Characteristics and Outcomes of Parkinson's Disease Individuals Hospitalized with COVID-19 in a New York City Hospital System

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ABSTRACT: Background: The coronavirus disease 2019 (COVID-19) pandemic has caused worse health outcomes among elderly populations with specific pre-existing medical conditions and chronic illnesses. There are limited data on health outcomes of hospitalized Parkinson's disease (PD) individuals infected with COVID-19.
Objectives: To determine clinical characteristics and outcomes in hospitalized PD individuals infected with COVID-19.
Methods: Individuals admitted to NewYork-Presbyterian with a diagnosis of PD were retrospectively identified using an electronic medical record system. Clinical characteristics and mortality were abstracted.
Results: Twenty-five individuals with PD, mostly male (76%) with a median age of 82 years (IQR 73–88 years), were hospitalized for COVID-19 infection. A total of 80% of individuals had mid-stage to advanced PD (Hoehn and Yahr 3–5) and 80% were on symptomatic pharmacologic therapy, most commonly levodopa (72%). The most common comorbidities were hypertension (72%) and mild cognitive impairment or dementia (48%). A total of 44% and 12% of individuals presented with altered mental status and falls, respectively. Mortality rate was 32% compared to 26% for age-matched controls ($P = 0.743$). Individuals who died were more likely to have encephalopathy during their admission (88% vs. 35%; $P < 0.03$).
Conclusion: PD individuals who require hospitalization for COVID-19 infection are likely to be elderly, have mid-stage to advanced disease, and be on pharmacologic therapy. Hypertension and cognitive impairment are common comorbidities in these individuals and encephalopathy during hospitalization is associated with risk of death. Altered mental status and falls are clinical presentations of COVID-19 infection in PD that clinicians should be aware of. A diagnosis of PD is not a risk factor for COVID-19 mortality.

Severe acute respiratory syndrome coronavirus 2 (SARS–CoV–2) rapidly caused a global pandemic beginning in early 2020. New York City (NYC) was one of the earliest epicenters in the United States (US), with over 19,984 confirmed deaths by December 2020.[1] The coronavirus disease 2019 (COVID-19) pandemic has particularly threatened the lives of the elderly population and those with chronic illnesses.[2] Advancing age, male sex, chronic hypertension, and other cardiovascular comorbidities have been identified as risk factors for worsened disease severity and mortality.[2] Parkinson's disease (PD) is a chronic neurodegenerative condition that impairs mobility and functionality and largely affects an elderly population[3] who also often have age-related comorbidities. Given their vulnerability, it is plausible that PD individuals may be at greater risk for COVID-19 and its

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associated sequelae. Several studies to date have found no increased risk of COVID-19 infection in PD individuals compared to the general population.[4–7] However, there may be increased risk to those with advanced age and disease to suffer more severe consequences including death.[8,9] Given the paucity of data on the impact and outcomes of COVID-19 disease in hospitalized PD individuals,[4,8,10] we examined the characteristics and outcomes of PD individuals who suffered from COVID-19 infection severe enough to require hospitalization.

Methods

This was a retrospective cohort study of PD individuals hospitalized with COVID-19. We used the Weill Cornell Medicine (WCM) COVID-19 data warehouse to identify COVID-19 individuals with a diagnosis of PD. The COVID-19 data warehouse included a comprehensive set of data automatically abstracted from the electronic medical records of individuals evaluated in the emergency department or hospitalized for polymerase chain reaction (PCR)-confirmed COVID-19 at NewYork-Presbyterian/Weill Cornell Medical Center and NewYork-Presbyterian/Lower Manhattan Hospital between March 17, 2020 and August 8, 2020. We used International Classification of Diseases tenth revision (ICD-10) code G20 and administration of any PD medications to identify those with PD. PD medications searched included any levodopa therapy, dopamine agonists, catechol-o-methyltransferase inhibitors, monoamine oxidase inhibitors, amantadine, trihexyphenidyl, and istradefylline. A study investigator with expertise in movement disorders (L.N.) manually reviewed the electronic medical records of these individuals to confirm the PD diagnosis and abstract data on demographics, clinical presentation, hospital course, and an estimated Hoehn and Yahr (H&Y) score. Total daily levodopa equivalent daily dose (LEDD) was calculated using a standard protocol.[11] In addition, we calculated the mortality rate in an age-matched cohort of patients without a diagnosis of PD who were hospitalized for COVID-19 during the same period. After extracting data on eligible individuals from the WCM COVID-19 data warehouse, we de-identified and maintained all chart-review data in REDCap (Research Electronic Data Capture, Vanderbilt University, Nashville, Tennessee).

