CHAPTER THREE

Prevalence and outcomes of Covid-19 in Parkinson's disease: Acute settings and hospital

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Abstract

The global explosion of COVID-19 necessitated the rapid dissemination of information regarding SARS-CoV-2. Hence, COVID-19 prevalence and outcome data in Parkinson's disease patients were disseminated at a time when we only had part of the picture. In this chapter we firstly discuss the current literature on the prevalence of COVID-19 in people with PD. We then discuss outcomes from COVID-19 in people with PD, specifically risk of hospitalization and mortality. Finally, we discuss specific contributing and confounding factors which may put PD patients at higher or lower risk from COVID-19.

1. Introduction

The coronavirus disease 2019 (Covid-19) pandemic, caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), has spread globally with a previously unseen rapidity. Its dominance around the world has meant that prevalence and outcome data from almost any population could be obtained within months of the pandemic. This data could be pulled from hospital admissions, hospital deaths, community prevalence and nursing homes. The global explosion of Covid-19 has necessitated rapid dissemination of information regarding SARS-CoV-2. In addition, the ease with which reasonably sized data set could be drawn together has meant that Covid-19 prevalence and outcome data in Parkinson's disease (PD) patients has been disseminated at a time when we only had part of the picture. Many people with PD (PwP) were concerned about the Covid-19 risk and it would always be challenging to assess this risk in the absence of good quality data. As each new publication came out, we have gained a better idea of the Covid-19 prevalence and outcomes in PD, although we are continuing to learn and understand this data.

The heterogeneity of PD, its ability to affect both young and old, and its relatively slow disease progression from highly active and independent functioning to highly dependent advanced disease means that prevalence and outcome data must be carefully considered within the population from which those data is drawn, taking confounding factors into account. For example, it should not be surprising that we might find differences in prevalence and outcomes between a cohort of PwP with advanced PD admitted acutely to hospital and a cohort of early-stage PwP who undertake a telephone survey in the community and who may well be isolating at home during the peak lockdown period of the first wave of the Covid-19 pandemic in case PD poses a significant risk to them in the setting of Covid-19.

The first goal of this chapter is to discuss the current literature on the prevalence of Covid-19 in PwP. We will then discuss outcomes from Covid-19 in PwP, specifically risk of hospitalization and mortality. Finally, we will discuss specific contributing and confounding factors which may put PwP at higher or lower risk from Covid-19.

Prior to this discussion, it is important to note that lockdowns during the pandemic had a profound effect on PwP. This aspect is beyond the scope of this chapter, but has been covered in detail elsewhere (Brown et al., 2020;

Fearon & Fasano, 2021; Prasad et al., 2020). Suffice to say that motor and non–motor symptoms of PD worsen during lockdowns (Fabbri et al., 2021), anxiety heightens (Shalash et al., 2020), impulsive–compulsive behaviors become more common (Yule, Pickering, McBride, & Poliakoff, 2021), sleep problems become more common (Kumar & Gupta, 2021), access to medications, physiotherapy and exercise become more problematic (Cheong et al., 2020; van der Kolk et al., 2019). Hence, the effect of the Covid–19 *pandemic* on PwP is a far more complex consideration than the impact of SARS-CoV-2 infection alone. Nevertheless, we will direct our focus toward the latter, merely acknowledging that it forms part of a bigger picture.

Firstly, however, we will discuss an important question. The interest in prevalence and outcomes in PwP had started even before we had any data on these parameters. Why, therefore, would we expect prevalence and outcomes of SARS-CoV-2 infection to be different in PwP compared with the general population?

2. Why should PwP be more or less susceptible to Covid-19?

Particular interest has surrounded SARS–CoV-2 infection in PwP since the beginning of the Covid-19 pandemic. A major driver of this interest was the emergence of post-encephalitic parkinsonism ("encephalitis lethargica") in the wake of the last major global viral pandemic, the H1N1 "Spanish" flu of 1914–1918 (von Economo, 1918). In the decades that followed the pandemic, it is estimated that up to 1 million people worldwide may have developed encephalitis lethargica (Ravenholt & Foege, 1982). In spite of the fact that the causal role of H1N1 in the pathogenesis of encephalitis lethargica is debated (Hoffman & Vilensky, 2017), the knowledge that certain viruses can demonstrate specific neurotropism for the basal ganglia, in addition to the fear that a pandemic of similar degree could lead to another epidemic of parkinsonism has forever been etched on the minds of the scientific and medical community. Even in the few years prior to the Covid-19 pandemic, vigilance for the return of encephalitis lethargica persisted in historic discussions on the topic (Hoffman & Vilensky, 2017).

It is not surprising, therefore, that immediately after the first reports of Covid-19 spreading globally, it was suggested that SARS-CoV-2 may have the potential to cause neurodegeneration and that we might expect a

significant increase in the incidence of post-infectious parkinsonism in the decades to come (Lippi, Domingues, Setz, Outeiro, & Krisko, 2020). Although clearly different viruses, SARS-CoV-2 and H1N1 viruses do share some common pathophysiological mechanisms, including mitochondrial dysfunction, lipid metabolism, proteostasis and stress responses, all of which have also been implicated in the pathophysiology of PD (Lippi et al., 2020). Nevertheless, this concept was debated vigorously in the scientific literature at the earlies stages of the pandemic (Gonzalez-Latapi, Fearon, Fasano, & Lang, 2021; Merello, Bhatia, & Obeso, 2021).

Even if SARS-CoV-2 did have the potential to lead to post-infectious parkinsonism, it does not necessarily follow that PwP would then be more susceptible to SARS-CoV-2 infection than the general population. However, further links between SARS-CoV-2 and PD were identified early on, particularly that dopamine may be involved in the pathophysiology of Covid-19. An alteration in dopamine synthetic pathways may be implicated in the pathophysiology of SARS-CoV-2, raising the question of whether alterations in dopamine metabolism could modulate the effect of SARS-CoV-2 infection. A co-expression link was also demonstrated between *DDC*, the gene which encodes for dopa decarboxylase (a major enzyme in dopamine synthetic pathways) and *ACE2*, the gene encoding one of the main receptors on the SARS-CoV-2 virus (Nataf, 2020). This is important because ACE2 is found in high quantities in dopaminergic neurons, which are decreased in PwP.

