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RESEARCH ARTICLE

Clinical features and outcomes of hospitalised patients with COVID-19 and Parkinsonian disorders: A multicentre UK-based study

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Abstract

Background

Parkinson's disease has been identified as a risk factor for severe Coronavirus disease 2019 (COVID-19) outcomes. However, whether the significant high risk of death from COVID-19 in people with Parkinson's disease is specific to the disease itself or driven by other concomitant and known risk factors such as comorbidities, age, and frailty remains unclear.

Objective

To investigate clinical profiles and outcomes of people with Parkinson's disease and atypical parkinsonian syndromes who tested positive for COVID-19 in the hospital setting in a multi-centre UK-based study.

Methods

A retrospective cohort study of Parkinson's disease patients with a positive SARS-CoV-2 test admitted to hospital between February 2020 and July 2021. An online survey was used to collect data from clinical care records, recording patient, Parkinson's disease and COVID-19 characteristics. Associations with time-to-mortality and severe outcomes were

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analysed using either the Cox proportional hazards model or logistic regression models, as appropriate.

Results

Data from 552 admissions were collected: 365 (66%) male; median (inter-quartile range) age 80 (74–85) years. The 34-day all-cause mortality rate was 38.4%; male sex, increased age and frailty, Parkinson's dementia syndrome, requirement for respiratory support and no vaccination were associated with increased mortality risk. Community-acquired COVID-19 and co-morbid chronic neurological disorder were associated with increased odds of requiring respiratory support. Hospital-acquired COVID-19 and delirium were associated with requiring an increase in care level post-discharge.

Conclusions

This first, multicentre, UK-based study on people with Parkinson's disease or atypical parkinsonian syndromes, hospitalised with COVID-19, adds and expands previous findings on clinical profiles and outcomes in this population.

Introduction

The Coronavirus disease 2019 (COVID-19) pandemic caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has spread worldwide since early 2020 with unprecedented speed [1]. Initial observations suggested that in the general population, poor outcomes due to SARS-CoV-2 were associated with particular demographic factors such as older age, and co-morbidities including hypertension, diabetes and coronary heart disease [2]. This has led to the development of clinical risk prediction models to identify risks of poor short-term outcomes due to the SARS-CoV-2 infection (mortality and hospital admission) and offer guidance to public health policymakers for clinical decision-making processes, prioritisation for vaccination, and targeted recruitment for clinical trials. Among them, the QCovid and the more recently developed QCovid3 risk algorithms, have identified Parkinson's disease (PD) as a risk factor for severe COVID-19 outcomes, despite vaccination (adjusted cause-specific hazard ratios for COVID-19 death after vaccination of 2.23 (1.79 to 2.78)) [3, 4]. Advanced age, frailty and impaired cough reflex are commonly observed in people with PD (PwP) and might contribute to their susceptibility to developing severe acute respiratory syndrome [5]. A variety of studies have investigated mortality in PwP and COVID-19 with figures ranging from 5% to 100% [6]; the wide range reflects the heterogeneity of methodologies used (case report, series, surveys, retrospective or prospective cohort studies) and cohort analysed (home-based vs hospitalised patients, early vs advanced patients, etc.) [7–19]. However, whether the factors associated with the significant high risk of death from COVID-19 in PwP are related to PD or to other concomitant and known risk factors such as comorbidities (hypertension, diabetes, pulmonary disease, obesity, immunosuppression, and dementia), older age (>60 years) and frailty remains unclear [6]. Participants in the COVID-19 PD UK study include inpatients with PD and related neurodegenerative diseases (atypical parkinsonian syndromes (APS) including multiple system atrophy (MSA), progressive supranuclear palsy (PSP), as well as dementia with Lewy bodies (DLB)). The COVID-19 PD UK study is the first to investigate the association of demographic, co-morbidity, COVID-19 and PD-specific factors with mortality and

severe outcomes of PwP who tested positive for COVID-19 admitted to a UK NHS trust hospital.

Methods

Study design and population

The COVID-PD UK study was a retrospective cohort study across 21 acute care settings in England. Approvals were obtained from the University of Plymouth Faculty Research Ethics and Integrity Committee (Ref: 2269) and the Health Research Authority (IRAS ID 285686). Members of the project team included PwP who were involved in all aspects of protocol and study development.

The study consisted of patients with a clinical diagnosis of PD, APS (including progressive supranuclear palsy, multiple system atrophy) or Parkinson's dementia syndrome (Parkinson's disease dementia (PDD) or dementia with Lewy bodies (DLB)) admitted to participating hospitals between 5th February 2020 and 31st July 2021, with a positive polymerase chain reaction (PCR) test. During this time, NHS PCR testing was to some degree heterogeneous, details of testing methodologies and implementation during the pandemic are summarised by the UK Health Security Agency [20]. Exclusion criteria were patients with a diagnosis of vascular parkinsonism and a COVID-19 positive test over 2 weeks prior to admission or at any time following discharge.

Clinical care teams completed an online survey (S1 File) on JISC (https://www.onlinesurveys.ac.uk/) using patients' clinical care records, extracting information from admission to at least 28 days following admission. Retrospective data collection began in February 2021 and the online survey closed on the 31st July 2021. Individuals were pseudo-anonymised by sites to allow for data clarification where required.

Sites were asked to enter data for all participants meeting the eligibility criteria during the data collection period. Sites were contacted by the study team to identify their method of identification of patients, including comprehensively selecting all patients or random sampling.

Data included patient, PD and COVID-19 related characteristics along with details of admission, discharge and participation in a COVID-19 related clinical trial. Comorbidities were chosen to allow comparison with the International Severe Acute Respiratory and emerging Infection Consortium (ISARIC) study of hospitalised COVID-19 patients in the UK [21]. Patient characteristics included age, sex, ethnicity, index of multiple deprivation (IMD), location pre-admission and clinical frailty score (CFS) [22]. PD related features captured included those considered neurological risk features in UK national guidance [23], such as significant cognitive impairment or psychosis, bulbar symptoms, significant respiratory compromise, significant autonomic neuropathy, as well as marked motor fluctuations and Hoehn and Yahr (H&Y) stage. PD features and comorbidities could be entered as unknown by site staff on the JISC survey. No imputation of missing data was performed, however, sites were asked to address unexpected responses and missing data during the querying process by checking patient care records and providing the study team with updated responses where necessary.

The wave of positive SARS-CoV-2 test was identified. Wave one: 23/03/2020 to 30/05/2020, corresponding to wild-type SARS-CoV-2, and wave two: 07/09/2020 to 22/05/2021 [24] corresponding to the emergence of alpha and delta variants in the UK [25].

Patients were classified as vaccinated if their positive SARS-CoV-2 test was over 14 days following their first vaccine dose. COVID-19 was classified as hospital-acquired if the positive SARS-CoV-2 test was more than 5 days following admission; otherwise, COVID-19 was classified as community-acquired.

