'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,

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

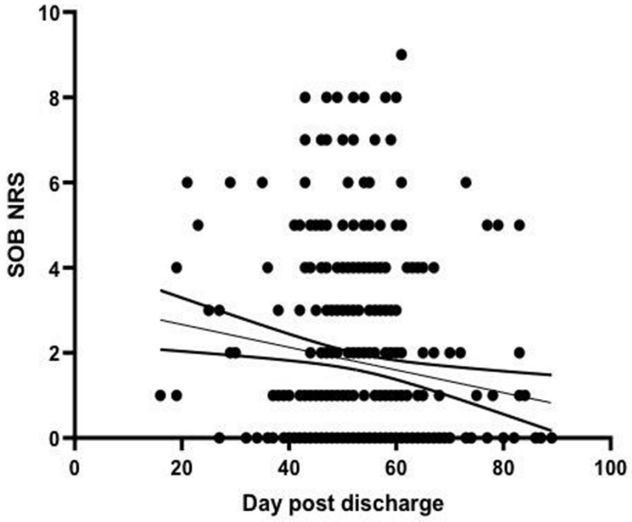

Figure 1 Patient reported breathlessness (0–10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90% CI. A higher score represents more severe breathlessness.

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

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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Supplementary Appendix

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

Mandal S, *et al. Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2020-215818

Detailed Method:

An attempt was made to contact every patient who had been discharged from our hospitals following an acute illness compatible with COVID-19, and who had tested positive using a nasopharyngeal swab for SARS-CoV-2.

We aimed to complete the review at between four and six weeks following hospital discharge. The timing and method of delivering the follow-up varied to reflect local Trust resources. The service was conducted from Royal Free London NHS Foundation Trust (Barnet and Hampstead sites), and University College London Hospitals NHS Foundation Trust, between April and June 2020.

The data presented here were collected as part of a novel service evaluation and in line with UK national guidance for such work (available at http://www.hra-decisiontools.org.uk/research/docs/DefiningResearchTable_Oct2017-1.pdf), ethics committee approval is not required. In addition, during COVID (https://www.hra.nhs.uk/covid-19-research/guidance-using-patient-data/) "*anonymised information can then be used in health and care research*". All appropriate service evaluation forms were completed and approved at our Trusts. All data were de-identified prior to analysis and the Authors had all necessary clinical administrative permissions to access the data.

A minimum dataset was agreed by members of the North Central London 'Assessing Recovery from COVID-19' (ARC) consortium and is attached as Appendix 1. We first collated a summary of the participants' medical history and details of the acute admission from the medical record. This was used to inform the need for further blood testing and imaging and to guide the follow-up discussion. All patients with abnormal blood tests and or chest radiograph findings at discharge were invited to have those tests repeated.

We specifically assessed current physical and psychological symptom burden (PHQ2 score), and the trajectory of symptom recovery. Subjective breathlessness, cough, fatigue and sleep quality were assessed on an eleven-point scale from 0-10 (where 0 represented 'I do not have this problem' to 10 = 'this symptom is very significant'). Participants were also asked to grade the maximum intensity of each symptom during the acute illness. Current breathlessness was assessed further using the Medical Research Council scale [1]. Participants were asked to rate their satisfaction with the call.

Most assessments were made by telephone, employing trained medical students and junior medical staff under the supervision of higher trainees and Consultants.

In addition to the agreed dataset, we agreed local onward pathways for referral to physical rehabilitation resources and psychological support, and/or further investigations. A copy of the consultation and actions was sent to the patient's primary care physician.

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The British Society of Thoracic Imaging (BSTI) classification [2] was used to code chest radiographs; follow-up chest radiographs were compared with the last radiograph obtained prior to discharge. Blood biomarkers were measured using standard laboratory analysers.

Data were recorded on an encrypted database and password protected NHS computer. Data analysis was conducted in SPSS (version 22) and GraphPad (version 8). Data were tested for normality and reported as mean and standard deviation (SD), median and interquartile range (IQR) or number (%) as appropriate. Comparison of symptoms at maximum and follow-up was achieved using a Wilcoxon Signed Rank test. Symptom trajectories were examined based on time from discharge to the follow-up assessment, using absolute values of symptom intensity as reported by the patient, and interpolation with 90% confidence intervals (CI). $p \leq 0.05$ was considered statistically significant.