Further evidence that PwP were an important cohort to study in the early stages of the pandemic arose from the possibility that amantadine, an antiviral agent used relatively widely in the treatment of PD, could be protective against Covid-19. Amantadine is FDA-approved for the treatment of influenza A and its antiviral properties led its early consideration as a treatment for Covid-19 (Araújo, Aranda-Martínez, & Aranda-Abreu, 2020). A number of mechanisms of action of amantadine targeting SARS-CoV-2 have been proposed to limit the toxic effects of Covid-19, including disrupting lysosomal gene expression and viral replication (Aranda Abreu, Hernández Aguilar, Herrera Covarrubias, & Rojas Durán, 2020; Smieszek, Przychodzen, & Polymeropoulos, 2020).

Finally, it was then postulated that α-synuclein may itself be protective against Covid-19 (Ait Wahmane et al., 2020). Neuronal expression of α-synuclein inhibits viral central nervous system (CNS) invasion and restricts the ability of RNA viruses to replicate in the brain (Massey & Beckham, 2016). Physiological α-synuclein has myriad roles, which includes immune cell recruitment and protection against pro-inflammatory

responses to infections (Labrie & Brundin, 2017). Depletion of α-synuclein in knockout mice leads to B- and T-cell deficiencies (Xiao, Shameli, Harding, Meyerson, & Maitta, 2014). Given this, it was proposed that peripheral overexpression of α-synuclein in PD may prevent neuroinvasion of SARS-CoV-2 (Ait Wahmane et al., 2020).

Taken together, this data has led to the expectation that PwP may be differently susceptible compared to the general population when it comes to risk of contracting Covid-19 and the severity of that illness. This idea had emerged long before we had relevant data on Covid-19 and PD risk. So, was this hypothesis borne out by the data which followed? We will explore this in the sections which follow.

3. Covid-19 prevalence in Parkinson's disease

It is important to state from the outset that whether there is an increased risk of Covid-19 in PwP remains a matter of debate. A number of small and larger studies have tried to answer this question, through case–control study design or by comparing prevalence in their selected group of PwP with prevalence in the general population in that region over a similar time period. Particularly in the early stages of the pandemic, study design and recruitment were undertaken at times in a rapid and ad hoc fashion out of necessity. This led to conflicting results scattered across a number of small studies initially, with critical mass for systematic reviews and meta-analyses only being reached more recently. The studies which report prevalence rates of SARS-CoV-2 among PwP are presented in Table 1. We will discuss these studies below and finally review the findings of the recent systematic reviews and meta-analyses.

The first reported neurological presentation of Covid-19 was in a PD patient (Filatov, Sharma, Hindi, & Espinosa, 2020). At that time, it was clear that Covid-19 affected elderly patients with chronic conditions to a greater extent, but it was not known whether PD itself was a specific risk factor for contracting SARS-CoV-2.

A large telephone-based case-control study from Lombardy in Italy (the region from which one-third of Italian cases of SARS-CoV-2 occurred during the first wave of the pandemic) demonstrated no difference in Covid-19 rates between 1486 PwP and 1207 familial controls (7.1% vs 7.6%) (Fasano, Cereda, et al., 2020). The PwP who contracted Covid-19 were younger, more likely to suffer from respiratory disease and obesity than unaffected patients. In addition, patients who avoided infection were more likely to be taking vitamin D supplementation. Although the PD group were

Table 1 Studies reporting prevalence figures relating to COVID-19 in PD.

Reference	Study Design	Total PD sample	PD	Controls	Risk factors
Fasano, Cereda, et al. (2020), Fasano, Elia, et al. (2020)	Phone survey	1486	7.1%	7.6%	Reduced risk from fewer weekly outings in PD cohort
Brown et al. (2020)	Online survey	5429	0.9%	1.8%	Smoking, heart disease, age, male sex
Del Prete et al. (2020)	Phone survey	740	0.9%	NA	Hypertension, diabetes,? age
Santos García et al. (2020)	Phone survey	568	2.6%	NA	Less advanced disease (possibly due to cocooning in more vulnerable advance), heart disease, amantadine (protective)
Salari, Etemadifar, Ashrafi, Ommi et al. (2021), Salari, Etemadifar, Zali, Aminzade, et al. (2021), Salari, Etemadifar, Zali, Medghalchi, et al. (2021)	Seroprevalence case-control study in asymptomatic individuals	90	25.6%	12.4%	None
Cilia et al. (2020)	Community-based case control study	141	8.5%	NA	No increased risk with advancing age or disease duration compared with COVID-19-negative
Artusi et al. (2020)	Phone survey	1407	0.57%	0.63%	Unclear if similar rates are due to lack of increased risk or due to increased self-isolation in at risk patients
Salari, Etemadifar, Ashrafi, Ommi, et al. (2021), Salari, Etemadifar, Zali, Aminzade, et al. (2021), Salari, Etemadifar, Zali, Medghalchi, et al. (2021)	Phone survey	647	11.28%	15.39%	None

older than their familial controls, they were less likely to be hospitalized. It was noted by the authors that the PD cohort appeared to be self-isolating to a greater degree than their family members who were surveyed (as measured by a lower number of weekly outings). A possible explanation for this finding may have been that families were cocooning the at-risk member of family (and as a result venturing out into the community relatively more frequently to run errands etc.). Irrespective of why this occurred, it may have underestimated true risk of being infected by SARS-CoV-2 in the PD cohort. At a similar time in the pandemic, a semi-structured telephone-based study in Germany reported that 73% of PwP had changed their behavior since the start of the Covid-19 pandemic in order to reduce the risk of infection (Zipprich, Teschner, Witte, Schönenberg, & Prell, 2020). Of these, 99% performed at least one specific preventive behavior, and 86.9% had reduced social contacts and stayed home. The proportion was higher in older patients, probably in light of higher perceived risk.

This theory might be further supported by a similar phone-based survey of 568 Spanish patients (Santos García et al., 2020). They found that 2.6% of patients reported a confirmed diagnosis of Covid-19. The Covid-19-negative group were more likely to experience motor fluctuations (61% vs 35.7%, $P=0.052$) and hallucinations (23.4% vs 0%, $P=0.025$), and there was a trend toward more prevalent dementia and behavioral disorders among the group who did not contract Covid-19. The authors similarly hypothesized that stricter prevention measures in this group with more complex PD may have led to these findings, however the Covid-19-positive cohort was small.