COVID-19 and non-COVID-19 symptoms at admission were recorded as free text and subsequently grouped by the research team into categories including altered mental state (delirium, confusion, obtundation, reduced oral intake), COVID-19 (pyrexia, cough, anosmia) and other respiratory symptoms. Symptoms were summarised for the community- and hospital-acquired COVID-19 patients separately.

The primary outcome of the study was death from any cause within 28-days of a COVID-19 positive test. Date of death was recorded as the Sunday following death to preserve anonymity. We therefore used death within 34-days as a proxy outcome; this assumption was explored in a sensitivity analysis. Secondary outcomes included the requirement for respiratory support (oxygen supplementation, continuous positive airway pressure, non-invasive ventilation or intubation), an increase in the level of care post-discharge and change in levodopa equivalent daily dose (LEDD).

Statistical methods

A summary of the data is presented using frequency and percentages for categorical variables of the non-missing sample, while means, standard deviations, medians and ranges are presented for continuous variables. Values entered as 'unknown' were coded to missing to ease the comparison between presence and absence of characteristics and due to the small group sizes of some unknown categories.

Survival within 34-days of a COVID-19 positive test was analysed using univariable and multivariable Cox proportional hazards models, using Schoenfeld's test to assess the assumption of proportional hazards. The requirement for respiratory support and an increase in care were modelled using univariable and multivariable logistic regression models. Model selection for the final multivariable models was conducted using backward elimination, whilst including variables of clinical interest: sex, age, ethnicity, diagnosis, wave of COVID-19 positive test and where COVID-19 was acquired, regardless of their statistical significance. For each outcome, the first-order interaction of wave and where COVID-19 was acquired was examined for statistical significance. In the multivariable models, site was included as a random effect to account for potential differences in practice and COVID-19 severity between UK regions during the pandemic.

Change in LEDD was found to occur in less than 25% of discharged individuals and was therefore analysed descriptively.

Sensitivity analyses were conducted for all outcomes using individuals with a positive SARS-CoV-2 test in wave two, sites that comprehensively selected their patients to enter over waves one and two and for the survival outcome, censoring at 28-days.

All analyses are presented with 95% confidence intervals and all tests are two-sided, where a p-value of < 0.05 is considered statistically significant. All analyses were conducted using R version 4.1.3 [26] using packages including survival [27], glmmTMB [28] and forester [29].

Results

Site staff from 21 hospitals entered 627 individual data sets; of these 17 were duplicates, 38 were excluded due to unverifiable data and 20 were excluded due to meeting the exclusion criteria. The final number of individual admission data sets included in the COVID-19 PD UK study was 552 compromising 385 community-acquired and 167 hospital-acquired COVID-19 infection episodes; the timing of these admissions is shown in Fig 1. Six sites entered data comprehensively over waves one and two (n = 242), while due to resource

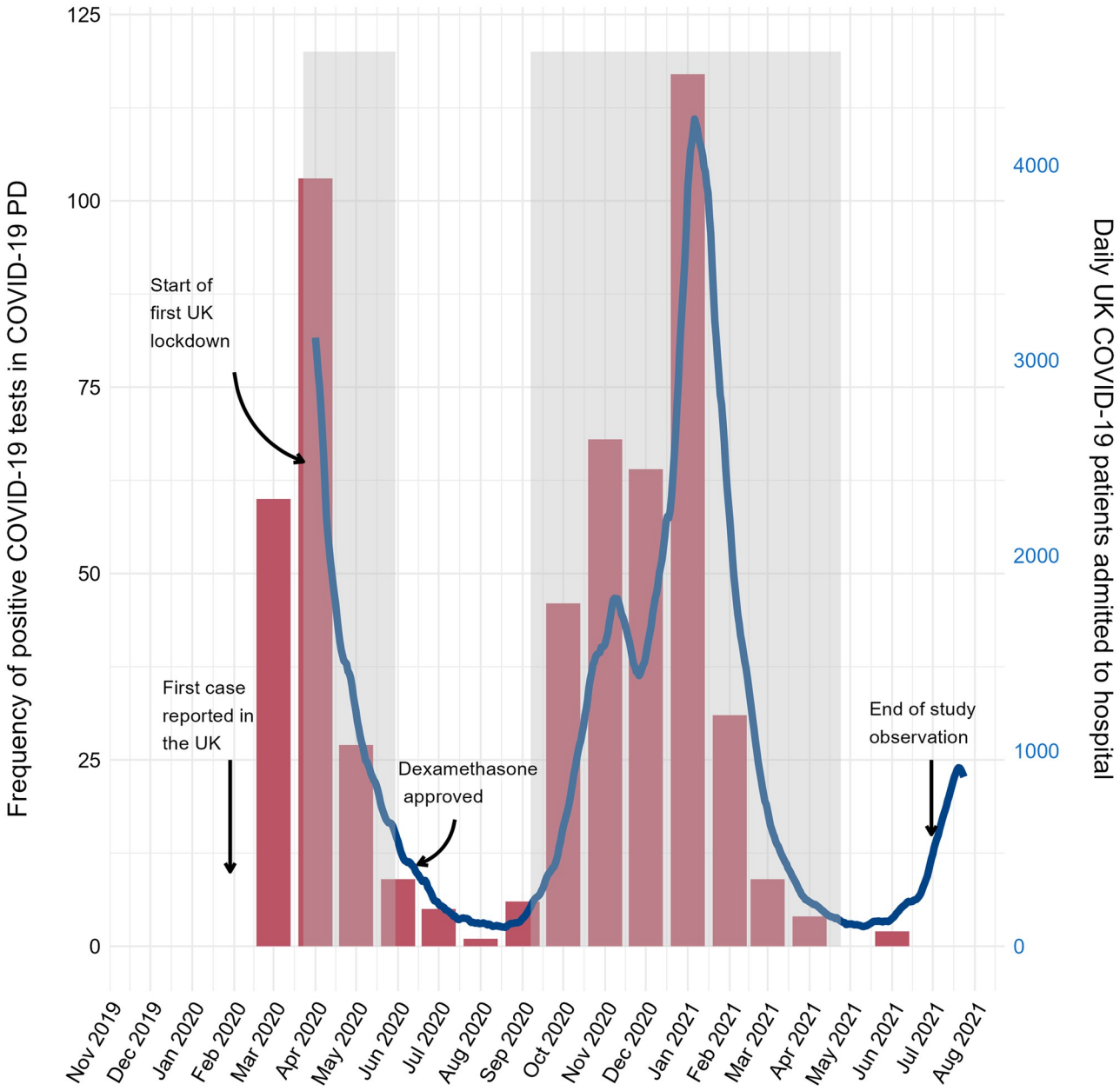

Fig 1. COVID-19 PD UK participants compared to UK daily hospital admissions. Positive COVID-19 cases captured in the COVID-19 PD UK study (red bar chart, left y-axis) by month, overlaid by UK daily COVID-19 hospital admissions [30] (blue line graph, right y-axis). Grey regions reflect COVID-19 wave one (23/03/2020–30/05/2020) and wave two (07/09/2020–22/05/2021) in the UK.

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constraints, the other sites submitted data for one of the two waves or entered data from a selection of patients.

