‘Long-COVID’: a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19

Swapna Mandal,1 Joseph Barnett,2 Simon E Brill,1 Jeremy S Brown ø,3,4 Emma K Denny,4 Samanjit S Harre,2 Melissa Heightman,3 Toby E Hillman,4 Joseph Jacob,5,6 Hannah C Jarvis,1 Marc C I Lipman ø,1,3 Sindhu B Naidu,1 Arjun Nair,6 Joanna C Porter ø,3,4 Gillian S Tomlinson,4,7 John R Hurst ø,1,3 ARC Study Group

ABSTRACT
Large numbers of people are being discharged from hospital following COVID-19 without assessment of recovery. In 384 patients (mean age 59.9 years; 62% male) followed a median 54 days post discharge, 53% reported persistent breathlessness, 34% cough and 69% fatigue. 14.6% had depression. In those discharged with elevated biomarkers, 30.1% and 9.5% had persistently elevated d-dimer and C reactive protein, respectively. 38% of chest radiographs remained abnormal with 9% deteriorating. Systematic follow-up after hospitalisation with COVID-19 identifies the trajectory of physical and psychological symptom burden, recovery of blood biomarkers and imaging which could be used to inform the need for rehabilitation and/or further investigation.

INTRODUCTION
Large numbers of people are being discharged from hospital following COVID-19 without systematic assessment of their recovery and need for rehabilitation or further investigation to detect complications. Initial reports are emerging of significant ongoing symptom burden termed ‘Long-COVID’, and of changes in lung function and imaging.

METHOD
We rapidly established a post-COVID follow-up service across three large London hospitals, collecting data to identify unmet health needs and to identify people requiring additional rehabilitation and/or investigation for complications. In brief, we aimed to follow up all SARS-CoV-2 positive COVID-19 admissions by phone or in person four-to-six weeks after discharge. Key symptoms were graded as absent, present on an 11-point (0–10) scale in which a higher score was more severe. We invited people with abnormal blood tests or imaging at discharge to repeat these. Imaging was classified using British Society of Thoracic Imaging criteria. Full details of our follow-up procedures and protocol are included as an online supplemental appendix.

RESULTS
This report summarises the clinical assessment of 384 patients reviewed a median of 54 (IQR 47–59) days following hospital discharge with COVID-19. Three hundred eighty-four patients represent 34% of the total number of patients with COVID-19 discharged during this period (online supplemental figure 1). Of the 479 patients we attempted to contact, we were able to complete the call in 395 (82%) and of these only 11 (2.8%) declined to participate. Data for 79 of the 95 patients in who we were unable to complete the follow-up demonstrate similar age, sex, ethnicity and comorbidity to those we were able to follow-up.

The characteristics of the 384 participating subjects, and a summary of their COVID-19 admission are reported in table 1. In brief, the population had a mean age of 59.9 years and were predominantly male. Only 34% had no reported comorbidity. Forty-three per cent were from a black, Asian or minority ethnic background. Eight per cent of the cohort was obese. The median length of hospital stay was 6.5 (4–10.75) days and 14.5% required admission to intensive care.

Patients graded their overall recovery health as a median (IQR) 90 (75–100)% compared with 100% best health. Recovery towards usual health was lower in those with comorbidity (as listed in table 1) compared with those without: 85 (70–100)% versus 92.5 (80–100)% p=0.007. Persistence of symptoms at follow-up, by level of acute respiratory support, is reported in table 1. Follow-up symptoms were least prevalent in those treated with oxygen alone. Further detail on the assessment of physical symptoms at follow-up is reported in online supplemental table 1, including symptom intensity in relation to maximum, and the proportions reporting the trajectory of symptoms to be improving, unchanged or deteriorating. For all symptoms at follow-up, there was a statistically significant improvement from maximum intensity to follow-up (p<0.0001). In those with persistent breathlessness, patients assessed earlier post discharge tended to have higher breathlessness scores (figure 1) suggesting a trend to improvement over time. The trajectory for cough, fatigue and sleep quality is illustrated in online supplemental figures 2–4. 14.6% of participants had a PHQ2 score of greater than 3 indicating significant depression.

