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Early View

Original article

Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia

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Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia

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Social media "take home" message:

At 2-month follow-up, survivors of severe COVID-19 pneumonia experience persistent symptoms, functional disability and mental health problems despite radiographic resolution occurring in the majority, highlighting the need for holistic follow-up care.

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ABSTRACT

BACKGROUND A standardised approach to assessing COVID-19 survivors has not been established, largely due to the paucity of data on medium- and long-term sequelae. Interval chest radiograph is recommended following community-acquired pneumonia, however its utility in monitoring recovery from COVID-19 pneumonia remains unclear.

METHODS Prospective single-centre observational cohort study. Patients hospitalised with severe COVID-19 pneumonia (admission duration ≥48hours and oxygen requirement ≥40% or critical care admission) underwent face-to-face assessment 4-6 weeks post-discharge. Primary outcome: radiological resolution of COVID-19 pneumonitis (Radiographic Assessment of Lung Oedema score <5). Secondary outcomes: clinical outcomes, symptom questionnaires, mental health screening (Trauma Screening Questionnaire, GAD-7, PHQ-9), physiological testing (4-metre gait speed (4MGS), 1-minute sit-to-stand test (STS)).

RESULTS 119 patients assessed between 3rd June and 2nd July 2020 at median (IQR) 61 (51-67) days post-discharge. Mean±SD age 58.7±14.4 years, body mass index 30.0 (25.9-35.2) kg/m^2, 62% male, 68% ethnic minority. Despite radiographic resolution of pulmonary infiltrates in 87%, mMRC breathlessness scores were above pre-COVID baseline in 46% and patients reported persistent fatigue (68%), sleep disturbance (57%) and breathlessness (32%). Screening thresholds were breached for post-traumatic stress disorder (25%), anxiety (22%) and depression (18%). 4MGS was slow (<0.8m/s) in 38%, 35% desaturated by ≥4% during STS. Of 56 thoracic computed tomography scans performed, 75% demonstrated COVID-related interstitial and/or airways disease.

CONCLUSIONS Persistent symptoms, adverse mental health outcomes and physiological impairment are common 2 months after severe COVID-19 pneumonia. Follow-up chest radiograph is a poor marker of recovery, therefore holistic face-to-face assessment is recommended to facilitate early recognition and management of post-COVID sequelae.

Introduction

Following alarmingly rapid global spread of the novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), COVID-19 was categorised as a pandemic on 11th March 2020 [1]. Acute manifestations of the disease are widely reported, with fever, cough and breathlessness recognised as the most common presenting symptoms [2]. Following the acute phase of illness, there is increasing anecdotal awareness of patients with "long COVID" in whom residual symptoms persist beyond the acute viral illness [3]. However, a robust evidence base on medium- and long-term physical and psychological sequelae of severe COVID-19 infection is currently lacking.

Drawing from experience from previous coronavirus global outbreaks (SARS-CoV-1 (SARS) in 2002-2004 and the Middle East respiratory syndrome-related coronavirus (MERS) in 2012) and our comprehensive understanding of outcomes following acute respiratory distress syndrome (ARDS) and critical illness, COVID-19 survivors are anticipated to be at risk of impaired lung function [4], interstitial lung disease [5], exercise limitation and impaired quality of life in the months and years following hospital discharge [4, 6, 7]. Given the 14% prevalence of post-traumatic stress disorder in critical illness survivors [8] and excess increase in mental distress observed amongst UK adults during the COVID-19 pandemic [9], the burden of mental health disorders following COVID-19 infection is expected to be high. With over 24 million cases now confirmed globally and the daily incidence continuing to climb [10], it is apparent that early recognition and management of complications amongst the increasing population of severe COVID-19 survivors, many of whom will have experienced multi-organ involvement, critical care admission and psychological trauma, is a clinical priority.

We aimed to prospectively investigate clinical, radiological, functional and psychological COVID-19 sequalae of severe COVID-19 pneumonia, and to identify factors associated with symptomatic and functional recovery.

