Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study

*The PHOSP-COVID Collaborative Group**

Summary

Background No effective pharmacological or non-pharmacological interventions exist for patients with long COVID. We aimed to describe recovery 1 year after hospital discharge for COVID-19, identify factors associated with patient-perceived recovery, and identify potential therapeutic targets by describing the underlying inflammatory profiles of the previously described recovery clusters at 5 months after hospital discharge.

Methods The Post-hospitalisation COVID-19 study (PHOSP-COVID) is a prospective, longitudinal cohort study recruiting adults (aged ≥18 years) discharged from hospital with COVID-19 across the UK. Recovery was assessed using patient-reported outcome measures, physical performance, and organ function at 5 months and 1 year after hospital discharge, and stratified by both patient-perceived recovery and recovery cluster. Hierarchical logistic regression modelling was performed for patient-perceived recovery at 1 year. Cluster analysis was done using the clustering large applications k-medoids approach using clinical outcomes at 5 months. Inflammatory protein profiling was analysed from plasma at the 5-month visit. This study is registered on the ISRCTN Registry, ISRCTN10980107, and recruitment is ongoing.

Findings 2320 participants discharged from hospital between March 7, 2020, and April 18, 2021, were assessed at 5 months after discharge and 807 (32·7%) participants completed both the 5-month and 1-year visits. 279 (35·6%) of these 807 patients were women and 505 (64·4%) were men, with a mean age of 58·7 (SD 12·5) years, and 224 (27·8%) had received invasive mechanical ventilation (WHO class 7–9). The proportion of patients reporting full recovery was unchanged between 5 months (501 [25·5%] of 1965) and 1 year (232 [28·9%] of 804). Factors associated with being less likely to report full recovery at 1 year were female sex (odds ratio 0·68 [95% CI 0·46–0·99]), obesity (0·50 [0·34–0·74]) and invasive mechanical ventilation (0·42 [0·23–0·76]). Cluster analysis (n=1636) corroborated the previously reported four clusters: very severe, severe, moderate with cognitive impairment, and mild, relating to the severity of physical health, mental health, and cognitive impairment at 5 months. We found increased inflammatory mediators of tissue damage and repair in both the very severe and the moderate with cognitive impairment clusters compared with the mild cluster, including IL-6 concentration, which was increased in both comparisons (n=626 participants). We found a substantial deficit in median EQ-5D-5L utility index from before COVID-19 (retrospective assessment; 0·88 [IQR 0·74–1·00]), at 5 months (0·74 [0·64–0·88]) to 1 year (0·75 [0·62–0·88]), with minimal improvements across all outcome measures at 1 year after discharge in the whole cohort and within each of the four clusters.

Interpretation The sequelae of a hospital admission with COVID-19 were substantial 1 year after discharge across a range of health domains, with the minority in our cohort feeling fully recovered. Patient-perceived health-related quality of life was reduced at 1 year compared with before hospital admission. Systematic inflammation and obesity are potential treatable traits that warrant further investigation in clinical trials.

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*The full writing group is listed at the end of the Article and a complete list of members of the PHOSP-COVID Collaborative Group is provided in the appendix (pp 3–12)

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See Online for appendix

Introduction

As of April, 2022, more than 500 million cases of SARS-CoV-2 infection have been reported worldwide,[1] with 21·7 million cases in the UK[2] and over 820 000 patients in the UK admitted to hospital for COVID-19. This population is at high risk of persisting health impairments 6 months after discharge associated with reduced physical function and health-related quality of life.[3–4] It is essential to understand both the longer-term trajectory of recovery to identify ongoing health-care needs and the required response by health-care systems and policy makers for this already large and ever-increasing population.

Much remains unknown about the longer-term sequelae of COVID-19. In the largest cohort study to date from Wuhan, China, nearly half of patients had persistent symptoms 12 months after discharge from hospital for COVID-19.[5] 6–12 months after discharge, patients had no change in 6-min walk distance, but

Research in context

Evidence before this study

We systematically searched PubMed and Embase databases for large studies (>1000 participants) reporting 1-year follow-up data for patients admitted to hospital with COVID-19, published between Jan 1, 2021, and Nov 7, 2021, without language restrictions. Search terms related to COVID-19 ("COVID-19", "COVID-2019", "SARS-CoV-2", "2019-nCoV", "2019-SARS-CoV-2"), hospitalisation ("hospital*"), and long-term follow-up ("survivor*", "recover*", "persistent", "follow up", "long term", "sequela*", "long Covid") were used. A large prospective cohort study from Wuhan, China (n=1276), showed that 49% of patients reported at least one persistent symptom during a follow-up clinic visit at 12 months after discharge from hospital with COVID-19; no significant improvement in exercise capacity was observed between 6-month and 12-month visits. Another two large cohort studies in China (n=2433) and Spain (n=1950) with 1-year follow-up data from telephone interviews showed that 45% (China study) and 81% (Spain study) of patients reported at least one residual COVID-19 symptom. However, no previous studies have compared the trajectories of COVID-19 recovery in patients classified by different clinical phenotypes, and we found no large studies investigating the association between systemic inflammation and ongoing health impairments after COVID-19 with or without hospitalisation.

Added value of this study

In a diverse population of adults following hospital admission with COVID-19, our large UK prospective, multicentre study reports several novel findings: the minority felt fully recovered at 1 year with minimal recovery from 5 months across any health domain; female sex and obesity were associated with being less likely to feel fully recovered at 1 year; several inflammatory mediators were increased in individuals with the most severe physical, mental health, and cognitive impairments compared with individuals with milder ongoing impairments.

Implications of all the available evidence

Both pharmacological and non-pharmacological interventions are urgently needed to improve the ongoing burden following hospitalisation for COVID-19 both for individuals and health-care systems. Our findings support the use of a precision-medicine approach with potential treatable traits of systemic inflammation and obesity.

had some improvement in the results of pulmonary imaging.[5]

The mechanisms underlying long-term persistence of symptoms are unknown. A potential hypothesis is that the hyperinflammation associated with acute COVID-19 leads to a persistent inflammatory state following COVID-19, associated with dysregulated immunity and multiorgan dysfunction. Although multiple studies have highlighted increased inflammatory markers, including interleukin-6 (IL-6), associated with severity of acute illness,[6,7] no large studies have investigated the association between systemic inflammation and ongoing health impairments after COVID-19.

No effective treatments exist for long COVID or post-COVID-19 condition. Long COVID is defined by the National Institute for Health and Care Excellence (NICE) as ongoing symptoms beyond 4–12 weeks after COVID-19 and post-COVID-19 condition by WHO as occurring "in individuals with a history of probable or confirmed SARS CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms and that last for at least 2 months and cannot be explained by an alternative diagnosis".[8,9] Improved characterisation of this population with an emphasis on elucidating underlying mechanisms is needed to identify potential therapeutic targets. We previously described four clusters of patients according to clinical recovery (very severe, severe, moderate with cognitive impairment, and mild) defined by severity of ongoing physical health, mental health, and cognitive impairment 5 months after a hospital admission with COVID-19.[3] We sought to answer the following questions using the ongoing Post-hospitalisation COVID-19 study (PHOSP-COVID) longitudinal study cohort: first, what proportion of patients discharged from hospital with COVID-19 felt fully recovered 1 year later and what are the characteristics associated with non-recovery? Second, are there inflammatory mediators associated with severity of ongoing health impairments and therefore potential therapeutic targets? Third, are there differences in the trajectory of recovery at 1 year after discharge across different health domains and between our previously described clusters?

Methods

Study design and participants

Recruitment in the PHOSP-COVID multicentre, prospective cohort study has been described previously.[3] In brief, we recruited patients aged 18 years and older who were discharged from 83 National Health Service (NHS) hospitals across the four UK nations following admission to a medical assessment unit or ward for confirmed or clinician-diagnosed COVID-19 before March 31, 2021. The current analysis involves participants who consented to attend two additional in-person research visits (tier 2, 39 sites; appendix p 16) within 1 year after discharge alongside routine clinical care.

Written informed consent was obtained from all study participants. The study was approved by the Leeds West Research Ethics Committee (20/YH/0225) and is registered on the ISRCTN Registry (ISRCTN10980107).

Procedures

Participants were invited to attend research visits at 2–7 months after discharge (5-month visit) and at

10–14 months (1-year visit). Participants were also able to attend a 1-year visit only if they were outside the time period for a 5-month visit at the time of consent and were discharged before Nov 30, 2020. The core set of data variables collected at each visit and included in this study are listed in the appendix (pp 17–18). These variables included baseline demographics, information about disease severity and treatment during their hospital admission, as well as symptoms using a bespoke study-specific questionnaire and other patient-reported outcome measures for anxiety (Generalised Anxiety Disorder 7-item scale [GAD-7]), depression (Patient Health Questionnaire-9 [PHQ-9]), post-traumatic stress disorder (Post-Traumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders* [PCL-5]), fatigue (Functional Assessment of Chronic Illness Therapy—Fatigue [FACIT-Fatigue]), breathlessness (Dyspnoea-12), and health-related quality of life (EQ-5D-5L), physical performance measures including the short physical performance battery (SPPB) and the incremental shuttle walk test (ISWT), cognitive impairment using the Montreal Cognitive Assessment (MoCA), and pulmonary function tests and blood test results reflecting multiorgan function and systemic inflammation obtained at clinical and research visits (appendix p 17). Patients were also asked to complete the EQ-5D-5L, Washington Group Short Set Functioning (WG-SS) scale, and visual analogue scale for breathlessness and fatigue retrospectively to assess their perceived pre-COVID-19 health (appendix pp 17–18). Plasma samples obtained at the 5-month visit were analysed using the Olink Explore 384 Inflammation panel (Uppsala, Sweden). Sample processing and assay details are provided in the appendix (p 13).

The primary outcome for this analysis was patient-perceived recovery, assessed using a study-specific questionnaire and the question "Do you feel fully recovered?"; participants could answer "yes", "no", or "not sure". Other secondary outcomes included symptoms since COVID-19 hospital admission that were collected on the bespoke study-specific questionnaire, validated patient-reported outcome questionnaires, and physiological measures (including physical performance and spirometry; appendix p 17).

Statistical analysis

Continuous variables were presented as median (IQR) or mean (SD). Binary and categorical variables were presented as n (%; by row or by column as indicated in table legends). Participants were stratified by patient-perceived recovery: yes (recovered), not sure, or no (not recovered).