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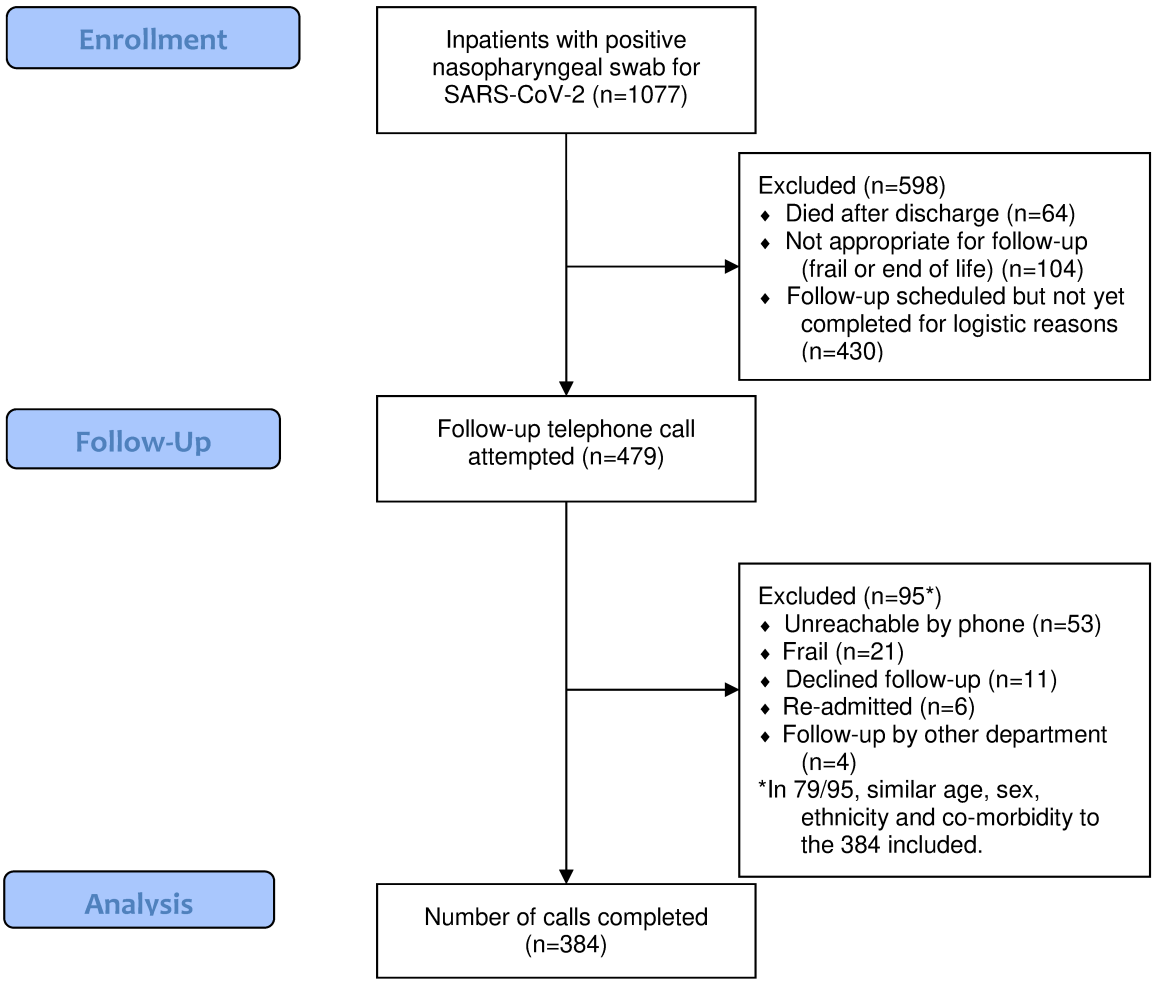
Additional Results:

SUPPLEMENTARY FIGURE 1: *Service participants.*



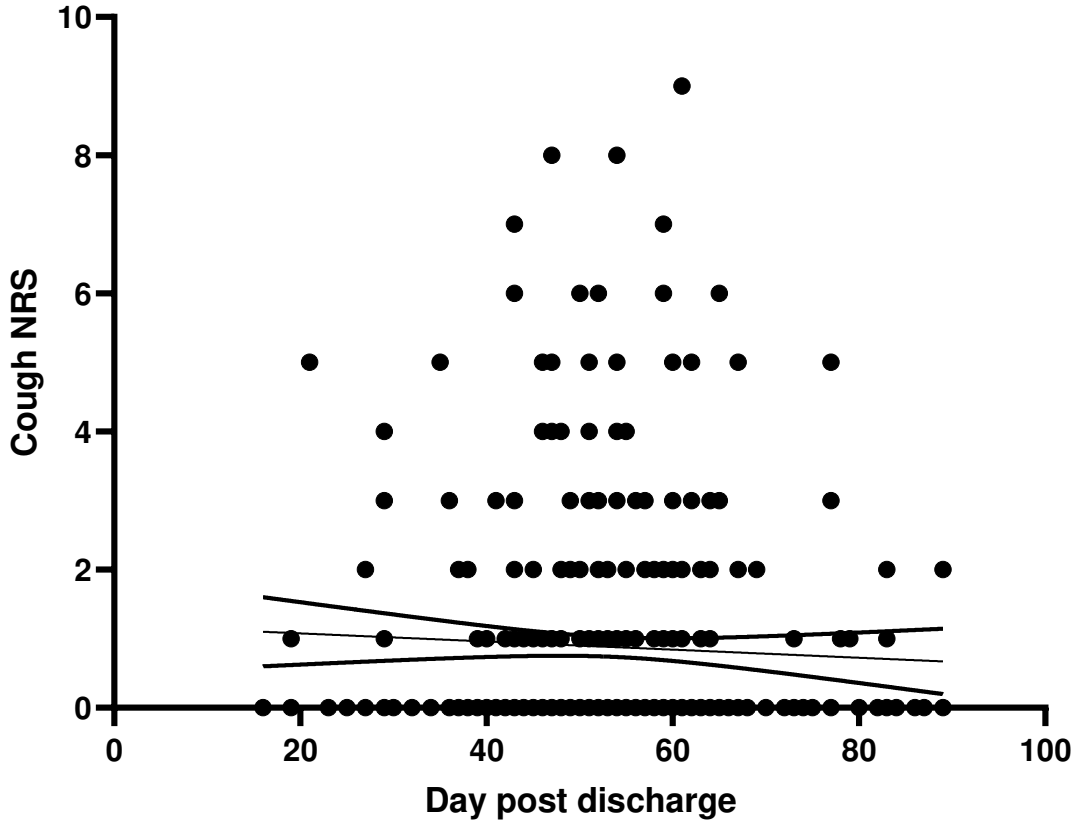
SUPPLEMENTARY TABLE 1: *Symptom recovery following discharge from hospital with COVID-19. Data presented as median (IQR).*

Symptom	Maximum Intensity	Intensity at Six Weeks	% reporting improving	% reporting unchanged	% reporting deteriorating
Breathlessness	7 (2-9)	1 (0-3)	80.8	18.6	0.6
Cough	3 (0-8)	0 (0-1)	74.5	24.1	1.4
Fatigue	8 (5-10)	2 (0-5)	80.4	18.5	1.2
Sleep Quality	5 (1-5)	3 (0-6)	66.2	29.7	4.2