Demographics and comorbidities

Patient demographics and diagnosis of parkinsonian syndrome details are presented in Table 1. The majority of the patients had PD (349/552 (63.2%)), with 170/552 (30.8%) having

Table 1. Patient demographics by diagnosis.

		Parkinson's disease	Parkinson's dementia syndrome	Atypical parkinsonian syndrome	Total
	N (% of total)	349 (63.2)	170 (30.8)	33 (6.0)	552 (100.0)
Age at admission (years)	N	349	170	33	552
	Median (IQR)	81 (74–86)	81 (76–85)	75 (70–78)	80 (74–85)
	[Min., Max.]	[43, 99]	[65, 101]	[45, 98]	[43, 101]
Disease duration (years)	N	339	168	33	540
	Median (IQR)	5 (3–9)	5 (3–9)	2 (1–4)	5 (2–9)
	[Min., Max.]	[0, 27]	[0, 29]	[0, 11]	[0, 29]
LEDD[a] (mg)	N	340	169	33	542
	Median (IQR)	450 (300–653)	375 (150–575)	200 (0–400)	400 (243–615)
	[Min., Max.]	[0, 2313]	[0, 2300]	[0, 800]	[0, 2313]
Sex	N	349	170	33	552
Male	N (%)	224 (64.2)	120 (70.6)	21 (63.6)	365 (66.1)
Female		125 (35.8)	50 (29.4)	12 (36.4)	187 (33.9)
Ethnicity[b]	N	349	170	33	552
White British	N (%)	298 (85.4)	152 (89.4)	26 (78.8)	476 (86.2)
Asian/British Asian (Indian)		10 (2.9)	3 (1.8)	2 (6.1)	15 (2.7)
White (any other background)		10 (2.9)	2 (1.2)	1 (3.0)	13 (2.4)
Asian/British Asian (Pakistani)		5 (1.4)	1 (0.6)	0 (0.0)	6 (1.1)
Other		26 (7.4)	12 (7.1)	4 (12.0)	42 (7.6)
Hoehn and Yahr	N	322	167	32	521
1–2	N (%)	49 (15.2)	5 (3.0)	0 (0.0)	54 (10.4)
2.5–3		125 (38.8)	41 (24.6)	8 (25.0)	174 (33.4)
4–5		148 (46.0)	121 (72.5)	24 (75.0)	293 (56.2)
Clinical frailty score	N	345	167	33	545
<5	N (%)	75 (21.6)	3 (1.8)	3 (9.1)	81 (14.8)
5–6		170 (49.3)	71 (42.5)	14 (42.4)	255 (46.8)
7–9		100 (29.0)	93 (55.7)	16 (48.5)	209 (38.3)
Location pre-admission	N	349	170	33	552
Local/community hospital	N (%)	3 (0.9)	3 (1.8)	1 (3.0)	7 (1.3)
Own Home/private residence		268 (76.8)	97 (57.1)	24 (72.7)	389 (70.5)
Residential or nursing home		78 (22.3)	70 (41.2)	8 (24.2)	156 (28.3)
IMD[c] decile	N	349	170	33	552
1–2	N (%)	63 (18.1)	28 (16.5)	5 (15.2)	96 (17.4)
3–4		77 (22.1)	23 (13.5)	4 (12.1)	104 (18.8)
5–6		77 (22.1)	37 (21.8)	9 (27.3)	123 (22.3)
7–8		69 (19.8)	38 (22.4)	8 (24.2)	115 (20.8)
9–10		63 (18.1)	44 (25.9)	7 (21.2)	114 (20.7)

[a]Levodopa equivalent daily dose (LEDD).

[b]For further breakdown of ethnicity, see S1 Table.

[c]Index of multiple deprivation (IMD).

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PDD/DLB). Only 33 (6.0%) of patients had APS. The median (interquartile range (IQR)) age at admission was 80 (74–85) years with 73.6% of patients over the age of 75 years; APS patients were younger (median (IQR) 75 (70–78) years), while 365/552 (66.1%) were male. The majority of patients were White British (476/552 (86.2%)); further details of the sample ethnicity can be found in S1 Table. Thirty-two patients were enrolled into COVID-19 therapeutic clinical

trials, including 21 in the RECOVERY trial [31]. Further information on Parkinson's and COVID-19 characteristics is provided in S1 Table.

More patients hospitalised with positive SARS-CoV-2 tests had community-acquired rather than hospital-acquired COVID-19 in both wave one (153/190 (80.5%)) and wave two (220/343 (64.1%)).

509/552 (92.2%) had at least one reported co-morbidity at admission, the most frequently reported being hypertension (251/542, 46.3%), dementia (218/535 (40.7%)), chronic cardiac disease (193/539 (35.8%)) and chronic kidney disease (117/535 (21.9%)) (see S1 Table).

Parkinsonian syndrome-related features

349/552 (63.2%) patients had PD, 170/552 (30.8%) had PDD/DLB and 33/552 (6.0%) patients had an atypical parkinsonian syndrome. Overall, 251/535 (46.9%) of the cohort had significant cognitive impairment and 154/493 (31.2%) had marked motor fluctuations. Bulbar symptoms were most common in APS patients (16/32 (50.0%) vs. 49/331, (14.8%) and 33/160 (20.6%) for PD and PDD/DLB, respectively) (see Fig 2 and S1 Table). Patients with PDD/DLB and APS more often had pre-morbid Hoehn and Yahr stages 4–5 (121/167 (72.5%) and 24/32 (75.0%), respectively) compared to PD patients (148/322 (46.0%).