A study from Piedmont, the region in Italy with the second highest number of Covid-19 cases after Lombardy, aimed to estimate the prevalence of Covid-19 in a large population of PwP and compare the infection rate with the general population of the same region (Artusi et al., 2020). They performed a telephone survey of 1407 PwP, asking for a laboratory-confirmed diagnosis of Covid-19. They found eight PwP (0.57%) who were Covid-19-positive. The prevalence in Piedmont in the general population of Piedmont over the same period was 0.63%. The authors point out once again that it cannot be determined whether this is due to equivalent risk of contracting Covid-19 or due to higher self-isolation in the PD cohort masking a greater underlying risk.

Another telephone-based study of PwP in Tuscany, Italy demonstrated a Covid-19 prevalence of 0.9% among the 740 PwP who responded (Del Prete et al., 2020). There was no non-PD control group in the study,

but estimated prevalence of Covid-19 in the region during that period was 0.18%–0.25%. All patients in the study who contracted Covid-19 were over the age of 60. However, the age profile of the Covid-19-negative group was similar. When comparing Covid-19-positive and Covid-19-negative patients, the former reported a significantly higher prevalence of hypertension ($P < 0.001$) and diabetes ($P = 0.049$), while no significant differences were found for the other comorbidities. There were no reported differences in anti-parkinsonian medications.

Hence increasing age does not appear to predispose to Covid-19 in PwP, as supported by another community-based case-control study from Lombardy, which found 12 of 141 PwP had tested positive for Covid-19 and when compared to the Covid-19-negative PD group, they were neither older nor of longer disease duration (Cilia et al., 2020). However, it is important to note that this study was likely underpowered to examine such a difference.

In an effort to reach an even larger cohort of PwP, Brown et al. surveyed users of Fox Insight, an online study that involves thousands of people with and without PD (Brown et al., 2020). 7209 users responded (5429 PwP and 1452 without PD). This represented 74% of all active Fox Insight users. 51 PwP (0.9%) and 26 (1.8%) respondents without PD reported a diagnosis of Covid-19. Covid-19-positive PwP were more likely to smoke (5.9% vs 1.6%, $P = 0.048$) and have a history of heart disease (20% vs 8.2%, $P = 0.008$) than those who were Covid-19-negative, and were more likely to be older, male, and less likely to have lung disease than Covid-19-positive respondents who did not have PD. Importantly, control subjects who contracted Covid-19 more often reported working in healthcare or as another essential worker which may have increased their exposure. The Covid-19-positive PD group were more likely to have a close contact with Covid-19 compared to the Covid-19-negative PD group (59% vs 7.7%, $P < 0.001$). Hence general exposure risk may have greatly impacted the above findings.

Using patients' reports as a means of estimating prevalence has limitations. The higher prevalence reported in the Lombardy studies above could be influenced by the fact that patients without molecular test confirmation were included, leading to a possible overestimation of prevalence. On the other hand, patient reports may not account for patients who may have been exposed to SARS-CoV-2 and remained asymptomatic or pauci-symptomatic. To this end, Salari et al. used commercially available enzyme-linked immunosorbent assay (ELISA) kits to estimate the seroprevalence of SARS-CoV-2 among PwP who did not have the symptomatic infection during the third wave of Covid-19 in Iran (Salari, Etemadifar, Zali, Medghalchi, et al., 2021).

Ninety PwP and 97 healthy controls were tested and 25.6% of PwP and 12.4% of controls tested positive for SARS-CoV-2 IgG antibody. Risk factors for those who were seropositive were not explored, but the authors reported that the proportion of PwP with positive IgG test who had no direct contact with Covid-19 patients was significantly higher than that of the same individuals in the control group.

In an effort to clarify the incongruity of the reported studies, Chambergo-Michilot et al. provided an analysis of the factors associated with Covid-19 prevalence in PwP (Chambergo-Michilot, Barros-Sevillano, Rivera-Torrejón, De la Cruz-Ku, & Custodio, 2021). The authors included six studies (four case-controlled studies and two cross-sectional studies) in their systematic review and meta-analysis. Two of these case–control studies and one cross-sectional study were felt not to have controlled their analysis for important factors. The pooled prevalence of Covid-19 in PD was 2% They found that the following factors were associated with contracting Covid-19 in PwP: obesity (OR: 1.79, 95% CI: 1.07–2.99, I^2: 0%), any pulmonary disease (OR: 1.92, 95% CI: 1.17–3.15, I^2: 0%) and Covid-19 contact (OR: 41.77, 95% CI: 4.77–365.56, I^2: 0%) and that vitamin D supplementation was associated with a lower odds ratio of contracting Covid-19 (OR: 0.50, 95% CI: 0.30–0.83, I^2: 0%). They did not find any significant association between Covid-19 in PD and hypertension, diabetes, cardiopathy, cancer, any cognitive problem, dementia, chronic obstructive pulmonary disease, renal or hepatic disease, smoking, and tremor.

El-Qushayri et al. subsequently performed a systematic review and meta-analysis of Covid-19 in PwP (El-Qushayri et al., 2021). Four studies which reported prevalence of Covid-19 in a total of 6878 PwP were included in the analysis. The pooled prevalence rate of Covid-19 was estimated at 2.12% (95% CI: 0.75–5.98). There was, however, significant heterogeneity among the pooled studies ($I^2 = 95\%$; $P < 0.001$) with the prevalence estimates in the included studies ranging from 0.94% to 8.51%. The authors examined possible co-founders by comparing comorbidities among Covid-19-positive PwP and Covid-19-negative PwP. They found significantly higher rates of diabetes mellitus (OR: 2.12, 95% CI: 1.06–4.23; $P = 0.033$) and immune compromise (OR: 2.06, 95% CI: 1.08–3.94; $P = 0.029$) among the Covid-19-positive group. No significant differences were observed in hypertension, obesity, dementia, chronic pulmonary disease, malignancy, or cardiomyopathy between groups. The effect of age or other demographic factors was not examined.