Methods

Study design and participants

This single-centre prospective observational cohort study was conducted at King's College Hospital, an urban university hospital in London (UK). We analysed the routine data of COVID-19 survivors

attending the King's College Hospital COVID-19 post-discharge clinical service. To identify patients hospitalised with COVID-19 pneumonia, we screened electronic medical records of consecutive patients aged 18 years and above hospitalised with PCR-confirmed COVID-19 on naso- and oro-pharyngeal swab between February and May 2020. In the UK healthcare system during the pandemic, patients presenting to the emergency department with symptoms consistent with COVID-19 were admitted to hospital if they were considered at higher risk of severe disease (based on age, comorbidities or social circumstances) and/or they had significantly abnormal vital observations or investigations (venous or arterial blood results, chest radiography). We defined severe COVID-19 pneumonia as requiring hospitalisation for ≥48 hours and a fraction of inspired oxygen (FiO_2) of ≥40% or intensive care unit (ICU) admission. Patients fulfilling these criteria and surviving to discharge were invited to attend clinic for face-to-face assessment in accordance with British Thoracic Society (BTS) Guidance [11]. Herein, we report the first month of prospectively collected data from consecutive patients assessed between 3rd June and 2nd July 2020. This study was approved by the Clinical Governance committee, King's College NHS Foundation Trust, judged to be a service evaluation exempt from NHS Research Ethics Committee review, since no *a priori* hypothesis testing, randomisation or treatment allocation was undertaken, and conducted according to the principles of the Declaration of Helsinki [12].

Data collection

Demographic and anthropometric data and inpatient clinical outcomes for all patients screened were obtained from medical records. A summary of follow-up data collected is provided in Table S1. Questionnaires were used to evaluate persistent symptoms, self-reported functional disability, depression, anxiety, post-traumatic stress disorder (PTSD) and cognition [13-20]. Functional disability was objectively assessed using the 4-metre gait speed (4MGS) and 1-minute sit-to-stand (STS) test [21, 22]. Admission, worst inpatient and follow-up radiographs were graded using the Radiographic Assessment of Lung Oedema (RALE) score [23]. Thoracic computed tomography (CT) scans were performed for patients with persistent chest radiograph abnormalities, respiratory symptoms or desaturation of ≥4% during STS. Additional methodological details are provided in the online supplement.

Outcomes

The primary outcome of this study was radiological resolution of COVID-19 pneumonia, in accordance with national guidelines [11]. Secondary outcomes included demographics, anthropometrics, inpatient clinical course, symptom questionnaires, mental health screening and physiological testing (STS repetitions and oxygen desaturation and 4MGS).

Statistical analysis

The aim of this study was to perform rapid characterisation of severe COVID-19 recovery, with no *a priori* hypothesis testing or sample size calculation. Consecutive survivors of confirmed severe COVID-19 pneumonia attending face-to-face assessments were included. Data are presented as mean±standard deviation (SD) or median (interquartile range (IQR)) for continuous variables depending on the normality of the data and frequency (percentage (%); 95% confidence interval) for categorical variables. Group comparisons were performed using independent t-tests and Chi square (χ^2) tests. Ordinal logistic regression modelling was used to identify factors associated with measures of COVID-19 recovery. Odds ratios (OR) (adjusted for age, sex and ethnicity) are presented. Statistical significance was concluded at the two-sided significance level of 0.05. Analyses were conducted with SPSS (version 26, IBM Corp, NY, USA).

Results

Baseline and inpatient characteristics

Between 3rd June and 2nd July 2020, 143 patients were invited to attend face-to-face assessment post-discharge, 119 attended. These patients had been hospitalised between 5th March and 28th May 2020, during which time a total of 898 patients were hospitalised with confirmed COVID-19, of whom 657 survived to discharge (Figure 1). Data for all patients hospitalised with COVID-19, those surviving to discharge and those that did not attend their post-COVID clinic appointment and between-group comparisons are provided in Tables S2-3. Baseline demographic and anthropometric characteristics at follow-up and patients' inpatient clinical course are presented in Table 1. Average age was

58.7±14.4 years, body mass index (BMI) was 30.0 (25.9-35.2)kg/m^2, 62% of patients were male and 70% self-reported as Black, Asian or minority ethnic (BAME). Charlson comorbidity index was 2 (1-4), 53% had pre-existing cardiovascular disease, 11% had obstructive lung disease, 7% had end-stage renal failure, 18% had no pre-existing comorbidities. Patients were moderately hypoxaemic at admission (PaO_2:FiO_2 169 (106-272)). 58% of patients were lymphopenic, 20% were thrombocytopenic. 41 (34%) were admitted to the intensive care unit (ICU), 34 (29%) received invasive mechanical ventilation, average ICU admission duration was 14.5 (7-27) days. Hospital length of stay for critical care patients was 30.8 ± 16.3 days and 9 (7-14.5) days for those receiving ward-based care. 70 (59%) experienced at least one complication attributable to COVID-19 (Table S4), of which acute kidney injury (35%) and venous thromboembolism (23%) were most common.