Missing data were reported within each variable and per category. Within visit, a χ^2 test was used to identify differences in proportions across multiple categories. To test differences across categories, ANOVA was used for normally distributed continuous data and Kruskal Wallis test for non-normally distributed continuous data. For paired data between the 5-month and 1-year visit, a McNemar's χ^2 test with continuity correction was used for binary variables and a McNemar's χ^2 test was used for variables with more than two levels. We used a paired *t* test for normally distributed continuous data and a Wilcoxon signed-rank test for non-normally distributed continuous data. As previously described,[3] univariable and hierarchical multivariable logistic regression models (admission hospital included as random effect) were used to explore risk factors associated with patient-perceived recovery. Missing data were addressed using multiple imputation (ten datasets, ten iterations, and final models combined using Rubin's Rules), with the outcome used in imputation models, but not itself imputed.

To assess any potential bias as a result of patients not yet attending their 1-year visit at the time of analysis (Oct 6, 2021), we compared characteristics and patient-perceived recovery between those who attended a 1-year visit with those who had not yet attended but were discharged from hospital during the same range of dates. Multiple imputation was used to complete missing outcomes for participants who had not yet attended their 1-year follow-up. The imputation model used age, sex, ethnicity, index of multiple deprivation, and WHO clinical progression scale and all comorbidity variables. Ten datasets with ten iterations were created and combined using Rubin's rules.

In this cohort, we repeated our previous unsupervised cluster analysis[3] of patient recovery, which was measured using symptom questionnaires (patient-reported outcome measures) and physical performance and cognitive assessment data (Dyspnoea-12, FACIT-Fatigue, GAD-7, PHQ-9, PCL-5, SPPB, and MoCA as continuous variables) from the 5-month visit (discharge dates March 7, 2020, to April 18, 2021) using the clustering large applications k-medoids approach.[10] Scores were centred, normalised, and transformed so that higher burden of disease represented higher values. A Euclidean distance metric was used and the optimal number of clusters chosen using a silhouette plot. Cluster membership was determined for each individual using 5-month visit data. Characteristics at 1 year and change in characteristics between 5 months and 12 months are presented as cluster-stratified tables. All tests were two-tailed and p values of less than 0·05 were considered statistically significant. We did not adjust for multiple testing.

Plasma protein concentrations were compared between clusters using the mildest recovery cluster as baseline and using multinomial regression with age, body-mass index (BMI), and number of comorbidities as covariates (appendix p 14). Significance was defined as a p value of less than 0·1 after false discovery rate adjustment for multiple testing.

We used R (version 3.6.3) with the *finalfit*, *tidyverse*, *mice*, *cluster*, *ggplot2*, *ggalluvial*, *radiant*, *dabestr*, and *recipes* packages for all statistical analyses.

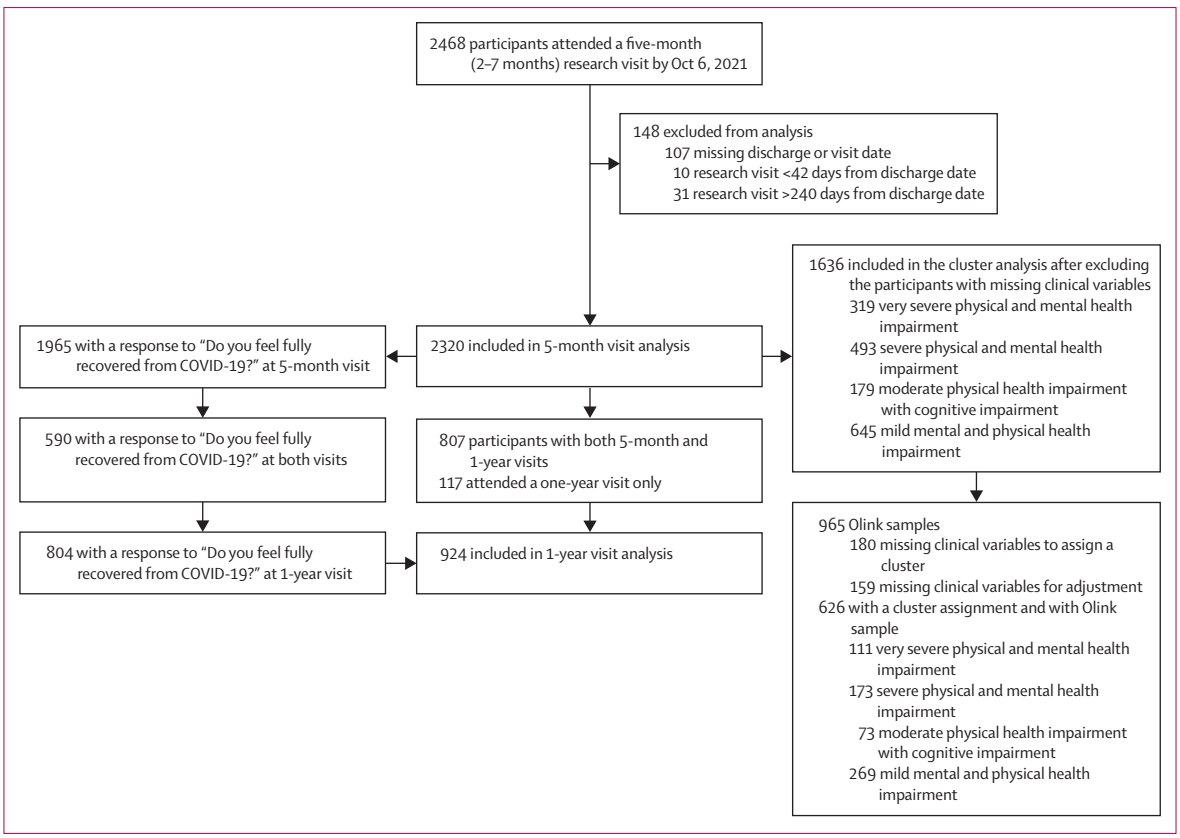


Figure 1: **Study profile**

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

At the time of analysis (Oct 6, 2021), 2468 participants (discharged from hospital between March 7, 2020, and April 18, 2021) had attended a 5-month visit (median 5 months [IQR 4-6] after discharge, 148 [6·0%] of whom were excluded; figure 1). 924 (37·4%) participants (discharged Feb 28, 2020, to Nov 28, 2020) returned for a 1-year visit (13 months [12–13] after discharge) and 807 (32·7%) participants attended both visits (figure 1). The individual and hospital admission characteristics including severity of acute illness were similar between those who attended the 5 five-month visit, 1-year visit, and both visits, except for the proportion of patients who received acute treatment with corticosteroids (table 1).

At 5 months, 1965 (84·7%) of 2320 patients, and at 1 year 804 (34·7%) patients, had both attended a research visit and answered whether or not they felt fully recovered (figure 1). At 5 months, 501 (25·5%) of 1965 patients felt fully recovered, with 385 (19·6%) feeling not sure and 1079 (54·9%) not recovered (figure 2A; appendix p 19). At 1 year, 232 (28·9%) of 804 patients felt fully recovered, 180 (22·4%) were not sure, and 392 (48·8%) were not recovered (figure 2A; appendix p 19). Similar proportions were observed in those with paired data (appendix p 22). The individual responses were also similar between 5 months and 1 year (appendix p 39).

In multivariable analysis, female sex (odds ratio [OR] 0·68 [95% CI 0·46–0·99]), BMI 30 kg/m² or greater (0·50 [0·34–0·74]), and receiving invasive mechanical ventilation (WHO category 7–9; 0·42 [0·23–0·76]) were all independent factors associated with being less likely to recover at 1 year (figure 2B; appendix p 25). We found no effect of receiving systemic corticosteroids (1·05 [0·66–1·65]) during the acute admission on patient-perceived recovery at 1 year for the whole cohort (figure 2B; appendix p 26). We also found no effect of time from discharge to the research visit (1·00 [1·00–1·01]).

751 participants discharged between Feb 28, 2020, and Nov 28, 2020, did not return for a 1-year visit but had similar characteristics and 5-month recovery status to the 924 participants who had attended (appendix p 27). The proportion of recovered patients was similar after imputation for outcome (499 [29·8%] of 1675).

For the 5-month dataset, the previously identified four clusters[3] were confirmed using participants with complete

data for the cluster analysis (n=1636; figure 1). The distribution of the four clusters was very severe physical and mental health impairment (n=319 [19·5%]), severe physical and mental health impairment (n=493 [30·1%]), moderate physical health impairment with cognitive impairment (n=179 [10·9%]), and mild mental and physical health impairment (n=645 [39·4%]; appendix p 29). 664 (86·7%) of 766 individuals included in the previous study[3] were reassigned to the same recovery cluster as before; the cluster of moderate with cognitive impairment had the most assignment alterations (60 [47·2%] of 127). Characteristics of individuals in each recovery cluster are shown in the appendix (p 30). Compared with the mild cluster, the very severe cluster had a higher proportion of women (165 [53·9%] of 306 *vs* 177 [28·4%] of 624) and obesity (BMI ≥30 kg/m²; 204 [70·8%] of 288 *vs* 288 [50·2%] of 568).