A third systematic review and meta-analysis which included a greater number of studies found a pooled prevalence of Covid-19 in PD cases of

5% (95% CI: 4%–6%) ($I^2 = 98.1\%$, $P < 0.001$), higher than the pooled prevalence reported in the two previous systematic reviews (Khoshnood et al., 2021). Another systematic review very clearly demonstrated that prevalence varied according to geography, with a prevalence of 2.6% in Spain, 0.9% in the US, and variable values in different regions of Italy, ranging from 7.1% to 8.5% in Lombardy, 0.9% in Tuscany, and 0.6% in Piedmont and in the Bologna district (Artusi et al., 2021).

In summary, there is no consistent evidence that people with PD are at greater risk from contracting Covid-19 compared with the general population. The region from which the data were drawn appear to play a significant role, as does the presence of comorbidities. The main confounder in community studies may be that PwP potentially self-isolated to a greater degree than the general population who had no perceived added risk from Covid-19. This behavior may have masked an increased predisposition to SARS-CoV-2 infection, but we simply cannot say with certainty from the current data. Next, we will consider what happens to PwP if they do contract Covid-19.

4. Covid-19 outcomes in Parkinson's disease

Intuitively, older patients with advanced PD, impaired cough reflex and respiratory muscle involvement would be particularly vulnerable to a severe acute respiratory syndrome. Muscular weakness can appear in PD, and could contribute to respiratory failure, which leads to death (Baille et al., 2018). However, data from the pre-Covid-19 era of elderly patients with pneumonia showed that patients with parkinsonism had significantly lower in-hospital mortality than those without (Jo et al., 2018). Hence, the above factors may not pose as great a risk for PwP with Covid-19 as one might expect. We will consider hospitalization and mortality outcomes separately.

4.1 Hospitalization

Similar to the prevalence data above, hospitalization data was reported in a number of small studies with varying rates reported. For example, the aforementioned Spanish telephone-based study suggested that approximately 33% of PwP who contracted Covid-19 were hospitalized, although the number of Covid-19-positive PD cases in this study was small (15 cases) (Santos García et al., 2020). However, a systematic review incorporating 13 studies reported a similar hospitalization rate of 28.6% among PwP with Covid-19 (Artusi et al., 2021). A more recent systematic review and meta-analysis which pooled

17 studies found a pooled prevalence of hospitalization in cases with Covid-19 infection of 49% (95%CI: 29%–52%) (I^2: 93.5%, $P < 0.001$) (Khoshnood et al., 2021).

It is important to note that PwP have an increased risk of being admitted to hospital, not only from Covid-19, but also due to PD-related complications (Temlett & Thompson, 2006). Furthermore, PwP are more likely to have comorbidities which further increases their risk of being admitted to hospital. The meta-analysis performed by Chambergo-Michelot and colleagues found hospitalization to be independently associated with Covid-19 and PD (OR: 11.78, 95% CI: 6.27–22.12, I^2: 0%) (Chambergo-Michilot et al., 2021).

Salari et al. found that although PwP were hospitalized because of the severity of Covid-19 more frequently than the rates in the general population, the rate of hospitalization among these patients was not significantly different from a simultaneously collected age-matched control group suggesting that advancing age may play a role (Salari, Etemadifar, Zali, Aminzade, et al., 2021).

Similarly, advanced disease, as expected, contributes to risk of hospitalization from Covid-19. The Fox Insight-based study demonstrated that longer PD-duration was associated with a higher risk of pneumonia, supplemental oxygen requirement and hospitalization among PwP who contracted Covid-19 (44% among disease duration > 9 years vs 14% among disease duration ≤ 9 years, OR 5.44, 95% CI 1.04–30.5, $P = 0.043$) (Brown et al., 2020). Mortality rate was not addressed in this study.

Interestingly, another study from Bologna, Italy of 696 subjects with PD, 184 with parkinsonism and 8590 control subjects found a 3-month hospitalization rate for Covid-19 of 0.6% in PD, 3.3% in parkinsonism, and 0.7% in controls (Vignatelli et al., 2021). This suggests that PD per se is not a risk factor for hospitalization, but that atypical parkinsonism may be a significant risk factor. The parkinsonism group (albeit a presumably heterogeneous group) will have included a significantly higher proportion of atypical parkinsonism who one expects to have a higher prevalence of dysphagia, cognitive impairment and gait impairment, all of which may contribute to hospitalization (and mortality). No studies specifically examining this risk in atypical parkinsonism has been undertaken to date.

4.2 Mortality

Seventeen studies have examined mortality in PD in the setting of Covid-19. The number of Covid-19 cases in the studies ranged from two to 694 cases, while reported mortality rates ranged from 5.2% to 100% (Table 2).

Table 2 Studies reporting mortality figures relating to COVID-19 in PD.

Reference	Study design	Total PD sample	PD	Controls	Risk factors
Antonini, Leta, Teo, and Chaudhuri (2020), Antonini, Leta, Teo, and Ray Chaudhuri (2020)	Case series	10 (10 COVID+)	40%	NA	Age, disease duration, use of advanced therapies
Hainque and Grabli (2020)	Case report	2 (2 COVID+)	100%	NA	STN DBS?
Kobylecki et al. (2020)	Hospitalized patients in a single center	58 (3 COVID+)	5.2%	NA	NA
Fasano, Cereda, et al. (2020), Fasano, Elia, et al. (2020)	Phone survey	1486 (105 COVID+)	5.7%	7.6%	NA
Artusi et al. (2020)	Phone survey	1407 (8 COVID+)	75%	NA	NA
Del Prete et al. (2020)	Phone survey	740 (7 COVID+)	14%	NA	NA
Fasano, Cereda, et al. (2020), Fasano, Elia, et al. (2020)	Multi-center case series	117 (117 COVID+)	19.7%	NA	Dementia, hypertension, disease duration
Sainz-Amo et al. (2020)	Single-center case series	211 (33 COVID+)	21%	NA	Cancer, hospital admission (no DA use, dementia)[a]
Vignatelli et al. (2021)	Prospective cohort study	696 (4 hospitalized with COVID-19)	25%	39%	Control group was matched for age and comorbidities
Salari, Etemadifar, Ashrafi, Ommi, et al. (2021), Salari, Etemadifar, Zali, Aminzade, et al. (2021), Salari, Etemadifar, Zali, Medghalchi, et al. (2021)	Hospitalized pts. patients in two referral centers	87 (87 COVID+)	35.6%	16.6%	Dementia (Age)

