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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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COVID-19. We sought to answer the following questions: ongoing physical health, mental health, and cognitive impairments, and mild) defined by severity of clinical recovery (very severe, severe, moderate with an emphasis on elucidating underlying mechanisms. 

had some improvement in the results of pulmonary imaging. 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, 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”. 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. 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. 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). Participants 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 χ² 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 χ² test with continuity correction was used for binary variables and a McNemar’s χ² 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,¹ 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 analysis² 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.⁹ 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.
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, 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 clusters3 were confirmed using participants with complete...
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, 73 (11·7%) in the cluster severe, 127 (20·4%) in the cluster moderate with cognitive impairment, and 269 (43·0%) in the mild cluster. Compared with the mild cluster, the very severe cluster had a higher proportion of women (165 [53·9%] of 306 vs 177 [58·0%] of 302), obesity (BMI ≥30 kg/m²; 204 [70·8%] of 288 vs 226 [38·7%] of 578), and physical health impairment (n=645 [39·4%]; appendix p 29). 664 (86·7%) of 766 individuals included in the previous study 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 [58·0%] of 302) and obesity (BMI ≥30 kg/m²; 204 [70·8%] of 288 vs 226 [38·7%] of 578).

After adjustment for 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).

The ten most common persistent symptoms at 1 year were fatigue (463 [60·1%] of 769), breathlessness (395 [51·4%] of 769), joint pain or aching muscles (442 [54·6%] of 809), physically slowing down (360 [44·6%] of 808), and limb weakness (377 [47·6%] of 808), fatigue (463 [60·1%] of 770 patients), achiness (442 [54·6%] of 809), physically slowing down (429 [52·9%] of 811), poor sleep (402 [52·3%] of 770), 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

| Characteristics of participants who had a 5-month visit, a 1-year visit, and both visits |
|---------------------------------|-----------------|-----------------|-----------------|
| Age at admission, years         | 58·0 (12·6)     | 58·9 (12·5)     | 58·7 (12·5)     |
| Sex                             |                |                |                |
| Female                          | 855 (39·0%)    | 219 (35·8%)    | 279 (35·6%)    |
| Male                            | 1238 (61·0%)   | 572 (64·2%)    | 505 (64·4%)    |
| Missing data                    | 117 (5·5%)     | 33 (3·5%)      | 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                          | 31·2 (27·7–35·1) | 31·5 (27·7–35·7) | 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 (13·9%)    | 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 (37·6%)    |
| 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 (0·0–3·0)    | 2 (0·0–3·0)    | 2 (0·0–3·0)    |
| 0                               | 642 (27·7%)    | 251 (27·2%)    | 213 (26·4%)    |
| 1                               | 468 (20·2%)    | 172 (18·6%)    | 154 (19·4%)    |
| ≥2                              | 1210 (52·2%)   | 501 (54·2%)    | 440 (54·5%)    |
| Admission duration, days        | 13 (9–18·2)    | 17 (24–7)      | 17 (22–4)      |
| Positive SARS-CoV-2 PCR          | 1916 (92·4%)   | 796 (90·8%)    | 700 (90·6%)    |
| Missing data                    | 246 (10·6%)    | 47 (5·1%)      | 34 (4·4%)      |
| Systemic steroids               | 1173 (54·2%)   | 251 (29·8%)    | 226 (30·2%)    |
| Missing data                    | 157 (6·8%)     | 81 (8·8%)      | 59 (7·3%)      |

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

**Do you feel fully recovered from COVID-19?**

- **5 months:**
  - Yes: 501 (25.5%)
  - Not sure: 385 (19.6%)
  - No: 1079 (54.9%)

- **1 year:**
  - Yes: 232 (28.9%)
  - Not sure: 180 (22.4%)
  - No: 392 (48.8%)

**Figure B**

**Age at admission, years**

- 50–59: 3.65 (0.87–15.27, p=0.076)
- <30: 3.09 (0.48–16.47, p=0.0028)
- 30–39: 1.88 (1.02–3.45, p=0.043)
- 40–49: 1.93 (1.19–3.32, p=0.0074)
- 60–69: 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 (1.92–8.52, 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=0.337)
- 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: 1.37 (0.83–2.27, p=0.216)
- ≥2 comorbidities: 0.75 (0.49–1.16, p=0.201)

**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 (0.73–2.26, 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)
- No: 1.00 (1.00–1.01, p=0.118)
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, 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).