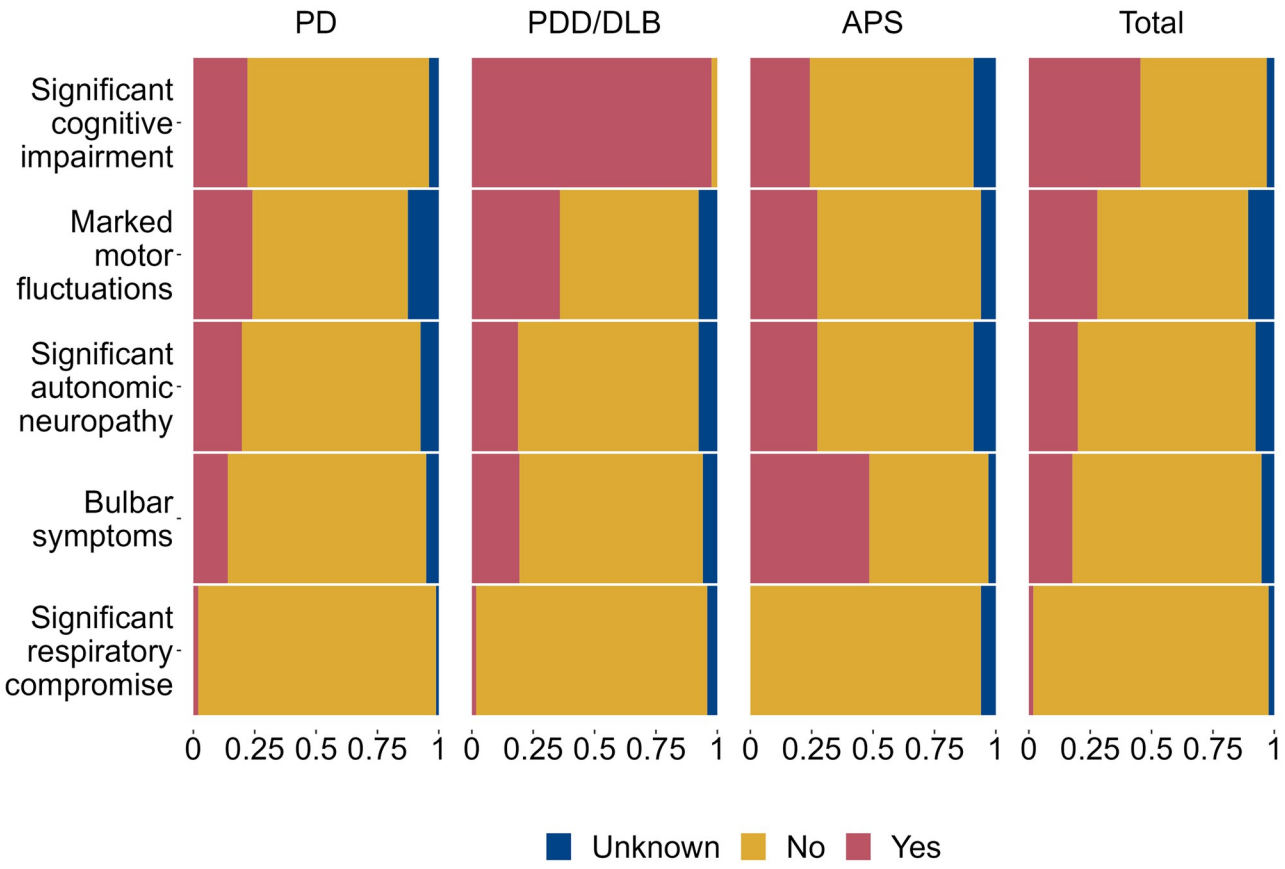

Fig 2. Clinical features of Parkinson's disease. Clinical features of Parkinson's as a proportion by diagnosis of Parkinson's disease. X-axis: proportion of feature within diagnosis. Abbreviations: Parkinson's disease (PD), Parkinson's dementia syndrome (PDD/DLB) and atypical parkinsonian syndrome (APS).

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Symptoms of COVID-19

The frequency of altered mental state and classical COVID-19 or respiratory symptoms for community- and hospital-acquired COVID-19 patients are presented in Fig 3A and 3B, respectively. Of patients with community-acquired COVID-19, 7.0% (27/385) had neither altered mental state nor classical COVID-19 or respiratory symptoms. This was the case in 25.1% (42/167) of the hospital-acquired COVID-19 patients. Altered mental state was the only feature of COVID-19 infection in 15/385 (3.9%) of community-acquired and 16/167 (9.6%) of hospital-acquired cases.

Length of stay

The time from positive test to discharge of patients who acquired COVID-19 in the community was shorter compared to those who acquired COVID-19 in hospital (median (IQR) of 12 (7–21) and 16 (5–28) days, respectively). For those discharged, 84% of community-acquired patients were discharged by day 28 compared to 75% of hospital-acquired patients (Fig 4). Time until discharge was longer for those with bulbar symptoms (median (IQR) of 17 (8–27) compared to 13 (6–23)), a chronic neurological disorder (19 (10–31) compared to 12 (6–22)), those in wave two compared to wave one (15 (6–27) and 12 (7–19), respectively) and those with delirium (15 (7–29) compared to 12 (6–21)). Time until discharge for further patient, COVID-19 and PD characteristics are detailed in S2 Table.

Outcomes

Mortality. Details of patient outcomes and discharge are provided in S1 Table. Of the 552 patients in the COVID-19 PD study, 212 (38.4%) died within 34-days of a COVID-19 positive test. Of these patients, 85.4% (181/212) died in hospital, 9.0% (19/212) died following discharge and 5.7% (12/212) died having been discharged to end-of-life care.

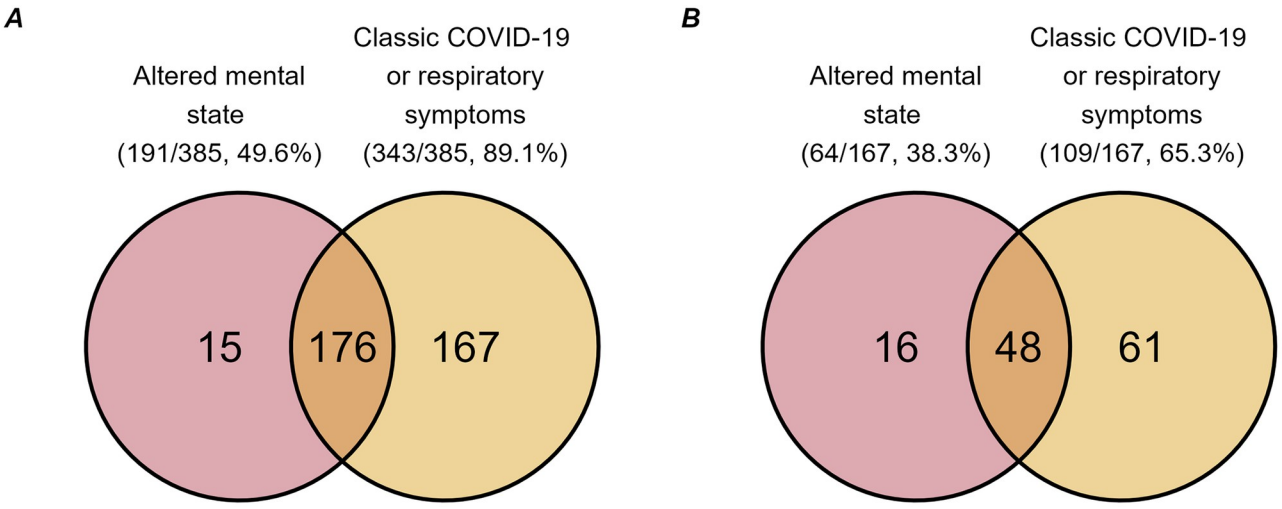

Fig 3. Symptoms of COVID-19. Frequency of altered mental state and classic COVID-19 or respiratory symptoms by where COVID-19 was acquired. A: The frequency of community acquired COVID-19 patients (total n = 385) by symptoms of altered mental state, classic COVID-19 or other respiratory symptoms during admission). B: The frequency of hospital acquired COVID-19 patients (total n = 167) with the symptoms of altered mental state and classic COVID-19 or respiratory symptoms (mild symptoms or respiratory support) associated with their COVID-19 infection.

