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

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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[1] termed 'Long-COVID', and of changes in lung function[2] and imaging.[3]

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, or 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.[4] 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 as 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,

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Table 1 Baseline characteristics, features of the acute COVID illness and symptom persistence at follow-up following hospital discharge

Subject characteristics	
Age (n=384, years)	59.9±16.1
Sex M:F (n=384, %)	62:38
Ethnicity (n=368)	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)
Comorbidities	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)
Smoking: current/ever/never (n=373, %)	2.7/23.3/60.9
Covid illness	
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

Data reported as mean (±SD), median (IQR) or % as appropriate.
*Persistence defined as symptom score ≥1.
IV, invasive ventilation.

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 returned to normal levels in the majority of patients at follow-up. Of those with abnormal discharge results and who attended for further blood tests, 7.3% of 247 patients had persisting lymphopaenia, 30.1% of 229 patients had elevated d-dimer and 9.5% of 190 patients had elevated C reactive protein (CRP). The d-dimer value was decreasing over time (online supplemental figure 5).

At presentation, 333/384 (87%) patients had a chest radiograph performed. Of these, 49 (15%) were normal, 188 (56%) were typical of COVID-19 and 96 (29%) were indeterminate for or unlikely to represent COVID-19. Of the radiographs classified as typical for COVID-19, 4 did not have a severity grading, 49/188 (26%) were reported as mild, 78/188 (41%) as moderate and 57/188 (30%) as severe.

Of the 244/384 (66%) patients that had follow-up radiographs, 151 (62%) radiographs were normal, 66 (27%) demonstrated

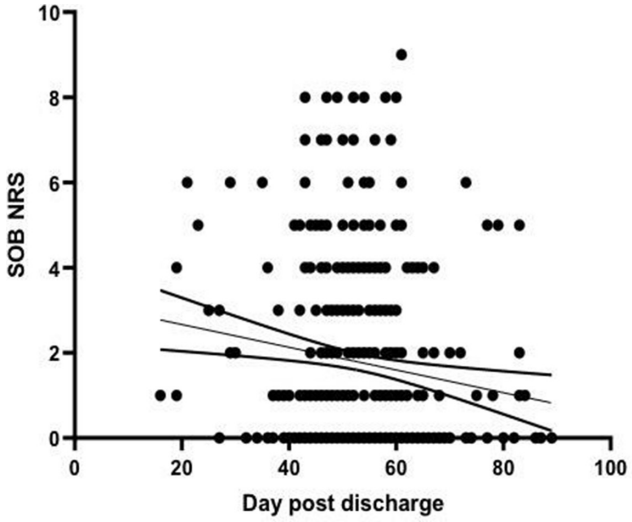

Figure 1 Patient reported breathlessness (0–10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90% CI. A higher score represents more severe breathlessness.

significant improvement, 4 (2%) were unchanged and 23 (9%) showed significant deterioration. Of the patients with radiographs that demonstrated worsening at follow-up, 2/23 (9%) had been normal at presentation, 10/23 (43%) had been typical for COVID-19 and 11/23 (48%) had been indeterminate for or unlikely to represent COVID-19.

14.8% of follow-up patients were deemed to require further assessment with CT chest imaging, pulmonary function tests, other investigations or a face-to-face review.

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 at follow-up, and 30.1% and 9.5% had persistently elevated d-dimer and CRP concentration respectively. COVID-19 is associated with increased risk of thrombosis[5] 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,[6] and initial data emerging from smaller COVID-19 cohorts.[1 7]

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

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Table 2 Blood investigations at admission to hospital, discharge and follow-up

	N	Admission	Predischarge	Follow-up
WCC ($\times 10^9$/L)	337	6.99 (5.07–9.29)	6.85 (5.44–8.71)	6.49 (5.6–7.8)
Platelets ($\times 10^9$/L)	337	218 (169–276.5)	334 (243–445)	247 (210–294)
Lymphocytes ($\times 10^9$/L)	337	0.95 (0.69–1.3)	1.23 (0.92–1.69)	1.94 (1.44–2.52)
D-dimer ng/mL	176	785 (510–1486)	878.5 (547.5–2522.5)	384 (242–665)
Ferritin µg/L	197	861 (430–1671)	795 (440–1458)	169 (86–271)
Creatinine µmol/L	335	84 (68–106)	71 (59.7–89)	80 (68–91)
ALT (iu/L)	288	36 (25–58.5)	46 (30–71.3)	26 (19–39)
AST (iu/L)	146	45 (31.8–68.5)	44 (27–67)	24 (20–30)
Glucose mmol/L	187	6.6 (5.5–7.9)	6.9 (5.2–8.5)	5.9 (5.2–7.2)
CRP mg/L	332	76 (36–157)	38 (16–78)	1 (1–4)

Data expressed as median (IQR).
ALT, alanine transaminase; AST, aspartate transaminase; CRP, C reactive protein; WCC, white cell count.

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 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.

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Contributors SM, SEB, JSB, MH, TEH, MCIL, JCP and JRH developed the clinical follow-up protocol. JB, JJ, SSH and AN developed and led the radiology protocols and analysis. SM, EKD, MH, HCJ, 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.

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