The results of blood investigations at admission, the last time point prior to discharge and follow-up, are reported in table 2. Overall, despite significant abnormalities at discharge, blood test results had...
Table 1  Baseline characteristics, features of the acute COVID illness and symptom persistence at follow-up following hospital discharge

<table>
<thead>
<tr>
<th>Subject characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (n=384, years)</td>
<td>59.9±16.1</td>
</tr>
<tr>
<td>Sex M:F (n=384, %)</td>
<td>62:38</td>
</tr>
<tr>
<td>Ethnicity (n=368)</td>
<td>British Caucasian 38.8% (n=139/368) Other Caucasian 17.1% (n=63/368) British Asian 6.5% (n=24/368) Other Asian 10.3% (n=38/368) Black British 6.8% (n=25/368) Other black 7.6% (n=28/368) Other ethnicity 13.9% (n=51/368)</td>
</tr>
<tr>
<td>Comorbidities</td>
<td>Hypertension 41.9% (n=155/370) Diabetes mellitus 27.2% (n=101/371) Asthma and or COPD 17.5% (n=65/371) Chronic kidney disease 11.0% (n=41/372) Ischaemic heart disease 9.7% (n=36/371)</td>
</tr>
<tr>
<td>Smoking: current/ever/never (n=373, %)</td>
<td>2.7/23.4/60.9</td>
</tr>
<tr>
<td>Covid illness</td>
<td>Duration of symptoms prior to admission (n=372, days) 7 (4–10) Level of care (n=367) Oxygen alone: 59.1% (n=217) ICU: 14.5% (n=54) Intubation: 7.1% (n=47) Length of stay (n=384, days) 6.5 (4–10.75) Clinical Frailty Score on Admission (n=384) 2 (2–3.75) Symptom persistence* (n=276) Breathlessness Oxygen alone/CPAP/IV (%) 54.8/63.3/57.7 Cough Oxygen alone/CPAP/IV (%) 32.2/36.7/46.2 Fatigue Oxygen alone/CPAP/IV (%) 67.3/73.3/76.9 Poor sleep quality Oxygen alone/CPAP/IV (%) 61.1/93.3/76.9</td>
</tr>
</tbody>
</table>

Data reported as mean (±SD), median (IQR) or % as appropriate.

*Persistence defined as symptom score ≥1.

Figure 1  Patient reported breathlessness (0–10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90% CI. A higher score represents more severe breathlessness.

DISCUSSION

Our data show that while symptom burden in subjects recovering from hospital admission with COVID-19 had generally improved at early follow-up, 53% reported persistent breathlessness, 34% persistent cough and 69% persistent fatigue. Fifteen per cent were depressed. Of people who attended for repeat imaging and blood tests because investigations on discharge had been abnormal, 9% had a deteriorating chest radiograph appearances and 9% had persistently elevated d-dimer and 9.5% had persistently elevated CRP concentration respectively. COVID-19 is associated with increased risk of thrombosis but the significance of the persistent elevation in d-dimer is unclear. Deteriorating chest radiograph appearances raise the possibility of developing lung fibrosis. These data are compatible with studies reporting longer term abnormalities in SARS survivors, and initial data emerging from smaller COVID-19 cohorts.

There are strengths and weaknesses to this analysis. We only included those who tested positive for SARS-CoV-2, and patients requiring prolonged ICU and inpatient stay may be underrepresented in this early analysis. Comparing against maximal symptoms risks recall bias and other symptoms such as chest pain may also be important. Not all participants were willing to take part in the review, or attend for investigations, potentially introducing selection bias. We cannot determine if these features are unique to COVID-19 or similar to those following admission for other critical respiratory illness.