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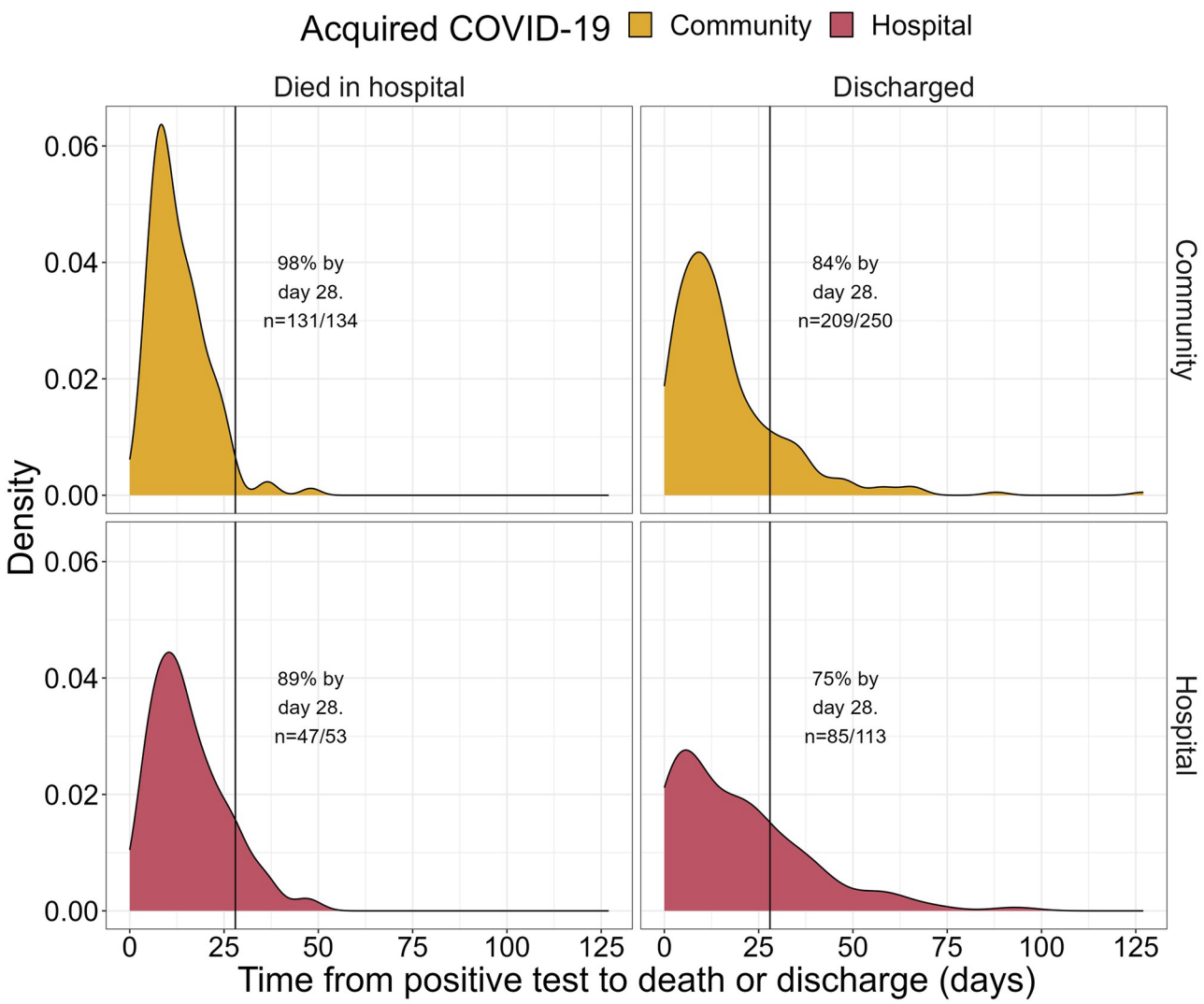

Fig 4. Time to discharge or death. Density plot of time to discharge or death from first positive SARS-CoV-2 test by place of COVID-19 acquisition (community or hospital). Two patients that remained in hospital following the study period have been omitted.

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Univariable and multivariable results of the Cox models for all-cause mortality are provided in S3 Table, along with the results from each sensitivity analysis. The results of the multivariable Cox proportional hazards model are presented in a forest plot in Fig 5. Increased risk of mortality within 34-days was associated with increased age (hazard ratio (HR) 1.05, with a 95% confidence interval (CI) 1.03 to 1.07) and PDD/DLB (HR 1.59 with 95% CI 1.14 to 2.20, reference: PD), after adjustment. Decreased risk of mortality was associated with female sex (HR 0.54, with a 95% CI 0.39 to 0.75), a pre-morbid CFS of <5 (HR 0.62, with a 95% CI 0.44 to 0.85, reference: 7–9), being vaccinated (HR 0.36, with a 95% CI 0.13 to 0.99) and having asymptomatic or mild respiratory COVID-19 symptoms (HR and 95% CI: 0.22, 0.12 to 0.39 and 0.27, 0.18 to 0.41, respectively, reference: respiratory support). No association was found after adjustment between mortality within 34-days and any other PD or COVID-19 features.

As the date of the Sunday following death was captured during the study as a proxy for date of death, all patients included in the primary analysis have been censored at 34-days, with eight patients dying between days 28 and 34. We have conducted a sensitivity analysis