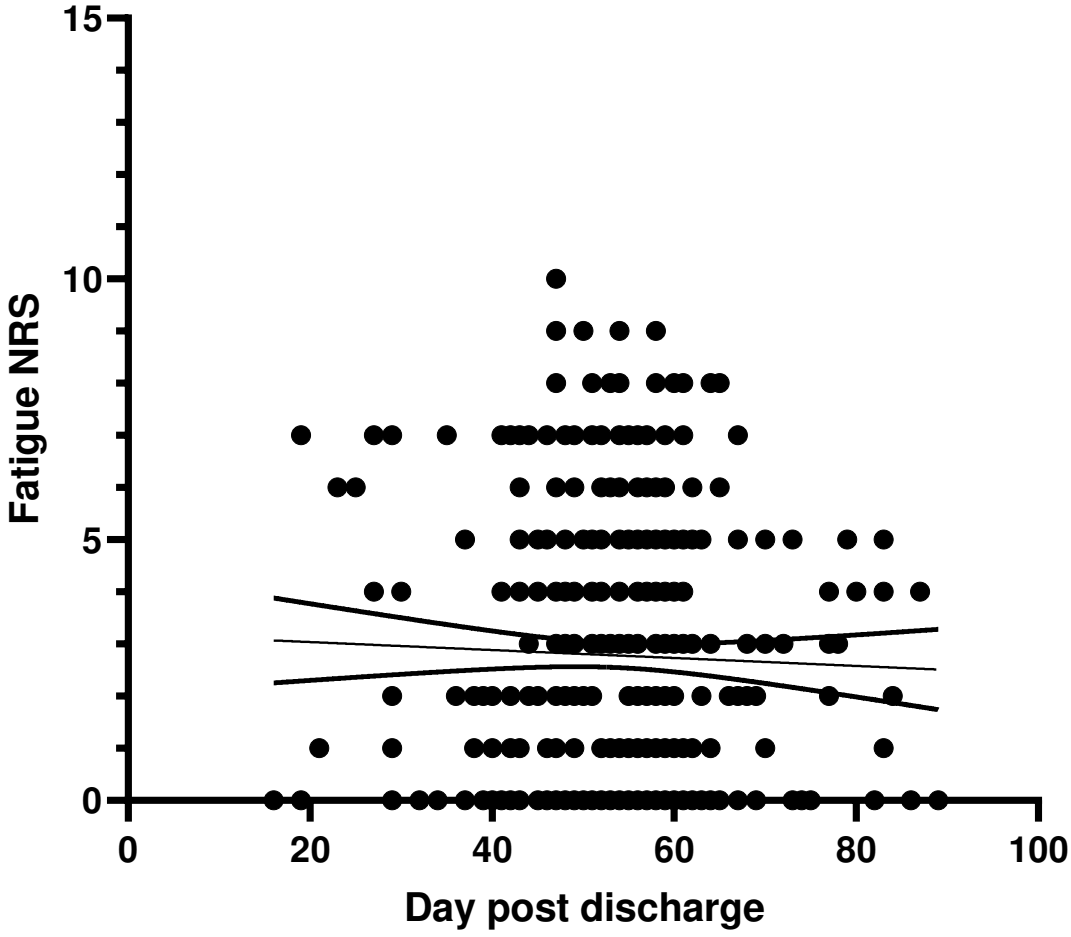
8.5% of people had persisting anosmia.

When looking at the four main symptoms (breathlessness, cough, fatigue and poor sleep quality), only 42/384 (11%) patients scored zero on all four of these symptoms at follow-up.