Table 1 Baseline characteristics at follow-up and inpatient clinical course

Age (years)	58.7 ± 14.4
18-29	4 (3.4; 0.8-6.7)
30-39	11 (9.2; 5.0-14.3)
40-49	13 (10.9; 6.7-15.1)
50-59	36 (30.3; 22.7-38.7)
60-69	27 (22.7; 16.0-28.6)
70-79	18 (15.1; 10.1-21.0)
80+	10 (8.4; 5.0-12.6)
Sex	
Female	45 (37.8; 29.4-46.2)
Male	74 (62.2; 53.8-70.6)
Ethnicity	
BAME (Yes/No)	83 (69.7; 61.3-78.2)
White	36 (30.3; 22.6-37.8)
Black	52 (43.7; 36.1-51.3)
Asian	18 (15.1; 10.1-20.2)
Mixed race	5 (4.2; 1.7-6.7)
Other	8 (6.7; 3.4-10.9)
Index of multiple deprivation score (n=115)	26.6 ± 9.7
Body Mass Index (kg/m^2) (n=118)	30.0 (25.9-35.2)
Underweight (<18.5)	0 (0.0)
Normal (18.5-24.9)	22 (18.6; 12.7-24.6)
Overweight (25-29.9)	35 (29.7; 22.9-37.3)
Obese (30-34.9)	30 (25.4; 19.5-33.1)
Severely obese (35-39.9)	20 (16.9; 11.0-22.0)
Morbidly obese (40-49.9)	9 (7.6; 4.2-11.0)
Super obese (50+)	2 (1.7; 0.0-4.2)
Smoking status (n=110)	
Never	82 (74.5; 67.3-82.7)
Ex-smoker	25 (22.7; 16.4-28.2)
Current	3 (2.7; 0.0-6.4)
Comorbidities	
Charlson comorbidity index	2 (1-4)
Any cardiovascular disease	63 (52.9; 44.5-61.8)
Hypertension	54 (45.4; 37.7-52.9)
Hyperlipidaemia	25 (21.0; 15.1-27.4)
Ischaemic heart disease/ heart failure	8 (6.7; 3.4-10.9)
Diabetes	41 (34.5; 26.4-42.9)
Immunosuppressed	16 (13.4; 8.4-18.5)

Obstructive lung disease	13 (10.9; 6.7-16.0)
Malignancy	12 (10.1; 5.9-14.3)
End stage renal failure	8 (6.7; 3.4-10.1)
Thyroid disease	7 (5.9; 2.5-9.2)
Mental health condition	6 (5.0; 2.5-7.6)
Cerebrovascular disease	5 (4.2; 1.7-6.7)
Admission PaO_2:FiO_2	168.8 (105.9-272.3)
PaO_2:FiO_2 severity (%)	
>300 (normal)	13 (14.6; 9.0-21.3)
200-300 (mild)	23 (25.8; 19.1-34.8)
100-199 (moderate)	32 (36.0; 28.1-44.9)
<100 (severe)	21 (23.6; 15.7-32.6)
Maximum respiratory support (%)	
FMO_2	71 (59.7; 51.3-67.2)
PAP	14 (11.8; 6.9-16.8)
IMV	34 (28.6; 21.0-37.0)
COVID-19 complications (%)	
None during admission	49 (41.2; 33.6-48.7)
VTE	27 (22.7; 16.8-29.4)
PE	23 (19.3; 12.6-26.1)
DVT	6 (5.0; 2.5-7.6)
AKI	41 (34.5; 25.2-43.7)
Deranged LFTs	17 (14.3; 9.2-20.2)
Delirium	18 (15.1; 10.1-20.2)
Hospital LOS (days)	12 (8-23)
LOS if admitted to ICU	30.8±16.3
LOS if not admitted to ICU	9 (7-14.5)
ICU admission (%)	41 (34.5; 26.9-42.9)
ICU LOS	14.5 (7-27)
Duration of IMV (days)	20.5 ± 14.0

Data presented as mean ± standard deviation, median (interquartile range) or frequency (proportion; 95% confidence interval). Abbreviations: BAME = Black, Asian or minority ethnic, PaO_2 = arterial partial pressure of oxygen, FiO_2 = fraction of inspired oxygen, LOS = length of stay, ICU = intensive care unit, IMV = invasive mechanical ventilation, FMO_2 = facemask oxygen, PAP = positive airway pressure therapy (including high-flow therapy, continuous positive airway pressure and non-invasive ventilation), VTE = venous thromboembolism, PE = pulmonary embolism, DVT = deep vein thrombosis, AKI = acute kidney injury, LFT = liver function tests.

