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Cross-sectional study evaluating the impact of SARS-CoV-2 variants on Long COVID outcomes in UK hospital survivors

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ABSTRACT

Objectives COVID-19 studies report on hospital admission outcomes across SARS-CoV-2 waves of infection but knowledge of the impact of SARS-CoV-2 variants on the development of Long COVID in hospital survivors is limited. We sought to investigate Long COVID outcomes, aiming to compare outcomes in adult hospitalised survivors with known variants of concern during our first and second UK COVID-19 waves, prior to widespread vaccination.

Design Prospective observational cross-sectional study.

Setting Secondary care tertiary hospital in the UK.

Participants This study investigated Long COVID in 673 adults with laboratory-positive SARS-CoV-2 infection or clinically suspected COVID-19, 6 weeks after hospital discharge. We compared adults with wave 1 (wildtype variant, admitted from February to April 2020) and wave 2 patients (confirmed Alpha variant on viral sequencing (B.1.1.7), admitted from December 2020 to February 2021).

Outcome measures Associations of Long COVID presence (one or more of 14 symptoms) and total number of Long COVID symptoms with SARS-CoV-2 variant were analysed using multiple logistic and Poisson regression, respectively.

Results 322/400 (wave 1) and 248/273 (wave 2) patients completed follow-up. Predictors of increased total number of Long COVID symptoms included: pre-existing lung disease (adjusted count ratio (aCR)=1.26, 95% CI 1.07, 1.48) and more COVID-19 admission symptoms (aCR=1.07, 95% CI 1.02, 1.12). Weaker associations included increased length of inpatient stay (aCR=1.02, 95% CI 1.00, 1.03) and later review after discharge (aCR=1.00, 95% CI 1.00, 1.01). SARS-CoV-2 variant was not associated with Long COVID presence (OR=0.99, 95% CI 0.24, 4.20) or total number of symptoms (aCR=1.09, 95% CI 0.82, 1.44).

Conclusions Patients with chronic lung disease or greater COVID-19 admission symptoms have higher Long COVID risk. SARS-CoV-2 variant was not predictive of Long COVID though in wave 2 we identified fewer admission symptoms, improved clinical trajectory and outcomes. Addressing modifiable factors such as length of stay and timepoint of clinical review following discharge may enable clinicians to move from Long COVID risk stratification towards improving its outcome.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ A systematic review highlights a greater Long COVID prevalence in adults with the wildtype variant versus other variants yet includes data on non-hospitalised individuals and non-sequenced SARS-CoV-2 variants. To date, no UK studies have analysed Long COVID burden in hospital survivors according to acute disease severity and sequenced SARS-CoV-2 variants.

WHAT THIS STUDY ADDS

⇒ This observational study demonstrates no association between SARS-CoV-2 variant and Long COVID outcomes in hospitalised adults with the wildtype and Alpha variants, but we demonstrate improved clinical outcomes in those with the Alpha variant. We identify Long COVID risk factors (chronic lung disease, greater COVID-19 admission symptoms) but importantly highlight modifiable factors such as reduced inpatient length of stay and earlier clinic review following discharge that may alter Long COVID trajectory.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ We highlight the need to accurately identify clinical determinants of Long COVID according to its presence and severity, sequenced variants and confounding factors to best modulate impact in high-risk groups, both during and following acute COVID-19.

INTRODUCTION

Background

As of 2 May 2023, an estimated 680 million cases of COVID-19 have been confirmed

worldwide, resulting in over 6.8 million deaths.[1] The UK was among the countries worst affected by the pandemic. By 5 March 2023, an estimated 2 million people (3% of the population) self-reported Long COVID (symptoms persisting for more than 4 weeks following SARS-CoV-2 infection and not explained by an alternative diagnosis). Twenty per cent reported their symptoms adversely affected their day-to-day activities.[2] The SARS-CoV-2 wildtype variant was dominant during the UK's first wave (from February 2020), with the Alpha variant replacing it in wave 2 (onset from October 2020). Twenty-nine per cent of self-reporters had acute COVID-19 before Alpha was the main variant (wave 1) and 12% reported symptoms during the Alpha period (wave 2).[2] These findings are not necessarily reflective of those clinically diagnosed with ongoing symptomatic COVID-19 or post-COVID-19. Additionally, as SARS-CoV-2 variants were not sequenced, these data may not depict accurately the relationship between SARS-CoV-2 variants and Long COVID.

Our research group documented the significant Long COVID burden[3] (69% fatigued, 53% breathless, 34% experiencing cough and 15% depressed) in a smaller number of our wave 1 patients (n=188; 384 total participants across three hospitals) at a median of 54 days from hospital discharge. These data concur with a systematic review of 15 studies[4] (time of follow-up ranging from 15 to 110 days) from viral infection, which found fatigue was the most prevalent Long COVID symptom (58%) and identified a high mental health burden (anxiety in 34% and depression in 32%). The UK National Institute for Health and Care Excellence (NICE) has acknowledged the range and diversity of ongoing symptoms within their recommendations for managing Long COVID.[5]

It remains important to identify risk factors for Long COVID in order to mitigate its possible effect. Arjun *et al*[6] (n=487 Indian adults) found a greater frequency of Long COVID (63% vs 23%) in those with severe acute COVID-19 (n=72) compared with moderate disease (n=415), including hospitalised and non-hospitalised individuals.

How might different SARS-CoV-2 variants contribute? A systematic review of 26 studies[7] concluded that infection with any of four SARS-CoV-2 variants (Alpha (B.1.1.7), Beta (B.1.351), Gamma (P.1) and Delta (B.1.617.2)) increased the risk of acute morbidity, with greater hospitalisation, intensive care admission and mortality, compared with wildtype variant. However, as clinical management has evolved over time, and several international secondary care studies[8–10] demonstrate less acute severe presentation, greater use of corticosteroid drug treatment and less invasive ventilation (IV) across their COVID-19 waves, it remains unclear how variant influences Long COVID outcomes when adjusting for these factors. These studies do not report data on sequenced variants of concern, or vaccination status, which also may modify Long COVID risk in survivors.

Spinicci *et al*[11] (n=428) identified Long COVID sequelae across differing SARS-CoV-2 variants in hospitalised Italian survivors. They identified a similar proportion of persistent symptoms across the wildtype variant (78%) and Alpha variant (72%) at a median of 53 days following hospital discharge (with greater prevalence of myalgia, brain fog and anxiety/depression in those with the Alpha variant). They performed multivariable analysis; female sex, advanced oxygen supplementation and use of immunosuppressant drugs were independently associated with a higher risk of developing Long COVID. This study did not include SARS-CoV-2 variant as an independent variable within this analysis, nor were the variants sequenced. This contrasts to Fernández-de-las-Peñas *et al*[12] (n=614) who used sequenced data in hospitalised patients. This study identified a higher prevalence of Long COVID with the Alpha variant (n=201) compared with wildtype variant (n=211) at 6 months (SD 1.2 months) versus 6.5 months (SD 1.0 months). However, this study did not account for confounding variables such as vaccinated individuals, yet they did identify that their patients with the Alpha variant were older and had a longer hospital stay (p<0.001) while those with the wildtype variant had more admission symptoms.

In comparison, Azzolini *et al*[13] evaluated a non-hospitalised group of healthcare personnel (2560 participants; 229 (31%) had Long COVID) and they divided the patients into groups by the main circulating variant of concern rather than sequenced variant. They demonstrated a lower prevalence of Long COVID in those with the Alpha variant (35.9% vs 48.1% wildtype). When adjusting for confounders, including vaccination status, they demonstrated no statistically significant association with variant type but did show an association with older age, higher body mass index, obstructive lung disease and Long COVID, and a lower probability in those receiving two or three vaccination doses.

These two studies solely contribute to the data comparing wildtype and Alpha variants within a systematic review[14] comparing Long COVID across SARS-CoV-2 variants in hospitalised and non-hospitalised patients (n=6 studies; n=355 infected with the wildtype variant; 512 with Alpha; 41 563 with Delta; 57 616 Omicron). This review identifies a higher prevalence of Long COVID in individuals with the wildtype variant compared with all other variants. Of note, the two included studies comparing the wildtype and Alpha variants differ in their population groups and use different definitions of Long COVID; Azzolini *et al*[13] used the NICE definition[15] of postacute COVID symptoms lasting for more than 4 weeks, whereas Fernández-de-las-Peñas *et al*[12] used the proposal by Soriano *et al*,[16] describing symptoms lasting for at least 2 months.

When examining vaccine outcome in specific SARS-CoV-2 variants on Long COVID outcomes in the UK, a large case–control observational study[17] (n=56 003) highlights differences in Delta versus Omicron variants alone. The relative odds of Long COVID were lower in people with the Omicron variant (0.24 (0.20–0.32)) versus Delta variant (0.50 (0.43–0.59)) following vaccination. This

study used self-reported data from the COVID Symptom Study app with no objective measures of acute illness severity, and identified the periods comparing Omicron and Delta, to be timepoints at which more than 70% of each variant had been identified. To date, no studies have analysed Long COVID burden in hospital survivors according to both disease severity, accurately sequenced SARS-CoV-2 variants and vaccination status.

METHODS

Study design

We established a virtual COVID-19 follow-up service.[3] The current study is an observational cross-sectional study comparing discharged hospital survivors from our peak wave 1 and 2 admissions in a single academic medical centre (Royal Free Hospital). We collected demographic data, comorbidities, admission severity, postdischarge Long COVID symptoms, viral sequences (using previously described methods[18]) and radiological burden to assess differences in clinical severity and Long COVID. Long COVID was defined as any one of 14 symptoms (displayed in table 3 and further described in the online supplemental material). Full details of our inclusion and exclusion criteria, treatment guidelines and statistical methods are included within the online supplemental material. Our follow-up protocols have previously been published[3] and we include details within the online supplemental material. Online supplemental figure 1 summarises the total number of patients with SARS-CoV-2 positive swabs or suspected COVID-19, admitted to our hospital, during the reporting period. Due to this study being conducted during the peak of the COVID-19 pandemic, it was not possible to have patient and public involvement contribution to the design and conduct of this study.

Study participants

Eligible participants included hospitalised adult patients (aged ≥18 years), presenting to hospital with symptoms or signs suggestive of COVID-19 during the first two UK waves, who had a clinical diagnosis of acute COVID-19 made by the admitting medical team (with or without a positive swab for SARS-CoV-2). Online supplemental figure 2 shows the numbers excluded from follow-up within each wave (including those with severe dementia, those too frail to participate in clinical follow-up, patients transferred from another hospital for ongoing care and hospital-acquired cases of COVID-19, defined as a positive swab 7–14 days following admission). Increased COVID-19-related admissions to our hospital were identified to start on 27 February 2020 and 20 October 2020 (according to positive PCR tests performed at our hospital, linked to hospital admissions). Participants were excluded from the analysis if they did not have the main variant of concern within their respective waves (identified as wildtype variant in wave 1 and Alpha variant in wave 2).

