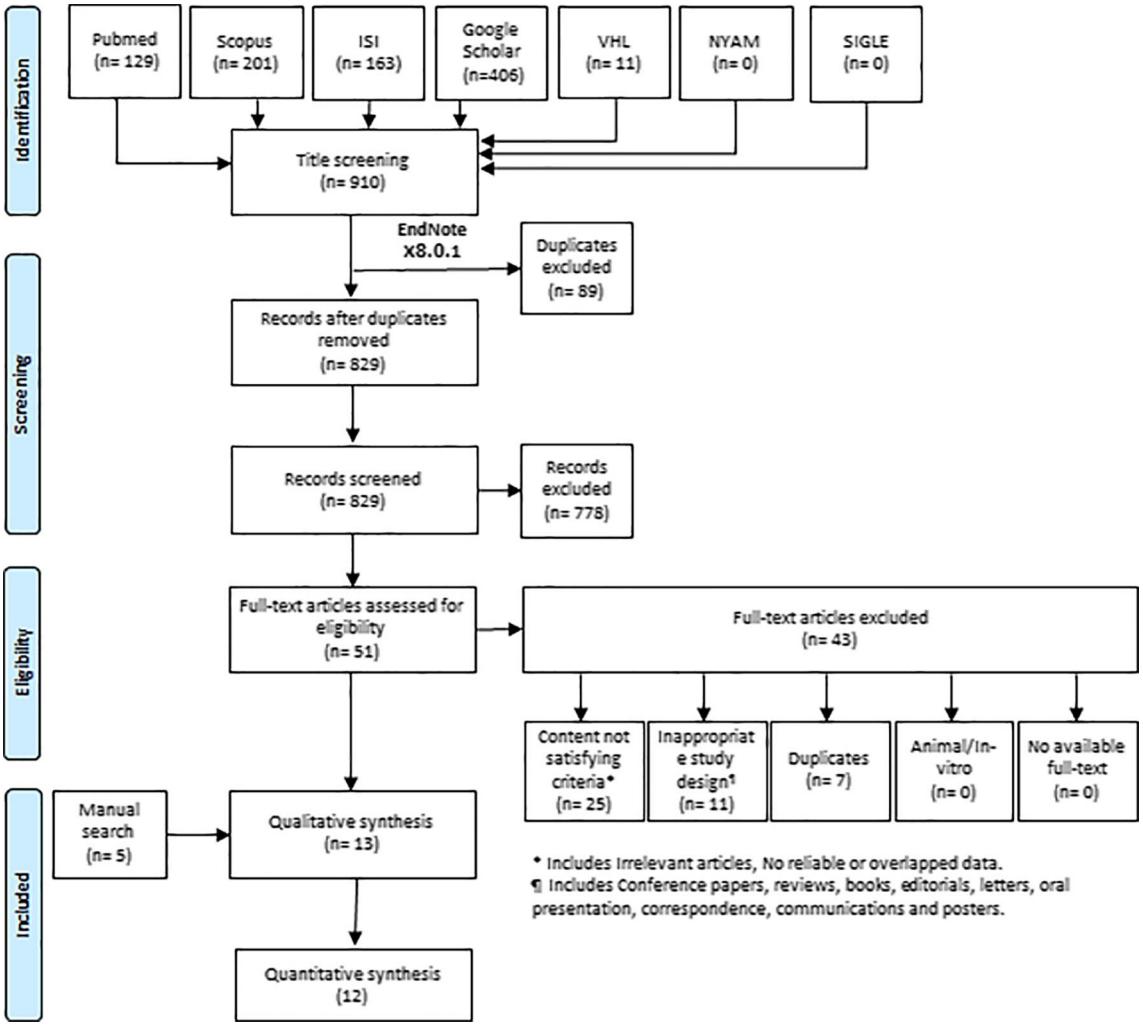

FIGURE 1 Preferred reporting items for systematic review and meta-analyses statement flow diagram of qualitative study selection process

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 papers[48–60] (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.

[a]median.

[b]range.