To conclude, we provide the first report of physical and psychological symptom burden, blood markers and chest imaging trajectory following discharge for a hospitalised episode of COVID-19. We have identified persisting symptoms and radiological abnormalities in a significant proportion of subjects. These data may assist with the identification of people outside expected recovery trajectories who could benefit from additional care.
Table 2  Blood investigations at admission to hospital, discharge and follow-up

<table>
<thead>
<tr>
<th>N</th>
<th>Admission</th>
<th>Predischarge</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>WCC (&gt;10^12/L)</td>
<td>337</td>
<td>6.99 (5.07–9.29)</td>
<td>6.85 (5.44–8.71)</td>
</tr>
<tr>
<td>Platelets (&gt;10^12/L)</td>
<td>337</td>
<td>218 (169–276.5)</td>
<td>334 (243–445)</td>
</tr>
<tr>
<td>Lymphocytes (&gt;10^12/L)</td>
<td>337</td>
<td>0.95 (0.69–1.3)</td>
<td>1.23 (0.92–1.69)</td>
</tr>
<tr>
<td>D-dimer ng/mL</td>
<td>176</td>
<td>785 (510–1486)</td>
<td>878.5 (547.5–2522.5)</td>
</tr>
<tr>
<td>Ferritin µg/L</td>
<td>197</td>
<td>861 (430–1671)</td>
<td>795 (440–1458)</td>
</tr>
<tr>
<td>Creatinine µmol/L</td>
<td>335</td>
<td>84 (68–106)</td>
<td>71 (59.7–89)</td>
</tr>
<tr>
<td>ALT (iul)</td>
<td>288</td>
<td>36 (25–58.5)</td>
<td>46 (30–71.3)</td>
</tr>
<tr>
<td>AST (iul)</td>
<td>146</td>
<td>45 (31.8–68.5)</td>
<td>44 (27–67)</td>
</tr>
<tr>
<td>Glucose mmol/L</td>
<td>187</td>
<td>6.6 (5.5–7.9)</td>
<td>6.9 (5.2–8.5)</td>
</tr>
<tr>
<td>CRP mg/L</td>
<td>332</td>
<td>76 (36–157)</td>
<td>38 (16–78)</td>
</tr>
</tbody>
</table>

Data expressed as median (IQR).

ALT, alanine transaminase; AST, aspartate transaminase; CRP, C reactive protein; WCC, white cell count.

rehabilitation and/or further investigation to detect post-COVID complications. Identifying which patients have persistent dyspnoea due to complications rather than deconditioning alone is an important question for future research.

Author affiliations
1 Respiratory Medicine, Royal Free London NHS Foundation Trust, London, UK
2 Department of Radiology, Royal Free London NHS Foundation Trust, London, UK
3 UCL Respiratory, University College London, London, UK
4 UCL Radiology, University College London Hospitals NHS Foundation Trust, London, UK
5 Centre for Medical Image Computing, University College London, London, UK
6 Department of Radiology, University College London Hospitals NHS Foundation Trust, London, UK
7 Infection and Immunity, University College London, London, UK

Twitter Samanjit S Hare @lungdiagnosis, Arjun Nair @lungradiologist and Joanna C Porter @djroporter

Acknowledgements This work was partially undertaken at UCLH/UCL which received a proportion of funding from the Department of Health NIHR Biomedical Research Centre funding scheme. JJ was supported by a Wellcome Trust Clinical Research Career Development Fellowship: 209553/Z/17/Z.


Contributors SM, SEB, JSB, MH, TEH, MCI, JCP and JRH developed the clinical follow-up protocol. JB, JI, SSS and AN developed and led the radiology protocols and analysis. SM, EKD, MH, HJC, SBN and GST delivered and supported the follow-up process at three hospital sites. SM led the initial data analysis. JRH developed the first draft of the manuscript. All authors revised the manuscript for important intellectual content and approved the final version for submission.

Funding The authors have not declared a specific grant for this research from any funding agency in the public, commercial or not-for-profit sectors.

Competing interests None declared.

Patient consent for publication Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

This article is made freely available for use in accordance with BMJ’s website terms and conditions for the duration of the covid-19 pandemic or until otherwise determined by BMJ. You may use, download and print the article for any lawful, non-commercial purpose (including text and data mining) provided that all copyright notices and trade marks are retained.

ORCID iDs
Jeremy S Brown http://orcid.org/0000-0002-5650-5361
Marc C I Lipman http://orcid.org/0000-0001-7501-4448
Joanna C Porter http://orcid.org/0000-0002-7307-169X
John R Hurst http://orcid.org/0000-0002-7246-6040

REFERENCES