We contacted participants for their follow-up assessment across a 39-day admission period in wave 1 and 60 days in wave 2. During the wave 2 admission period, more patients were admitted and discharged (wave 1: n=851 vs wave 2: n=1340). We identified 607 vs 1015 eligible for follow-up in each wave. We analysed outcomes in wave 1 (those with wildtype variant (n=400; no other variant of concern arose during this period and whole genome sequencing was unavailable)) and wave 2 participants confirmed to have the Alpha variant (n=273). The case fatality rate for our cohort during these periods was 29% vs 22% (p<0.001), respectively. There were no cases of reinfection from wave 1 presenting in wave 2. Two patients in wave 2 had received partial vaccination (ie, received one of two doses) before being admitted to hospital.

We further categorised our patients using the three-level WHO inpatient disease severity[19] of non-severe, severe and critical COVID-19. For ease of description, in this paper we have renamed these terms as mild, moderate and severe COVID-19. Mild includes those with no signs of severe or critical disease and moderate disease includes those with oxygen saturations >90% breathing room air, signs of pneumonia or severe respiratory distress. Severe disease includes those with sepsis, shock, acute respiratory distress syndrome or those requiring life-sustaining respiratory support (continuous positive airway pressure (CPAP), high flow nasal oxygen (HFNO), non-invasive ventilation or IV). Our hospitalisation admission criteria did not change between our first two waves, but non-pharmaceutical interventions (contact tracing) and newer pharmaceutical interventions had been implemented (dexamethasone, antiviral biological therapies[20–22] and vaccination roll-out in those clinically vulnerable[23]).

Statistical methods

Please see the online supplemental material for detailed information on statistical analyses used.

RESULTS

Participants

Participants' descriptive analyses are given in table 1 (baseline demographics), table 2 (clinical characteristics of our cohorts) and table 3 (clinical outcomes). Descriptive data according to acute COVID-19 disease severity subgroups are shown in online supplemental tables 1–4 and supplemental figures 3–5. Unadjusted and adjusted multiple logistic regressions evaluating associations with the prevalence of Long COVID symptoms (determined as a self-report of one or more of 14 symptoms) are shown in online supplemental tables 8 and 9, respectively. Unadjusted and adjusted multiple Poisson regressions evaluating associations with the total number of Long COVID symptoms are shown in tables 4 and 5, respectively.

Missing values were removed using listwise deletion. One hundred and nineteen patients had at least one missing value for symptoms after discharge. Even though

Table 1 Baseline demographics and comorbidities in wave 1 and 2 participants

Variable	Wave 1 (n=400)	Wave 2 (n=273)	P value
Baseline characteristics and demographics			
Age, median (IQR), years	n=400 61 (50–74)	n=273 62 (52–75)	0.68
Male gender (%)	247/400 (62)	153/273 (56)	0.14
Ethnicity (%)			
White	200/395 (51)	135/251 (54)	0.44
Black, Asian and minority ethnic	195/395 (49)	116/251 (46)	
Never smokers (%)	215/341 (63)	152/233 (65)	0.60
BMI, median (IQR), kg/m^2	n=285 26.8 (24.1–29.4)	n=171 27.8 (24.7–32.1)	**0.01**
Clinical Frailty Score, median (IQR)	n=332 2 (2–4)	n=260 3 (2–3)	**<0.01**
Co-morbidities			
Hypertension (%)	182/386 (47)	110/273 (40)	0.08
Any cardiac disease (%)	76/400 (19)	44/273 (16)	0.34
Cerebrovascular disease (%)	30/386 (8)	16/273 (6)	0.34
Diabetes (%)	109/372 (29)	71/273 (26)	0.36
Any lung condition (%)	66/400 (17)	48/273 (18)	0.71
Chronic kidney disease (%)	70/388 (18)	27/273 (10)	**<0.01**
Any mental health disorder (%)	63/400 (16)	33/273 (12)	0.18

Bold values denote statistical significance at the p<0.05 level.
BMI, body mass index;

we found an association between missingness on symptoms after discharge and some predictor variables such as ethnicity and cohort, sensitivity analysis indicated that our results were robust to missingness (through a comparison of the results of listwise deletion to those from multiple imputation—data not shown).

Descriptive data: baseline characteristics and demographics

Genotyping

Whole genome sequencing was not available for wave 1 participants but given this early timepoint of the pandemic, we have assumed the majority of wave 1 patients had the wildtype variant in line with UK data detailing distribution of SARS-CoV-2 variants.[24] In wave 2 patients, 273 out of 309 with samples available for sequencing were found to have the Alpha variant (B.1.1.7).

Patients were of similar age (61 years (50–74) vs 62 years (52–75), p=0.68), gender distribution (males; 62% vs 56%, p=0.14) and ethnicity across the two waves (table 1). Wave 1 patients had statistically lower body mass index (26.8 kg/m^2 (24.1–29.4) vs 27.8 kg/m^2 (24.7–32.1), p=0.01) and lower Clinical Frailty Scores (2 (2–4) vs 3 (2–3), p<0.01). Wave 1 patients had more prevalent chronic kidney disease (18% vs 10%, p<0.01; table 1). Two participants in wave 2 received one vaccination dose prior to infection onset (at 8 and 9 days, respectively). See online supplemental table 1 and supplemental figure 3 for demographic data according to acute inpatient severity subgroups.

Descriptive data: admission data

Wave 1 patients received less non-invasive respiratory support such as CPAP or HFNO (3% vs 10%, p<0.01), had a greater number of admissions to intensive care (16% vs 11%, p=0.04) and more patients were invasively ventilated (13% vs 4%, p<0.01). Wave 1 patients received less corticosteroid treatment (4% vs 79%, p<0.001), fewer novel agents (6% vs 35%, p<0.001) and had a longer length of stay (8 days (5–13) vs 6 days (3–9), p<0.001). See online supplemental table 2 and supplemental figure 4 for admission data according to acute COVID-19 severity subgroups. Admission blood results are summarised in online supplemental table 5, with no significant differences seen between waves 1 and 2.

Outcome data: clinical outcomes at follow-up consultation

We sought to contact patients for their initial clinical review at 6 weeks following discharge and achieved this in 322/400 (81%) in wave 1 versus 248/273 (91%) in wave 2. This represented 27% and 21% of all patients admitted and discharged during each study period (online supplemental figure 1). Patients had an earlier clinical review in wave 2 (54 days (46–66) vs 74 days (66–97) for wave

Table 2 Inpatient admission data for wave 1 and 2 participants

Admission characteristics			
	Wave 1 (n=400)	**Wave 2 (n=273)**	**P value**
Total number of admission symptoms, median (IQR), days	n=386 4 (3–6)	n=273 3 (2–4)	**<0.001**
Chest X-ray—reported as classical or probable disease (%)	202/378 (53)	197/264 (75)	**<0.001**
NEWS2, median (IQR)	n=372 5 (2–7)	n=259 4 (2–6)	0.88
Treatment escalation plan—full escalation (%)	318/400 (80)	249/273 (91)	**<0.001**
Length of stay, median (IQR)	n=400 8 (5–13)	n=273 6 (3–9)	**<0.001**
Maximum respiratory support			**<0.001**
Post hoc comparison* (%)			
No respiratory support	77/400 (19)	53/273 (19)	**1.00**
Oxygen treatment	258/400 (65)	177/273 (65)	**1.00**
CPAP or HFNO	13/400 (3)	27/273 (10)	**<0.01**
NIV	2/400 (1)	5/273 (2)	**0.99**
IV	50/400 (13)	11/273 (4)	**<0.01**
Total days of CPAP, NIV and IV treatment, median (IQR), days	n=55 8 (4–28)	n=32 6 (2–10)	**<0.01**
Received corticosteroid treatment (%)	14/338 (4)	215/273 (79)	**<0.001**
Received novel drugs (antiviral or monoclonal antibody treatment) (%)	23/375 (6)	96/273 (35)	**<0.001**
Intensive care admission (%)	64/400 (16)	29/273 (11)	**0.04**
Pulmonary embolism (%)	22/400 (6)	12/270 (4)	0.54

Bold values denote statistical significance at the p<0.05 level.
*Post hoc p values are Bonferroni adjusted.
CPAP, continuous positive airway pressure; HFNO, high flow nasal oxygen; IV, invasive ventilation ; NEWS2, National Early Warning Score 2; NIV, non-invasive ventilation.

1 patients, p<0.001). Table 3 summarises physical and mental symptom burden and radiological outcomes at follow-up.

Long COVID prevalence was higher in wave 1 (83% vs 76%, p<0.001) as was the total number of Long COVID symptoms (3 (1–5) vs 2 (1–4), p<0.001). Impaired sleep quality (52% vs 37%, p<0.001), myalgia (24% vs 13%, p=0.001), anosmia (12% vs 5%, p<0.01), chest pain (11% vs 6%, p=0.03) and focal weakness (14% vs 6%, p=0.001) were more common in wave 1 patients but there were no statistically significant differences in other individual symptoms. Wave 1 versus wave 2 patients demonstrated less self-reported improvement in sleep quality: 61% vs 80%; breathlessness: 76% vs 88%; and cough: 70% vs 87% (p<0.001 for all variables). The degree of self-reported improvement in fatigue remained similar across both cohorts (88% vs 89%, p=0.49).

Wave 1 patients had a trend to higher scores for depression (Patient Health Questionnaire ≥3; 15% vs 10%, p=0.06) and greater post-traumatic stress (Trauma Screening Questionnaire ≥5; 15% vs 3%, p<0.001) at clinical review following discharge.

Fewer wave 1 chest radiographs had improved at clinical review following hospital discharge (18% vs 24%, p<0.001). Of those attending for blood tests at this review, a statistically lower persisting raised white cell count (6.5×10^9/L (5.6–7.8) vs 7.2×10^9/L (6.1–8.5), p<0.01), platelet count (242×10^9/L (207–290) vs 272×10^9/L (233–333), p<0.001), fibrinogen (3.3 g/dL (2.8–3.8) vs 3.6 g/dL (3.2–4.2), p<0.001), ferritin (138 µg/L (65–249) vs 172 µg/L (82–361), p=0.02) and C-reactive protein (1 mg/L (1–3) vs 2 mg/L (1–6), p<0.001) were seen in wave 1 patients, suggesting persistent inflammatory changes in wave 2 patients (see online supplemental table 6). Patients with at least one Long COVID symptom had a higher white cell count (6.4×10^9/L (5.5–7.5) vs 7.0×10^9/L (5.9–8.4), p=0.02) and lymphocyte count (1.9×10^9/L (1.5–2.4) vs 2.1×10^9/L (1.6–2.7)) compared with those without any Long COVID symptoms (see online supplemental table 7).

Fewer wave 1 patients reported feeling back to their baseline health status (51% vs 82%, p<0.001). At 11 weeks, 51% of wave 1 patients had returned to work, if employed, compared with 59% of wave 2 patients who had returned to work at 8 weeks (p=0.18). Figure 1 illustrates symptom, radiological and functional recovery at follow-up, comparing wave 1 and 2 participants.