Parihar et al. (2021)	Retrospective review of admitted pts. (1 hospital in NYC)	70 (53 COVID+)	35.8%	NA	Age > 70, advanced PD, meds reduction, Black race
Nwabuobi et al. (2021)	Retrospective review of admitted pts. (1 hospital in NYC)	25 (25 COVID+)	32%	26%	Encephalopathy during admission
Xu et al. (2021)	Cross-sectional online survey (1 center)	46 (46 COVID+)	13%	NA	None
Zhai et al. (2021)	Retrospective review of admitted pts. (1 hospital in Wuhan)	10 (10 severe COVID)	30%	40.6	None
Fathi et al. (2021)	Multicenter study of hospitalized patients	259 (259 COVID+)	35.1%	29.5%	None
Salari, Etemadifar, Ashrafi, Ommi, et al. (2021), Salari, Etemadifar, Zali, Aminzade, et al. (2021), Salari, Etemadifar, Zali, Medghalchi, et al. (2021)	Phone survey	647 (73 COVID+)	10.9%	NA	None
Zhang et al. (2020)	COVID-19 Medical record database analysis	694 (694 COVID+)	21.3%	5.5%	None

[a]Lack of DA use and dementia did not survive the multivariate analysis.
Abbreviations: DA: Dopamine agonist; STN DBS: subthalamic nucleus deep brain stimulation.

As mentioned above, the first reported case of neurological complications of Covid-19 was in a patient with PD (Filatov et al., 2020). This 74-year-old man presented with encephalopathy in the setting of Covid-19 pneumonia and was admitted to the intensive care unit critically ill. Importantly this patient also had atrial fibrillation, a prior cardioembolic stroke and chronic obstructive pulmonary disease. This single case highlights the multiple confounding factors which must be considered when assessing the contribution of PD itself to outcomes from Covid-19 in PD.

The earliest assessment of Covid-19 outcomes in PD was a small case series of 10 Covid-19-positive PwP from the UK and Italy (Antonini, Leta, Teo, & Chaudhuri, 2020). Four of these patients died leading to an early, but worrying implication that PwP had a 40% risk of dying if they contracted Covid-19. This caused significant concerns when it was published (Antonini, Leta, Teo, & Ray Chaudhuri, 2020; Raphael, 2020) and it is likely that this impacted behavior in PwP, leading to extra caution and self-isolation. However, all patients in that study had advanced disease and age (mean age of 78.3 years). Two of the four patients who died in this series had an advanced therapy in the form of intrajejunal levodopa. However, two of the six patients who recovered also had advanced therapies (one had undergone deep brain stimulation, while another had an intrajejunal levodopa pump), suggesting that advanced therapies alone may not be a good predictor of mortality. This series highlighted early two important confounders in Covid-19 outcomes of PwP, namely advanced age and advanced disease (albeit extract from a small sample size).

The early concern that PwP with advanced therapies might be at higher risk was further compounded by a case series of just two PwP treated with subthalamic nucleus deep brain stimulation (STN-DBS), whose SARS-CoV-2 infection presented atypically and had poor outcomes (Hainque & Grabli, 2020). Both patients died within days of acute respiratory distress syndrome. However, Salari et al. found no risk of worse outcomes in 44 of 647 PwP who had undergone DBS surgery in their study (Salari, Etemadifar, Zali, Aminzade, et al., 2021). The relatively small numbers of infected patients included in these studies clearly highlight the difficulties in calculating meaningful estimates for outcomes.

Subsequently, a number of studies reported a *lower* mortality rate from Covid-19 among PwP. Analysis of admissions to hospital in PwP during the early stages of the pandemic with a three-year period prior to the pandemic revealed 13 deaths (22.4% of hospitalizations) during the pandemic compared with 6.5% of hospitalizations previously (Kobylecki, Jones, Lim, Miller, & Thomson, 2020). However, only three deaths during the

pandemic period related to Covid-19 (in-hospital mortality 5.2%). This highlights the important effect of delay in seeking medical attention for other illnesses (e.g., cardiac issues), which may be reflected better by total excess mortality during the pandemic in PwP rather than Covid-19-related deaths alone.

A telephone survey of 1486 PwP in Italy (105 Covid-19 positive) similarly reported no significant difference in mortality from Covid-19 among PwP when compared to familial controls (5.7% vs 7.6%, $P=0.20$) (Fasano, Cereda, et al., 2020). Interestingly, another Italian study found that mild-to-moderate Covid-19 may be contracted independently of age and PD duration and that PwP with mid-stage PD do not seem to have an overall worse outcome than non-PD population (Cilia et al., 2020). Two further Italian studies reported much higher mortality rates of 14% (1 of 7 Covid-19-positive PwP) and 75% (6 of 8 Covid-19-positive PwP) respectively (Artusi et al., 2020; Del Prete et al., 2020). The demographic and clinical features of the examined cohorts must be considered, in particular whether patients with advanced PD and those living in nursing homes or other long-term care facilities were included. From the current data it appears that those studies with lower reported mortality had included fewer institutionalized patients and patients with advanced disease.

Supporting this, a multi-center study of 117 community-dwelling PwP with Covid-19 from 21 tertiary referral centers in Italy, Iran, Spain and the UK examined predictors of outcomes (Fasano, Elia, et al., 2020). Overall mortality was 19.7% and predictors of poor outcome included coexistent dementia (26.1% vs 8.5%, $P=0.049$) and duration of PD (11.7 ± 8.8 vs 6.6 ± 5.4 years, $P=0.029$). In addition, there was a trend toward increased mortality with hypertension (63.6% vs 37.6%, $P=0.054$). Thus, once again, patients with advanced PD are most at risk, although the overall mortality was lower than in previous studies. Given that much of these data are derived from Italian patients, it is helpful to consider what the mortality from Covid-19 was in the general population in these regions. Case-fatality rates of individuals dying in relation to Covid-19 in Italy over similar periods were 9.5% for people over 50 years of age and 12.8% for people over 70 years of age (Onder, Rezza, & Brusaferro, 2020).