Follow-up characteristics

Median (IQR) times between hospital admission and discharge to follow-up assessment were 76 (71-83) days and 61 (51-67) days, respectively. Time between discharge and clinic assessment and current modified Medical Research Council Breathlessness scale (mMRC) is displayed in Figure 2. 57 patients (48%) utilised hospital services following hospital discharge: 23 (40%) attended outpatient appointments for monitoring of inpatient complications (haematology, renal, diabetes), 16 (28%) attended the Emergency Department, 9 (16%) were re-hospitalised, 9 (16%) attended planned outpatient appointments for pre-existing co-morbidities.

Questionnaire scores are displayed in Figure 3. mMRC scale at follow-up was 1 (0-2) and pre-COVID was 0 (0-1), 55/115 (46.2; 37.8-54.6) had not returned to pre-COVID mMRC baseline. The association between current mMRC scale and time between discharge and clinic assessment was weak (R^2 <0.001, p=0.82). Post-COVID Functional Status (PCFS) scale was ≥2 in 47/115 (40.9; 33.0-47.8). Of those whose mMRC breathlessness scale had not returned to pre-COVID baseline, 11/55

(20.0%; 10.0-31.2) had no pre-existing comorbidity. Comorbid obstructive lung disease was associated with failure of mMRC recovery to baseline (OR 5.06 p=0.02 95%CI 1.33 to 19.2) and PCFS ≥2 (OR 2.84 p=0.047 95%CI 1.01 to 7.98) (Table 2).

Median number of persistent symptoms was 4 (IQR 2-5), 11% of patients reported no persistent symptoms. Burdensome breathlessness (numerical rating scale (NRS) breathlessness ≥4) was present in 37/115 (32.2% (95%CI 25.2-40.0). Persistent cough (NRS ≥1) was present in 49/115 (42.6; 33.9-52.2) and burdensome (NRS ≥4) in 8/115 (7.0; 3.5-10.4). 78/115 (67.8; 60.0-76.5) reported fatigue, 65/115 (56.5; 47.3-66.1) reported sleep disturbance and 57/115 (49.6; 40.9-58.3) reported pain. Where stated, pain was most commonly reported in the shoulder (9, 29%), chest (7, 23%), lower limbs (6, 19%) and back (4, 13%). Pre-morbid obstructive lung disease was associated with persistent (NRS ≥1) breathlessness (OR 8.04 p=0.03 95%CI 0.19 to 21.4) and cough (OR 3.43 p=0.04 95%CI 0.98 to 12.0), but not burdensome (NRS ≥4) breathlessness or cough (OR 1.97 p=0.26 95%CI 0.60 to 6.47 and OR 2.27 p=0.37 95%CI 0.38 to 13.7, respectively). There were no associations between the presence or absence of pre-existing comorbidities and persistent fatigue, sleep disturbance or pain. PHQ-9 score was ≥9 in 20/111 (18.0; 11.7-23.4), GAD-7 was ≥9 in 25/113 (22.1; 15.0-29.8). 28/113 (24.8; 18.1-31.9) scored ≥6 on the Trauma Screen Questionnaire. 21/97 (21.6; 14.4-28.9) scored ≥8 on the 6-item Cognitive Impairment Test.