Subgroup analyses

Long COVID prevalence was no different when categorised according to inpatient severity. Wave 1 patients with

Table 3 Clinical outcomes at follow-up consultation for wave 1 and 2 participants

Variable	Wave 1 (n=323)	Wave 2 (n=248)	P value
Days since discharge (days) (median, IQR)	n=322 74 (60–97)	n=237 54 (46–66)	**<0.001**
Mental health outcomes			
Patient Health Questionnaire-2 Score (≥3) (%)	47/305 (15)	23/232 (10)	0.06
Trauma Screening Questionnaire Score (≥5) (%)	44/297 (15)	8/248 (3)	**<0.001**
Functional recovery			
Number returned to work, if employed (%)	76/149 (51)	75/128 (59)	0.18
Numerical rating score asking how close to 100% do you feel, median (IQR)	n=287 90 (75–100)	n=221 85 (70–95)	**0.02**
Participants reporting feeling back to normal (%)	159/312 (51)	69/84 (82)	**<0.001**
Current Clinical Frailty Score at follow-up, median (IQR)	n=352 3 (2–4)	n=164 3 (2–6)	**<0.001**
Long COVID symptoms at follow-up consultation			
Long COVID prevalence (at least one out of 14 symptoms listed below)	262/316 (83)	188/248 (76)	**<0.001**
Long COVID total number of symptoms (out of 14 symptoms listed below), median (IQR)	n=316 3 (1–5)	n=248 2 (1–4)	**<0.001**
Prevalence of individual Long COVID symptoms (total of 14 symptoms, ie, reporting >1 on numerical rating score)			
Breathlessness (%)	152/316 (48)	115/232 (50)	0.71
Cough (%)	81/316 (26)	70/231 (30)	0.23
Impaired sleep quality (%)	163/311 (52)	86/230 (37)	**<0.001**
Fatigue (%)	199/311 (64)	150/232 (65)	0.87
Myalgia (%)	76/315 (24)	32/248 (13)	**0.001**
Anosmia (%)	39/314 (12)	12/248 (5)	**<0.01**
Chest pain (%)	34/314 (11)	14/248 (6)	**0.03**
Chest tightness (%)	39/315 (12)	22/248 (9)	0.18
Confusion (%)	48/314 (15)	27/248 (11)	0.13
Diarrhoea (%)	18/314 (6)	8/248 (3)	0.16
Peripheral oedema (%)	36/314 (12)	24/248 (10)	0.50
Abdominal pain (%)	20/314 (6)	9/248 (4)	0.15
Focal weakness (%)	44/315 (14)	14/248 (6)	**0.001**
Anorexia (%)	21/314 (7)	10/248 (4)	0.17
Subjective physical symptoms—improvement in symptoms from discharge to follow-up consultation			
Breathlessness (%)	213/280 (76)	207/235 (88)	**<0.001**
Cough (%)	194/279 (70)	201/231 (87)	**<0.001**
Impaired sleep quality (%)	168/273 (61)	183/228 (80)	**<0.001**
Fatigue (%)	241/275 (88)	209/234 (89)	0.49
Other physical symptom variables at follow-up consultation			
MRC Dyspnoea Scale 0–5, median (IQR)	n=294 2 (1–3)	n=134 2 (1–3)	0.42
Radiology outcomes at follow-up consultation			
	n=309	n=189	**<0.001**
Normalised (%)	212 (69)	124 (66)	
Significantly improved (%)	55 (18)	46 (24)	
Not significantly improved (%)	2 (1)	11 (6)	
Worsened (%)	29 (9)	8 (4)	

Bold values denote statistical significance at the p<0.05 level.
MRC, Medical Research Council.

Table 4 Simple Poisson regression models for total number of Long COVID symptoms following discharge

Unadjusted Poisson regression coefficients for 'total number of Long COVID symptoms following discharge'		
Predictor variable	**Count ratio (95% CI)**	**P value**
Variant, Alpha	0.78 (0.70, 0.86)	**<0.001**
Sex, male	0.91 (0.82, 1.01)	0.06
Ethnicity, white	0.97 (0.88, 1.07)	0.56
Age (years)	1.00 (1.00, 1.00)	0.46
Length of stay (days)	1.01 (1.01, 1.01)	**<0.001**
BMI (kg/m^2)	1.00 (0.98, 1.00)	0.28
Days after discharge (days)	1.01 (1.00, 1.01)	**<0.001**
Total number of COVID-19 symptoms on admission	1.09 (1.07, 1.12)	**<0.001**
Clinical Frailty Score (rated 1–9)	1.01 (0.96, 1.03)	0.89
Pre-existing lung disease	1.27 (1.12, 1.43)	**<0.001**
Any cardiac disease	1.05 (0.93, 1.20)	0.42
Diabetes	1.07 (0.95, 1.20)	0.24
Immunosuppressed	1.02 (0.87, 1.19)	0.78
Chronic kidney disease	1.06 (0.91, 1.23)	0.42
Pulmonary embolism	0.90 (0.71, 1.11)	0.33
Duration of symptoms at admission (days)	1.01 (1.00, 1.02)	0.08
Treated with novel drug	0.95 (0.83, 1.07)	0.41
Treated with corticosteroids	0.92 (0.83, 1.03)	0.14
Any respiratory support	1.10 (0.97, 1.26)	0.42
Vaccinated before admission	0.36 (0.06, 1.10)	0.14

BMI, body mass index.

mild and moderate acute diseases had a greater total number of Long COVID symptoms than similar wave 2 patients (mild, 3 (1–5) vs 2 (0–3), p=0.02; moderate, 3 (1–5) vs 2 (1–4), p=0.01). See online supplemental tables 3 and 4 for analysed differences in symptoms, mental health and functional recovery according to acute COVID-19 severity subgroups.

Association between Long COVID presence according to acute COVID-19 severity, treatment and SARS-CoV-2 variants

A multiple logistic regression model for the presence of Long COVID (ie, one of 14 symptoms exhibited) revealed a significant association with a greater number of COVID-19 admission symptoms (adjusted OR=1.32, 95% CI 1.05, 1.67) (see online supplemental tables 8 and 9). There was no association between partial vaccination status and Long COVID.

Association between total number of Long COVID symptoms according to acute COVID-19 severity, treatment and SARS-CoV-2 variants

A multiple Poisson regression model found a greater total number of Long COVID symptoms were associated with pre-existing lung disease (adjusted count ratio (aCR)=1.26, 95% CI 1.07, 1.48) and more COVID-19 admission symptoms (aCR=1.07, 95% CI 1.02, 1.12). A lesser association was seen with longer length of stay (aCR=1.02, 95% CI 1.00, 1.03) and later clinical review after discharge (aCR=1.00, 95% CI 1.00, 1.01). A lower aCR for the total number of Long COVID symptoms was observed with the development of pulmonary embolism (PE) (aCR=0.57, 95% CI 0.38, 0.83) (see tables 4 and 5). There was no association between partial vaccination status and total number of Long COVID symptoms.

In both multiple regression models, after controlling for other predictors, there were no significant differences in the presence of at least one Long COVID symptom or the total number of Long COVID symptoms after hospital discharge between the wildtype and Alpha variants.

DISCUSSION

In this prospective cross-sectional study of hospitalised UK adults with COVID-19 who survived to follow-up after discharge, we report key determinants of Long COVID presence and total symptom number in people infected with different SARS-CoV-2 variants.

Key results

Contributory factors to Long COVID

After adjusting for confounders, we demonstrate a shift in wave 2 towards a reduction in the presence of Long COVID but not the total number of Long COVID

Table 5 Multiple Poisson regression model for total number of Long COVID symptoms following discharge

Adjusted Poisson regression coefficients for 'total number of Long COVID symptoms following discharge'		
Predictor variable	**Count ratio (95% CI)**	**P value**
Intercept	1.87 (1.04, 3.35)	0.04
Variant, Alpha	1.09 (0.82, 1.44)	0.57
Sex, male	0.99 (0.85, 1.14)	0.85
Ethnicity, white	0.96 (0.84, 1.11)	0.60
Age (years)	1.00 (0.99, 1.00)	0.65
Length of stay (days)	1.01 (1.00, 1.03)	**<0.01**
BMI (kg/m^2)	0.99 (0.98, 1.01)	0.27
Days after discharge (days)	1.00 (1.00, 1.01)	**0.03**
Total number of COVID-19 symptoms on admission	1.07 (1.02, 1.12)	**<0.01**
Clinical Frailty Score (rated 1–9)	1.01 (0.95, 1.07)	0.68
Pre-existing lung disease	1.26 (1.06, 1.48)	**<0.01**
Any cardiac disease	1.10 (0.90, 1.34)	0.35
Diabetes	0.94 (0.78, 1.11)	0.46
Immunosuppressed	1.12 (0.90, 1.39)	0.29
Chronic kidney disease	1.04 (0.84, 1.29)	0.71
Pulmonary embolism	0.57 (0.38, 0.83)	**<0.01**
Duration of symptoms at admission (days)	1.01 (0.99, 1.02)	0.28
Treated with novel drug	1.04 (0.83, 1.28)	0.74
Treated with corticosteroids	1.02 (0.78, 1.34)	0.86
Any respiratory support	0.85 (0.70, 1.05)	0.12
Vaccinated before admission	0.44 (0.07, 1.41)	0.26

Bold values denote statistical significance at the p<0.05 level.
BMI, body mass index.

symptoms (neither association being statistically significant). We do, however, find a lower prevalence of at least one Long COVID physical symptom (and all individual symptoms) in wave 2 and improved mental (less post-traumatic stress) and functional recovery (as more participants felt they were back to their baseline at follow-up).

We find that patients with pre-existing lung disease and/or more COVID-19-related symptoms at admission are at greatest risk of Long COVID. Although these factors are not directly modifiable, our data highlight that these patients may need increased input during their hospital admission (such as improved therapeutics and acute management aimed at reducing length of stay, in addition to earlier postdischarge follow-up) to help improve their Long COVID trajectory. Our findings differ from a UK prospective multicentre UK cohort study (n=327)[25] which identified worse outcomes in people under the age of 50, females and those with a higher severity of acute disease. Our results in part concur with a pooled meta-analysis[26](n=38 studies) identifying risk factors solely predictive of Long COVID development, which are not linked with the severity of the acute SARS-CoV-2 infection. This study highlighted an association with female sex (n=7; OR=1.48, 95% CI 1.17 to 1.86, p=0.01) and pulmonary disease, obesity and diabetes as independent comorbidities. Our data highlight the heterogeneity in research data evaluating predictive factors of Long COVID in hospitalised individuals with different SARS-CoV-2 variants. We highlight the continued importance of performing research to evaluate predictors in different populations, and the limited ability of predictors of poor outcomes during the acute illness to predict Long COVID.

Although we cannot infer causation for our improved recovery demonstrated in wave 2, we can offer plausible explanations for this. We find no association between inpatient disease severity (according to WHO criteria), inpatient treatments (novel drugs/respiratory support) and Long COVID outcomes. This is consistent with a smaller (n=96) intensive care study[27] that found no association with the presence or severity of cognitive dysfunction in patients receiving different anti-inflammatory therapies (dexamethasone or tocilizumab), and where 91% were invasively ventilated.