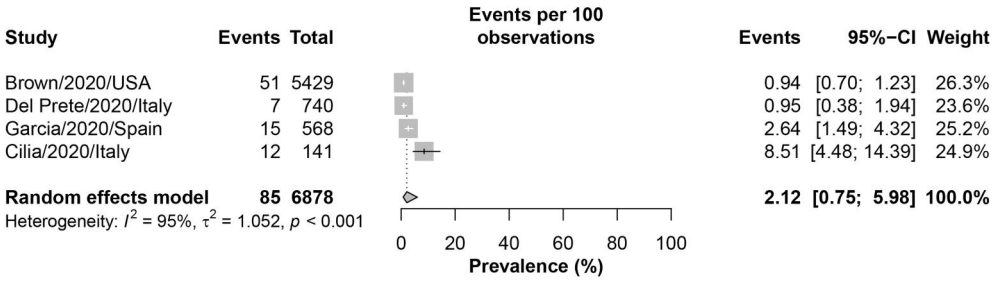

FIGURE 2 Prevalence of COVID-19 in Parkinson's disease patients (represented by the pooled event rate and the corresponding 95% CI)

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

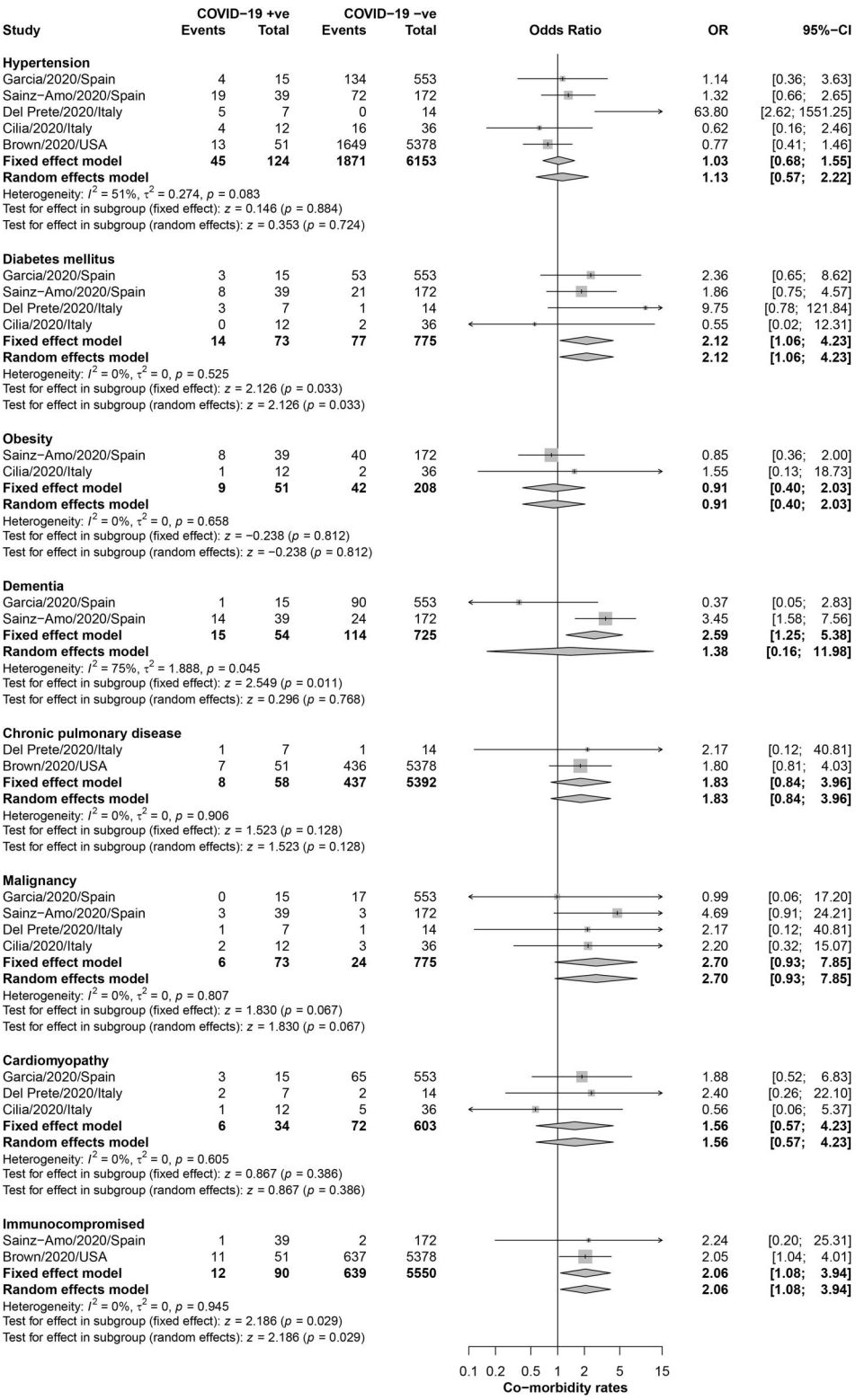

FIGURE 3 Comparison of comorbidities in Parkinson's disease (PD) patients with COVID-19 and PD patients without Covid-19 (represented by the pooled odds ratio and the corresponding 95% CI)