Physiological outcomes are displayed in Table 3. Resting SpO_2 was <94% in 2 (1.7%). 115 (97%) patients completed the 4MGS. Mean 4MGS was 0.87±0.29 m/s, 44 (38%) had a 4MGS <0.8 m/s. 109 (92%) completed the STS. The number of repetitions performed were below the 2.5 percentile in 56 (52%). 39 (35%) desaturated by ≥4%, 13 (11.5%) desaturated to ≤88%. There were no adverse events during physiological testing. There were no associations between pre-morbid obstructive lung disease and physiological functional impairment (OR 0.68 p=0.61 95%CI 0.16 to 2.95) (Table 2), however cardiovascular disease was associated with a 4MGS <0.8 m/s (OR 3.95 p=0.003 95%CI 0.42 to 2.49). There were no associations between pre-existing comorbidities and exertional oxygen desaturation (≥4%) during STS testing. There was no relationship between age categories (as defined in Table 1) and persistent post-COVID symptoms, self-reported functional disability (mMRC not returned to baseline or PCFS scale ≥2) or physiological impairment (4MGS <0.8 m/s or oxygen desaturation ≥4%).

Table 2 Ordinal logistic regression to identify factors associated with measures of COVID-19 recovery

	mMRC recovery to pre-covid baseline				**PCFS ≥ 2**				**Physiological functional impairment**				**Positive mental health screening**			
Variable	Adjusted OR	p-value	95%CI		Adjusted OR	p-value	95%CI		Adjusted OR	p-value	95%CI		Adjusted OR	p-value	95%CI	
			Lower	Upper			Lower	Upper			Lower	Upper			Lower	Upper
Age	0.85	0.219	0.66	1.10	0.86	0.237	0.66	1.11	1.00	0.982	0.81	1.23	0.66	**0.003**	0.50	0.87
Sex	1.07	0.848	0.54	2.12	1.12	0.748	0.56	2.22	0.84	0.656	0.39	1.81	0.68	0.358	0.30	1.54
BAME	0.63	0.234	0.29	1.35	0.68	0.243	0.36	1.29	1.81	**0.071**	0.95	3.46	0.77	0.548	0.32	1.82
IMD	1.38	0.076	0.97	1.95	1.16	0.417	0.81	1.68	0.73	0.072	0.52	1.03	1.53	0.061	0.98	2.40
Obese (BMI>30 kg/m^2)	1.64	0.177	0.80	3.34	1.17	0.645	0.59	2.32	0.75	0.415	0.37	1.50	1.61	0.292	0.66	3.89
Current smoker	0.88	0.752	0.39	1.96	1.15	0.715	0.54	2.43	1.27	0.546	0.59	2.74	1.46	0.431	0.57	3.72
Co-morbid diabetes	0.81	0.589	0.39	1.72	0.80	0.601	0.36	1.82	1.58	0.243	0.73	3.39	1.33	0.550	0.52	3.37
Co-morbid hypertension	0.73	0.366	0.37	1.44	0.81	0.576	0.38	1.71	1.62	0.271	0.69	3.84	1.76	0.210	0.73	4.25
Co-morbid obstructive lung disease	5.06	**0.017**	1.33	19.24	2.84	**0.047**	1.01	7.98	0.68	0.605	0.16	2.95	2.47	0.059	0.97	6.31
Total comorbidities	1.03	0.823	0.82	1.28	1.09	0.495	0.86	1.38	1.20	0.142	0.94	1.53	1.34	0.060	0.99	1.81
Hospital LOS	1.04	0.706	0.84	1.29	1.21	0.099	0.97	1.52	1.14	0.180	0.94	1.37	0.94	0.596	0.75	1.18
FMO_2 maximum respiratory support	0.86	0.715	0.39	1.92	0.48	**0.060**	0.22	1.03	0.44	**0.023**	0.21	0.89	0.85	0.735	0.32	2.22
PaO_2:FiO_2	0.96	0.677	0.77	1.19	0.89	0.393	0.68	1.16	1.00	0.999	0.80	1.25	0.88	0.338	0.67	1.15
ICU admission	1.22	0.657	0.51	2.94	2.57	**0.026**	1.12	5.90	2.44	**0.029**	1.10	5.42	1.26	0.643	0.47	3.42
ICU for IMV	1.36	0.503	0.56	3.30	3.27	**0.008**	1.36	7.84	2.65	**0.017**	1.19	5.91	1.23	0.688	0.45	3.36