A few studies have compared outcomes in Covid-19-positive PwP with Covid-19-positive controls. An Iranian study of 12,909 hospitalized Covid-19-positive individuals (87 of whom had PD) from two university hospitals demonstrated a case fatality of 35.6% among PwP who contracted Covid-19 compared to 19.8% among those who did not have PD (Salari, Etemadifar, Ashrafi, Ommi, et al., 2021). Although there was no significant difference in

age between the two cohorts, Alzheimer's disease as an underlying condition was more frequent in deceased PwP in comparison to survived PD patients ($P<0.01$). Examination of clinical characteristics and mortality in 25 PwP admitted to a large referral center in New York revealed that 72% of these patients had comorbid hypertension and 48% had mild cognitive impairment or dementia (Nwabuobi et al., 2021). The authors found that the mortality rate in PwP did not differ significantly from age–matched controls (32% vs 26%, $P=0.743$). Interestingly, 44% of them presented with altered mental status and individuals who died were more likely to have encephalopathy during their admission (88% vs 35%; $P<0.03$). A study of cases of severe Covid-19 admitted to a hospital in Wuhan found mortality among the 10 PwP was non–significantly lower than those without PD (30% vs 46%, $P>0.05$) (Zhai et al., 2021). The authors highlight that PwP with older age, longer PD duration, and late-stage PD may be highly susceptible to critically severe Covid-19 infection and poor outcome.

With regards to other factors which might predict poor outcomes from Covid-19 in PD, a comparison of 29 PwP with severe Covid-19 (hospitalized or death) with 182 PwP who contracted mild Covid-19 or were Covid-19–negative found a positive association between worse outcome and institutionalization (28% vs 5%, $P<0.0001$), dementia (38% vs 15%, $P=0.0026$) and concomitant cancer (10% vs 2%, $P=0.0353$) (Sainz-Amo et al., 2020). They also demonstrated a negative association with dopamine agonist use (17% vs 74%, $P=0.0155$), although one might argue that dopamine agonists are less frequently used in older patients or those with advanced disease. The overall mortality in this study was 21%.

Another study examining 70 PwP admitted to a single hospital in New York found that the 53 patients who were Covid-19–positive had a significantly higher mortality than the 17 Covid-19–negative patients who were admitted to hospital (35.8% vs 5.9%, $P=0.028$) (Parihar, Ferastraoaru, Galanopoulou, Geyer, & Kaufman, 2021). PwP older than 70 years of age, those with advanced disease, those with reductions in their medications, and non-Hispanics (largely comprised of Black/African-Americans) had a statistically significant higher mortality rate, if infected with SARS-CoV-2. The latter point suggests that socioeconomic factors may contribute to mortality in this setting. Importantly, PD did not increase mortality rates from SARS-CoV-2 infection when age was controlled. Similarly, Xu et al. surveyed 46 PD patients who reported Covid-19 positivity to their movement disorders specialist at a university institution (Xu et al., 2021). They found a mortality rate of 13%, but did not find sufficient evidence that PD is an independent risk factor for severe Covid-19 and death. A study which

included PwP, patients with a diagnosis of parkinsonism and a control group matched to the PD cohort (and therefore of advanced age and with comparable comorbidities) found a high case fatality rate for those hospitalized with Covid-19 in all groups (PD: 25%; parkinsonism 50%; matched controls 39%) (Vignatelli et al., 2021).

One study specifically aimed at comparing the case fatality of Covid-19-positive PwP with Covid-19-positive PwP by analysis of the TriNetX COVID-19 research network, a health research database with deidentified medical records of over 50 million patients (Zhang, Schultz, Aldridge, Simmering, & Narayanan, 2020). Among 78,355 Covid-19 patients without PD, 5.5% died compared with 21.3% of the 694 PwP with Covid-19. The PD and non-PD groups had different age distribution (median age 79 vs 50), sex distribution (female 39.8% vs 55.3%), and racial composition (African American 9.7% vs 19.7%). Logistic regression demonstrated that the mortality risk in PwP is significantly higher than that of the general population (odds ratio 1.27), even when controlling for these age, sex, and race differences. To address residual confounders, the authors then matched five Covid-19 patients without PD to each PD patient with the exact age, sex, and race and performed a conditional logistic regression which demonstrated that PwP had a significantly higher risk of dying from Covid-19 compared to patients without PD (OR = 1.30, 95% CI: 1.13–1.49, $P < 0.001$). However, crucially the database lacked information on comorbid risk factors for Covid-19 which could influence mortality.

Hence, mortality estimates in PwP with Covid-19 are broadly spread with figures ranging from 5.2% to 100% (Table 2). More recently, four systematic reviews and meta-analyses have helped to clarify risk. El-Qushayri and colleagues performed a systematic review which included 13 studies, encompassing 8649 PD patients and 88,710 controls (El-Qushayri et al., 2021). Hospitalization was reported in eight studies (263 patients) with a pooled rate of 39.89% for PwP (95% CI: 27.09–58.73). Length of hospital stay was comparable in PwP with Covid-19 and Covid-19-positive patients without PD (cumulative mean difference: 2.69, 95% CI: −6.99–12.37; $P = 0.586$). The pooled rate of Intensive Care Unit (ICU) admission was 4.7% (95% CI: 1.56–14.16). The total mortality rate for PwP was found to be 25.1% (95% CI: 16.37–38.49) with no significant differences between Covid-19 patients with PD and without PD (OR: 1.42, 95% CI: 0.26; 7.70; $P = 0.687$). It is important to note that, there was significant heterogeneity observed among studies with respect to rates of hospitalization and mortality. Moreover, these analyses do not consider age, other demographic factors, or geographic factors including race/ethnicity or comorbidities.

Another systematic review calculated a pooled mortality rate of 18.9% in PwP with Covid-19 (Artusi et al., 2021). Importantly, from six of the studies included which reported cases in nursing homes, 46.8% of Covid-19-positive PwP were living in a nursing home. A third systematic review and meta-analysis included 12 studies with 103,874 Covid-19 patients to examine in-hospital outcomes of PwP with COVID-19 (Putri et al., 2021). They assessed not only mortality in these patients, but also severe Covid-19. The latter was defined as any of the following: (1) respiratory distress ($\geq$30 breaths per min); (2) oxygen saturation at rest $\leq$93%; (3) ratio of the partial pressure of arterial oxygen (PaO2) to a fractional concentration of oxygen inspired air (fiO2) $\leq$300 mmHg; or (4) critical complication (respiratory failure, septic shock, and or multiple organ dysfunction/failure) or admission into ICU. They found that PD was associated both with severe Covid-19 (OR 2.61 (95% CI 1.98–3.43), $P < 0.00001$), and mortality (RR 2.63 (95% CI 1.50–4.60), $P = 0.0007$]). The authors subsequently performed a meta-regression which determined that the above findings were affected by age ($P = 0.05$), but not by gender ($P = 0.46$), hypertension ($P = 0.44$), diabetes ($P = 0.58$), or dementia ($P = 0.23$). Finally, the meta-analysis which included the largest number of studies to date (21 studies) found pooled prevalence of mortality in PD Covid-19 cases was 12% (95% CI: 10%–14%) ($I^2 = 97.6\%$, $P < 0.001$) (Khoshnood et al., 2021).