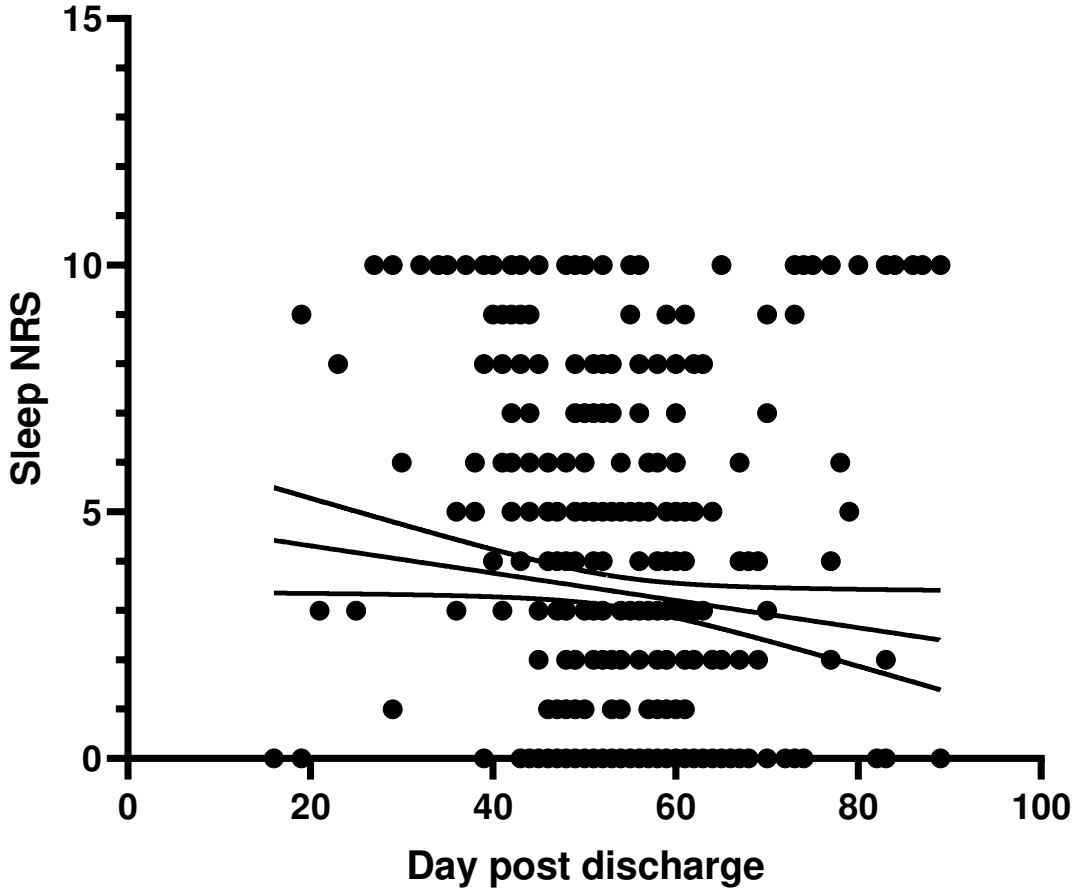
SUPPLEMENTARY FIGURE 2*: Patient reported cough intensity (0-10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90%CI. A higher score represents more burdensome symptoms.*



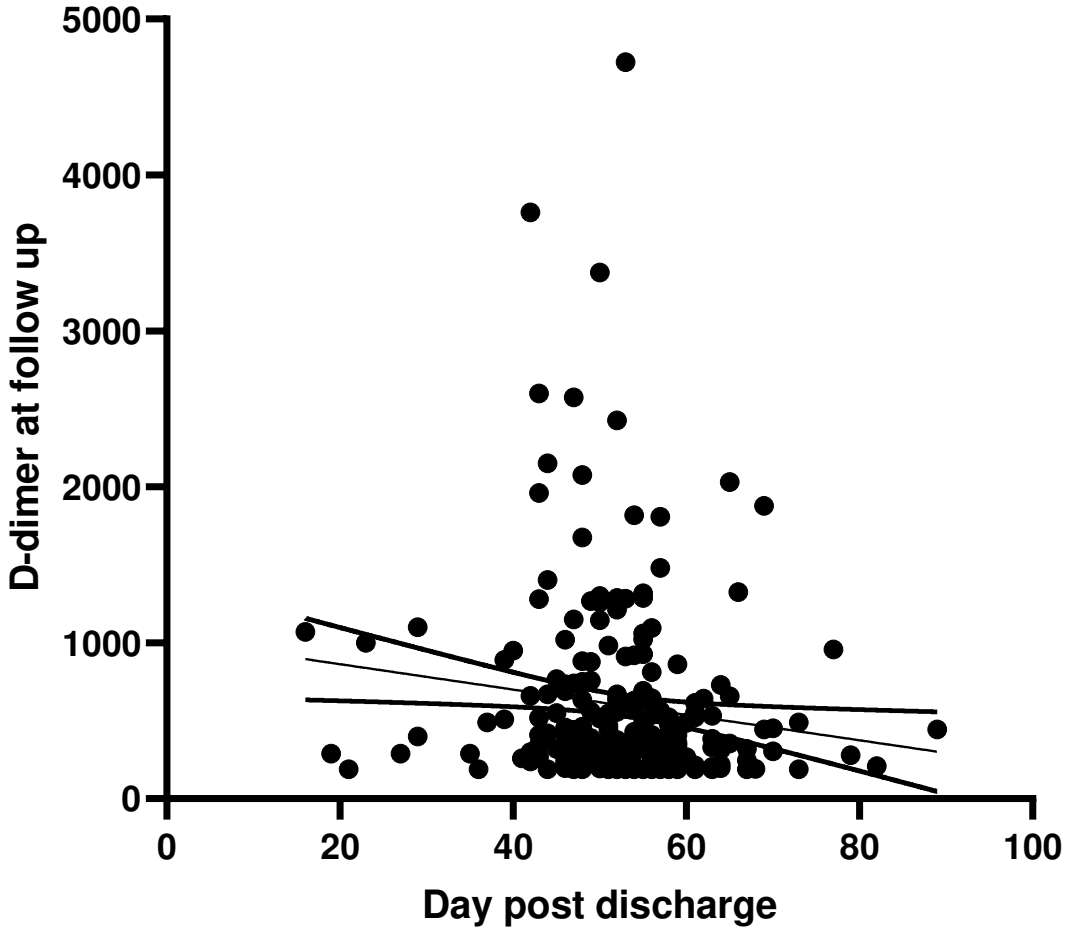
SUPPLEMENTARY FIGURE 3*: Patient reported fatigue intensity (0-10 scale) versus time of follow-up from hospital discharge. Each circle represents an individual patient at follow-up, with interpolation line and 90%CI. A higher score represents more burdensome symptoms.*