However, we did identify weaker associations between a shorter length of stay and a lower number of Long COVID symptoms. This may be a proxy for the reduced severity of disease seen in wave 2 and the more effective treatments used. We also can explain the apparent paradox of an association between pulmonary thromboembolic disease

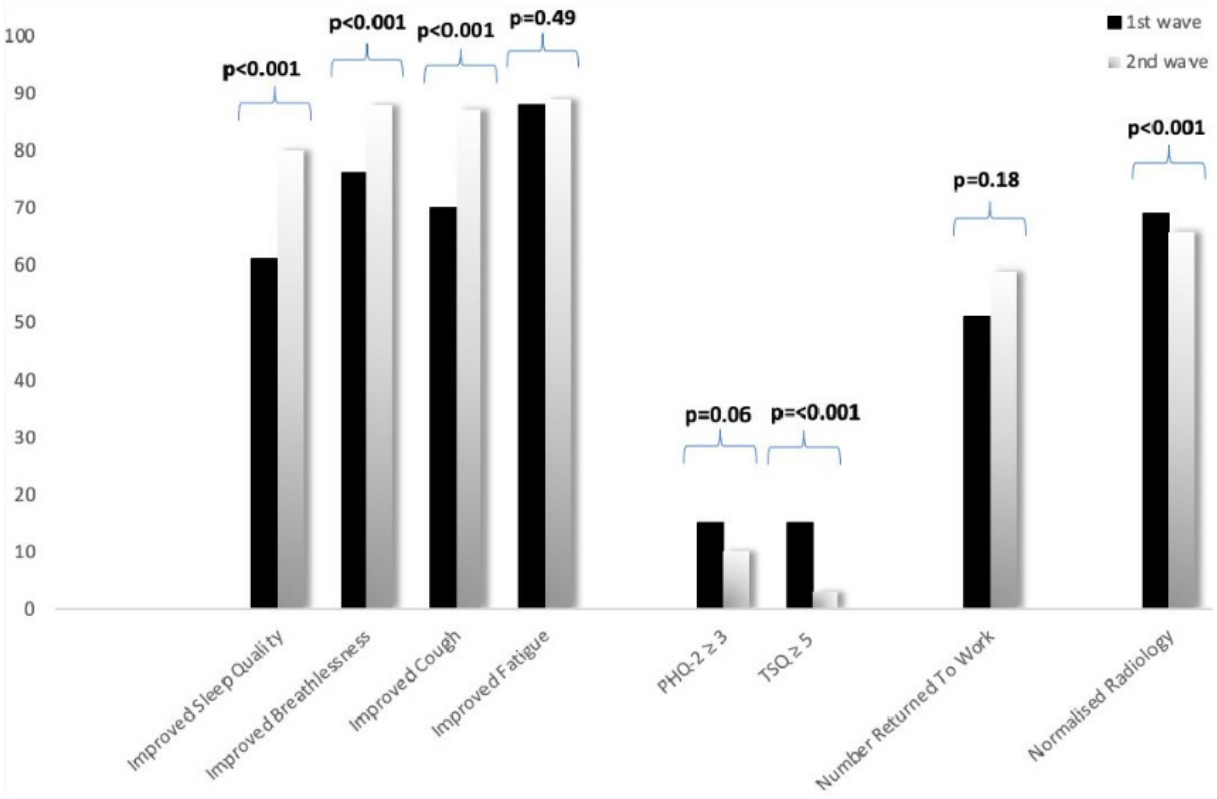

Figure 1 Clinical outcomes at initial clinical review of wave 1 and 2 participants. PHQ, Patient Health Questionnaire; TSQ, Trauma Screening Questionnaire.

(PE) and less Long COVID symptoms as representing a 'healthy survivor' effect, that is, those people who had their PE diagnosed and received treatment for it did better than those that were unrecognised and resulted in more hypoxia.[28] These associations therefore do point towards an improvement in acute clinical care in wave 2.

After adjusting for confounders, neither variant was associated with worse Long COVID outcomes. This may be expected given that in the UK, the Alpha and wildtype variants had similar mortality (n=45) and odds of intubation (n=31) in eligible patients (although when analysed in a relatively small population).[29] We address the limitation of this study by evaluating Long COVID outcomes and the limited knowledge in this area.

When looking for a plausible explanation for improved wave 2 recovery, a lower number of COVID-19 admission symptoms were identified across all severity groups. This may be attributable by proxy to the Alpha variant which may have resulted in less severe disease and a shorter hospital stay. However, other explanations for improved holistic recovery in wave 2 include a greater morbidity from the wildtype SARS-CoV-2 variant, limited treatments in wave 1 or an improved SARS-CoV-2 T cell response after a first variant infection, which could offer protection against more severe infection in wave 2.[30] Lastly, individuals have been forced to accept a 'new normal' following the pandemic, adapting to its challenges and finding a way of adjusting to life, such as returning to work despite new health considerations.[31]

Lastly, there is a suggestion that a later clinical review following hospital discharge is associated with an increased number of Long COVID symptoms. This may be explained by patients waiting longer for clinical support and therapeutic interventions, and so having worse mental and physical health. Although there was no statistical increase in the proportion of wave 2 patients returning to work, despite a higher proportion feeling back to normal, this may be explained by the expectation of a clinical review in wave 2 providing them with certainty to return. We certainly demonstrate a similar proportion of patients returning to work in wave 2 at an earlier timepoint (8 weeks vs 11 weeks). These associations reinforce the concept of a Long COVID minimisation strategy that can deliver effective treatments during the acute admission, and also target groups at greatest risk (ie, those with more admission symptoms and/or chronic lung disease), with earlier support following hospital discharge.

Strengths and limitations

Strengths of our data include a large sample size with a high number of patients contacted for their initial clinical review. We also report on Long COVID outcomes according to sequenced viral variants in comparison to other published studies that rely on the most prevalent variant of concern during the data capture period. We compare patient characteristics at peak admission periods, which represent comparable timepoints of clinical strain when managing a large volume of inpatient

admissions. This is a realistic representation of outcomes as we include swab negative patients clinically suspected to have COVID-19. We also evaluate beyond Long COVID prevalence, presenting data on the total number of symptoms, self-reported trajectory, mental health and functional recovery.

Limitations include single centre data and unequal comparative admission and follow-up periods. The latter is reflective of improved clinical and logistical processes allowing earlier clinical review in wave 2, and identification of suitable patients who would have otherwise been missed. When evaluating recovery by severity, the largest population was the moderate group and may therefore display more representative follow-up outcomes. We excluded patients who had died from our analysis and note data are biased towards survivors. Selection bias may exist as our analyses can only represent those who we could contact and were prepared to be reviewed by us. Plus, patients with very prolonged intensive care unit/in-hospital stays may have still been in hospital at the time of what would have been their planned review.

Interpretation

Our study demonstrates no significant association between SARS-CoV-2 variants (wildtype and Alpha) and Long COVID outcomes in adults admitted to our hospital. Our findings concur with Azzolini *et al*[13] who compare a non-hospitalised group thought to be infected with the same variants as ours (although confirmatory sequencing was not performed). However, we differ from the hospitalised cohort data presented by Fernández-de-las-Peñas *et al*[12] who found a higher prevalence of Long COVID in those with the Alpha variant (without adjusting for confounders such as vaccination, age and length of hospital stay). Our study has similarities to Spinicci *et al*,[11] who compared predominantly unvaccinated individuals. However, our study differs from this in that we identify a reduction in the sequelae of all Long COVID physical symptoms in association with the Alpha variant. This may be explained, though, by our greater use of viral sequencing to identify the relevant strains. We contrast to Antonelli *et al*[17] who compare later waves (Delta vs Omicron; with both periods following widespread vaccination) and we predominantly reflect on outcomes in unvaccinated individuals and are confident of variant strain within each wave (no other variant of concern had been identified in wave 1 and we included participants with confirmed variant on viral sequencing in wave 2). In comparison to Arjun *et al*,[6] we present data on associations of prevalence of one symptom alone and the total number of Long COVID symptoms within a hospitalised cohort that were predominantly unvaccinated. Our study therefore appears to be the first international work to address research gaps in Long COVID by reporting on the association of inpatient trajectory and SARS-CoV-2 variants according to sequenced variant.

We acknowledge the significant association of vaccination on Long COVID outcomes as 15 studies[32] (6030 UK participants) have demonstrated that fully vaccinated individuals (matched with unvaccinated individuals) are half as likely to have symptoms lasting at least 28 days (OR=0.51, 95% CI 0.32 to 0.82, p=0.005), yet those partially vaccinated had a similar probability (OR=1.04, 95% CI 0.86 to 1.25). A large systematic review[33] (n=2584 studies; 17 256 654 individuals) demonstrated that vaccination reduced risks of odds of Long COVID (with two doses more effective than one), though only two studies investigated longer follow-up periods of up to 6 months. When evaluating the risk for individuals with ongoing Long COVID symptoms following one vaccination dose, seven studies demonstrated an improvement in symptoms, yet four reported no change or worsening of Long COVID symptoms. In the latter group, one study[34] identified an increased antibody titre ratio in those with worsening symptoms, suggesting this was a consequence of an excessive immune response to vaccination. Our data capture was before full vaccination roll-out in the UK (the first vaccine was offered to those clinically vulnerable at the onset of the second wave). Therefore, only two of our participants within wave 2 had received a partial vaccination (one dose) before their admission. When adjusting for vaccination in our cohort, we identify different clinical predictors beyond vaccination that influence Long COVID prevalence and total number of Long COVID symptoms within our cohort. The reported lessons learnt on recovery differences are therefore attributable to factors beyond vaccination.

Generalisability

We demonstrate greater holistic wave 2 recovery, including improved mental health outcomes and functional recovery in those with mild and moderate acute COVID-19 diseases. This is encouraging as these groups represented the majority of our inpatient admissions and more of these patients were for full treatment escalation (reinforcing the importance of delivering appropriate inpatient clinical care for patients). It remains important to recognise that reduction in Long COVID symptom prevalence alone does not necessarily link to functional recovery.

Our clinical service provided an earlier clinical review in wave 2, which required considerable support and input to maintain given the larger clinical cohorts. The trend towards positive impact on Long COVID prevalence and improved mental and physical health outcomes reinforces the importance of adequately resourced and timely clinical review following hospital discharge.

Summary

In summary, we report the first UK comparison of patient recovery in hospital survivors across two variants of COVID-19. Although we do not demonstrate an association between SARS-CoV-2 variant, Long COVID prevalence and total number of Long COVID symptoms, we do demonstrate a shift towards improved clinical and functional outcomes in wave 2 patients.

Our data indicate that hospitalised patients with chronic lung disease and/or more COVID-19 admission symptoms are at risk of an increased number of Long COVID symptoms (the latter of which may be related to variant strains). We suggest that there need to be efficient care pathways developed which can include tackling modifiable clinical risk factors such as the length of hospital stay, as well as ensuring early and adequate follow-up after discharge. Through this and future treatments it may be possible to minimise Long COVID risk and improve patient outcomes.

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Contributors AS, SBN, SM and ML conceived and conducted the design and organisation of this observational study. AS, CN, SBN and GS conducted a literature search. AJS, HMB, CN, AS and NGJ collected the data. Data analysis was performed by AS, CS, SM and CO. Data interpretation and verification was performed by AS, SM, JRH, MCL, CS and CO. The first draft of the manuscript was written by AS. All authors contributed to the writing of the final approved manuscript. SM is the guarantor for this manuscript.