In summary, PwP are at significant risk of poor outcomes and death from SARS-CoV-2 infection. Based on the currently available studies and meta-analyses, the mortality rate appears to be most likely in the range of 18%–25%. However, whether this risk is specific to PD itself or is largely driven by advanced age and other comorbidities is unclear. If we have learned anything from the heterogeneity PD and the specifics of the studies described in this chapter, it is reasonable to assume that pooled mortality rates do not capture the nuances of which PwP are at risk and why. We will discuss some of these factors in more detail in the next section.

5. Reported modulators of Covid-19 risk in Parkinson's disease

5.1 Canonical Covid-19 risk factors

In large studies of the general population, hypertension, diabetes, pulmonary disease, obesity and immunosuppression have been consistently shown to be independent risk factors for Covid-19 (Alqahtani et al., 2020; de Siqueira et al., 2020; Zheng et al., 2020). These risk factors are so common in the

general population that it is almost impossible to adjust for these confounders when studying any specific population with Covid-19. In many of the studies outlined in this chapter, authors have noted that cardiovascular comorbidities are considerable contributors to the Covid-19 risk in PD (Antonini, Leta, Teo, & Chaudhuri, 2020; Artusi et al., 2020; Bhidayasiri, Virameteekul, Kim, Pal, & Chung, 2020; Cilia et al., 2020; Del Prete et al., 2020; Fasano, Elia, et al., 2020). Diabetes is a frequent comorbidity in PwP (Bhidayasiri et al., 2020). Furthermore, Covid-19-positive PwP have been shown in one study to be more likely to suffer from chronic obstructive pulmonary disease than their Covid-19 negative counterparts (Fasano, Cereda, et al., 2020). In fact, an analysis of hospital data in Germany of in-patients with PD from the year 2018 found a strikingly high prevalence of what we now know to be Covid-19 risk comorbidities (Richter, Bartig, Krogias, & Tönges, 2020). Approximately half of PwP had hypertension, 15%–20% had diabetes mellitus, 10%–15% had cardiovascular disease and 6%–15% had chronic kidney disease. Hence these canonical risk factors for Covid-19 continually seep into these PD studies – the contribution, albeit poorly quantified, is undeniable.

5.2 Vitamin D

As mentioned above vitamin D has been highlighted to potentially reduce the risk of Covid-19 in one study (Fasano, Cereda, et al., 2020). This was, however, further consolidated by a meta-analysis which found vitamin D supplementation to be associated with a lower odds ratio of contracting Covid-19 among PwP (OR: 0.50, 95% CI: 0.30–0.83, I^2: 0%) (Chambergo-Michilot et al., 2021). This supports the independent suggestion that vitamin D could reduce the risk of Covid-19 infection in the general population via a number of mechanisms, including reducing the concentration of pro-inflammatory cytokines (Mitchell, 2020). Vitamin D deficiency may contribute to Covid-19 susceptibility (Ilie, Stefanescu, & Smith, 2020; Mitchell, 2020) and is a common comorbidity in PD (Ding et al., 2013). This has prompted some authors to propose vitamin D replacement as a therapy against both Covid-19 and PD (Azzam, Ghozy, & Azab, 2022; Behl et al., 2021; Hribar, Cobbold, & Church, 2020). It is clear that dedicated studies are needed to examine the effect of vitamin D on Covid-19 risk in PwP.

5.3 Age, disease severity and dementia

Early data from Wuhan showed clear evidence of the association between Covid-19 and older, frail patients with multiple pathologies (Meng et al., 2020). It is clear that increasing age is also a significant risk factor for

Covid-19 and PD prevalence increases with age, but other confounders may also be at play when examining Covid-19 prevalence in PD. Age greater than 60 is a significant determinant of mortality from Covid-19 in the general population (Bonanad et al., 2020). It is precisely in this age group that we see the highest prevalence of PD. Older people tend to present more atypically in the setting of SARS-CoV-2 infection (D'Adamo, Yoshikawa, & Ouslander, 2020). This phenomenon may be even more prominent in older people with PD where worsening of motor symptoms may be the only presenting symptom and, hence, mask the symptoms of Covid-19, leading to delayed treatment and poor outcomes (Fearon & Fasano, 2021). Furthermore, typical Covid-19 symptoms, such as fatigue, anosmia, subjective changes in temperature or limb pain, are also part of the spectrum of non-motor PD symptoms, which these patients experience every day. Anosmia, which was one of the earliest symptoms which people were told to look out for following the emergence of SARS-CoV-2 is present in over 96% of PwP (Tarakad & Jankovic, 2017).

However, the case fatality does seem to be higher in PwP compared to the general population of similar age (4.5% in people over 60 years of age (Verity et al., 2020)). Hence, other factors such as cognitive impairment, institutionalization and frailty may contribute to the observed increased risk. Indeed, dementia is an age-independent risk factor for severity and death in Covid-19 in hospitalized patients (Tahira, Verjovski-Almeida, & Ferreira, 2021). For comparison, taking all patients with dementia (which will include some PwP) the prevalence of Covid-19 is 13% (Bianchetti et al., 2020). A retrospective case-control study from Spain compared demographics of 39 Covid-19-positive PwP to 172 Covid-19-negative PD controls (Sainz-Amo et al., 2020). Covid-19-positive cases were more likely to be institutionalized and have co-existent dementia (36% vs 14%, $P = 0.0013$). A comparison of mortality in a large number of hospitalized patients (259 with PD) in a multi-center study found no difference in the 28-day mortality risk between PwP and other patients (Fathi, Taghizadeh, Mojtahedi, Zargar Balaye Jame, & Markazi Moghaddam, 2021). They did, however, find a significant increase in 28-day mortality risk among the 363 patients with Alzheimer's disease also included in the analysis.