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

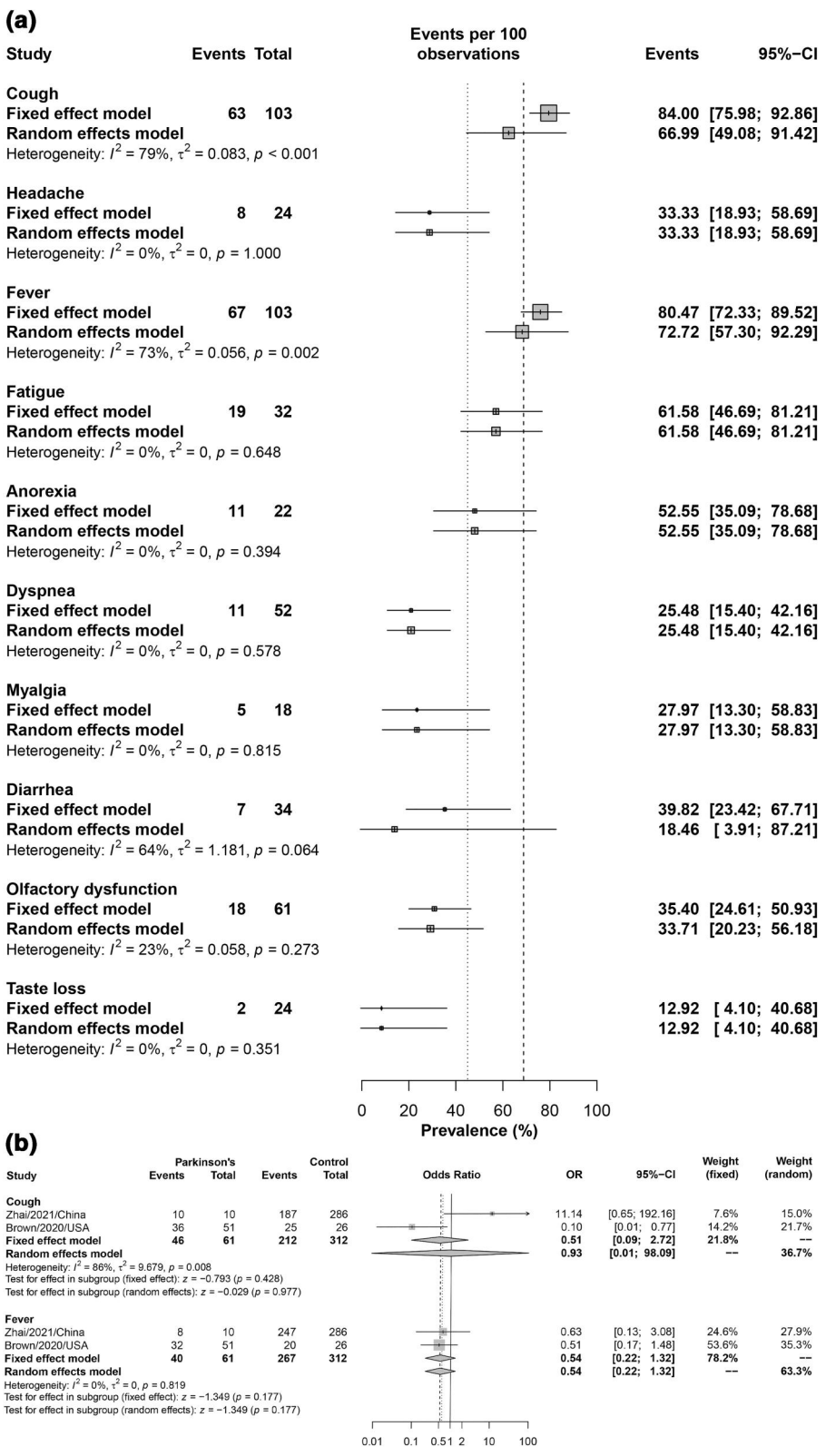

FIGURE 4 Manifestations of COVID-19 in Parkinson's disease (PD) patients. (a): Prevalence of manifestations (represented by the pooled event rate and the corresponding 95% confidence interval [CI]); (b): Comparison of the manifestations in PD patients with COVID-19 to COVID-19 without PD (represented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