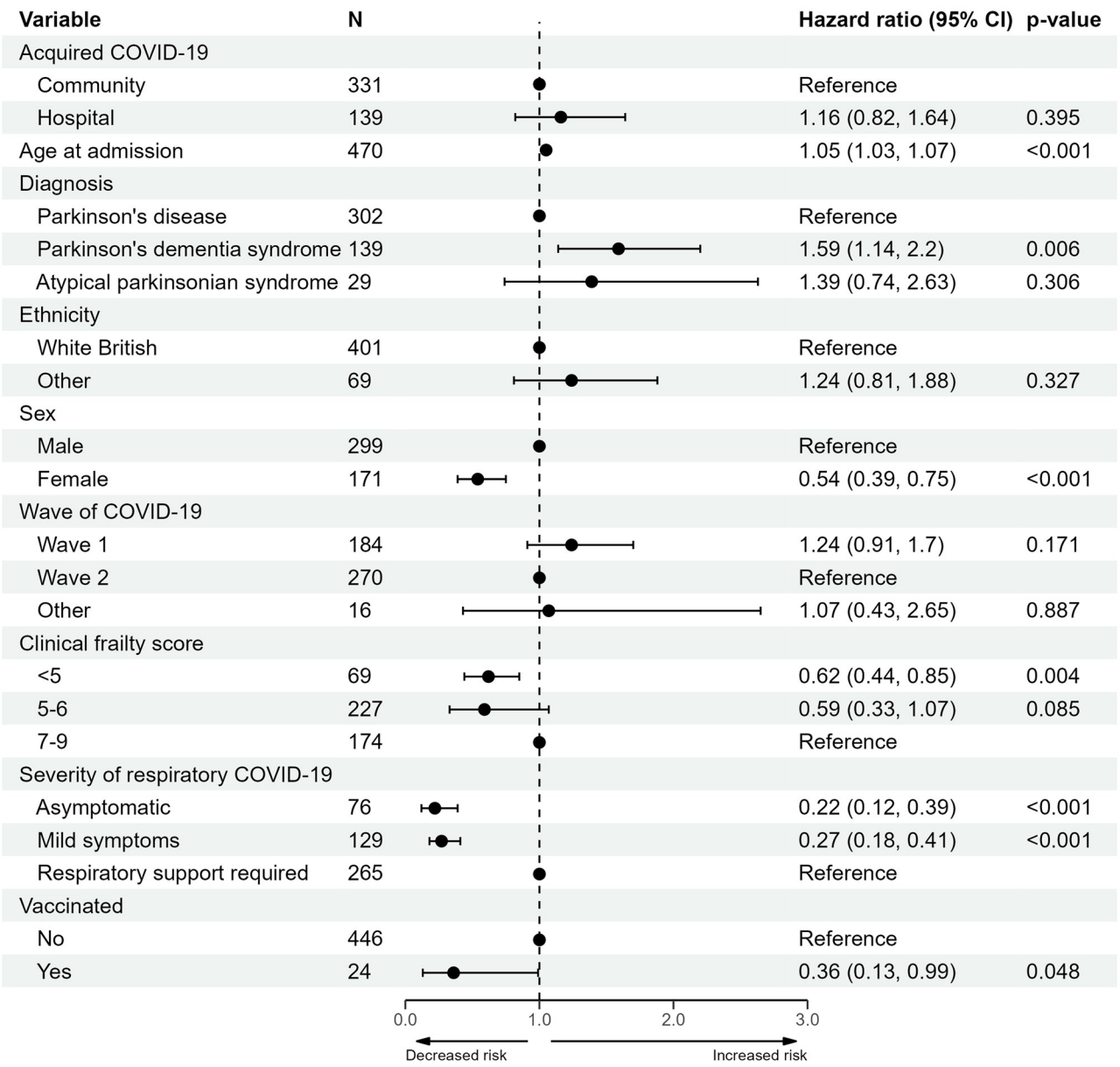

Fig 5. Forest plot of the multivariable Cox proportional hazards model of mortality within 34-days of a COVID-19 positive test. Abbreviations: confidence interval (CI).

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investigating the effect of 28-day censoring; all sensitivity analyses found no substantial changes to the final mortality model (S3 Table).

Requirement for respiratory support. Nine patients (1.6%) in the study were admitted to high-dependency care (HDU) or intensive care units (ICU). Over half of patients received respiratory support while in hospital (291/552, 52.7%) with the majority of these (266/291, 91%) receiving oxygen supplementation; 28.3% (156/552) had mild symptoms not requiring support and 19.0% (105/552) were asymptomatic from a respiratory perspective. Patients with asymptomatic and mild symptoms were combined to compare the odds of requiring respiratory support.

A forest plot presenting the results of the multivariable model is shown in Fig 6 (details of univariable and sensitivity analyses in S4 Table. Increased odds of requiring respiratory support were found to be associated with presence of a co-morbid chronic neurological disorder (odds ratio (OR) 1.81, with a 95% CI 1.06 to 3.09) and community-acquired COVID-19 (OR of hospital-acquired 0.54, with a 95% CI 0.36 to 0.81, reference: community) after adjustment. Sex, age, ethnicity and Parkinsonian syndrome diagnosis were not found to be associated with requiring respiratory support. Sensitivity analyses found no substantial changes to the multivariable model.

Increase in care requirement post-discharge. Increase in care was determined by change in location between admission and discharge, calculated for patients living at home prior to admission who were discharged from hospital. Of these 264 patients, 115 individuals (43.6%) had an increase in care and 149 (56.4%) remained at their pre-admission location at discharge. Results of the analysis are provided in S5 Table, while a forest plot of the multivariable results is provided in Fig 7. Increase in level of care post-discharge was associated with delirium associated with COVID-19 infection (OR 2.07, with a 95% CI 1.48 to 3.86) and hospital-acquired COVID-19 (OR 2.01, with a 95% CI 1.10 to 3.65).