A significant number of studies have suggested that advanced PD may be a prominent risk factor for poor outcomes from Covid-19 (Antonini, Leta, Teo, & Chaudhuri, 2020; Artusi et al., 2020; Brown et al., 2020; Fasano, Elia, et al., 2020; Zhai et al., 2021). On the other hand, mild-to-moderate Covid-19 appears to be contracted independently of age and disease duration in PD and mid-stage PwP have a similar outcome from Covid-19 than

the non-PD population (Cilia et al., 2020). Another study similarly found no difference in age or disease duration in symptomatic Covid-19 PwP compared to those who were Covid-19-negative. However, the finding that patients with parkinsonism have a much higher risk of hospitalization from Covid-19 compared to PwP or controls suggests that disease complexity and progression may play a significant role in determining outcomes (Vignatelli et al., 2021).

An important group of patients who were frequently omitted from the studies outlined in this chapter are those in residential care. A systematic review published in April 2021 estimated that from six studies in the literature which included nursing home residents 46.8% of Covid-positive PwP in the literature (n = 22/47) were living in a nursing home (Artusi et al., 2021). In a retrospective observational study of 18 patients (13 PD, 5 non-PD) hospitalized in a rehabilitation unit, 23% of the PwP had advanced therapies (one intra-jejunal levodopa, one STN-DBS, one MRI-guided focused ultrasound thalamotomy) (Sorbera et al., 2021). The authors found that 77% of PD and 60% of non-PD tested positive for Covid-19 and that there was no difference in Covid-19 disease course between the PD and non-PD groups. Another study of 12 residential care patients who were hospitalized due to a SARS-CoV-2 outbreak in the care home, reported that all patients had mild Covid-19 symptoms (Buccafusca et al., 2021). Most of the PwP had a long disease duration and multiple comorbidities, however none required ICU admission or died. However, a large prospective cohort study of 1538 residents in Dutch nursing homes, 14 of whom had PD, found a higher mortality among those with PD when adjusted for age, sex and comorbidities (HR 1.49, 95% CI 1.11–2.00, $P=0.007$) (Rutten et al., 2020).

5.4 Parkinson's disease medications

As mentioned above, the potentially protective role of amantadine, as an antiviral agent, naturally led to its study in PD cohorts. A telephone-based study found that none of the 568 patients receiving amantadine (16.5%) in the study developed Covid-19 (Santos García et al., 2020). Similarly a small number of Covid-19-positive PwP taking amantadine did not manifest symptoms of the disease in another study (Rejdak & Grieb, 2020) and other case reports have reported similar results (Aranda-Abreu, Aranda-Martínez, & Araújo, 2020; Cortés Borra, 2020). The potential role for amantadine in Covid-19 treatment is further supported by a drug screen gene expression study suggesting that amantadine might be effective in reducing replication and infectivity of SARS-CoV-2 (Smieszek et al., 2020). The protective role of amantadine has not been confirmed by other studies (Fasano, Elia, et al., 2020).

Two studies have demonstrated that patients with a worse outcome were less likely to be on dopamine agonists (Fasano, Elia, et al., 2020; Sainz–Amo et al., 2020). However, this most likely reflects the fact they are more rarely prescribed in patients with advanced disease and higher baseline frailty. Other studies have not demonstrated differences in concomitant medication use (Cilia et al., 2020; Fasano, Cereda, et al., 2020), although they have found that PwP and COVID–19 might require higher doses of levodopa.

6. Conclusion

There have been extensive attempts to clarify two important questions in PwP since the start of the Covid–19 pandemic: (1) Are PwP at higher risk for contracting Covid–19; and (2) if they do contract Covid–19, is PD a specific risk factor for poor outcomes from the infection? Unfortunately, the rapidity with which Covid–19 has swept across the globe has made constructing large well-designed studies to examine these questions in a rigorous fashion problematic.

The data collected so far does not indicate that PD itself is a specific risk factor for developing Covid–19. A broad range of prevalence rates have been reported to date and much of this may relate to the specific study design (e.g., seroprevalence vs self-reported phone-based questionnaire) or geographical factors. One major confounder has been that PwP may potentially self-isolated to a greater degree than the general population, hence, reducing their risk of exposure. This behavior may have masked a true increased predisposition to a SARS-CoV-2 infection.

PwP are at significant risk of poor outcomes and death from a SARS-CoV-2 infection. However, whether this risk is specific to PD itself or is largely driven by advanced age, advanced disease and frailty or by other comorbidities is unclear. Irrespective of the mechanisms of the risk of poor outcomes from Covid–19, PwP are a cohort for whom exposure to SARS-CoV-2 should be minimized to avoid these outcomes. The unfortunate downside of minimizing exposure risk in PwP is the negative effects of isolation. Social isolation is a known risk factor for poor outcomes in the general population (Pantell et al., 2013). The pandemic has led to significantly worse stress, depression, anxiety, physical activity and quality of life for PwP than healthy controls (Shalash et al., 2020). Lack of access to physiotherapy and aerobic exercise removes a crucial intervention which protects against progression of parkinsonian symptoms in these patients

(van der Kolk et al., 2019). This co–existence of anxiety, stress, isolation and physical inactivity is a particularly detrimental combination for PwP (Helmich & Bloem, 2020) and worsening of motor and non-motor symptoms of PD have been demonstrated (Fabbri et al., 2021) in addition to worsening of standard cognitive test scores (Palermo et al., 2020). We will undoubtedly see the long-term negative outcomes of prolonged isolation and limited access to exercise and social interaction in people who may have, for example, young-onset PD and may be at the early stages of a progressive neurodegenerative illness. Like all considerations which have been undertaken since the start of the Covid–19 pandemic, one must weigh up these negative consequences of isolation in PwP with the risk of poor outcome outlined above. As a final point, it is important to note that the current data is almost entirely drawn from the pre-vaccination era of the pandemic and a re-evaluation of the Covid–19 risk in vaccinated PwP is desperately needed. An early population study from the UK indicates that PD still increases the risk of poor outcome among vaccinated patients (Hippisley-Cox et al., 2021).

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