To assess comparative data on mortality rates among hospitalized PD patients without COVID-19, we used all-payer claims data on all discharges from all non-federal acute care hospitals in Arkansas, Florida, Georgia, Iowa, Maryland, Massachusetts, Nebraska, New York, Utah, Vermont, and Wisconsin (https://www.hcup-us.ahrq.gov/db/state/siddbdocumentation.jsp). Data were available from calendar year 2016 for all 11 states; from 2017 for all states except New York; and from 2018 for Florida, Iowa, Maryland, Nebraska, Vermont, and Wisconsin. Using ICD-10 code G20, we identified hospitalized PD patients and calculated their in-hospital mortality rate.

Statistical analyses were performed using Stata (version 15.1; StataCorp). χ^2 and Fisher's exact test were used to analyze differences between categorical variables. We used the Wilcoxon rank sum test to analyze differences between continuous variables. Statistical significance was based on a 2-tailed α of <0.05. Given the exploratory nature of the analysis, no corrections were made for multiple comparisons. The WCM Institutional Review Board approved this study and waived the requirement for informed consent.

Results

Demographics

We identified 25 individuals with a diagnosis of PD who were evaluated in the emergency department or hospitalized with COVID-19. All patients were admitted and treated primarily for COVID-19 infection. Men comprised 76% of individuals (Table 1). The median age of the group was 82 years (IQR = 73–88 years). The majority of individuals identified as White (59%), whereas 27% and 14% identified as Asian and African-American, respectively. Two-thirds (68%) of individuals presented to the hospital from home, and others were brought in from assisted living facilities (12%) or nursing homes (20%).

Clinical Characteristics

On review of records, no identified PD patient had apparent features of atypical parkinsonism. A total of 80% of individuals had moderate to severe PD symptoms (H&Y 3–4, 40%; H&Y 5, 40%) (Table 1). Median disease duration was 6 years (IQR = 2.5–10.5), but this data was only available in 11 individuals. The median duration from COVID-19 symptom onset to hospital admission was 4 days (IQR = 1–10 days). A majority of individuals were on pharmacologic treatment for PD, with levodopa being the most common medication (72%) and dopamine agonists, the second most common (28%). Median LEDD was 300 (IQR = 75–451). Two individuals had a deep brain stimulation (DBS) device. The most common comorbidities were hypertension (72%), mild cognitive impairment (MCI) or dementia (48%), cardiac disease (44%), and diabetes (40%). Common presenting symptoms included fever, altered mental status, cough, shortness of breath, and generalized weakness (Fig. 1). Both motor and non-motor PD symptoms were reported to worsen in 8 individuals, including tremor, rigidity, gait difficulty and falls, constipation, urinary incontinence, dizziness, confusion, and hallucinations.

Clinical Outcomes

All but 1 individual was admitted into the hospital for further management. Most individuals (80%) required supplemental oxygen at some point during hospitalization, typically on initial presentation (Table 1). Half (52%) of the individuals suffered from encephalopathy during hospitalization, manifesting as confusion,

TABLE 1 *Characteristics of hospitalized Parkinson's disease individuals stratified by death*