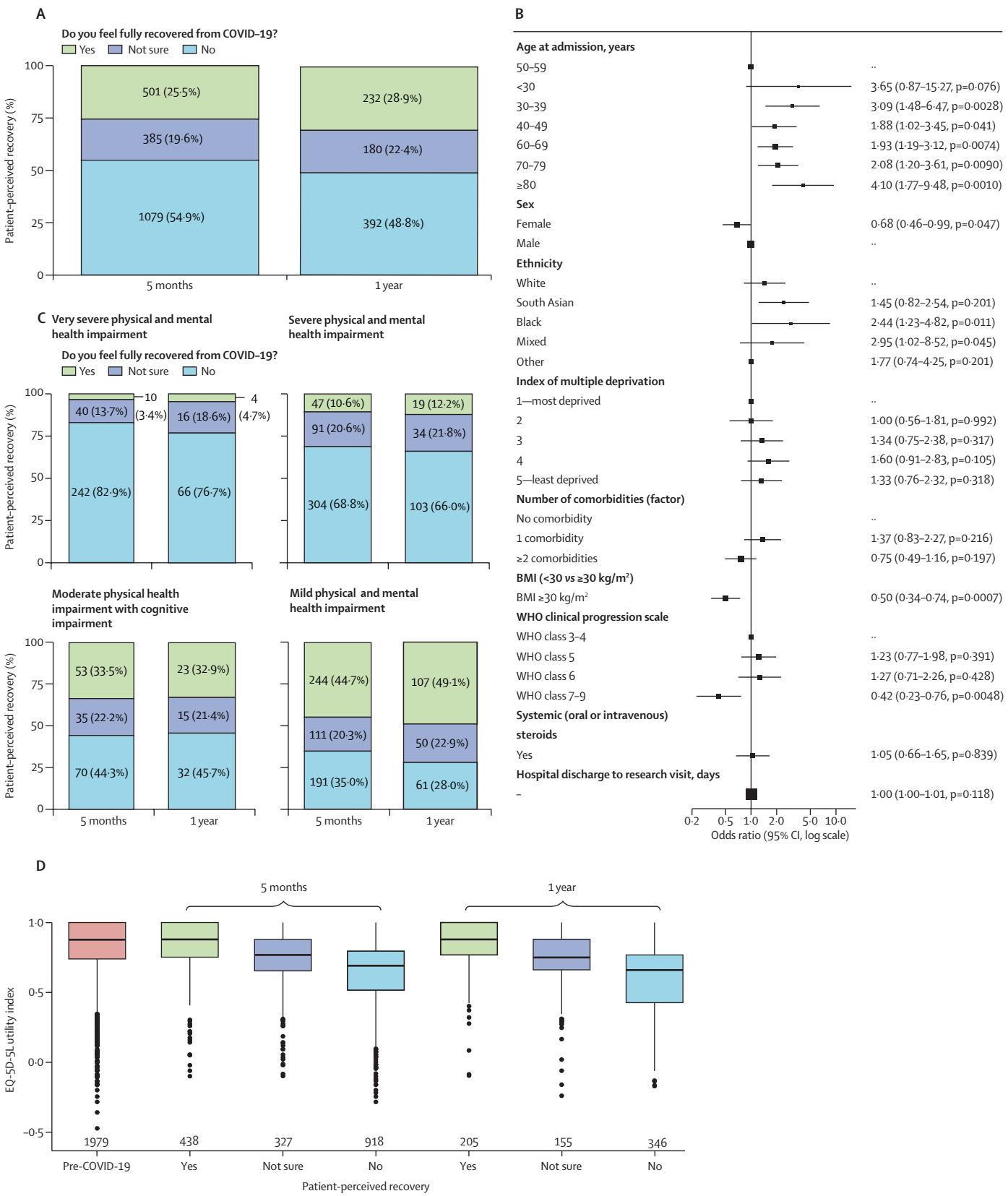
After quality control, plasma proteome data for 296 protein features and complete clinical data for cluster assignment were available at 5 months for 626 participants: 111 (17·7%) in the very severe cluster, 173 (27·6%) in the severe cluster, 73 (11·7%) in the cluster moderate with cognitive impairment, and 269 (43·0%) in the mild cluster. Age, BMI, and two or more comorbidities were associated with cluster membership, whereas receiving invasive mechanical ventilation during the acute illness was not (analysis done in participants with plasma proteome data and a cluster assignment; appendix p 32). After adjustment for age, BMI, and comorbidity count, 13 proteins were significantly increased in participants in the very severe recovery cluster compared with those in the mild cluster (appendix p 33; figure 3). These proteins were trefoil factor 2 (TFF2), transforming growth factor α (TGFA), lysosomal associated membrane protein 3 (LAMP3), CD83 molecule (CD83), galectin-9 (LGALS9), urokinase plasminogen activator surface receptor (PLAUR), interleukin-6 (IL-6), erythropoietin (EPO), FMS-related receptor tyrosine kinase 3 ligand (FLT3LG), agrin (AGRN), secretoglobin family 3A member 2 (SCGB3A2), follistatin (FST), and C-type lectin domain family 4 member D (CLEC4D; appendix p 33). Additionally, IL-6 and CD70 molecule were significantly increased in the moderate with cognitive impairment cluster compared with the mild cluster (appendix p 34).

The ten most common persistent symptoms at 1 year after discharge were fatigue (463 [60·1%] of 770 patients), aching muscles (442 [54·6%] of 809), physically slowing down (429 [52·9%] of 811), poor sleep (402 [52·3%] of 769), breathlessness (395 [51·4%] of 769), joint pain or swelling (382 [47·6%] of 803), slowing down in thinking (377 [46·7%] of 808), pain (359 [46·6%] of 770), short-term memory loss (360 [44·6%] of 808), and limb weakness (341 [41·9%] of 813; appendix p 35). Overall, symptoms were unchanged in prevalence from 5 months to 1 year, with small reductions in rates of limb weakness (47·6% at 5 months *vs* 41·7% at 1 year; p=0·010), paraesthesia (40·6% *vs* 35·2%; p=0·014), and balance problems (34·9% *vs* 30·0; p=0·0076). We found either no or minimal improvement in patient-reported outcome measures, physical function, cognitive impairment, or

	Complete 5-month visit (n=2320)	Complete 1-year visit (n=924)	Completed both visits (n=807)
Age at admission, years	58·0 (12·6)	58·9 (12·5)	58·7 (12·5)
Sex			
Female	855 (39·0%)	319 (35·8%)	279 (35·6%)
Male	1338 (61·0%)	572 (64·2%)	505 (64·4%)
Missing data	127 (5·5%)	33 (3·6%)	23 (2·9%)
Ethnicity			
White	1685 (75·4%)	681 (74·7%)	596 (74·5%)
South Asian	262 (11·7%)	102 (11·2%)	94 (11·8%)
Black	154 (6·9%)	68 (7·5%)	57 (7·1%)
Mixed	46 (2·1%)	19 (2·1%)	18 (2·2%)
Other	87 (3·9%)	42 (4·6%)	35 (4·4%)
Missing data	86 (3·7%)	12 (1·3%)	7 (0·9%)
Index of multiple deprivation score			
1 (most deprived)	517 (22·6%)	187 (20·4%)	163 (20·4%)
2	533 (23·3%)	186 (20·3%)	163 (20·4%)
3	404 (17·7%)	175 (19·1%)	155 (19·4%)
4	396 (17·3%)	160 (17·5%)	137 (17·2%)
5 (least deprived)	438 (19·1%)	207 (22·6%)	180 (22·6%)
Missing data	32 (1·4%)	9 (1·0%)	9 (1·1%)
Body-mass index			
Median (IQR)	31·2 (27·7–36·1)	31·5 (27·7–35·8)	31·5 (27·7–35·7)
<30 kg/m²	840 (41·1%)	349 (40·3%)	316 (41·2%)
≥30 kg/m²	1204 (58·9%)	517 (59·7%)	451 (58·8%)
Missing data	276 (11·9%)	58 (6·3%)	40 (5·0%)
Smoking status			
Never	1085 (54·7%)	429 (53·2%)	350 (52·8%)
Ex-smoker	864 (43·5%)	369 (45·7%)	301 (45·4%)
Current	36 (1·8%)	9 (1·1%)	12 (1·8%)
Missing data	335 (14·4%)	117 (12·7%)	144 (17·8%)
WHO clinical progression scale			
WHO class 3–4	385 (16·9%)	171 (18·6%)	145 (18·0%)
WHO class 5	959 (42·2%)	342 (37·1%)	299 (37·1%)
WHO class 6	517 (22·7%)	167 (18·1%)	139 (17·2%)
WHO class 7–9	412 (18·1%)	241 (26·2%)	224 (27·8%)
Missing data	47 (2·0%)	3 (0·3%)	0
Comorbidities			
Median number of comorbidities	2·0 (0·0–3·0)	2·0 (0·0–3·0)	2·0 (0·0–3·0)
0	642 (27·7%)	251 (27·2%)	213 (26·4%)
1	468 (20·2%)	172 (18·6%)	154 (19·1%)
≥2	1210 (52·2%)	501 (54·2%)	440 (54·5%)
Admission duration, days	13·9 (18·2)	17·0 (24·7)	17·8 (22·1)
Positive SARS-CoV-2 PCR	1916 (92·4%)	796 (90·8%)	700 (90·6%)
Missing data	246 (10·6%)	47 (5·1%)	34 (4·2%)
Systemic steroids	1173 (54·2%)	251 (29·8%)	226 (30·2%)
Missing data	157 (6·8%)	81 (8·8%)	59 (7·3%)

Data are n (%), mean (SD), or median (IQR). Percentages are calculated by category after exclusion of missing data for that variable.

Table 1: **Characteristics of participants who had a 5-month visit, a 1-year visit, and both visits**


A
Do you feel fully recovered from COVID-19?
Yes
Not sure
No
Patient-perceived recovery (%)
100
75
50
25
0
501 (25·5%)
385 (19·6%)
1079 (54·9%)
232 (28·9%)
180 (22·4%)
392 (48·8%)
5 months
1 year
B
Age at admission, years
50–59 ..
<30 3·65 (0·87–15·27, p=0·076)
30–39 3·09 (1·48–6·47, p=0·0028)
40–49 1·88 (1·02–3·45, p=0·041)
60–69 1·93 (1·19–3·12, p=0·0074)
70–79 2·08 (1·20–3·61, p=0·0090)
≥80 4·10 (1·77–9·48, p=0·0010)
Sex
Female 0·68 (0·46–0·99, p=0·047)
Male ..
Ethnicity
White ..
South Asian 1·45 (0·82–2·54, p=0·201)
Black 2·44 (1·23–4·82, p=0·011)
Mixed 2·95 (1·02–8·52, p=0·045)
Other 1·77 (0·74–4·25, p=0·201)
Index of multiple deprivation
1—most deprived ..
2 1·00 (0·56–1·81, p=0·992)
3 1·34 (0·75–2·38, p=0·317)
4 1·60 (0·91–2·83, p=0·105)
5—least deprived 1·33 (0·76–2·32, p=0·318)
Number of comorbidities (factor)
No comorbidity ..
1 comorbidity 1·37 (0·83–2·27, p=0·216)
≥2 comorbidities 0·75 (0·49–1·16, p=0·197)
BMI (<30 vs ≥30 kg/m²)
BMI ≥30 kg/m² 0·50 (0·34–0·74, p=0·0007)
WHO clinical progression scale
WHO class 3–4 ..
WHO class 5 1·23 (0·77–1·98, p=0·391)
WHO class 6 1·27 (0·71–2·26, p=0·428)
WHO class 7–9 0·42 (0·23–0·76, p=0·0048)
Systemic (oral or intravenous) steroids
Yes 1·05 (0·66–1·65, p=0·839)
Hospital discharge to research visit, days
– 1·00 (1·00–1·01, p=0·118)
0·2
0·5
1·0
2·0
5·0
10·0
Odds ratio (95% CI, log scale)
C
Very severe physical and mental health impairment
Do you feel fully recovered from COVID-19?
Yes
Not sure
No
Patient-perceived recovery (%)
40 (13·7%)
10 (3·4%)
242 (82·9%)
16 (18·6%)
4 (4·7%)
66 (76·7%)
Severe physical and mental health impairment
47 (10·6%)
91 (20·6%)
304 (68·8%)
19 (12·2%)
34 (21·8%)
103 (66·0%)
Moderate physical health impairment with cognitive impairment
53 (33·5%)
35 (22·2%)
70 (44·3%)
23 (32·9%)
15 (21·4%)
32 (45·7%)
Mild physical and mental health impairment
244 (44·7%)
111 (20·3%)
191 (35·0%)
107 (49·1%)
50 (22·9%)
61 (28·0%)
5 months
1 year
D
5 months
1 year
EQ-5D-5L utility index
1·0
0·5
0·0
−0·5
1979
438
327
918
205
155
346
Pre-COVID-19
Yes
Not sure
No
Yes
Not sure
No
Patient-perceived recovery

organ function at 1 year compared with 5 months after discharge (paired data in table 2 and presented stratified by patient-perceived recovery in appendix p 19). At 1 year, 147 [21·5%] of 684 patients had clinically relevant symptoms of anxiety, 169 (24·9%) of 680 participants had clinically relevant symptoms of depression, 68 (10·0%) of 680 had post-traumatic stress disorder, and 55 (8·8%) of 623 had significant cognitive impairment (table 2). Measures of symptoms and physical function were significantly different across participants who reported being fully recovered, not sure, or not fully recovered at 5 months and 1 year, but cognitive impairment and measures of organ function were not (except for forced vital capacity; table 2). Health-related quality of life was significantly different across participants who reported being fully recovered, not sure, or not recovered at both 5 months and 1 year (figure 2D; appendix p 19).