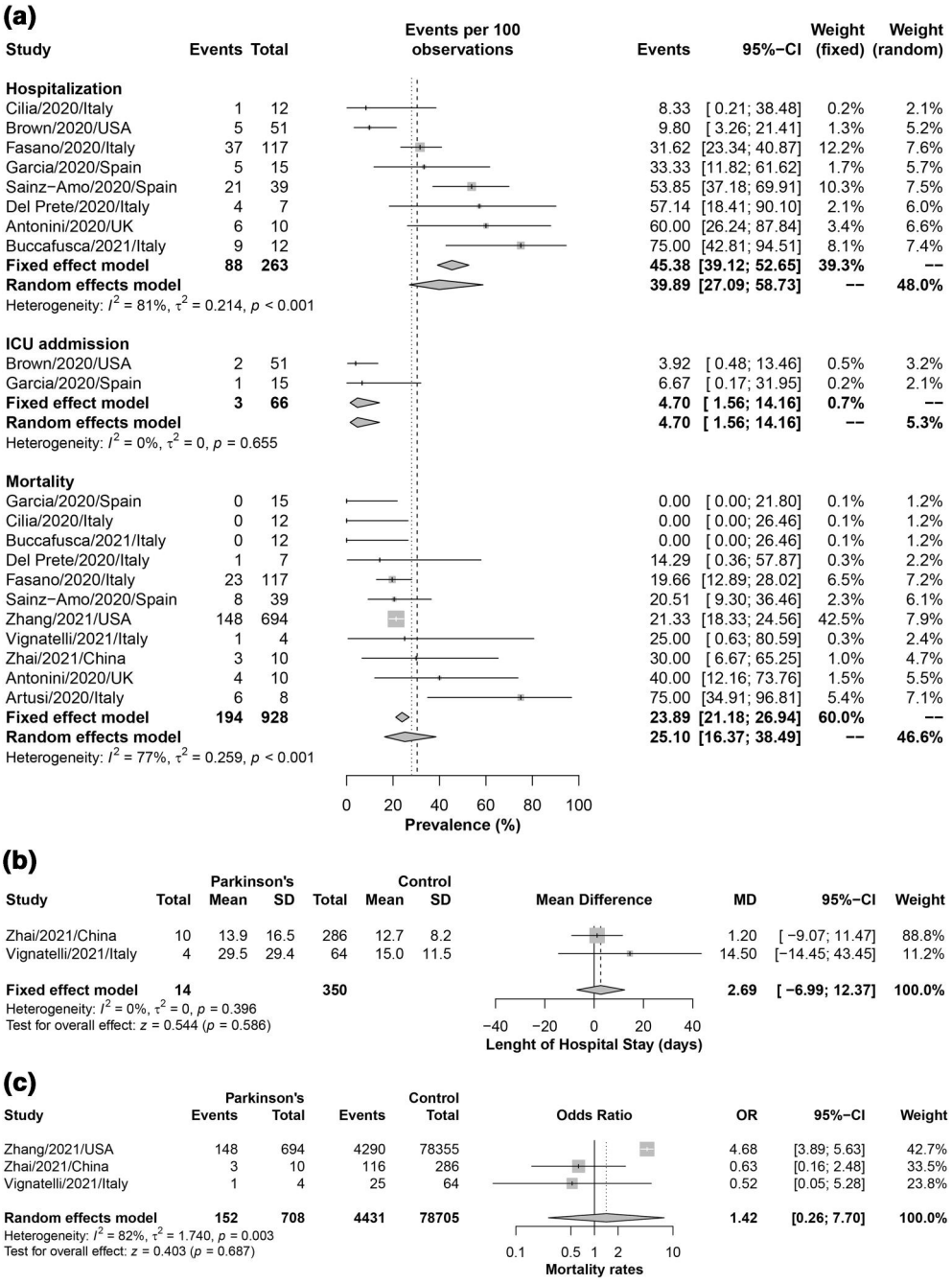

FIGURE 5 Outcomes of COVID-19 in Parkinson's disease (PD) patients. (a): Prevalence of patients' outcomes (represented by the pooled event rate and the corresponding 95% confidence interval [CI]); (b): Comparison of COVID -19 patients with PD to COVID-19 patients without PD in terms of length of hospital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

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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*. 2021;e2278. https://doi.org/10.1002/rmv.2278