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Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study involves human participants and was approved by the HRA and Health and Care Research Wales (HRA number 20/HRA/4928). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

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Supplementary Material

Saigal A, *et al. BMJ Open Respir Res* 2023; 10:e001667. doi: 10.1136/bmjresp-2023-001667

Detailed Method:

An attempt was made to contact every patient who had been discharged from our hospitals following an acute illness compatible with COVID-19 (i.e. suspected COVID-19), or who had tested positive using a nasopharyngeal swab for SARS-CoV-2. We aimed to complete the review between six and twelve weeks following hospital discharge. The service was conducted from Royal Free London NHS Foundation Trust and data were collected as part of a novel service evaluation and in line with UK national guidance. All data were de-identified prior to analysis and the authors had all necessary clinical administrative permissions to access the data.

Participants and Setting

We collected demographic data, co-morbidities, admission severity, symptoms, viral sequences and radiological burden, to assess differences in clinical severity and Long-COVID. Data were collected through electronic case note review and using a real time data analytics tool (Open Health Care UK). We included all people aged ≥ 18 years, who had been admitted to our inpatient wards with symptoms or signs suggestive of COVID-19, during the first two UK waves; Wave1:29th February- 5th April 2020 and Wave 2: 10th December 2020 – 8th February 2021. Patients were eligible for this study if a clinical diagnosis of acute COVID-19 was made by the admitting medical team (with or without a positive swab for SARS-CoV-2). We excluded patients from follow up and analysis if: they were unable to participate in a clinical telephone follow-up call due to severe dementia, were too frail to engage in clinical follow-up, or had hospital-acquired COVID-19 (defined as a positive swab 7-14 days following admission). Participants were also excluded from this study if they had been admitted to another hospital and their care was subsequently transferred to our service. Further, when analysing Long-COVID outcomes, we excluded participants if, when genotyping was performed, they did not have main the variant of concern within that Wave (wildtype variant for Wave 1 and alpha variant for Wave 2). Genotyping was not available for Wave 1 participants, however no other variant of concern had been identified as emerging over this time. Supplementary Figure 1 summarises the total number of patients with COVID-19 positive swabs or suspected COVID-19, admitted to our hospital, during which our data were obtained.

Variables and data sources

A minimum dataset (of fourteen Long-COVID symptoms) was agreed (3) by members of the North Central London 'Assessing Recovery from COVID-19' (ARC) consortium. All patients with abnormal blood tests and or chest radiograph findings at discharge were invited to have those tests repeated. We specifically assessed current physical and psychological symptom burden (Patient Health Questionnaire-2 score (PHQ-2) (35), Trauma Screening Questionnaire score (TSQ) (36)), and the trajectory of symptom recovery. Subjective breathlessness, cough, fatigue and sleep quality were assessed on an eleven-point scale from 0-10 (where 0 represented 'I do not have this problem' to 10 = 'this symptom is very significant'). Participants were also asked to grade the maximum intensity of each symptom during the acute illness. Current breathlessness was assessed further using the Medical Research Council scale (37). Participants were asked to rate their satisfaction with the call. In addition to the agreed dataset as detailed in the manuscript, we agreed local onward pathways for referral to physical rehabilitation resources and psychological support, and/or further investigations. A copy of the consultation and actions was sent to the patient's primary care physician. The British Society of Thoracic Imaging (BSTI) classification (38) was used to code chest radiographs; follow-up chest radiographs were compared with the last radiograph obtained prior to discharge. Blood biomarkers were measured using standard laboratory analysers.

Treatments available during study period

Participants were given treatment as per guidelines issued by the Royal Free London NHS Foundation Trust, which have been updated several times during the pandemic. From the 29/06/2020, Dexamethasone and Remdesivir were indicated if supplemental oxygen and respiratory support was needed (although Remdesivir was not indicated if patients were invasively ventilated). Tocilizumab was indicated in severe COVID-19 in combination with patients receiving steroid therapy from 23/11/2020. Standard dose anticoagulation of LMWH was offered to adults with COVID-19 who needed supplemental oxygen or respiratory support and treatment dose was indicated in those who were identified to be at risk or have associated complications of PE at the time of this study.

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Sample Size

For the multiple Poisson regression model, we estimated the average number of Long-COVID symptoms to be 3 in Wave 1 and 2.5 in Wave 2 (based on Arjun [6] et al findings). Based on the other confounders in the model explaining 10% of the total variance in number of Long-COVID symptoms among patients, a sample of 514 (257 in each group) was estimated to be required to achieve 90% power with 5% level of significance. For the multiple logistic regression model, an estimation of Long-COVID prevalence as 75% in wave 1 and 62% in wave 2 (based on both Arjun et al and Spinicci [11] et al), and the other confounders in the model explaining 10% of the total variance in Long-COVID presence among patients, a sample of 504 (252 in each group) was estimated to be required to achieve 90% power with 5% level of significance. Therefore, taking the larger of the two sample sizes and accounting for 10% of patients being potentially lost to follow-up, the required total sample size was estimated as 572.

Study Size

We initially used convenience sampling to identify the first 400 adults within each wave (Wave 1 and 2) who had a clinical diagnosis of COVID-19 (with or without a positive swab for SARS-CoV-2) and had been contacted as part of their follow-up. Patients were then excluded from the analysis if they were found to have an alternative variant to the main variant of concern identified in Wave 1 and 2. Wave 1 was identified to be wild type variant (n=400; all data was included as no whole genome sequencing was available and no other variant of concern had arisen before April 2020). Wave 2 was identified as the alpha variant (n=273), with all 273 participants confirmed on viral sequencing.

Study Bias

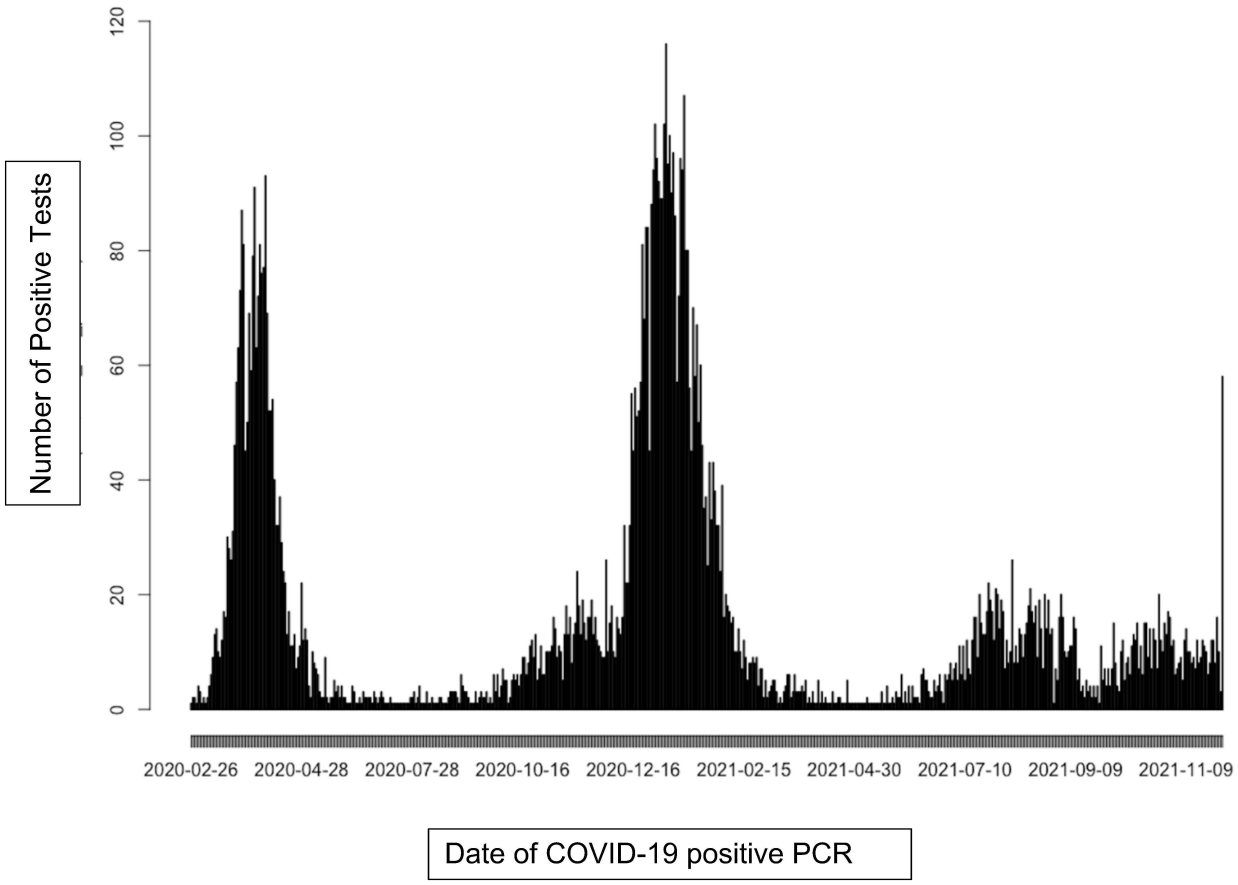
As our study's focus was on Long-COVID outcomes in hospital survivors, we did not analyse characteristics for those who had died. We compared baseline characteristics of the survivors in Waves 1 (n=400) and 2 (n=273), and included those lost to follow-up in these descriptive baseline analyses. To minimise selection bias however, up to a maximum of three telephone calls were made to contact eligible individuals for their follow-up call. Recall bias may have been present in the dataset as severity of symptoms are self-reported, however our focus here is the presence rather than severity of symptoms. Detection and performance bias could not be altered due to lack of blinding of both participants and assessors. We included regression analyses to minimise any confounding in the associations between clinical variables and Long-COVID outcomes.