In addition to higher proportions of women and obesity (appendix p 30), at 1 year the very severe cluster was associated with a lower proportion of patients who reported feeling fully recovered (4 [4·7%] of 86 *vs* 107 [49·1%] of 218; figure 2C; reduced exercise capacity [ISWT 44·4% predicted *vs* 72·4% predicted]; greater number of symptoms [20 *vs* 4]; and greater proportion of patients with increased C-reactive protein concentration >5 mg/L [38·4% *vs* 14·5%]) compared with the mild cluster (table 3; figure 4A). A comparison of health outcomes across the four clusters between the 5-month and 1 year timepoints (n=602) showed minimal change across the two timepoints for the four clusters (table 3). In the very severe cluster, symptoms of anxiety, depression, breathlessness, and fatigue significantly improved between 5 months and 1 year, but with minimal change in physical performance and no overall change in systemic inflammation measured by C-reactive protein concentration (table 3). Cognitive impairment significantly improved at 1 year in the moderate with cognitive impairment cluster and was unchanged in the other clusters (table 3). Compared with patient-perceived health before COVID-19, decrements were seen at 5 months and sustained at 1 year across health-related quality of life (EQ-5D-5L; figure 4B), disability (WG-SS), and severity of breathlessness and fatigue experienced in the past 24 h (appendix p 43).

Figure 2: **Patient-perceived recovery at 1 year**
(A) Compared with patient-perceived recovery at 5 months. (B) Risk factors for being less likely to recover. (C) Compared according to the four clusters. (D) Compared with health-related quality of life (assessed by the EQ-5D-5L utility index). WHO clinical progression scale classes are as follows: 3–4 indicates no continuous supplemental oxygen needed; 5 indicates continuous supplemental oxygen only; 6 indicates continuous positive airway pressure or bi-level positive pressure ventilation or high-flow nasal oxygen; and 7–9 indicates invasive mechanical ventilation or other organ support. The forest plot of the patient and admission characteristics associated with patient-perceived recovery at 1 year used multivariable logistic regression and multiple imputation. EQ-5D-5L score before COVID-19 was retrospectively completed by participants. BMI=body-mass index.

Discussion

In adults admitted to hospital with COVID-19 in the UK, we found that a minority of participants felt fully recovered 1 year after hospital discharge, with minimal improvement after a 5-month assessment. The most common ongoing

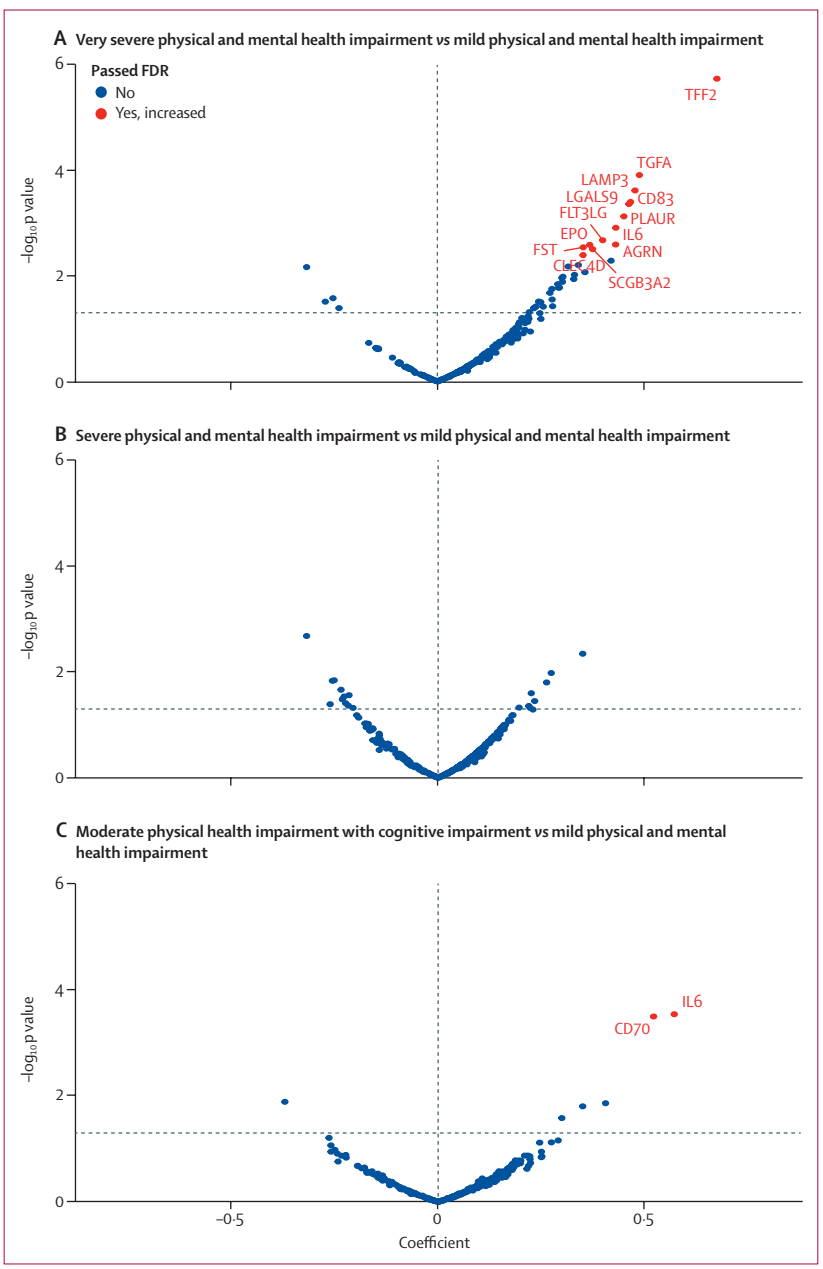


Figure 3: **Volcano plots representing multinomial regression association results for comparison of 296 proteins between the four clinical phenotypes**
Results corrected for age, body-mass index, and number of comorbidities, comparing 296 proteins between very severe physical and mental health impairment and mild physical and mental health impairment clusters (A), severe physical and mental health impairment and mild physical and mental health impairment clusters (B), and moderate physical health impairment with cognitive impairment and mild physical and mental health impairment clusters (C). The red horizontal line represents an unadjusted p<0·05 threshold. Proteins that were significantly differentially expressed (compared with the reference mild cluster) after FDR adjustment are indicated in red; FDR cutoff used was 0·1. FDR=false detection rate.

	5-month visit (n=1965)				Paired data at 5-month and 1-year visits (n=807)			
	Recovered	Not sure	Not recovered	p value	Pairs with available data	5 months	1 year	p value
Total	501 (25·5%)	385 (19·6%)	1079 (54·9%)	NA	590	151 (25·6%)	168 (28·5%)	0·12
Time to review from discharge, days	166 (127–191)	165 (122–191)	157 (119–189)	0·040	807	178 (156–197)	384 (359–409)	<0·0001
Body-mass index								
Overall	29·4 (26·6–33·5)	31·5 (28·0–36·3)	31·6 (28·0–36·4)	<0·0001	602	30·7 (27·3–35·0)	31·1 (27·5–35·5)	<0·0001
<30 kg/m²	230 (54·5%)	131 (40·2%)	360 (38·8%)	<0·0001	602	275 (45·7%)	255 (42·4%)	0·021
≥30 kg/m²	192 (45·5%)	195 (59·8%)	568 (61·2%)	..	..	327 (54·3%)	347 (57·6%)	..
Symptoms, n	3 (1–7)	8 (4–15)	14 (8–20)	<0·0001	619	9 (4–16)	9 (4–17)	0·010
Fatigue VAS score	0·0 (0·0–2·0)	2·0 (0·0–5·0)	5·0 (2·0–8·0)	<0·0001	521	3·0 (0·0–6·0)	3·0 (0·0–6·0)	0·090
Breathlessness VAS score	0·0 (0·0–1·0)	1·5 (0·0–4·0)	4·0 (1·0–6·0)	<0·0001	524	2·0 (0·0–5·0)	2·0 (0·0–5·0)	0·052
Anxiety (GAD-7 score >8)	53 (11·3%)	81 (22·6%)	339 (33·4%)	<0·0001	684	164 (24·0%)	147 (21·5%)	0·13
Depression (PHQ-9 score ≥10)	47 (9·9%)	96 (26·7%)	426 (42·0%)	<0·0001	680	181 (26·6%)	169 (24·9%)	0·25
Post-traumatic stress disorder (PCL-5 score ≥38)	18 (3·8%)	34 (9·5%)	202 (20·0%)	<0·0001	680	83 (12·2%)	68 (10·0%)	0·055
Dyspnoea-12 score	2·1 (4·8)	5·1 (7·1)	8·9 (8·8)	<0·0001	702	6·0 (8·1)	5·5 (7·7)	0·040
FACIT-Fatigue score	43·6 (8·8)	36·5 (11·2)	29·1 (12·8)	<0·0001	679	35·7 (12·9)	36·3 (12·5)	0·070
SPPB score ≤10	181 (38·9%)	166 (46·0%)	582 (58·8%)	<0·0001	685	318 (46·4%)	309 (45·1%)	0·53
ISWT distance, m	487·6 (274·7)	431·4 (242·3)	384·6 (249·4)	<0·0001	509	453·6 (262·8)	468·2 (267·8)	0·017
ISWT % predicted	63·5 (30·7)	57·8 (28·1)	52·5 (28·7)	<0·0001	429	60·1 (29·4)	61·2 (28·7)	0·22
MoCA score <23	66 (16·5%)	39 (12·4%)	147 (15·8%)	0·26	623	89 (14·3%)	62 (10·0%)	0·0013
MoCA score (adjusted)* <23	57 (14·3%)	36 (11·4%)	125 (13·4%)	0·52	623	72 (11·6%)	55 (8·8%)	0·034
FEV_1 <80% predicted	43 (21·4%)	43 (27·7%)	131 (27·9%)	0·20	287	67 (23·3%)	63 (22·0%)	0·64
FVC <80% predicted	40 (19·9%)	33 (21·4%)	155 (33·2%)	0·00030	281	79 (28·1%)	63 (22·4%)	0·018
BNP ≥100 ng/L or pro-NT-BNP ≥400 ng/L	27 (8·7%)	24 (10·3%)	35 (5·2%)	0·014	335	30 (9·0%)	29 (8·7%)	1·0
HbA_{1c} ≥6·0% (DCCT/NGSP)	6·1 (1·2%)	6·2 (1·3%)	6·2 (1·3%)	0·60	399	140 (35·1%)	130 (32·6%)	0·21
eGFR <60 mL/min per 1·73 m²	49 (12·0%)	35 (11·3%)	101 (11·4%)	0·94	564	73 (12·9%)	79 (14·0%)	0·45
C-reactive protein concentration >5 mg/L	83 (20·9%)	75 (23·9%)	239 (27·1%)	0·052	557	126 (22·6%)	133 (23·9%)	0·52
EQ-5D-5L utility index	0·88 (0·75–1·00)	0·77 (0·65–0·88)	0·69 (0·52–0·80)	<0·0001	585	0·74 (0·64–0·88)	0·75 (0·62–0·88)	0·95
EQ-5D-5L VAS	85·0 (72·2–91·2)	75·0 (60·0–85·0)	70·0 (50·0–80·0)	<0·0001	586	75·0 (60·0–90·0)	75·0 (60·0–90·0)	0·43
WG-SS-SCo	0·0 (0·0–2·0)	2·0 (0·5–3·0)	3·0 (1·0–8·0)	<0·0001	548	2·0 (0·0–4·0)	2·0 (0·0–4·0)	0·73