SUPPLEMENTARY FIGURE 4*: Patient reported impairment in sleep quality (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 burdensome symptoms.*



SUPPLEMENTARY FIGURE 5*: D-dimer versus time of follow-up after hospital discharge with COVID-19. Each circle represents an individual patient at follow-up, with interpolation line and 90%CI.*



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Clinical Data Proforma

NCEL ARC – Post admission clinical information

The **N**orth **C**entral and **E**ast **L**ondon – **A**ssessing **R**ecovery from **C**OVID project (NCEL-ARC) is a collaborative effort to define the recovery of patients from COVID in a safe and effective way, whilst allowing comparison across different areas of NCEL.

This document outlines the initial dataset that is suggested to ensure that the key clinical features of this illness, and subsequent recovery are recorded in a consistent way across clinical services. This will allow patterns of disease, complications, and long term sequelae to be recognised efficiently, and described accurately for the benefit of patients experiencing this disease in the future.

Patients should be contacted between 4-6 weeks after their hospital admission for assessment.

This is a clinical project, aimed at providing appropriate follow-up care to the following patients, to ensure resolution of symptoms, and identify those who require additional input from Respiratory Services and onward referral / signposting to other teams and services.

Patients to be included:

- Adults discharged from hospital with a confirmed diagnosis of COVID19 – **(Swab +ve cohort)**

Adults are defined as patients seen in adult clinics. This will vary locally, and is likely to include patients aged 16-18 at some centres.

The collection of information for these consultations will include a variety of sources – EPR, PACS, etc. These forms are intended to simplify this process, and set out the minimum dataset agreed by the NCL ARC working group.

The collection of full information for each patient is likely to be beyond that which can be extracted during a typical clinic visit, and much of the information is static, and extractable from computer systems. The 'script' for consultations is predominantly pages 5 and 6. The collection of additional information can be delegated to others engaged in this project, or conducted at a different time to the clinical contact.

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Baseline Information

PATIENT DETAILS:

NAME DOB SEX MRN

NHS no: Ethnic Group ***(See gov.uk guide for categorisation)***

Shielding status: Not / Voluntary shielding / extremely vulnerable / letter issued by HCP

THIS CALL:

Date and Time

Unreachable?

Unable to complete? - Why? e.g. language / refused / died

Clinician completing call (Name and position):

First Admission details – please record additional admissions on duplicate forms.

Admitting Site:

Date of admission: Estimated day of illness on admission:

Date of Discharge:

Rockwood (Clinical Frailty Score) on admission:

TEP status during admission: DNACPR / Not for NIV/CPAP / For NIV/CPAP / FULL

Smoking Status on admission: current smoker/ex-smoker/never smoker

PACK YEARS:

At time of FU: current smoker/ex-smoker/never smoker

If still smoking offer referral to smoking cessation services:

Agreed to referral Yes☐ No☐

Maximum Respiratory Support: none / O2 / CPAP / NIV / IV: Max FiO2____

Total number of days on CPAP___ NIV___ IPPV____

Last available SpO2 _____ / FiO2 prior to discharge_____

Currently requiring carers? Yes☐ No☐

Level of care in place: OD/BD/TDS/QDS Residential Home / Nursing Home

INVESTIGATIONS

Bloods:

Swab result: Swab Date: No swab ☐

Item	Admission	Follow Up
Hb g/dL		
Neutrophils x10^9/L		
Lymphocytes x10^9/L		
D-dimer ng/mL		
Ferritin mcg/L		
Creatinine mcmol/L		
Glucose mmol/L		
CRP mg/L		
BNP ng/L		

Radiology:

Chest xray on admission (date): normal / typical COVID / indeterminate / abnormal other

If available – radiologist estimation of severity:

Chest x-ray at follow up visit(date) : normal / typical COVID / indeterminate / abnormal other

If available – radiologist estimation of severity:

Was a CT performed? Date of first CT:

Lung ultrasound? BSTI Score ___/36

Pulmonary Embolism: confirmed / excluded / not investigated

Limb DVT: confirmed / excluded / not investigated

Additional: Any specific issues identified on discharge summary for follow up?

COMORBIDITIES

Free text, list major co-morbidities

Hypertension ☐	Anaemia ☐
Type II DM ☐	Active solid organ cancer ☐
Type I DM ☐	Solid organ cancer in remission ☐
Dyslipidaemia ☐	Organ transplant / other immunosuppressed eg HIV ☐
IHD ☐	Autoimmune disease requiring current immunosuppression ☐
Heart failure ☐	Autoimmune disease not requiring immunosuppression ☐
AF / arrhythmia ☐	GORD ☐
Cerebrovascular disease ☐	Depression ☐
COPD ☐	Anxiety ☐
Asthma ☐	Other mental health disorder☐
ILD ☐	**Lung Function if available pre-morbid**
CKD ☐	Date – FEV1 (%)
Height ____ Weight ____	FVC (%)
BMI:	DLCO (%)

MEDICATION / NOVEL Treatments

Have there been any changes in medication since discharge? Yes☐ No☐

If yes what has changed_____

Treated with systemic corticosteroids? Y / N

Was the patient enrolled in any trials of treatment for COVID 19? If so – which trial(s) and which treatments did they receive (if known)?

Follow-up questions

On a scale of 1-10 (where 0 = I do not have this problem and 10 = this symptom is very significant), please rate the following symptoms. Also grade the severity at maximum and in general whether staying the same, getting better or getting worse.

	0	1	2	3	4	5	6	7	8	9	10	Max	Trajectory
Breathlessness													S / B / W
Cough													S / B / W
Fatigue													S / B / W
Sleep quality													S / B / W

Current exercise tolerance: "on a good day, on a flat surface, how far are you able to walk before you have to stop"_____ (distance in yards / m)

MRC Dyspnoea Scale: /5

ET limited by: breathlessness ☐ fatigue ☐ Other☐

Rockwood (Clinical Frailty Score) at Follow Up:

Ask about persistence of:

Myalgia ('aching in our muscles') Yes☐ No☐

Anosmia ('reduced sense of smell') Yes☐ No☐

Loss of Taste Yes☐ No☐

Ongoing Other Symptoms:

Chest pain ☐	Confusion/fuzzy head ☐
Chest tightness ☐	Diarrhoea ☐
Peripheral oedema ☐	Abdo pain☐
Focal weakness/numbness ☐	Anorexia ☐

Any other persistent symptoms_____

How close to 100% of your usual best health do you currently feel? _____

Would you feel able to return to work if permitted? Full Time / Part Time / Not at all

Mandal S, *et al. Thorax* 2020;0:1–3. doi: 10.1136/thoraxjnl-2020-215818

PSYCHOLOGICAL

PHQ2: Over the last 2 weeks, how often have you been bothered by the following problems?

Little interest or pleasure in doing things

Feeling down, depressed or hopeless

On this scale: Not at all (0), Several days (score 1), More than half the days (score 2), Nearly every day (score 3).

Score of 3 or more is positive

Evidence of depression/anxiety – direct patient to relevant IAPT services / GP if out of area

FREE TEXT FOR OTHER CONCERNS:

_____

_____

COMPLETION:

Opportunity to answer any questions

Would you be willing to be contacted again to take part in research? No / Yes
Did you find this call useful? Yes / No / Not Sure

_____