	Total (n = 25)	Alive (n = 17)	Died (n = 8)	*P* value
Age, median (IQR), y	82 (73–88)	81 (68–89)	83.5 (79.5–87)	0.56
Male	19 (76)	14 (82)	5 (63)	0.34
Delay in presentation, median (IQR), days	4 (1–10)	7 (2–13)	1 (0.5–4.5)	0.02
Race[a]/ethnicity[b]				
White	13 (59)	9 (64)	4 (50)	0.82
Asian	6 (27)	3 (21)	3 (38)	
African American	3 (14)	2 (14)	1 (13)	
Hispanic	2 (8)	1 (6)	1 (13)	0.56
Place of residence				
Home	17 (68)	12 (71)	5 (63)	0.99
Nursing home	5 (20)	3 (18)	2 (25)	
Assisted living	3 (12)	2 (12)	1 (13)	
PD treatment				
LEDD, median (IQR)	300 (75–451)	300 (200–451)	312 (3–490)	0.75
Levodopa	18 (72)	13 (76)	5 (63)	0.64
Dopamine agonist	7 (28)	4 (24)	3 (38)	0.64
COMT inhibitor	2 (8)	1 (6)	1 (13)	0.99
Amantadine	1 (4)	1 (6)	(0)	0.99
MAOB inhibitor	1 (4)	1 (6)	(0)	0.99
Anticholinergics	0 (0)	–	–	
DBS	2 (8)	1 (6)	1 (13)	0.99
Intestinal levodopa	0 (0)	–	–	
Hoehn & Yahr				
1–2	5 (20)	4 (24)	1 (13)	0.87
3–4	10 (40)	7 (41)	3 (38)	
5	10 (40)	6 (35)	4 (50)	
Comorbidities				
Hypertension	18 (72)	11 (65)	7 (88)	0.36
MCI or dementia	12 (48)	7 (41)	5 (63)	0.41
Cardiac disease	11 (44)	8 (47)	3 (38)	0.99
Diabetes	10 (40)	5 (29)	5 (63)	0.19
Pulmonary disease	3 (12)	2 (12)	1 (13)	0.99
Renal disease	2 (8)	1 (6)	1 (13)	0.99
Hepatic disease	1 (4)	1 (6)	(0)	0.99
Cancer	1 (4)	1 (6)	(0)	0.99
Smoker	0 (0)	–	–	
Obesity	0 (0)	–	–	

(Continues)

TABLE 1 *Continued*

	Total (n = 25)	Alive (n = 17)	Died (n = 8)	*P* value
Complications				
Supplemental oxygen	20 (80)	12 (71)	8 (100)	0.14
Encephalopathy	13 (52)	6 (35)	7 (88)	0.03
Renal failure	7 (28)	4 (24)	3 (38)	0.64
ICU admission	4 (16)	3 (18)	1 (13)	0.99
Intubation	2 (8)	1 (6)	1 (13)	0.99
Other[c]	0 (0)	–	–	
Treatment				
Antibiotics	19 (76)	11 (65)	8 (100)	0.13
Hydroxychloroquine	15 (60)	10 (59)	5 (63)	0.99
Remdesivir	0 (0)	–	–	
Length of stay, median (IQR), days	10 (5–15)	–	–	
Disposition				
Home[d]	8 (32)	–	–	
Rehabilitation facility	6 (24)	–	–	
Skilled nursing facility	2 (8)	–	–	
Assisted living	0 (0)	-	–	
Continued hospitalization	1 (4)	–	–	
Death	8 (32)	–	–	