Data are n, n (%), mean (SD), or median (IQR). Percentages are calculated by category after exclusion of missing data for that variable. BNP=brain natriuretic peptide. DCCT/NGSP=Diabetes Control and Complications Trial and National Glycohemoglobin Standardization Program criteria. eGFR=estimated glomerular filtration rate. FACIT=Functional Assessment of Chronic Illness Therapy. FVC=forced vital capacity. GAD-7=Generalized Anxiety Disorder 7-item scale. ISWT=incremental shuttle walk test. MoCA=Montreal Cognitive Assessment. NA=not applicable. NT-BNP=N-terminal brain natriuretic peptide. PCL-5=Post-Traumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders*. PHQ-9=Patient Health Questionnaire-9. SPPB=short physical performance battery. VAS=visual analogue scale. WG-SS-SCo=Washington Group Short Set of Functioning Severity Continuum. *Adjusted for education.

***Table 2*: Patient-reported outcome measures, physical function, and organ function at 5 months, stratified by patient-perceived recovery and compared with outcome 1 year after hospital discharge**

symptoms were fatigue, muscle pain, physically slowing down, poor sleep, and breathlessness. The major risk factors for not feeling fully recovered at 1 year were female sex, obesity, and receiving invasive mechanical ventilation during the acute illness. We found substantial impairments in health-related quality of life at 5 months and 1 year compared with retrospective self-reported scores before COVID-19. Cluster analysis using the 5-month assessments corroborated four different clusters: very severe, severe, moderate with cognitive impairment, and mild, which were based on the severity of physical, mental, and cognitive impairments with similar characteristics to those previously reported.[3] We showed that obesity, reduced exercise capacity, a greater number of symptoms, and increased serum C-reactive protein concentration were associated with the more severe clusters.[3] In the largest post-hospital cohort with systemic inflammatory profiling to date, inflammatory mediators consistent with persistent lung and systemic inflammation were increased in the very severe, moderate with cognitive impairment, and mild clusters. We therefore highlight traits to identify individuals at high risk of non-recovery and potential targetable pathways for interventions.

Comparing the systemic inflammatory profiling at 5 months after discharge between the very severe and mild cluster, the most increased protein concentration, TFF2, is

	Very severe physical and mental health impairment				Severe physical and mental health impairment				Moderate physical health impairment with cognitive impairment				Mild mental and physical health impairment			
	Pairs	5 months	1 year	p value	Pairs	5 month	1 year	p value	Pairs	5 months	1 year	p value	Pairs	5 months	1 year	p value
Time to review, days	99	174 (136–204)	393 (354–413)	..	176	176 (152–193)	386 (358–409)	..	75	174 (155–199)	378 (363 – 405)	..	252	180 (163 – 194)	388 (364 – 407)	..
Symptom count	80	19.5 (16–25)	20 (14–26)	0·30	141	13 (8–17)	13 (8–18)	0·11	61	7·5 (5 – 11)	9 (5 – 12)	0·22	188	4 (1 – 7)	4 (1 – 7·5)	0·75
Anxiety (GAD-7 score ≥8)	88	93·2	70·5	0·00010	152	24·3	23·0	0·89	70	5·7	14·3	0·077	225	1·3	3·6	0·13
Depression (PHQ-9 score ≥ 10)	87	96·6	80·5	0·0012	152	32·2	27·0	0·28	70	2·9	7·1	0·37	225	0·9	3·1	0·18
Post-traumatic stress disorder (PCL-5 score ≥38)	88	65·9	47·7	0·0046	152	3·3	6·6	0·23	68	0·0	1·5	NA	223	0·0	0·4	NA
Dyspnoea-12 score	89	18·0 (9·6%)	15·2 (10·0%)	0·0028	167	6·5 (5·8%)	5·7 (5·9%)	0·11	67	2·9 (3·7%)	4 (5·4%)	0·066	238	1·5 (2·4%)	1·4 (2·5%)	0·64
FACIT-Fatigue score	88	17·4 (8·9%)	21·8 (12·0%)	0·00010	152	30·6 (8·9%)	33·5 (10·1%)	<0·0001	69	42·0 (7·4%)	39·1 (8·5%)	0·0052	225	45·8 (4·8%)	45·0 (6·6%)	0·043
Physical performance																
SPPB score ≤10	86	68·6	69·8	1·0	164	48·8	46·3	0·67	70	80·0	70·0	0·096	239	23·0	26·4	0·34
ISWT distance, m	65	308 (225)	332 (233)	0·14	122	454 (262)	476 (286)	0·056	45	349 (200)	355 (155)	0·72	172	552 (254)	571 (268)	0·070
ISWT % predicted*	58	40·7 (24·7%)	44·4 (27·2%)	0·14	105	59·9 (27·3%)	62·4 (30·5%)	0·11	39	56·5 (30·8%)	57·3 (26·1%)	0·72	138	71·6 (27·9%)	72·4 (26·3%)	0·62
Cognitive impairment																
MoCA score <23	88	22·7	15·9	0·15	161	5·6	5·6	1·0	62	59·7	32·3	0·00050	232	3·9	3·0	0·75
MoCA (adjusted) score <23	88	20·5	13·6	0·11	161	3·7	4·3	1·0	62	53·2	29·0	0·0023	232	1·7	2·6	0·68
Organ function																
FEV_1 % <80% predicted	28	35·7	25·0	0·25	61	21·3	18·0	0·72	33	21·2	27·3	0·72	86	18·6	22·1	0·55
FVC % <80% predicted	27	51·9	37·0	0·13	60	25	18·3	0·22	33	36·4	27·3	0·45	86	22·1	23·3	1·0
C-reactive protein concentration >5 mg/L	73	34·2	38·4	0·51	118	30·5	27·1	0·45	52	7·7	21·2	0·046	165	13·9	14·5	1·0

Data are n, n (%), mean (SD), or median (IQR). Missing data are not included in %. FACIT=Functional Assessment of Chronic Illness Therapy. FVC=forced vital capacity. GAD-7=Generalized Anxiety Disorder 7-item scale. ISWT=incremental shuttle walk test. MoCA=Montreal Cognitive Assessment. NA=not applicable. PCL-5=Post-Traumatic Stress Disorder Checklist for the *Diagnostic and Statistical Manual of Mental Disorders*. PHQ-9=Patient Health Questionnaire-9. SPPB=short physical performance battery. *Adjusted for education.