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
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 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 available data

Artic...s on respiratory function

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

| Time to review from discharge, days | 5-month visit (n=1965) | 5-month visit (n=1965) | 5-month visit (n=1965) | 5-month visit (n=1965) | 5-month visit (n=1965) | 5-month visit (n=1965) |
|-----------------------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|-----------------------|
| Total                             | 501 (25·5%)           | 385 (19·6%)           | 1079 (54·9%)          | NA                    | 501 (25·5%)           | 385 (19·6%)           |
| Recovered                         | 2·0 (0·0–4·0)         | 0·73                  | 0·070                 | 0·0                  | 2·0 (0·0–4·0)         | 0·73                  |
| Not sure                          | 166 (127–191)         | 165 (122–191)         | 157 (119–189)         | 0·040                 | 166 (127–191)         | 165 (122–191)         |
| Not recovered                      | 157 (119–189)         | 157 (119–189)         | 157 (119–189)         | 0·040                 | 157 (119–189)         | 157 (119–189)         |
| p value                           | 0·12                  | 0·0001                | 0·0001                | 0·0001                | 0·12                  | 0·0001                |
| Pairs with available data         | 501 (25·5%)           | 385 (19·6%)           | 1079 (54·9%)          | NA                    | 501 (25·5%)           | 385 (19·6%)           |
| 5 months                          | 590                   | 151 (25·6%)           | 168 (28·5%)           | 0·12                  | 590                   | 151 (25·6%)           |
| 1 year                            | 384 (359–409)         | 384 (359–409)         | 384 (359–409)         | 0·0001                | 384 (359–409)         | 384 (359–409)         |

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)      |
| <30 kg/m²                        | 230 (54·5%)           | 131 (40·2%)           | 360 (38·8%)           | <0·0001               | 602                   | 25·7 (45·7%)          |
| ≥30 kg/m²                        | 192 (45·5%)           | 195 (59·8%)           | 568 (61·2%)           | <0·0001               | 602                   | 31·1 (27·5–35·5)      |

Symptoms, n                      | 3 (1–7)               | 8 (4–15)              | 14 (8–20)             | <0·0001               | 619                   | 9 (4–16)              |

Fatigue VAS score                | 0 (0.0–2.0)           | 2 (0.0–5.0)           | 5 (0.0–8.0)           | <0·0001               | 521                   | 3 (0.0–6.0)           |

Breathlessness VAS score         | 0 (0.0–1.0)           | 1 (0.0–4.0)           | 4 (0.0–6.0)           | <0·0001               | 524                   | 2 (0.0–5.0)           |

Anxiety (GAD-7 score ≥8)         | 53 (11·3%)            | 81 (22·6%)            | 339 (34·4%)           | <0·0001               | 684                   | 164 (24·0%)           |

Depression (PHQ-9 score ≥10)      | 47 (9·9%)             | 96 (26·7%)            | 426 (42·0%)           | <0·0001               | 680                   | 181 (26·6%)           |

Post-traumatic stress disorder (PCL-5 score ≥10) | 18 (3·8%) | 34 (9·5%) | 202 (20·0%) | <0·0001 | 680 | 83 (12·2%) | 68 (10·0%) | 0·055 |

Paired data at 5-month and 1-year visits (n=807)

| Recovered                         | 2·0 (0·0–4·0)         | 0·73                  | 0·070                 | 0·0                  | 2·0 (0·0–4·0)         | 0·73                  |
| Not sure                          | 166 (127–191)         | 165 (122–191)         | 157 (119–189)         | 0·040                 | 166 (127–191)         | 165 (122–191)         |
| Not recovered                      | 157 (119–189)         | 157 (119–189)         | 157 (119–189)         | 0·040                 | 157 (119–189)         | 157 (119–189)         |
| p value                           | 0·12                  | 0·0001                | 0·0001                | 0·0001                | 0·12                  | 0·0001                |
### Table 3: Comparison of the change in patient-reported outcome measures between 5 months and 1 year