COMT, catechol-o-methyl transferase; DBS, deep brain stimulation; ICU, intensive care unit; IQR, interquartile range; LEDD, levodopa equivalent daily dose; MAOB, monoamine oxidase type-B; MCI, mild cognitive impairment.
[a]Data missing: 3.
[b]Data missing: 10.
[c]Mechanical circulatory support, seizure, stroke, hepatic failure, dialysis.
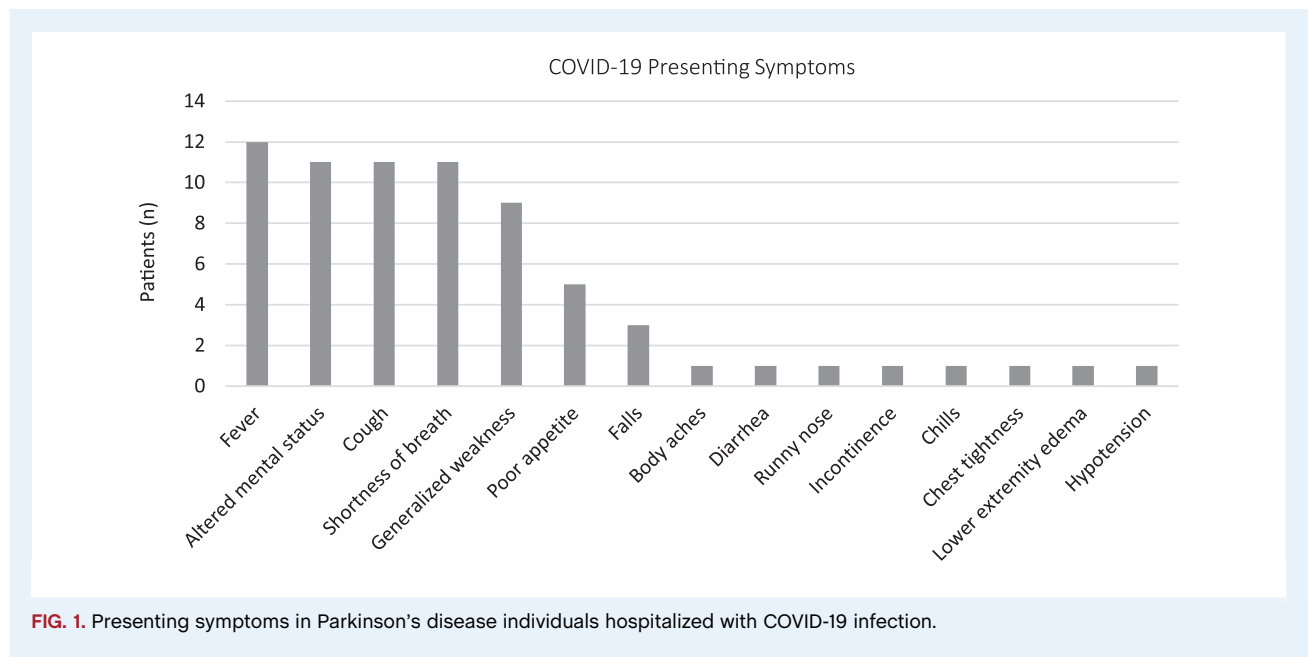[d]One individual was discharged to home hospice.

FIG. 1. Presenting symptoms in Parkinson's disease individuals hospitalized with COVID-19 infection.

hallucination, delirium, or reduced consciousness. Renal failure occurred in 28% of individuals. Four individuals required Intensive Care Unit care and 2 were intubated. Three-quarters (76%) of individuals were treated with antibiotics and 60% received hydroxychloroquine; none received remdesivir. There were no changes made to PD medication regimen during hospitalization. Hospital length of stay ranged from 0 to 43 days (median 10 days, IQR = 5–15 days). The mortality rate was 32%; another 32% of individuals went home (including one individual to home hospice) and 24% were discharged to rehabilitation facilities. There was no significant difference in mortality rate between the PD cohort and age-matched controls (32% vs. 26%; $P = 0.74$).

Using all-payer claims data from 11 US states during 2016 to 2018, we identified 109,274 hospitalized PD patients. Their mean age was 77 (SD = 10) and 41.7% were female. These patients were significantly younger than the PD patients with COVID-19 at our institution ($P < 0.001$). Of the 109,274 patients identified in our all-payer claims data, 3042 (2.8%) died during the hospitalization; this mortality rate was significantly lower than the mortality of PD patients hospitalized with COVID-19 at our institution during our study period ($P < 0.001$).