***Table 3*: Comparison of the change in patient-reported outcome measures between 5 months and 1 year**

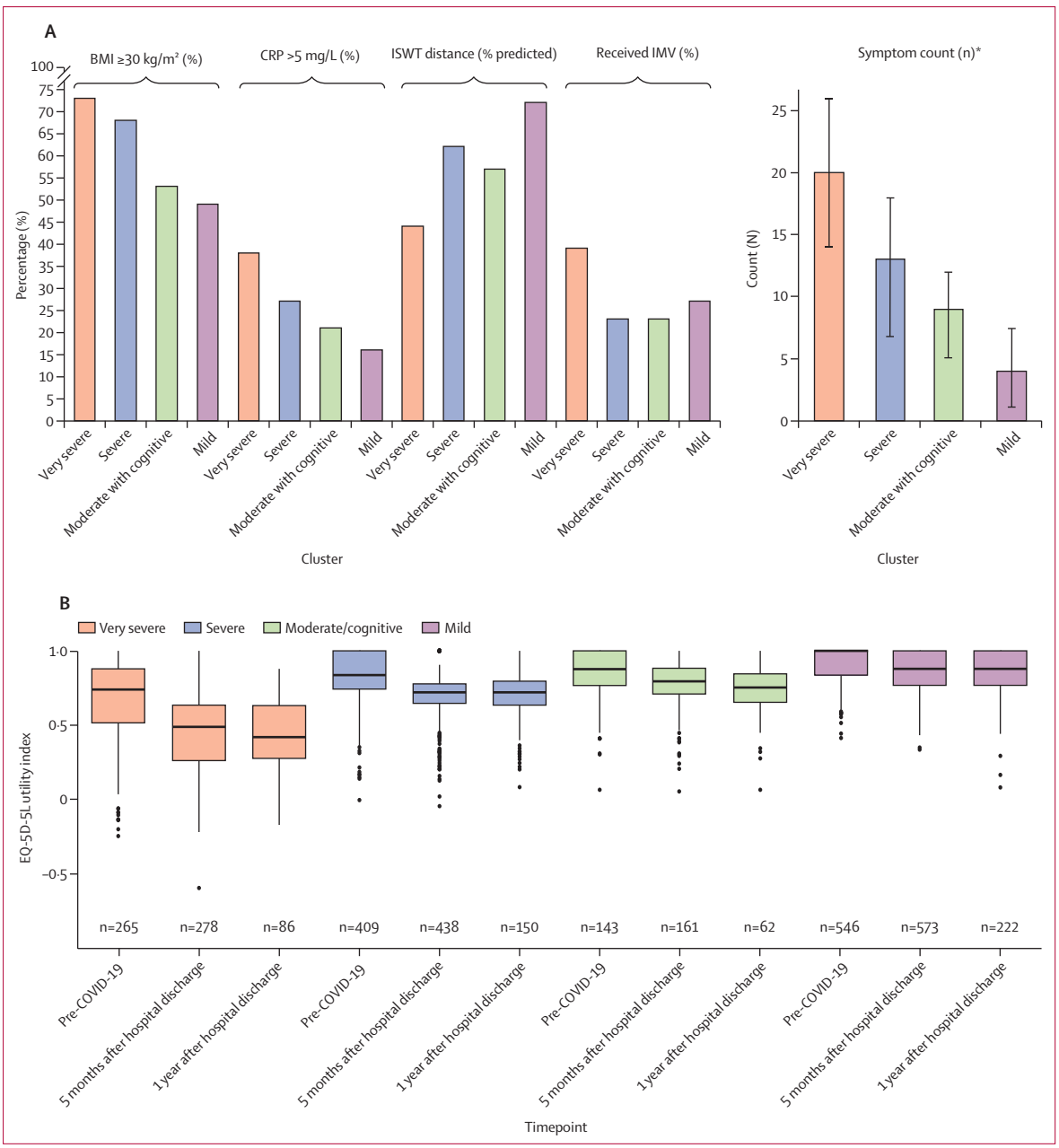


Figure 4: **Characteristics associated with the four recovery clusters**
(A) Patient characteristics, CRP concentration, exercise performance, and symptom count across the four clusters (error bars indicate IQR). (B) Health-related quality of life across the four clusters assessed before hospitalisation (patient estimate), and at 5 months and 1 year after discharge. EQ-5D-5L utility index stratified by cluster and pre-hospital health status assessed retrospectively. Very severe indicates the very severe physical and mental health impairment cluster, severe indicates the severe physical and mental health impairment cluster, moderate with cognitive indicates the moderate physical health impairment with cognitive impairment cluster, and mild indicates the mild physical and mental health impairment cluster. BMI=body-mass index. CRP=mean C-reactive protein concentration assessed at 1 year. IMV=invasive mechanical ventilation. ISWT=incremental shuttle walk test distance percentage predicted assessed at 1 year. *Median number of symptoms at 1 year.

a protein released with mucin from mucosal epithelium including lung and gastric mucosa. TFF2 has postulated roles in repair of damaged epithelium[11] and, in combination with interferon-κ, reduced duration of infection in a small open-label randomised controlled trial of patients with acute COVID-19.[11] In a study[6] of patients during acute illness with COVID-19 using Olink Proteomics, IL-6 was the most upregulated protein at day 7 among patients who developed acute respiratory distress syndrome (ARDS) and subsequently died. Similarly, other proteins that we identified such as LAMP3, Gal-9, and CD83 are involved in T-cell macrophage and dendritic cell activation and were

associated with increased morbidity and mortality during acute COVID-19 infection.[12–14] These changes suggest persistent mucosal epithelial abnormalities and inflammatory cell activation. Increased serum concentrations of the C-terminal fragment of agrin have been reported in older adults (aged age 65–87 years) with sarcopenia, possibly related to breakdown of the neuromuscular junction.[15] The increased agrin concentrations seen here might therefore have contributed to the high prevalence of physical impairment. Interestingly, in the moderate with cognitive impairment cluster versus the mild cluster, IL-6 and CD70 concentrations were increased, suggesting possible neuroinflammation contributing to the cognitive impairment because CD70 has been implicated in inflammation in the CNS[16] via a role in differentiation of proinflammatory pathogenic lymphocytes. We found small improvements at 1 year in cognition in the moderate with cognitive impairment cluster, indicating that some of this deficit was not pre-existing and is potentially modifiable; however, considerable deficit persisted at 1 year. The associations with the inflammatory mediators remained after adjusting for age, BMI, and number of comorbidities, and the proportion having received invasive mechanical ventilation was similar across the clusters—all factors known to be associated with systemic inflammation.[17] Taken together, the increased mediators provide biological plausibility for the persistent severe impairments seen in physical health, mental health, and cognitive impairment after COVID-19.

The limited recovery from 5 months to 1 year after hospitalisation in our study across symptoms, mental health, exercise capacity, organ impairment, and quality-of-life is striking. There are few similar detailed, prospective, longitudinal studies for patients hospitalised with COVID-19, but in this larger cohort we support those findings of minimal recovery.[18–20] Although the large-scale study from Wuhan, China, suggests a greater magnitude of recovery compared with our findings, new-onset symptoms persisted in half of the patients (620 of 1272).[5] Notably, the Wuhan cohort included a smaller proportion of patients with severe acute illness than ours did, with only 1% requiring invasive mechanical ventilation and 7% requiring high flow nasal oxygen or continuous positive airway pressure. The Wuhan cohort also had fewer pre-existing comorbidities and a higher proportion of never-smokers compared with patients in our study. In patients with non-COVID-19-related ARDS, little recovery in health-related quality of life is observed beyond 6 months after hospital discharge, but larger improvements in walking distance have been found[21,22] than we report following COVID-19 in our cohort, over 70% of whom did not receive invasive mechanical ventilation. In non-hospitalised patients after COVID-19, the proportion that develop long COVID appears to be lower than in those admitted to hospital with COVID-19.[23,24]

The responses for patient-perceived recovery were discriminatory across all the patient-reported outcome measures and exercise measures, providing additional validity for this outcome measure. We found female sex and obesity were major risk factors for not recovering at 1 year, supporting results from smaller cohorts[25] and non-hospitalised cohorts.[26–28] Female sex was similarly associated with worse recovery for fatigue, mental health, and lung function at 12 months in the Wuhan cohort.[5] In our clusters, female sex and obesity were also associated with more severe ongoing health impairments, including reduced exercise performance and health-related quality of life at 1 year, potentially highlighting a group that might need higher-intensity interventions such as supervised rehabilitation. Health-related quality of life before COVID-19 was substantially greater than at 5 months after discharge across all four clusters, indicating that the persistent burden of impaired physical and mental health is not simply explained by pre-existing morbidity. The total number and range of ongoing symptoms at 1 year was striking, positively associated with the severity of long COVID, and emphasises the multisystem nature of long COVID. Other studies have shown that the number of symptoms during the acute illness was associated with the likelihood of developing long COVID.[29] Whether the number of ongoing symptoms—a simple, widely available measure—could underpin a future risk score deserves further attention. Taken together, we suggest that our data will help to inform decisions about patient stratification for follow-up after hospital discharge. We advocate a proactive approach because of the high proportion of patients who do not recover, highlighting the usefulness of a screening questionnaire to assess whether patients feel fully recovered; the total number of symptoms might be a guide to the intensity or complexity of care required. Similar to our 5-month data[3], we highlight the need for a holistic assessment including mental health, physical function, and cognitive impairment. Any assessment of ongoing organ impairment will need to be further individualised.

No specific therapeutics exist for long COVID and our data highlight that effective interventions are urgently required. Our findings of persistent systemic inflammation, particularly in those in the very severe and moderate with cognitive impairment clusters, suggest that these groups might respond to anti-inflammatory strategies. The upregulation of IL-6 suggests that anti-IL-6 biologics that were successful for patients admitted to hospital with COVID-19[30] might also have a place in the treatment of long COVID. Similarly, activation of the urokinase-type plasminogen activator receptor pathway suggests that IL-1 activation might play a role, with soluble uPAR a biomarker in acute COVID-19 associated with good response to the recombinant IL-1 receptor antagonist anakinra.[31] Impaired exercise capacity was also associated with the more severe clusters and showed minimal improvement at 1 year (below the minimum clinically important difference for other long-term

conditions).[32–34] Available therapies for some adults with long COVID include rehabilitation,[35] but the optimal exercise prescription is contentious because of concerns of post-exertional symptom exacerbation. Our data suggest a high prevalence of musculoskeletal symptoms including muscle ache, fatigue, breathlessness, physically slowing down, and limb weakness.[5,16] This finding supports the need to investigate rehabilitation in combination with other therapies to improve skeletal muscle function, such as mitochondrial energetics, mitophagy enhancers, and drugs to combat cell senescence (associated with ageing).

The concordance of the severity of physical and mental health impairment in long COVID highlights the need not only for close integration between physical and mental health care for patients with long COVID, including assessment and interventions, but also for knowledge transfer between health-care professionals to improve patient care. The finding also suggests the need for complex interventions that target both physical and mental health impairments to ameliorate symptoms. However, specific therapeutic approaches to manage post-traumatic stress disorder might be needed.[36] With obesity being associated with both non-recovery and severity of long COVID, whether weight reduction using combined pharmacological and non-pharmacological approaches can ameliorate long COVID warrants further investigation. Beyond diet and lifestyle interventions, GLP-1 analogues have been reported to achieve clinically important weight reduction in adults.[37]

Our cohort study is ongoing, and we report these 1-year findings to help direct clinical care and further investigation. However, there are limitations. There will be selection bias for participants returning for a 1-year visit, although we have not found overt differences between the demographics or 5-month recovery status between attendees and non-attendees of the 1-year visit. Our cohort has a higher proportion of patients with COVID-19 requiring invasive mechanical ventilation than is typically seen in UK hospitals,[38] and therefore our results might not be directly generalisable to the wider population. We also had a lower-than-expected proportion of women, which might mean that the wider population have worse outcomes than we report because women appear to have worse recovery. To reduce uncertainty of the effect of pre-existing illness, we asked participants whether they felt fully recovered (ie, back to their normal selves). We also asked participants retrospectively to estimate their pre-COVID-19 health status, including the most prevalent symptoms, disability, and health-related quality of life; we recognise that there might be recall bias. Data linkage to electronic patient records is in process but not currently available; therefore, in the current report, pre-existing comorbidities were self-reported and data regarding hospital admissions and mortality in the first year are unavailable. Our study suggests that persistent inflammation might underlie ongoing impairment in some participants; the specific mechanisms underlying this signal require further investigation and replication. We described several associations with more severe health impairments at 1 year. Our findings cannot confirm causality but suggest that these associations should be further investigated as part of mechanistic studies and clinical trials. Our results require interpretation in the context of the COVID-19 pandemic. Our 1-year findings included patients discharged from hospital in 2020 and therefore would not include those infected with newer SARS-CoV-2 variants such as B.1.1.529 (omicron) and included patients who would not have been vaccinated before contracting COVID-19. Although our data are relevant to patients discharged under similar conditions, further research is needed to understand the effect of current acute care, newer SARS-CoV-2 variants, and vaccination status before and after contracting COVID-19.