Statistical Methods

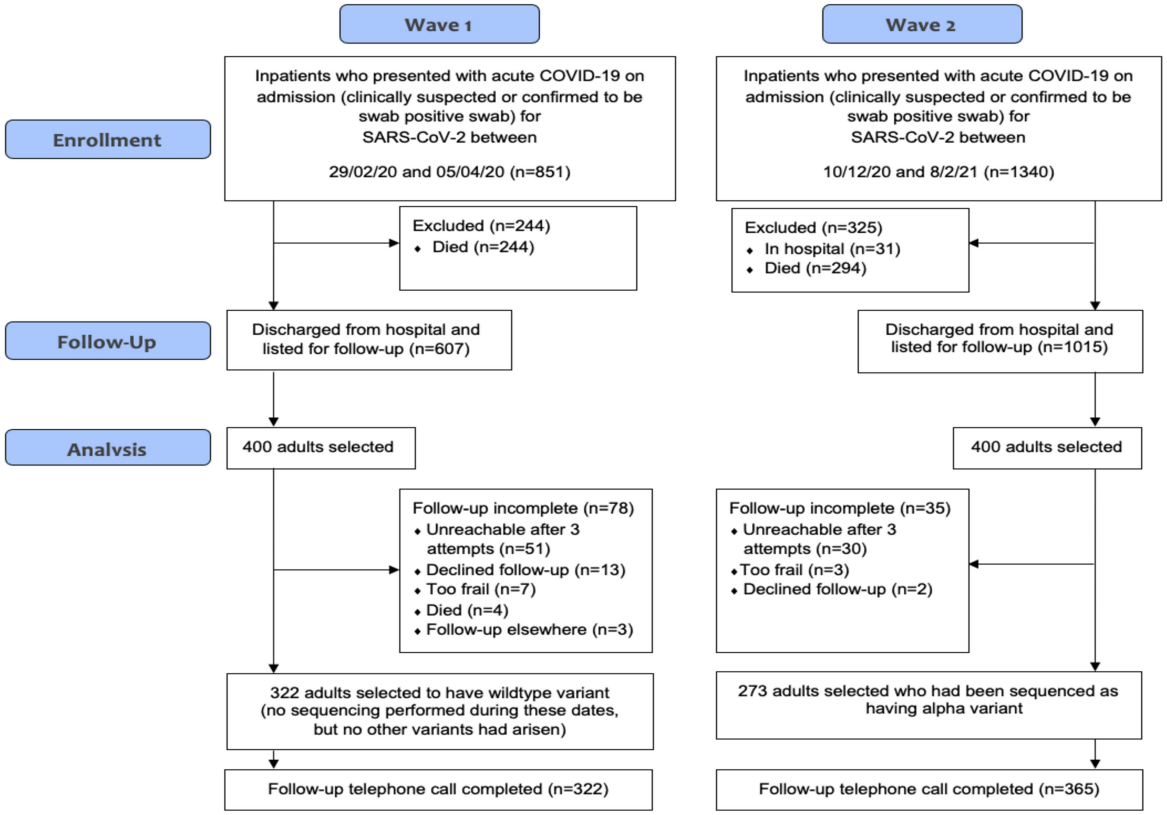
The data were analysed using IBM SPSS statistics for Macintosh (Version 28) and statistical software R (version 4.1.2). Descriptive data (displayed in Table 1, 2 and 3 and Supplementary Tables 1-7) were tested for normality, and Wave 1 and 2 characteristics summarised using mean and standard deviation (SD) for continuous variables if the normality assumption was satisfied (non-normally distributed variables were summarised using median and interquartile range (IQR)). Ordinal variables were summarised using median and IQR and frequencies (%) were used for binary and nominal categorical variables. Descriptive analyses comparing physical symptoms, mental health and functional outcomes between Wave 1 and 2, including subgroup analyses for mild, moderate and severe disease, used two-sample t-test for normally distributed variables and Mann-Whitney U test whenever the parametric assumptions were not satisfied. Chi-squared tests were used for categorical data that satisfied the parametric assumption, with Fisher's exact tests employed when the parametric assumption was not satisfied.

A multiple logistic regression model was constructed to examine the associations between presence of Long-COVID (self-report of at least one of fourteen symptoms) with a fixed set of covariates including SARS-CoV-2 variants, baseline demographics and inpatient disease severity (Supplementary Table 8). A multiple Poisson regression model examined the association between total number of Long-COVID symptoms (the total number of symptoms out of the fourteen) with the covariates (Table 4). All tests of significance were two-tailed and a p-value of ≤0·05 was considered statistically significant. More detailed information is provided in the Supplement on descriptive statistical analyses used and for evaluation of Wave 1 and 2 according to acute inpatient severity.

Supplementary Figure 1: Graphs Illustrating Positive COVID-19 Polymerase Chain Reaction (PCR) Tests During Wave 1 and 2 Admissions



Supplementary Figure 2: Service participants in first and second wave

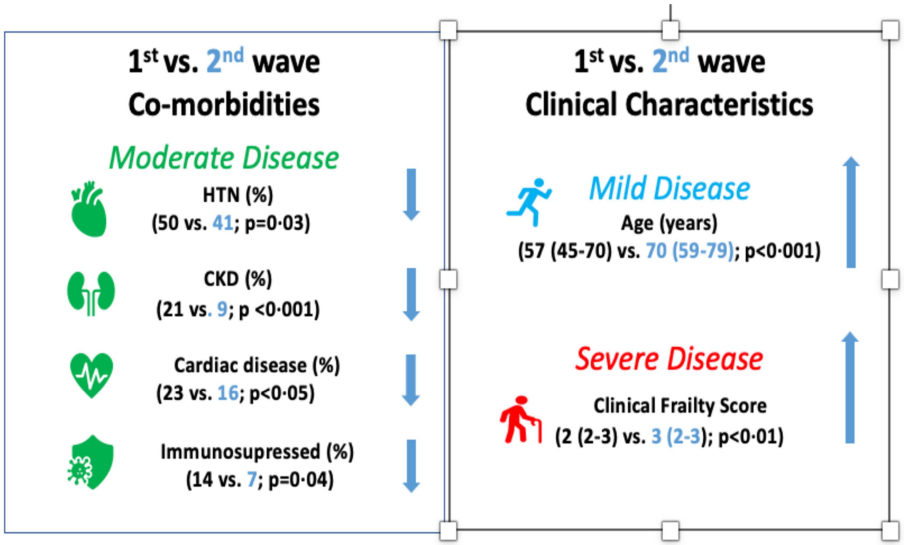


Supplementary Table 1: Comparing Baseline Demographics According to Clinical Severity of COVID-19

Variable	Wave 1 (N = 400)			Wave 2 (N = 273)			p-value		
Demographics and lifestyle									
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Age (years) (Median, IQR)	N = 77 57 (45-70)	N = 258 63 (51-77)	N = 65 58 (50-66)	N = 53 70 (59-79)	N = 177 62 (52-76)	N = 43 53 (47-63)	**<0·001**	0·36	0·09
Gender - Male N (%)	35/78 (45)	163/257 (63)	48/65 (74)	33/79 (42)	164/263 (62)	29/43 (67)	0·70	0·80	0·47
Ethnicity - White N (%)	43/76 (57)	132/256 (52)	25/63(40)	38/73 (52)	132/250 (53)	20/39 (51)	0·58	0·78	0·25
Smoking - Ex/current N (%)	25/63 (40)	74/220 (34)	27/58 (47)	22/59 (37)	84/230 (37)	17/42 (40)	0·79	0·52	0·55
BMI (kg/m^2) (Median, IQR)	N = 58 26·3 (22·4-29·4)	N = 179 26·7 (23·9-29·4)	N = 47 27·3 (25·8-30·7)	N = 30 27.8 (24·1-33·5)	N = 114 27·5 (23.8-31·8)	N = 27 28·7 (26·7-32·6)	0·10	0·07	0·15
Clinical Frailty Score (Median, IQR)	N = 51 2 (2-6)	N = 225 2 (2-5)	N = 56 2 (2-3)	N = 50 3 (3-4)	N = 171 3 (2-3)	N = 39 3 (2-3)	0·08	0·44	**<0·01**
Underlying co-morbidities and clinical conditions									
Hypertension N (%)	23/66 (35)	128/254 (50)	31/65 (48)	23/53 (43)	107/263 (41)	18/43 (42)	0·34	**0·03**	0·55
Any cardiac disease N (%)	14/77 (18)	58/257 (23)	4/65 (6)	12/53 (22)	41/263 (16)	4/43 (9)	0·53	**<0·05**	0·54
Cerebrovascular disease N (%)	7/65 (11)	22/255 (8)	1/65 (2)	5/53 (9)	15/263 (6)	2/43 (5)	0·81	0·20	0·34
Diabetes N (%)	21/66 (32)	70/246 (29)	18/60 (30)	18/53 (34)	44/177 (25)	9/43 (21)	0·80	0·41	0·30
Any lung condition N (%)	14/77 (18)	40/258 (16)	12/65 (19)	13/53 (25)	30/177 (17)	5/43 (12)	0·38	0·69	0·34
CKD N (%)	8/66 (12)	54/257 (21)	8/65 (12)	10/53 (19)	15/177 (9)	2/43 (5)	0·31	**<0·001**	0·18
Immunosupressed N (%)	4/77 (5)	35/258 (14)	7/65 (11)	4/53 (8)	13/177 (7)	5/43 (12)	0·58	**0·04**	0·89
Any Mental Health Disorder (N, %)	14/77 (18)	42/258 (16)	7/65 (11)	7/53 (13)	21/177 (12)	5/43 (12)	0·45	0·20	0·89

Supplementary Figure 3: Comparing Baseline Demographics According to Clinical Severity of COVID-19

Wave 1 mild patients were younger; 57 (45-70) vs. 70 (59-79) years; p <0·001. Wave 1 moderate disease patients had greater co-morbidity; hypertension (50 vs. 41%; p=0·03), cardiac disease (23 vs. 16%; p<0·05) and chronic kidney disease (21 vs. 9%; p<0.001) and a higher proportion were immunosuppressed 14 vs. 7% (16 vs. 10%; p=0·04). Wave 1 severe patients demonstrated a lower clinical frailty score (2 (2-3) vs. 3(2-3); p<0·001).



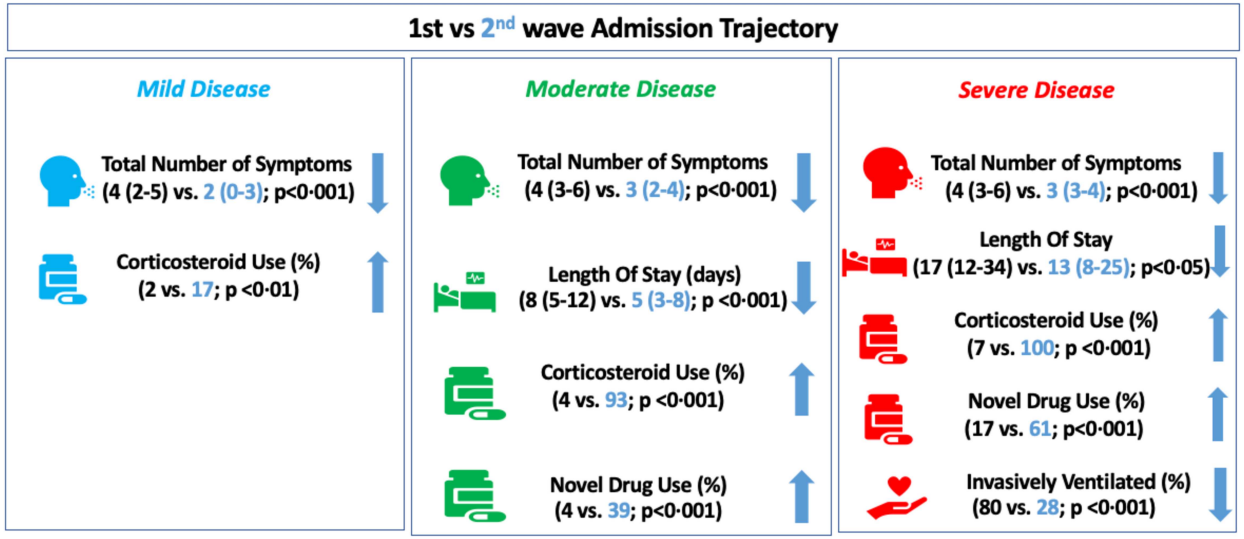
Supplementary Table 2: Comparing Inpatient Admission Trajectory According to Clinical Severity of COVID-19