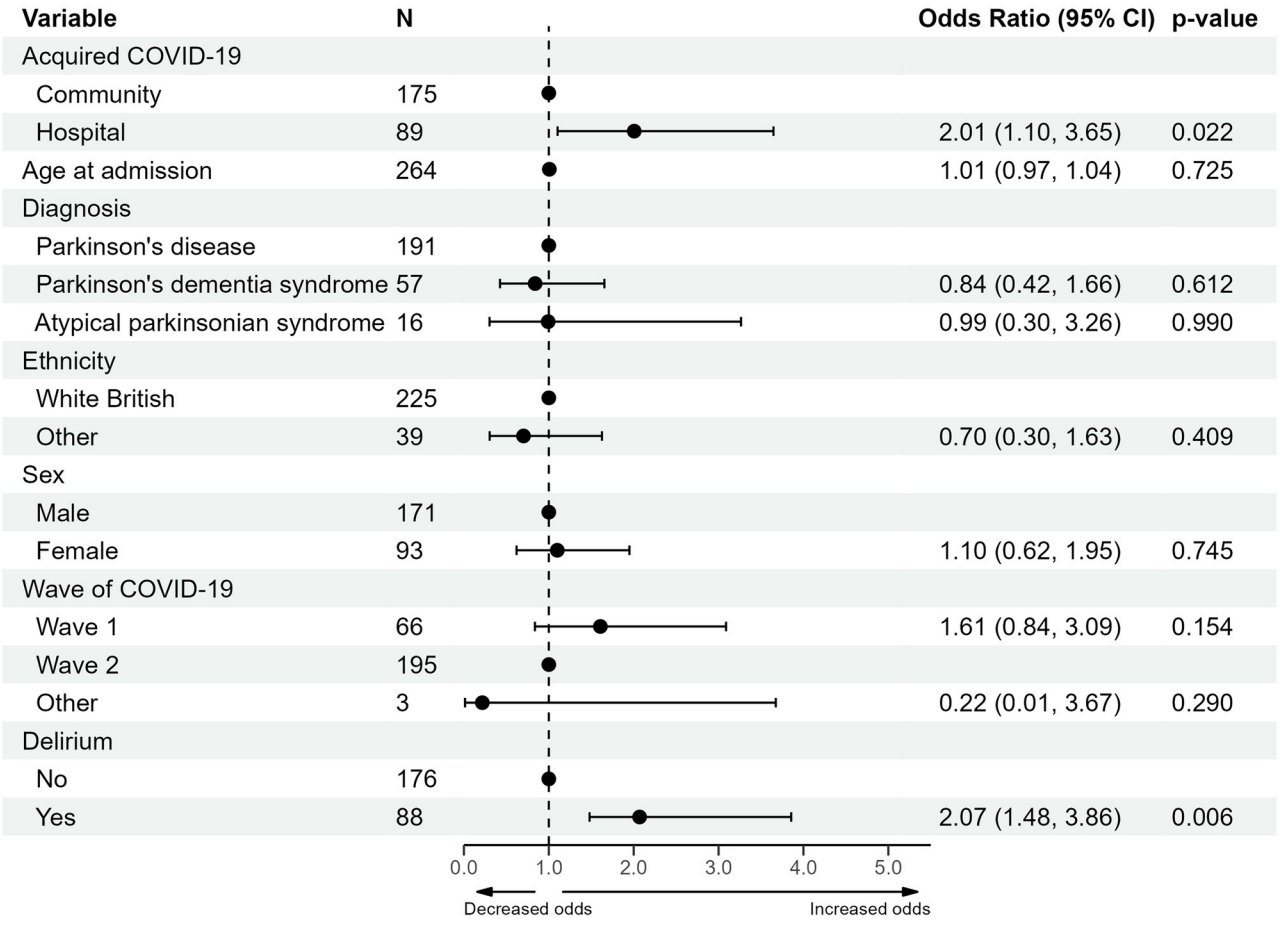

Fig 6. Forest plot of the multivariable logistic regression model of the requirement for respiratory support. Abbreviations: confidence interval (CI).

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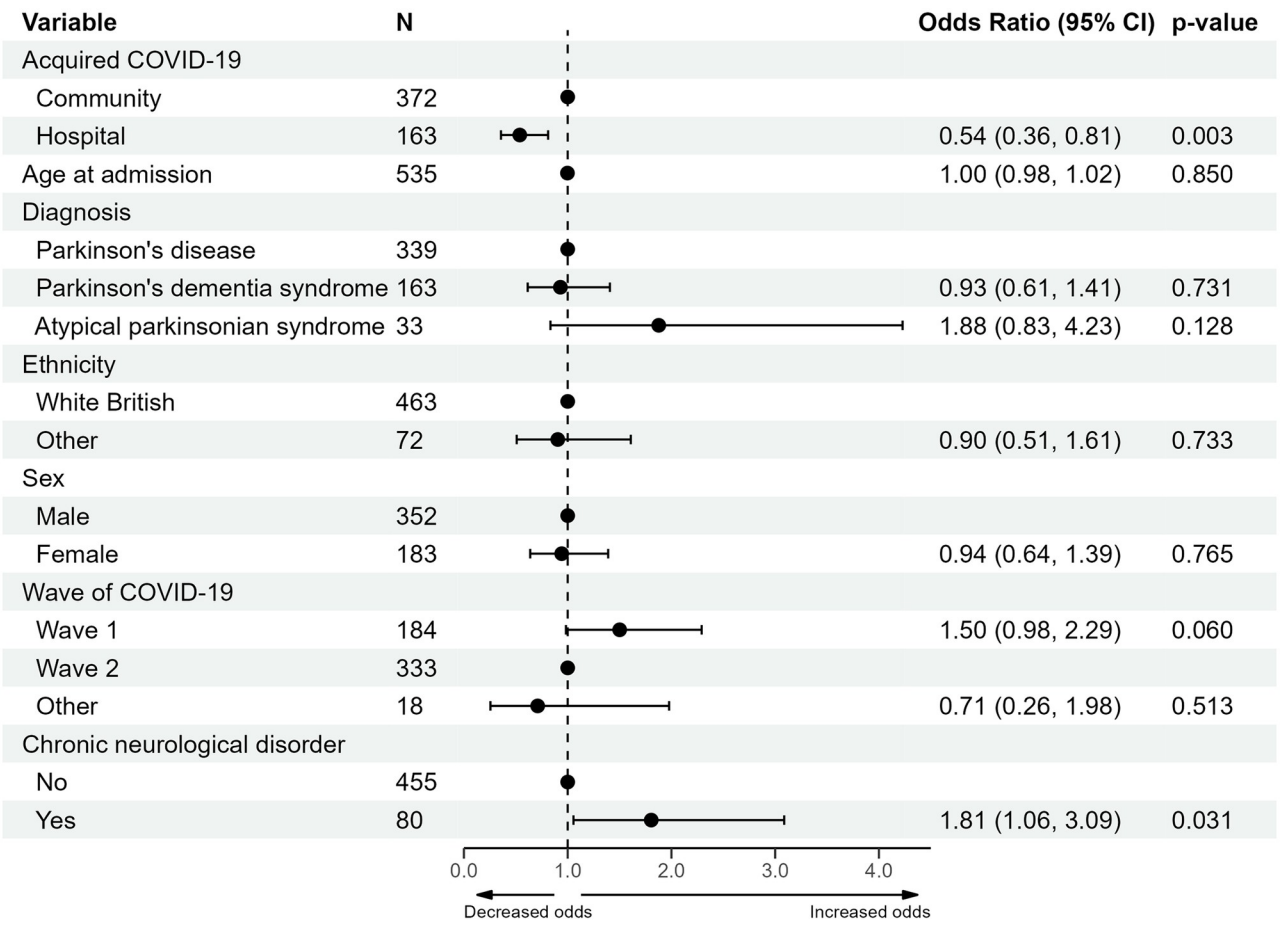

Fig 7. Forest plot of the multivariable logistic regression model of an increase in care post-discharge for patients admitted from their own home. Delirium is considered as delirium associated with COVID-19 infection. Abbreviations: confidence interval (CI).

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Change in levodopa equivalent daily dose. Change in LEDD (mg) was calculated for the 359 individuals who were discharged and had both admission and discharge medication documented. There was no change in LEDD between admission and discharge for 76.0% of individuals (273/359), while 13.4% (48/359) had a decrease in LEDD and 10.6% (38/359) had an increase in LEDD. We observed no indication of an association between variables of clinical interest, diagnostic category and change in LEDD.

Discussion

This is the first multicentre UK-based study to investigate demographics, comorbidities, clinical profiles and outcomes of PwP and APS who tested positive for COVID-19 in the hospital setting. The most common clinical presentations of COVID-19 in PwP and APS with community- and hospital-acquired COVID-19 were classic COVID-19 or respiratory symptoms and altered mental state. Comorbidities frequently reported were hypertension, dementia, chronic cardiac disease, and chronic kidney disease with an overall 34-day mortality rate of 38.4%. Increased age, male sex and diagnosis of PDD/DLB were associated with increased risk of mortality, while low pre-morbid CFS (<5), being vaccinated, and asymptomatic COVID-19 or mild respiratory symptoms were associated with reduced risk of mortality. Finally, while

increased risk of requiring respiratory support was associated with presence of a co-morbid chronic neurological disorder and community-acquired COVID-19, patients with hospital-acquired COVID-19 and delirium required a higher level of care at discharge. Overall, our study extends previous findings on clinical features and outcomes of hospitalised PwP and APS with COVID-19.

In relation to demographics, our cohort of parkinsonian patients had a median age at admission of 80 years which was higher than one of the cohorts of hospitalised non-parkinsonian patients with COVID-19 [21]. Of note, 73.4% (256/349) of our cohort of PD patients were over the age of 75 years compared to 56.3% of the estimated PD population in England [32]. Our cohort included more male (66.1%) than female (33.9%) patients. Overall, these results are in line with known increased prevalence of PD in the elderly and in men [12, 13, 33, 34], as well as older age and male sex being risk factors for hospitalisation with COVID-19 generally [21, 35].