In summary, our study highlights an urgent need for health-care services to support this large and rapidly increasing patient population in whom a substantial burden of symptoms exists, including reduced exercise capacity and large decrements in health-related quality of life 1 year after hospital discharge. Without effective treatments, long COVID could become a highly prevalent new long-term condition. Our study also provides a rationale for investigating treatment strategies for long COVID with a precision-medicine approach to target treatments to the relevant phenotype to restore health-related quality of life.

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The manuscript was initially drafted by RAE, CEBr, and LVW, and further developed by the writing committee. CEBr, RAE, LVW, OE, HJCM, AShi, ASi, MJD, ABD, NIL, AShe, JDC, L-PH, AH, MM, KP, and BR made substantial contributions to the conception and design of the work. RAE, ASi, MS, RMS, VCH, RA, PB, CEBo, JSB, GC, NDB, NE, CE, JF, NH, JRH, MGJ, DP, PP, NMR, SLR-J, AMS, DGW, JDC, L-PH, AH, MM, and WD-CM made substantial contributions to the acquisition of data. CEBr, RAE, LVW, OCL, MR, OE, HJCM, MS, TC, MJD, ADS, JRG, WG, NJG, LGH, SH, LSH, JJ, RGJ, JML, WD-CM, GPM, SN, PJMO, JCP, JQ, MJR, JTS, MGS, SJS, MTo, KEL, RST, AB, ABD, SK, NIL, AShe, MTh, BZ, JDC, L-PH, AH, MM, KP, BR, EMH, LH-W, and

DT made contributions to the analysis, or interpretation of data for the work. All authors contributed to data interpretation, critical review and revision of the manuscript, and final approval of the version to be published. RAE, HJCM, and OCL have accessed and verified the data. RAE, CEBr, and LVW were responsible for the decision to submit the manuscript, and are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

Declaration of interests

AB declares that their institute was awarded a grant from the UK National Institute for Health Research (NIHR) to complete this work and receives consulting fees from Roche, Merck, and GlaxoSmithKline. ADS declares grants to their institutes from GlaxoSmithKline, US COPD Foundation, Pfizer, and AstraZeneca; consulting fees were provided to their institute from 30T and personal consultations fees were received from AstraZeneca and Gilead; payments for lectures and presentations were received from GlaxoSmithKline, AstraZeneca, and Gilead; travel support to attend meetings was provided by GlaxoSmithKline and AstraZeneca; personal and institutional payments were received for participation on a data safety monitoring board/advisory board from Bayer. AH declares that their institute was awarded a grant from UK Research and Innovation (UKRI) and NIHR to complete this work, and from NIHR Manchester Clinical Research Facility to support study delivery and NIHR Manchester Biomedical Research Centre (BRC) for personal funding and institutional payments to support grant-funded research from NIHR, UK Medical Research Council (MRC), Cystic Fibrosis Trust, Cystic Fibrosis Foundation, North West Lung Centre Charity, and Moulton Trust; the author declares consulting fees from Mylan Pharmaceuticals for advisory board participation and payment from Vertex Pharmaceuticals for educational presentation, participation on a clinical trials advisory board, and writing a review article. AH's non-paid roles include chair of the Cystic Fibrosis Clinical Trials Accelerator Program, deputy chair of the NIHR Respiratory Translational Research Collaboration, and director of a university spin-out company (Mi-trial). AMS declares a grant to their institute from UKRI/NIHR to complete this work, and research grants from the British Heart Foundation, MRC, and NIHR-BRC. AShe declares a grant to their institute from UKRI, and unremunerated participation on AstraZeneca Thrombotic Thrombocytopenic Taskforce and Scottish and UK Governments COVID-19 advisory groups. BR declares payments from the British Heart Foundation Oxford Centre of Research Excellence, NIHR Oxford BRC, and UKRI for grants and contracts; and consulting fees from Axcella Therapeutics. CE declares funding from GlaxoSmithKline for an investigator-led research project. CEBr declares that their institute was awarded a grant from UKRI/NIHR to complete this work; the author reports grants from GlaxoSmithKline, AstraZeneca, Sanofi, Boehringer Ingelheim, Chiesi, Novartis, Roche, Genentech, Mologic, and 4DPharma; and consultancy fees paid to their institution from GlaxoSmithKline, AstraZeneca, Sanofi, BI, Chiesi, Novartis, Roche, Genentech, Mologic, 4DPharma, and Teva. CEBo declares that their institute was awarded a grant from UKRI/NIHR and institutional support from NIHR Nottingham BRC to complete this work; the author reports grants to support the Dynamo Study (DYNamic Assessment of Multi Organ level dysfunction in patients recovering from Covid-19) and The Nottingham Recovery from COVID-19 Research Platform (NoRCoRP) post-COVID project from NIHR Nottingham BRC and Nottingham University Hospitals Research and Innovation Department and Nottingham Hospitals Charity. DGW declares support from an Advanced Fellowship from NIHR. DP declares that their institute was awarded a grant from NIHR and MRC, and holds leadership roles within the British Thoracic Society. GC declares grants to their institution from GlaxoSmithKline, AstraZeneca, British Lung Foundation, Mereo, and Arrowhead Pharmaceutials; personal payments from GlaxoSmithKline and AstraZeneca for educational meetings and presentations; conference registration fees paid for by GlaxoSmithKline; and unpaid participation as chair of the Lothian Respiratory Managed Clinical Network and Act on COPD Group in Scotland for AstraZeneca. GPM declares a grant to their institute from UKRI/NIHR to complete this work; grants from the British Heart Foundation and MRC; support for attending meetings from the British and Irish Society for Minimally Invasive Cardiac Surgery; leadership in the British Society for Cardiovascular MRI; and receipt of research software from Circle CVi. JRH declares consultancy fees from AstraZeneca; speaker fees from Boehringer Ingelheim and Takeda; travel grants from AstraZeneca; participation on an advisory board for AstraZeneca; an unpaid leadership role with the British Thoracic Society; and a donation of oximeters from Nonin. JCP declares grants to their institution from UKRI, LifeArc, and MRC; payment fees from The Limbic; and advisory board membership at Carrick Therapeutics and AstraZeneca. JDC declares grants from AstraZeneca, Boehringer Ingelheim, Insmed, Novartis, Gilead Sciences, and Genentech; and consulting fees from AstraZeneca, Boehringer Ingelheim, Insmed, Novartis, Gilead Sciences, Chiesi, Zambon, and Genentech. JJ declares consulting fees from Boehringer Ingelheim, Roche, GlaxoSmithKline, and National Health Service X (NHSX, a joint organisation for digital data and technology); speaker fees from Boehringer Ingelheim, Roche, GlaxoSmithKline, and Takeda; support for meeting attendance from Boehringer Ingelheim; participation on advisory boards at Boehringer Ingelheim and Roche; and UK patent application number 2113765.8 (a patent for a computer algorithm for medical image analysis). LH-W declares a grant from NIHR unrelated to the submitted work; acting as independent chair of the NIHR HTA Committee for Colour COPD trial; and membership of the American Thoracic Society Pulmonary Rehabilitation Assembly Web and Planning Committees. L-PH declares that their institution received grants from UKRI, Regenerative Medicine Platform, Celgene, British Lung Foundation, and Oxford Boehringer Ingleheim; the author is on the advisory board for the CATALYST trial and acts as chair of the Respiratory Translational Research Collaboration. LVW declares research funding unrelated to the submitted work from GlaxoSmithKline and Orion; consulting fees unrelated to the submitted work from Galapagos; a Wellcome Conference speaker honorarium; travel support from Genentech; advisory board participation for Galapagos; and an associate editor role for the European Respiratory Journal. MGJ declares that their institute was awarded a grant from Boehringer Ingelheim. MGS declares that their institute was awarded a grant from NIHR, MRC, and Health Protection Research Unit in Emerging and Zoonotic Infections, University of Liverpool, to complete this work; the author is an independent external and non-remunerated member of Pfizer's external data monitoring committee for their mRNA vaccine programme; chair of the Infectious Disease Scientific Advisory Board for Integrum Scientific; minority share owner in Integrum Scientific; and a non-remunerated independent member of HMG Scientific Group for Emergencies and the UK New Emerging Respiratory Virus Threats Advisory Group (NERVTAG). MJD declares payments to their institution from AstraZeneca, Novo Nordisk, Boehringer Ingelheim, and Janssen, outside the submitted work; consulting fees from Novo Nordisk, Eli Lilly, and Boehringer Ingelheim; personal fees for lectures and presentations from Novo Nordisk, Sanofi-Aventis, Eli Lilly, Boehringer Ingelheim, AstraZeneca, and Napp Pharmaceuticals; and acting as a member of RESiliENT Trial Steering Committee and Chair of the European Association for the Study of Diabetes writing group. MJR declares a grant from NIHR for the HTA SOS Trial and NIHE EME Programme study (OSMOTIC); and current employment by Roche on a 1-year academic/industry senior clinical fellowship. NE received donations of COVID-19 lateral flow tests for a pilot project from Mologics. NIL declares acting as director of research at the Intensive Care Society UK. PJMO declares co-funding from MRC and GlaxoSmithKline (INFLAMMAGE), part of the EMINENT consortium to promote inflammation research; consulting fees from Janssen, Seqiris, and Valneva; payments for speaking from Janssen and Seqirus; and acting as member and vice-chair of NERVTAG. PP declares grants from NIHR to the institute to support remote rehabilitation after COVID-19. RGJ declares a commercial contract with PatientMPower to provide an app and spirometers with no payments by PatientMPower for the study; payments to their institution from AstraZeneca, Biogen, Galecto, GlaxoSmithKline, RedX, and Pliant; consulting fees from Bristol Myers Squibb, Daewoong, Veracyte, Resolution Therapeutics, and Pliant; payments for lectures from Chiesi, Roche, PatientMPower, and AstraZeneca; participation on advisory boards at Boehringer Ingelheim, Galapagos, and Vicore; a leadership role at NuMedii; and acting as a trustee for Action for Pulmonary Fibrosis. RAE declares that their institute was awarded a grant from UKRI/NIHR to complete this work; the author declares speaker fees from Boehringer Ingelheim and unpaid