Variable	Wave 1 (N = 400)			Wave 2 (N = 400)			p-value		
	Mild	Moderate	Severe	Mild	Moderate	Severe			
Total number of admission symptoms, Median (IQR)	N = 65 4 (2-5)	N = 256 4 (3-6)	N = 65 4 (3-6)	N = 53 2 (0-3)	N = 177 3 (2-4)	N = 43 3 (3-4)	**<0·001**	**<0·001**	**<0·001**
Duration of symptoms at admission, Median (IQR), days	N = 63 5 (2-7)	N=252 7 (4-11)	N=65 7 (7-10)	N = 32 4 (1-7)	N=153 8 (5-10)	N=42 8 (6-9)	0·38	0·73	0·51
For Full Escalation as part of Treatment Escalation Plan, (%)	63/77 (82)	195/258 (76)	60/65 (92)	44/53 (83)	162/177 (92)	43/43 (100)	0·33	**<0·001**	0·18
Length of stay, Median (IQR), days	N = 64 4 (2-8)	N = 257 8 (5-12)	N = 65 17 (12-34)	N = 53 3 (2-7)	N = 177 5 (3-8)	N = 43 13 (8-25)	0·36	**<0·001**	**<0·05**
Treated with corticosteroids (%)	1/65 (2)	10/231 (4)	3/41 (7)	9/53 (17)	164/177 (93)	43/43 (100)	**<0·01**	**<0·001**	**<0·001**
Received novel drug (%)	3/67 (5)	10/249 (4)	10/59 (17)	1/79 (1)	69/177 (39)	26/43 (61)	0·43	**<0·001**	**<0·001**
Pulmonary embolus (%)	1/77 (1)	10/258 (4)	11/65 (17)	1/53 (2)	6/176 (3)	5/41 (12)	0.79	0.80	0.51
Intubation (%)	0/78 (0)	0/256 (0)	52/65 (80)	0/53 (0)	0/177 (0)	12/43 (28)	**N/A**	**N/A**	**<0·001**

Supplementary Figure 4: Comparing Inpatient Admission Trajectory According to Clinical Severity of COVID-19

We looked for differences in total number of admission symptoms, length of stay, drug treatments received and complications such as pulmonary emboli and need for intensive care. All groups of wave 1 patients experienced greater COVID-19 admission symptoms (mild: 4 (2-5) vs. 2 (0-3); p <0·001, moderate: 4 (3-6) vs. 3 (2-4); p <0·001, severe: 4 (3-6) vs. 3 (3-4); p <0·001.

Wave 1 moderate and severe patients had a significantly higher length of stay (moderate; (8 (5-12) vs. 5 (3 -8) days, p=<0.001; severe (17 (12-34) vs. 13 (8-25) days; p<0·05) and were less likely to have received novel drug treatments (moderate: 4 vs. 39%; p<0·001, severe: 17 vs. 61%; p<0·001). A higher proportion of Wave 1 severe patients were invasively ventilated (80 vs. 28%; p <0·001).



Supplementary Table 3: Comparing Radiological, Mental Health and Functional Outcomes According to Clinical Severity of COVID-19

Variable	Wave 1 (N = 322)			Wave 2 (N = 365)			p-value		
	Mild	Moderate	Severe	Mild	Moderate	Severe	Mild	Moderate	Severe
Days since discharge at which follow-up call completed, Median (IQR), days	N = 63 72 (60-95)	N = 205 71 (58-93)	N = 54 91 (70-116)	N = 39 56 (45-82)	N = 161 53 (46-61)	N = 37 63 (51-81)	**<0·001**	**<0·001**	**<0·001**
Radiological Recovery									
Number of CXR normalised N (%) Number of CXRs improved N (%) Numbers of CXRs not improved N (%)	37/46 (80) 6/46 (13) 3/46 (7)	139/206 (67) 40/206 (19) 27/206 (13)	35/57 (61) 9/57 (16) 13/57 (23)	27/38 (71) 9/38 (24) 2/38 (5)	77/119 (65) 28/119 (24) 14/119 (12)	20/32 (63) 9/32 (28) 23/32 (72)	0·66	**<0·001**	0·21
Mental Health Recovery									
Patient Health Questionnaire 2 score (≥3) (%)	10/59 (17)	26/193 (14)	11/52 (21)	2/36 (6)	15/155 (10)	6/41 (15)	0·11	0·28	0·42
Trauma Screening Questionnaire score (≥5) (%)	9/58 (16)	22/187 (12)	13/52 (25)	1/40 (3)	6/166 (4)	1/42 (2)	**0·04**	**<0·01**	**<0.01**
Functional Recovery									
Number returned to work, if employed (%)	13/26 (50)	42/94 (45)	18/29 (62)	8/13 (62)	32/86 (37)	15/28 (54)	0·50	0·31	0·52
Visual analogue score reporting how close to 100% participants' feel (%)	N = 56 95 (80-100)	N = 182 90 (75-99)	N = 49 80 (60-95)	N = 34 90 (69-100)	N = 148 85 (70-95)	N = 39 80 (65-90)	0·10	0·15	0·42
Participants reporting feeling back to normal (%)	40/63 (64)	102/197 (52)	17/52 (33)	10/14 (72)	47/54 (87)	12/16 (75)	0·57	**<0·001**	**<0·01**
Current clinical frailty score, Median (IQR)	N = 69 3 (2- 4)	N = 225 3 (2-4)	N = 58 3 (2-4)	N = 39 3 (2-6)	N = 101 3 (2-6)	N = 24 4 (2-6)	0·17	**<0·01**	0·06
Social circumstances (Independent) (%)	37/63 (59)	124/201 (62)	35/54 (65)	20/38 (53)	116/157 (74)	28/40 (70)	0·34	**<0·001**	0·87
MRC dyspnoea scale, Median (IQR)	N = 53 2 (1-3)	N = 195 2 (1-2)	N = 46 2 (1-3)	N = 28 3 (2- 4)	N = 85 2 (1-3)	N = 22 1 (1-3)	**<0·01**	0·59	**0·03**

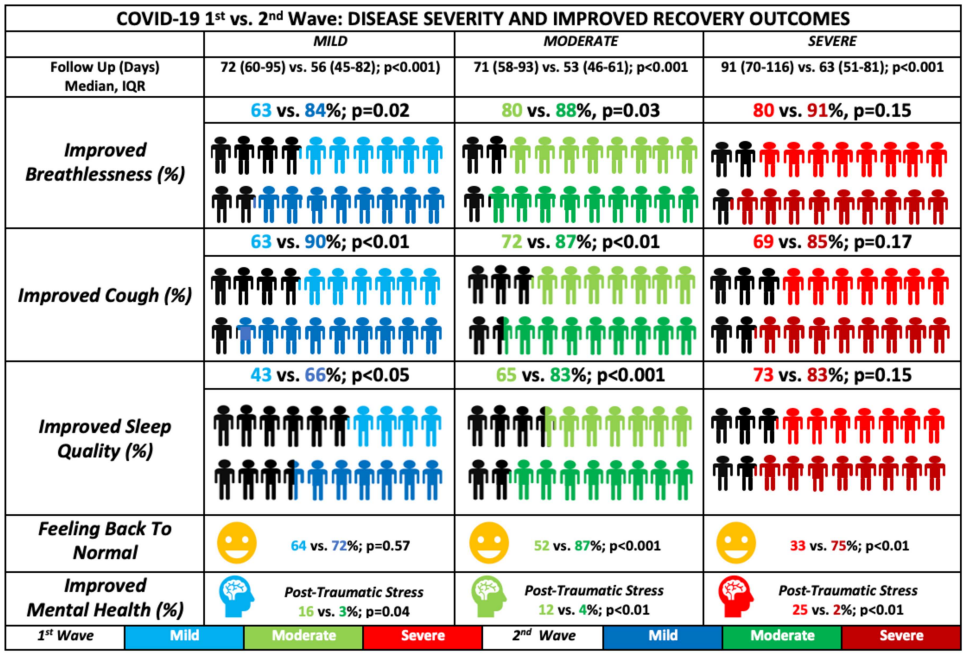
Supplementary Table 4: Comparing Physical Recovery Outcomes According to Clinical Severity of COVID-19

Physical Recovery									
Percentage of Persistence Symptoms at Follow-up i.e. Scoring > 1 on Numerical Rating Scale (0-10)									
	Wave 1 (N = 322)			**Wave 2 (N = 365)**					
Variable	**Mild**	**Moderate**	**Severe**	**Mild**	**Moderate**	**Severe**	**p -value**		
Long-COVID prevalence (any one of fourteen symptoms listed below)	50/63 (79)	165/200 (83)	47/53 (89)	26/40 (65)	126/166 (76)	36/42 (86)	0·11	0·12	0·67
Long-COVID severity (total number out of 14 symptoms listed below)	N = 63 3 (1-5)	N = 200 3 (1-5)	N = 53 4 (2-5)	N = 40 2 (0-3)	N = 166 2 (1-4)	N = 42 3 (1-4)	**0·02**	**0·01**	0·15
Long-COVID symptoms (maximum of 14 symptoms)									
Breathlessness N (%)	21/63 (33)	99/199 (50)	31/53 (59)	11/37 (30)	76/154 (49)	28/41 (68)	0·71	0·94	0·33
Cough N (%)	13/63 (21)	56/200 (28)	12/53 (23)	6/37 (16)	47/153 (31)	17/41 (42)	0·59	0·59	0·05
Sleep Quality N (%)	30/63 (47)	99/195 (51)	34/53 (64)	12/37 (32)	55/152 (36)	19/41 (46)	0·14	**<0.01**	0·08
Fatigue N (%)	37/63 (59)	125/195 (64)	37/53 (70)	19/37 (51)	101/154 (66)	30/41 (73)	0·47	0·77	0·72
Myalgia N (%)	13/63 (21)	45/199 (23)	18/52 (35)	5/40 (13)	20/166 (12)	7/42 (17)	0·29	**<0·01**	0·05
Anosmia N (%)	12/63 (19)	21/199 (11)	6/52 (12)	0/40 (0)	11/166 (7)	1/42 (2)	**<0·01**	0·19	0·09
Chest pain N (%)	8/63 (13)	20/200 (10)	6/52 (12)	1/40 (3)	10/166 (6)	3/42 (7)	0·07	0·17	0·47
Chest tightness N (%)	9/63 (14)	25/199 (13)	5/52 (10)	3/40 (8)	13/166 (8)	6/42 (14)	0·30	0·14	0·48
Confusion/Fuzzy head N (%)	13/63 (21)	28/199 (14)	7/52 (14)	5/40 (13)	15/166 (9)	7/42 (17)	0·29	0·14	0·66
Diarrhoea N (%)	6/63 (10)	7/199 (4)	5/52 (10)	2/40 (5)	5/166 (3)	1/42 (2)	0·40	0·79	0·15
Peripheral oedema N (%)	8/63 (13)	20/199 (10)	8/52 (15)	5/40 (13)	16/166 (10)	3/42 (7)	0·98	0·90	0·22
Abdominal Pain N (%)	7/63 (11)	13/199 (7)	0/52 (0)	2/40 (5)	5/166 (3)	2/42 (5)	0·28	0·12	0·11
Focal Weakness N (%)	7/63 (11)	24/199 (12)	13/53 (25)	0/40 (0)	10/166 (6)	4/42 (10)	**0·03**	**0·05**	0·06
Anorexia N (%)	6/63 (10)	13/199 (7)	2/52 (4)	2/40 (5)	6/166 (4)	2/42 (5)	0·40	0·21	0·83
Percentage Of Patients Demonstrating Improvement In Symptoms at Follow-up									
Breathlessness improved	37/59 (63)	137/172 (80)	39/49 (80)	32/38 (84)	137/155 (88)	38/42 (91)	**0·02**	**0·03**	0·15
Cough improved	37/59 (63)	123/171 (72)	34/49 (69)	34/38 (90)	132/152 (87)	35/41 (85)	**<0·01**	**<0·01**	0·17
Fatigue improved	45/58 (78)	149/169 (88)	47/48 (98)	32/38 (84)	142/155 (92)	35/41 (85)	0·46	0·43	**<0·05**
Sleep Quality improved	25/58 (43)	108/167 (65)	35/48 (73)	25/38 (66)	124/149 (83)	34/41 (83)	**<0.05**	**<0·001**	0·15

Supplementary Figure 5: Comparing Physical Recovery Outcomes According to Clinical Severity of COVID-19

We analysed differences in physical symptoms, mental health, radiological outcomes and functional recovery according to acute COVID-19 severity. Wave 1 mild and moderate patients reported a greater total number of Long-COVID symptoms (mild; 3(1-5) vs. 2(0-3), p=0.02, moderate; 4(2-5) vs. 3(1-4), p=0.01. Fewer Wave 1 mild and moderate disease patients reported self-improvement in their symptoms of breathlessness (mild; 63 vs. 84%, p=0·02, moderate; 80 vs. 88%, p=0·03), cough (mild; 63 vs. 90%, p<0·01, moderate; 72 vs. 87%, p<0·01) and sleep quality (mild; 43 vs. 66%, p=0.05, moderate; 65 vs. 83%, p<0·001). However, more Wave 1 severe patients experienced improved self-reported fatigue (98 vs. 85%; p<0·05).