Compared to those who survived, individuals who died had a shorter time from symptom onset to presentation (1 [IQR = 0.5–4.5] vs. 7 [IQR = 2–13] days; $P < 0.023$). In addition, individuals who died were more likely to have encephalopathy during their admission (88% vs. 35%; $P < 0.03$). There were no other statistically significant associations with mortality among other variables of interest, although we lacked power for these comparisons (Table 1).

Discussion

This report adds to the limited data on PD individuals affected by COVID-19 infection, especially in the United States. We determined that hospitalized PD individuals tended to be elderly, have mid-stage to advanced disease, have hypertension, and be on pharmacologic PD therapy. Altered mental status was a common presenting symptom in PD individuals, sometimes in the absence of respiratory symptoms. COVID-19 outcomes in PD individuals were poor, with one-third dying and only one-third being discharged to home. Most importantly, a diagnosis of PD did not increase mortality rate.

Older age, longer disease duration[9] and advanced therapy such as DBS or levodopa infusion therapy have all been associated with increased susceptibility to COVID-19 infection with poor outcomes[8] in the few studies available. Our findings also include those with mid-stage to advanced disease and on any pharmacologic therapy, collectively suggesting that advanced disease could be the main risk factor for severe COVID-19 infection in PD. Data on disease duration was limited in our cohort, hence, we could not analyze its impact on hospitalization or mortality. Elderly and advanced disease individuals may represent a particularly vulnerable population, given factors such as higher chance

of respiratory compromise and poor mobility. However, compared to the general population, PD individuals do not seem to have a higher rate of hospitalization.[4] Our cohort had a high prevalence of hypertension (72%), an uncommon comorbidity in PD,[12] similar to smoking[13] (that was not evident in our group as expected). This may suggest that the subset of PD individuals with comorbid hypertension may be more susceptible to hospitalization, because we now know chronic hypertension is one of the major risk factors for worsened COVID-19 disease severity and mortality.[2] Approximately half (48%) of our cohort had a diagnosis of MCI or dementia. This is not surprising because the cumulative prevalence of PD dementia can reach 75% after 10 years of disease, especially in older individuals with more severe disease.[14] Of those 12 individuals, 7 experienced encephalopathy during their hospital course. MCI and dementia are known risk factors for mortality in PD.[15,16] This association was not present in our cohort; however, we did find that individuals who had encephalopathy during hospitalization had a statistically significant higher mortality rate, possibly an indirect effect of their comorbidity. None of our subjects had obesity, also linked to severe manifestation of the infection, perhaps because of omission from the electronic medical record.

Only a few studies have determined symptomatologic presentation of COVID-19 in PD individuals.[7,17] Awareness of these symptoms are important for people with PD and their caregivers, in addition to clinicians. Many individuals presented with symptoms seen in the general COVID-19 population including fever, cough, and shortness of breath.[2] However, in our PD cohort, altered mental status was a common presentation, similar to findings by de Marcaida et al (61%),[17] manifesting as confusion, hallucinations, or reduced consciousness. This presenting symptom was more common in individuals who died (75% vs. 29%; $P < 0.081$) and may partly explain the earlier presentation of these individuals, as change in mental status suggests a more fulminant disease process, and hence, would trigger earlier care seeking. Other important symptoms to recognize include generalized weakness (fatigue) and impaired mobility/falls, similarly reported by Antonini et al[8] to be present in PD individuals with COVID-19. Clinicians should consider COVID-19 testing in PD individuals who present with these symptoms with or without pulmonary symptoms. A few individuals also had documented worsening of motor and/or non-motor symptoms, which is likely a secondary response to concurrent infection.[18] The limited documentation of PD symptomatology and lack of changes to PD medications could suggest a reduced focus on PD during hospitalization, especially at a time when uncovering the complexities and management of SARS-CoV-2 is the main focus. This supports the implementation of measures to optimize management of PD during hospital admissions, such as the PD Hospitalization and Coronavirus Preparedness Fact Sheet developed by the Parkinson's Foundation.[19]