roles with European Respiratory Society Assembly 01.02 Pulmonary Rehabilitation secretary and American Thoracic Society Pulmonary Rehabilitation Assembly programme committee. SH declares grants from the European Commission and NIHR; consulting fees from Eli Lilly, Zealand Pharma, Novo Nordisk, and Mylan; honorary payments from Novo Nordisk; and payment for expert testimony from the Crown Prosecution Service. SN declares research grant from Axcella. SLR-J declares a grant to their institute from UKRI/NIHR and salary support from Clinical Research Network to complete this work; grants from UKRI, NIHR, Global Challenges Research Fund, and European and Developing Countries Clinical Trials Partnership (EDCTP) for unrelated studies; participation on a data safety monitoring board for two trials (Bexero for gonococcal infection in Kenya and inactivated COVID-19 vaccine trial in Zimbabwe); and previously acting as president of the Royal Society of Tropical Medicine and Hygiene. TC declares a grant to their institute from NIHR Biomedical Research Centre at South London and Maudsley NHS Foundation Trust to complete this work; a grant from NIHR for the CLOCK study; speaker fees from Hello Self, the British Association for Behavioural and Cognitive Psychotherapies, and UK Department of Health; unpaid participation on the National Institute for Health and Care Excellence guideline committee on Post/Long COVID; leading the Persistent Physical Symptom service as part of their paid employment; and having authored a published self-help book on fatigue for which he received payments. WD-CM declares grants from NIHR, British Lung Foundation, and NHSX; payments for lectures from Munipharma, Novartis, and European Conference and Incentive Services DMC; participation on a monitoring board for Jazz Pharmaceuticals; and funds for blood analysis from GlaxoSmithKline. AShi, ASi, JML, MM, and NDB declare that their institute was awarded a grant from UKRI/NIHR to complete this work. LGH declares grants for acting as an academic lead for the UK MRC Consortium for Stratified Medicine in Severe Asthma; industrial pharma partners incude Amgen, AstraZeneca, Medimmune, Janssen, Novartis, Roche/Genentech, GlaxoSmithKline, and Boehringer Ingelheim; project grant funding was received from Medimmune, Novartis UK, Roche/Genentech, and GlaxoSmithKline. All other authors declare no competing interests.

Data sharing

The protocol, consent form, definition and derivation of clinical characteristics and outcomes, training materials, regulatory documents, requests for data access and other relevant study materials are available online at https://www.phosp.org.

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References

1 Johns Hopkins University. Coronavirus resource centre. https://coronavirus.jhu.edu/map.html (accessed April 19, 2022).
2 UK Government. Coronavirus (COVID-19) in the UK. https://coronavirus.data.gov.uk (accessed April 19, 2022).
3 Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021; **9:** 1275–87.
4 Huang C, Huang L, Wang Y, et al. 6-month consequences of COVID-19 in patients discharged from hospital: a cohort study. *Lancet* 2021; **397:** 220–32.
5 Huang L, Yao Q, Gu X, et al. 1-year outcomes in hospital survivors with COVID-19: a longitudinal cohort study. *Lancet* 2021; **398:** 747–58.
6 Filbin MR, Mehta A, Schneider AM, et al. Longitudinal proteomic analysis of severe COVID-19 reveals survival-associated signatures, tissue-specific cell death, and cell-cell interactions. *Cell Rep Med* 2021; **2:** 100287.
7 Thwaites RS, Sanchez Sevilla Uruchurtu A, Siggins MK, et al. Inflammatory profiles across the spectrum of disease reveal a distinct role for GM-CSF in severe COVID-19. *Sci Immunol* 2021; **6:** eabg9873.
8 National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19. Updated November, 2021. https://www.nice.org.uk/guidance/ng188 (accessed Dec 12, 2021).
9 WHO. A clinical case definition of post COVID-19 condition by a Delphi consensus. Oct 6, 2021. https://www.who.int/publications/i/item/WHO-2019-nCoV-Post_COVID-19_condition-Clinical_case_definition-2021.1 (accessed Dec 12, 2021).
10 Kaufman L, Rousseeuw PJ. Clustering large applications (Program CLARA). In: Finding groups in data: an introduction to cluster analysis. New Jersey: John Wiley & Sons, Inc, 2008: 126–63.
11 Fu W, Liu Y, Liu L, et al. An open-label, randomized trial of the combination of IFN-κ plus TFF2 with standard care in the treatment of patients with moderate COVID-19. *EClinicalMedicine* 2020; **27:** 100547.
12 Tserel L, Jõgi P, Naaber P, et al. Long-Term Elevated inflammatory protein levels in asymptomatic SARS-CoV-2 infected individuals. *Front Immunol* 2021; **12:** 709759.
13 Fraser DD, Patterson EK, Slessarev M, et al. Endothelial injury and glycocalyx degradation in critically ill coronavirus disease 2019 patients: implications for microvascular platelet aggregation. *Crit Care Explor* 2020; **2:** e0194.
14 Laudanski K, Jihane H, Antalosky B, et al. Unbiased analysis of temporal changes in immune serum markers in acute COVID-19 infection with emphasis on organ failure, anti-viral treatment, and demographic characteristics. *Front Immunol* 2021; **12:** 650465.
15 Hettwer S, Dahinden P, Kucsera S, et al. Elevated levels of a C-terminal agrin fragment identifies a new subset of sarcopenia patients. *Exp Gerontol* 2013; **48:** 69–75.
16 Dhaeze T, Tremblay L, Lachance C, et al. CD70 defines a subset of proinflammatory and CNS-pathogenic T_H1/T_H17 lymphocytes and is overexpressed in multiple sclerosis. *Cell Mol Immunol* 2019; **16:** 652–65.

17 Griffith DM, Vale ME, Campbell C, Lewis S, Walsh TS. Persistent inflammation and recovery after intensive care: a systematic review. *J Crit Care* 2016; **33:** 192–99.

18 Fernández-de-Las-Peñas C, Guijarro C, Plaza-Canteli S, Hernández-Barrera V, Torres-Macho J. Prevalence of post-COVID-19 cough one year after SARS-CoV-2 infection: a multicenter study. *Lung* 2021; **199:** 249–53.

19 Maestre-Muñiz MM, Arias Á, Mata-Vázquez E, et al. Long-term outcomes of patients with coronavirus disease 2019 at one year after hospital discharge. *J Clin Med* 2021; **10:** 2945.

20 Latronico N, Peli E, Calza S, et al. Physical, cognitive and mental health outcomes in 1-year survivors of COVID-19-associated ARDS. *Thorax* 2021; published online Sept 29. https://doi.org/10.1136/thoraxjnl-2021-218064.

21 Dowdy DW, Eid MP, Dennison CR, et al. Quality of life after acute respiratory distress syndrome: a meta-analysis. *Intensive Care Med* 2006; **32:** 1115–24.

22 Parry SM, Nalamalapu SR, Nunna K, et al. Six-minute walk distance after critical illness: a systematic review and meta-analysis. *J Intensive Care Med* 2021; **36:** 343–51.

23 Whitaker M, Elliott J, Chadeau-Hyam M et al. Persistent symptoms following SARS-CoV-2 infection in a random community sample of 508 707 people. *medRxiv* 2021; published online July 3. https://doi.org/10.1101/2021.06.28.21259452 (preprint).

24 Blomberg B, Mohn KG, Brokstad KA, et al. Long COVID in a prospective cohort of home-isolated patients. *Nat Med* 2021; **27:** 1607–13.

25 Wynberg E, van Willigen HDG, Dijkstra M, et al. Evolution of COVID-19 symptoms during the first 12 months after illness onset. *Clin Infect Dis* 2021; published online Sept 2. https://doi.org/10.1093/cid/ciab759.

26 Thompson EJ, Williams DM, Walker AJ, et al. Risk factors for long COVID: analyses of 10 longitudinal studies and electronic health records in the UK. *medRxiv* 2021; published online July 10. https://doi.org/10.1101/2021.06.24.21259277.

27 UK Office of National Statistics. COVID-19 https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/conditionsanddiseases/bulletins/prevalenceofongoingsymptomsfollowingcoronaviruscovid19infectionintheuk/2december2021 (accessed Dec 6, 2021).

28 Boscolo-Rizzo, P, Guida, F, Polesel, J, et al. Sequelae in adults at 12 months after mild-to-moderate coronavirus disease 2019 (COVID-19). *Int Forum Allergy Rhinol* 2021; **11:** 1685–88.

29 Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med* 2021; **27:** 626–31.

30 Ghosn L, Chaimani A, Evrenoglou T, et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. *Cochrane Database Syst Rev* 2021; **3:** CD013881.

31 Kyriazopoulou E, Poulakou G, Milionis H, et al. Early treatment of COVID-19 with anakinra guided by soluble urokinase plasminogen receptor plasma levels: a double-blind, randomized controlled phase 3 trial. *Nat Med* 2021; **27:** 1752–60.

32 Evans RA, Singh SJ. Minimum important difference of the incremental shuttle walk test distance in patients with COPD. *Thorax* 2019; **74:** 994–95.

33 Nolan CM, Delogu V, Maddocks M, et al. Validity, responsiveness and minimum clinically important difference of the incremental shuttle walk in idiopathic pulmonary fibrosis: a prospective study. *Thorax* 2017; **73:** 680–82.

34 Parreira VF, Janaudis-Ferreira T, Evans RA, Mathur S, Goldstein RS, Brooks D. Measurement properties of the incremental shuttle walk test: a systematic review. *Chest* 2014; **145:** 1357–69.

35 Spruit MA, Holland AE, Singh SJ, Tonia T, Wilson KC, Troosters T. COVID-19: interim guidance on rehabilitation in the hospital and post-hospital phase from a European Respiratory Society and American Thoracic Society-coordinated international task force. *Eur Respir J* 2020; **56:** 2002197.

36 Martin A, Naunton M, Kosari S, Peterson G, Thomas J, Christenson JK. Treatment guidelines for PTSD: a systematic review. *J Clin Med* 2021; **10:** 4175.

37 Wilding JPH, Batterham RL, Calanna S, et al. Once-weekly semaglutide in adults with overweight or obesity. *N Engl J Med* 2021; **384:** 989–1002.

38 Docherty AB, Mulholland RH, Lone NI, et al. Changes in in-hospital mortality in the first wave of COVID-19: a multicentre prospective observational cohort study using the WHO Clinical Characterisation Protocol UK. *Lancet Respir Med* 2021; **9:** 773–85.