PD patients in our study were more frequently in the advanced motor phases of the disease (46% H&Y 4–5) than the general PD population (16.4% H&Y 4–5 [36]), although with similar prevalence of significant cognitive impairment (23.0% vs 24–31% in PD in the community [37]) and marked motor fluctuations (27.5% vs 29% in PD in the community [38]). In relation to frailty, which is known to be strongly associated with PD and mortality [39, 40], 78.3% of PD patients in our study were pre-morbidly frail (CFS $\geq$ 5), which is higher than a previously reported proportion of PwP with frailty in an ambulant community PwP population (33%) [41]. Our finding is similar to previously reported levels of frailty in hospitalised PwP, where it has been found to predict mortality [42]. Patients within our study were found to have an increased level of frailty compared to the reported cohorts of patients hospitalised with COVID-19 generally [43–45].

Irrespective of the modality of infection (hospital or community-acquired), the most common clinical presentations in our cohort of hospitalised parkinsonian patients with COVID-19 were classic COVID-19 symptoms including fever, shortness of breath, hyposmia and cough or respiratory symptoms in agreement with previous findings in the general population and in PwP [13, 21]. However, we found 49.6% of community-acquired and 38.3% of hospital-acquired COVID-19 infections in our cohort also had altered mental state, with no respiratory symptoms in 3.9% and 9.6% respectively. Patients with altered mental state associated with COVID-19 were more likely to require increased care on discharge in our study. This aligns with findings from a single-centre study on hospitalised patients with COVID-19, where patients with delirium were less likely to be discharged home, and more frequently discharged to other hospitals, nursing homes or rehabilitation institutes [46]. Inconsistent results on the contribution of delirium to mortality in COVID-19 have been published [47], and our data supports a lack of association. Although altered mental state is a common neurological manifestation of COVID-19 in hospitalised patients in general (up to 32%) [48–50], our data suggests that hospitalised PwP or APS and COVID-19 present more frequently with altered mental state than the general population, in line with previous findings and as expected in a population of patients with known central nervous system neurodegeneration [12]. Cognitive impairment is frequently observed in PwP and APS and represents a well-known risk factor for development of delirium [51].

In our study, the most frequently reported comorbidities at admission were hypertension (46.3%), dementia (40.6%), chronic cardiac disease (35.8%), and chronic kidney disease (21.9%). These results only partly mirror those of the ISARIC study [21], which was based on UK hospitalised patients with COVID-19, where only 13.5% of patients were reported with dementia. This discrepancy might be due to the fact that cognitive impairment is an intrinsic feature of PD and APS as previously mentioned [51]; in addition, our cohort included 170

patients with PDD/DLB who present with dementia as per diagnostic criteria [52]. It is also worth mentioning that most PwP are non-smokers, which can partly explain the lower prevalence of chronic pulmonary disease in our cohort of patients than in the ISARIC study [53].

In relation to length of stay, the median time from positive test to discharge in our study was 12 and 16 days for patients with community- and hospital-acquired COVID-19, respectively, which is longer than data from other UK, US and Iranian cohorts (median hospital stay of 5, 10 and 7 days, respectively) [9, 12, 54] reflecting possible differences in study methodology, health care settings, spatial and temporal spread of the pandemic as well as intrinsic features of the study populations.

Our study showed an overall 34-day mortality rate of 38.4% which is in line with data deriving from other US and European cohorts of hospitalised PD patients with COVID-19 of 35.8% and 35.4%, respectively [13, 55]. These mortality rates appear to be higher compared with data from the general population with COVID-19 hospitalised over the same period (overall mortality rate of 25%) [56], adding to the evidence that PwP have a significant risk of poor outcomes [6]. Risk factors for increased mortality in our study were increased age, male sex and diagnosis of PD dementia while protective factors were low CFS (<5), being vaccinated, and COVID-19 with no or mild respiratory symptoms, in agreement with the literature on the general population and PD patients [4, 13, 21].

PwP/APS were more likely to require respiratory support if they had community-acquired COVID-19 or a co-morbid chronic neurological disorder. In our study, requirement for respiratory support was collected as a measure of severity of respiratory COVID-19. This might have unintentionally excluded individuals with worse respiratory COVID-19 than mild symptoms but did not have respiratory support available to them. Alternatively, there may have been individuals with mild symptoms that did not require respiratory support but received oxygen supplementation as a precaution.

We found that patients with hospital-acquired COVID-19 and delirium had increased risk of a requiring a higher level of care at discharge (residential or nursing home or a local hospital). Development of delirium can signpost the presence of an underlying cognitive impairment which might become manifest during the infection and hospitalisation and, ultimately, have a detrimental effect on autonomy in performing activities of daily living [57].

Limitations of the study include the retrospective nature of the survey, perhaps contributing to the level of unknown or missing responses. The study was designed to collect data only from PwP; therefore, we cannot ascertain the risk from COVID-19 of PwP compared to the general population. Limited data on patients from diverse ethnicities were available and, therefore, we were unable to compare risks of poor COVID-19 outcomes between specific ethnic groups. The small number of APS patients limited our ability to evaluate outcomes within this group. COVID-19 testing policy in the UK changed during the course of the study and testing of asymptomatic patients and routine testing of hospital in-patients was uncommon during wave one; however, to account for the change in testing we have adjusted for wave in each model and conducted sensitivity analyses focused on wave two only, where we observed no substantial changes to any outcomes.

Conclusion

In this first, multicentre, UK-based study we found that compared with published data on COVID-19 admissions, PwP or APS hospitalised with COVID-19 have increased mortality and are more likely to require an increase in care level post-discharge. These findings may be attributable to an increased proportion of PwP/APS having dementia and cardiovascular co-morbidities, with COVID-19-associated delirium. PwP admitted with COVID-19 were older

than community-dwelling PwP/APS, with more advanced Parkinson's and higher pre-morbid frailty. Our study expands previous findings on clinical profiles and outcomes of hospitalised PwP and APS with COVID-19.

Supporting information

S1 File. Data collection questionnaire.
(PDF)

S1 Checklist. STROBE statement—Checklist of items that should be included in reports of observational studies.
(DOCX)

S1 Table. Summary of patient, Parkinson's and COVID-19 characteristics by diagnosis.
(DOCX)

S2 Table. Time from positive COVID-19 test to discharge by patient characteristics.
(DOCX)

S3 Table. Univariable, multivariable and multivariable sensitivity analysis results from Cox proportional hazards models of mortality within 34 days of COVID-19 positive test.
(DOCX)

S4 Table. Univariable, multivariable and sensitivity analyses from mixed effects logistic regression models of requiring respiratory support.
(DOCX)

S5 Table. Univariable, multivariable and sensitivity analyses from mixed effects logistic regression models of increase in care.
(DOCX)

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