Levels of COVID-19 mortality in PD have been reported in the general community (5.7%),[7] in hospitalized individuals (40%)[8] and a combination of both (19.7%).[9] Our mortality rate of 32% reflects individuals who were hospitalized and with more severe illness than the general COVID-19 population, explaining

the high mortality rate. We found that a diagnosis of PD was not associated with an increased risk of mortality in hospitalized individuals, which is consistent with prior studies.[4,7] Although disease severity was not statistically significant, 50% of individuals in our study who died had H&Y score of 5. Hospital mortality in PD has been shown to affect those with more advanced disease (H&Y score >3).[20] However, none of the deaths were associated with PD. We did not find any significant effect of PD medications or LEDD on mortality. There are several hypotheses with regard to the potential therapeutic role of PD medications in COVID because of possible co-expression of dopa decarboxylase, and angiotensin–converting enzyme 2, the main receptor to SARS-CoV2.[21] Amantadine interferes with viroporin protein channel involved in the release of RNA in SARS coronavirus and potential mechanisms have been proposed for reduction of the viral load and severity of the disease in PD patients.[22] A comprehensive assessment of comorbidities associated with severity and prognosis of COVID-19 showed chronic kidney disease, chronic obstructive pulmonary disease (COPD), and hypertension are major factors that contribute to increased disease severity and worse prognosis.[23] In our cohort, none of the measured comorbidities had a significant effect on mortality, possibly because of insufficient power to detect differences.

Our study is the first study from NYC, a once epicenter of the COVID-19 pandemic. The cohort is reflective of the general Parkinson's disease population in NYC cared for by both neurologists and general practitioners. A major strength is that despite ICD codes being used to determine diagnosis and comorbidities, an additional electronic medical record review was performed by a movement disorders specialist to confirm diagnosis and hospitalization parameters. Our study has several limitations. One limitation is that there is certainly a possibility that a small percentage of individuals were misdiagnosed as Parkinson's disease, instead of an atypical parkinsonism, because often many parkinsonian patients are. Second, results were obtained in a small study population; hence, we are underpowered to show statistical differences between subgroups. A larger cohort follow-up and longitudinal studies would allow for a more thorough evaluation of PD risk factors for severe COVID-19 infection and the prognosis of individuals who are affected. In addition, we could not comment on relationship between disease duration and health outcomes, given limited data. We also could not assess the relationship between changes in PD medications and the risk of mortality, because none of the PD patients had adjustments to their PD medications. Finally, we lacked comparative data on the usual PD mortality or incidence of PD hospitalization at our institution; however, we were able to compare our cohort to hospitalized PD patients in 11 states in the United States.

In conclusion, this report adds to the scarce data on clinical impact of COVID-19 infection on people with PD, especially in the United States. We highlight risk factors for hospitalization that should be recognized by clinicians managing people with PD including older age, mid-stage to advanced disease, pharmacologic therapy and comorbidity of hypertension and cognitive impairment. In addition, we emphasize the need for clinicians and caregivers to recognize altered mental status and gait difficulty/falls as possible presenting symptoms of COVID-19 infection in those with PD. Finally, we reestablish that PD is not a risk factor for COVID-19 mortality. Studies comprising larger cohorts of PD individuals with COVID-19 infection, including long-term follow up, are needed to confirm findings from our study, identify potential risk factors for severe infection, hospitalization or mortality, determine long-term sequelae of the illness, and detect potential interactions between severe infection and chronic neurodegeneration.

Acknowledgments

Author Roles

(1) Research project: A. Conception, B. Organization, C. Execution; (2) Statistical Analysis: A. Design, B. Execution, C. Review and Critique; and (3) Manuscript Preparation: A. Writing the First Draft, B. Review and Critique.

L.N.: 1A, 1B, 1C, 2A, 2C, 3A, 3B
C.Z.: 2A, 2B, 2C, 3B
A.L.: 3B
H.S.: 3B
C.H.: 3B
H.S.: 3B
H.K.: 3B

L.N. takes responsibility for the integrity of the data and the accuracy of the data analysis

Disclosures

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