|                          | 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 months 1 year p value               | Pairs 5 months 1 year p value                            | Pairs 5 months 1 year p value            |
| Time to review, days     | 99 (136–204)                                      | 176 (152–393)                              | 75 (358–409)                                             | 252 (163–194)                           |
| Symptom count            | 80 (16–25)                                        | 141 (8–17)                                 | 61 (5–11)                                                | 188 (1–7)                               |
| Anxiety (GAD-7 score ≥8) | 88 (93–0)                                         | 152 (243)                                  | 70 (57)                                                  | 70 (5)                                  |
| Depression (PHQ-9 score >10) | 87 (96–66)                                      | 152 (322)                                  | 70 (29)                                                  | 70 (2)                                  |
| Post-traumatic stress disorder (PCL-5 score >10) | 88 (65–9)                                        | 152 (33)                                  | 70 (2)                                                  | 70 (2)                                  |
| Dyspnoea-12 score        | 89 (180–9)                                        | 167 (65–9)                                 | 67 (29)                                                  | 67 (29)                                 |
| FACIT-Fatigue score      | 88 (17–4)                                         | 152 (306–9)                                | 69 (420)                                                  | 69 (420)                                |
| Physical performance     |                                                   |                                            |                                                          |                                         |
| SPPB score ≤10           | 86 (68–6)                                        | 164 (488–9)                                | 70 (80–9)                                                | 239 (230)                               |
| ISWT distance, m         | 65 (308–9)                                        | 122 (454–9)                                | 45 (349–9)                                               | 172 (552)                               |
| ISWT % predicted*        | 58 (40–7)                                         | 105 (339–9)                                | 39 (56–9)                                                | 138 (71–6)                              |
| Cognitive impairment     |                                                   |                                            |                                                          |                                         |
| MoCA score <23           | 88 (22–7)                                        | 161 (56–9)                                 | 62 (597–9)                                               | 232 (39–9)                              |
| MoCA (adjusted) score <23| 88 (22–7)                                        | 161 (56–9)                                 | 62 (597–9)                                               | 232 (39–9)                              |
| Organ function           |                                                   |                                            |                                                          |                                         |
| FEV1 % <80 predicted     | 28 (35–7)                                         | 61 (21–3)                                  | 33 (21–2)                                                | 86 (18–6)                               |
| PFC % ≥40% predicted     | 27 (5–19)                                         | 60 (25–18)                                 | 33 (21–2)                                                | 86 (18–6)                               |
| C-reactive protein       | 73 (34–2)                                         | 118 (293)                                  | 52 (27–1)                                                | 86 (18–6)                               |

Data are n, n (%), mean (SD), or median (IQR). Missing data are not included in %. 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.
a protein released with mucin from mucosal epithelium including lung and gastric mucosa. TFF2 has postulated roles in repair of damaged epithelium11 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 study4 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

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**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.
associated with increased morbidity and mortality during acute COVID-19 infection. 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. 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 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. 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. 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). 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 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.

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 and non-hospitalised cohorts. Female sex was similarly associated with worse recovery for fatigue, mental health, and lung function at 12 months in the Wuhan cohort. 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. 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, 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 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. 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). Available therapies for some adults with long COVID include rehabilitation, 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. 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. 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.

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, and therefore our results might not be directly generalisable to the wider population. We also had a lower-than-expected proportion of data. CEBr, RAE, LVW, OE, RJG, Jenkins, Janet M Lord, William D-C Man, Gerry P McCann, Stefan Neubauer, Peter J M Openshaw, Joanna C Porter, Matthew J Rowland, Janet T Scott, Malcolm G Semple, Sally J Singh, David Thomas, Mark Toskes, Keir E Lewis, Ryan S Thwaites, Andrew Briggs, Annemarie B Docherty, Steven Kerr, Nazir I Lone, Jennifer Quint, Aziz Sheikh, Mathew Thorpe, Bang Zheng, James D Chalmers, Ling-Pei Ho, Alex Horsley, Michael Marks, Krissnnaa Poinasamy, Betty Ramam, Ewen M Harrison, Louise V Wain, Christopher E Brightling.

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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.phosph.org.

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