Wave 1 mild, moderate and severe patients reported more symptoms of post-traumatic stress (TSQ ≥5; mild; 16 vs. 3%, p=0.04, moderate; 12 vs. 4%, p<0·01, severe; 25 vs. 2%, p<0.01). A lower proportion of Wave 1 moderate and severe disease patients reported that they overall felt back to normal (moderate; 52 vs. 87%, p<0·001, severe; 33 vs 75%, p<0.01). The greatest overall number of improved outcomes is demonstrated in those with moderate disease.



Supplementary Table 5: Blood investigations at admission to hospital for first and second wave participants

Variable	Wave 1 N = 400	Wave 2 N = 273	p-value
White Cell count ($\times 10^9$/L)	N = 322 6.5 (4.9-8.8)	N = 255 6.4 (5.0-8.0)	0.21
Platelets ($\times 10^9$/L)	N = 321 203 (157-258)	N = 268 210 (175-265)	0.42
Neutrophils ($\times 10^9$/L)	N = 322 5.0 (3.2-7.0)	N = 255 4.8 (3.4-6.7)	0.36
Lymphocytes ($\times 10^9$/L)	N = 322 0.9 (0.7-1.3)	N = 255 1.0 (0.7-1.3)	0.37
Fibrinogen (g/dL)	N = 223 5.7 (4.8-6.3)	N = 219 5.5 (4.8-6.1)	0.77
D dimer (ng/mL)	N = 217 859 (558-1678)	N = 213 806 (517-1363)	0.84
Ferritin (ug/L)	N = 217 794 (430-1604)	N = 230 721 (406-1359)	0.73
Creatinine (umol/L)	N = 321 88 (71-115)	N = 249 79 (66-99)	0.55
Bilirubin (umol/L)	N = 296 7 (6-11)	N = 265 8 (6-12)	0.53
ALT (iu/L)	N = 287 33 (22-57)	N = 229 32 (22-56)	0.83
AST (iu/L)	N = 225 45 (32-71)	N = 143 40 (31-65)	0.19
Glucose (mmol/L)	N = 191 6.4 (5.6-8.1)	N = 247 6.5 (5.7-8.5)	0.15
CRP (mg/L)	N = 318 77 (35-140)	N = 253 71 (27-119)	0.90
Troponin (ng/L)	N = 235 13 (6-29)	N = 201 9 (6-19)	0.58
BNP (ng/L)	N = 36 526 (101-1476)	N = 225 157 (50-425)	0.49

Supplementary Table 6: Blood investigations at follow-up for first and second wave participants

Variable	Wave 1	Wave 2	p-value
White Cell count ($\times 10^9$/L)	N = 195 6.5 (5.6-7.8)	N = 143 7.2 (6.1-8.5)	**<0.01**
Platelets ($\times 10^9$/L)	N = 195 242 (207-290)	N = 144 272 (233-333)	**<0.001**
Neutrophils ($\times 10^9$/L)	N = 195 3.7 (2.8-4.6)	N = 143 4.0 (3.1-5.0)	**0.03**
Lymphocytes ($\times 10^9$/L)	N = 196 2.0 (1.5-2.6)	N = 143 2.2 (1.6-2.7)	0.05
Fibrinogen (g/dL)	N = 183 3.3 (2.8-3.8)	N = 127 3.6 (3.2-4.2)	**<0.001**
D dimer (ng/mL)	N = 181 408 (257-782)	N = 127 501 (286-879)	0.09
Ferritin (ug/L)	N = 182 138 (65-249)	N = 131 172 (82-361)	**0.02**
Creatinine (umol/L)	N = 190 81 (69-95)	N = 68 69 (58-89)	**<0.001**
Bilirubin (umol/L)	N = 189 7 (5-10)	N = 146 7 (5-11)	0.54
ALT (iu/L)	N = 189 24 (18-36)	N = 145 23 (17-35)	0.50
AST (iu/L)	N = 184 24 (19-29)	N = 134 22 (19-29)	0.27
Glucose (mmol/L)	N = 175 5.8 (5.1-7.3)	N = 173 5.7 (5.0-7.5)	0.69
CRP (mg/L)	N = 190 1 (1-3)	N = 146 2 (1-6)	**<0.001**
Troponin (ng/L)	N = 178 8 (4-16)	N = 128 8 (5-13)	0.77
BNP (ng/L)	N = 174 77 (50-205)	N = 132 60 (50-184)	0.51

Supplementary Table 7: Blood investigations at follow-up, comparing patients with at least one Long-COVID symptom

Variable	No Long-COVID symptoms	At least 1 Long-COVID symptom	p-value
White Cell count ($\times 10^9$/L)	N = 73 6.4 (5.5-7.5)	N = 331 7.0 (5.9-8.4)	**0.02**
Platelets ($\times 10^9$/L)	N = 73 258 (209-302)	N = 332 261 (219-309)	0.60
Neutrophils ($\times 10^9$/L)	N = 73 3.5 (2.8 -4.7)	N = 331 3. 9 (2.9- 4.9)	0.17
Lymphocytes ($\times 10^9$/L)	N = 73 1.9 (1.5-2.4)	N = 331 2.1 (1.6-2.7)	**0.04**
Fibrinogen (g/dL)	N = 64 4 (3-4)	N = 307 4 (3-4)	0.69
D dimer (ng/mL)	N = 61 370 (225-581)	N = 306 447 (285-817)	0.11
Ferritin (ug/L)	N = 64 185 (71-373)	N = 304 156 (79-305)	0.22
Creatinine (umol/L)	N = 51 80 (69-102)	N = 245 77 (66- 92)	0.46
Bilirubin (umol/L)	N = 71 7 (5-10)	N = 331 7 (5-10)	0.92
ALT (iu/L)	N = 72 24 (18-36)	N =329 24 (18-36)	0.82
AST (iu/L)	N = 69 23 (19-30)	N = 312 23 (19-28)	0.90
Glucose (mmol/L)	N = 60 5.8 (5.2-6.6)	N = 307 5.8 (5-7.5)	0.63
CRP (mg/L)	N = 74 2 (1-4)	N = 329 2 (1-5)	0.31
Troponin (ng/L)	N = 63 6 (5-16)	N = 302 8 (5-15)	0.58
BNP (ng/L)	N = 62 78 (50-217)	N = 303 70 (50 -189)	0.49

Supplementary Table 8: Simple Logistic Regression Model for at least one Long-COVID symptom following discharge

Unadjusted Logistic Regression Coefficients for "at least one Long-COVID symptom following discharge"		
Predictor Variable	**OR (95 % CI)**	**Wald test p-value**
Variant = alpha	0.65 (0.43, 0.98)	**0·04**
Sex = Male	0·77 (0.50, 1.17)	0.23
Ethnicity = White	0.95 (0.61, 1.45)	0.79
Age (years)	1.01 (1.00, 1.03)	0.06
Length of stay (days)	1.02 (1.00, 1.05)	**0.04**
BMI (kg/m^2)	1.01 (0.97, 1.06)	0·57
Days post discharge (days)	1.01 (1.00, 1.02)	0·08
Total number of COVID-19 symptoms on admission	1.21 (1.07, 1.36)	**<0.01**
Clinical frailty Score (rated 1-9)	1.01 (0.88, 1.17)	0·88
Pre-existing lung disease	1.45 (0.82, 2.71)	0·22
Diabetes	1.45 (0·89, 2.45)	0·15
Immunosuppressed	1.59 (0.80, 3.54)	0·22
Chronic Kidney Disease	0.89 (0.49, 1.69)	0·70
Pulmonary Embolism	1.14 (0.49, 3.13)	0·77
Duration of symptoms at admission (days)	1.03 (0.98, 1.08)	0·27
Treated with Novel Drug	0.80 (0.49, 1.34)	0·38
Treated with Corticosteroids	0.83 (0.54, 1.28)	0·40
Any respiratory Support	1.53 (0.92, 2.49)	0·10
Any cardiac disease	1.11 (0.66, 1.97)	0.70
Vaccinated before admission	0.26 (0.01, 6.67)	0.35

Supplementary Table 9: Multiple Logistic Regression Model for at least one Long-COVID symptom following discharge

Adjusted Logistic Regression Coefficients for "at least one Long-COVID symptom following discharge"		
Predictor Variable	**OR (95 % CI)**	**Wald test p-value**
Intercept	0.21 (0.11, 3.65)	0·29
Variant = alpha	0.99 (0.24, 4.20)	0·98
Sex = Male	0·93 (0.45, 1.89)	0·85
Ethnicity = White	0.84 (0.42, 1.65)	0·61
Age (years)	1.02 (0.99, 1.05)	0·15
Length of stay (days)	1.06 (1.99, 1.14)	0·11
BMI (kg/m^2)	1.01 (0.95, 1.08)	0·71
Days post discharge (days)	1.00 (1.00, 1.02)	0·81
Total number of COVID-19 symptoms on admission	1.32 (1.05, 1.67)	**0·02**
Clinical frailty Score (rated 1-9)	1.10 (0.83, 1.50)	0·52
Pre-existing lung disease	1.41 (0.58, 3.80)	0·47
Diabetes	1.48 (0·62, 3.88)	0·39
Immunosuppressed	2.68 (0.69, 17.99)	0·21
Chronic Kidney Disease	0.74 (0.24, 2.58)	0·61
Pulmonary Embolism	0.40 (0.09, 2.15)	0·24
Duration of symptoms at admission (days)	1.02 (0.95, 1.11)	0·57
Treated with Novel Drug	0.92 (0.35, 2.58)	0·88
Treated with Corticosteroids	1.03 (0.25, 4.40)	0·97
Any respiratory Support	0.98 (0.35, 2.55)	0·96
Any cardiac disease	1.05 (0.38, 3.18)	0.93
Vaccinated before admission	0.18 (0.01, 5.33)	0.26

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