No inpatient complications	0.94	0.872	0.46	1.92	0.82	0.592	0.40	1.69	0.74	0.416	0.37	1.52	1.12	0.808	0.45	2.80
Inpatient VTE	2.26	0.066	0.95	5.37	2.21	**0.040**	1.04	4.72	1.51	0.261	0.74	3.08	1.34	0.542	0.53	3.39
Worst RALE score	1.51	**0.005**	1.13	2.02	1.09	0.566	0.81	1.48	0.95	0.767	0.69	1.31	0.94	0.701	0.66	1.32
Follow-up RALE score	2.04	0.290	0.55	7.62	1.42	0.479	0.54	3.74	2.22	0.159	0.73	6.72	0.87	0.834	0.24	3.13
Normal CT	0.92	0.909	0.23	3.70	0.62	0.502	0.16	2.47	0.76	0.654	0.23	2.51	0.22	0.052	0.05	1.01
NRS breathlessness	8.04	**0.000**	3.62	17.84	4.21	**0.000**	1.94	9.10	1.77	0.149	0.82	3.83	4.34	**0.004**	1.58	11.95
NRS cough	1.63	0.166	0.82	3.26	1.79	0.091	0.91	3.51	1.18	0.652	0.57	2.46	1.38	0.442	0.61	3.15
NRS fatigue	3.16	**0.002**	1.51	6.62	4.66	**0.000**	2.08	10.44	1.09	0.827	0.51	2.33	3.58	**0.012**	1.32	9.70
NRS pain	2.60	**0.007**	1.31	5.19	6.54	**0.000**	2.98	14.35	0.77	0.487	0.38	1.59	9.62	**0.000**	3.65	25.38
NRS sleep disturbance	6.06	**0.000**	2.96	12.38	6.47	**0.000**	2.92	14.36	1.32	0.437	0.66	2.65	7.24	**0.000**	2.42	21.62
Positive 6CIT	1.28	0.554	0.57	3.32	0.96	0.949	0.32	2.89	1.05	0.918	0.44	2.47	0.71	0.563	0.22	2.29
4MGS <0.8 m/s	1.36	0.432	0.63	3.11	2.33	**0.040**	1.04	5.21					3.86	**0.004**	1.52	9.77
STS desaturation ≥4%	0.90	0.781	0.43	2.96	0.83	0.600	0.42	1.65					0.60	0.250	0.25	1.43
STS repetitions <2.5 percentile	1.55	0.256	0.73	1.88	4.03	**0.000**	1.90	8.55					2.91	**0.038**	1.06	7.99
Positive mental health screen	7.03	**0.000**	2.77	2.89	12.13	**0.000**	5.03	29.26	2.24	**0.046**	1.01	4.93				
Positive PHQ-9	31.36	**0.000**	10.32	17.82	21.26	**0.000**	8.29	54.49	2.93	**0.033**	1.09	7.86				
Positive GAD-7	9.71	**0.000**	3.23	95.36	13.20	**0.000**	5.03	34.65	1.72	0.256	0.67	4.39				
Positive Trauma Screen	5.26	**0.000**	2.13	29.20	7.41	**0.000**	3.27	16.79	1.84	0.153	0.80	4.27				
Positive PCFS	2.21	**0.000**	1.57	12.97					1.51	**0.003**	1.15	1.98	2.89	**0.000**	2.09	4.01
Pre-covid mMRC					1.57	**0.030**	1.04	2.36	1.49	**0.020**	1.06	2.08	1.60	**0.027**	1.06	2.42
Current mMRC					2.48	**0.000**	1.74	3.54	1.32	0.079	0.97	1.80	2.68	**0.000**	1.83	3.91

Odd ratios adjusted for age and sex. mMRC = modified Medical Research Council score for breathlessness, PCFS = post-covid functional scale, OR = odd ratio, 95%CI = 95% confidence interval, BAME = Black, Asian or minority ethnic, IMD = index of multiple deprivation score, BMI = body mass index, LOS = length of stay, FMO_2 = facemask oxygen, PaO2:FiO2 = arterial partial pressure of oxygen to fraction of inspired oxygen ratio, ICU = intensive care unit, IMV = invasive mechanical ventilation, VTE = venous thromboembolism, RALE = radiographic assessment of lung oedema, CT = computed tomography, NRS = numerical rating score, 6CIT = 6-item cognitive impairment test, 4MGS = 4-metre gait speed, STS = sit-to-stand

Table 3 Physiological outcomes

Resting observations (n=119)	
Median (IQR) SpO_2 (%)	98 (97-99)
Mean ± SD Heart rate (beat/min)	86 ± 13
Median (IQR) Systolic blood pressure	137 (126-151)
Mean ± SD 4MGS (m/s) (n=115)	0.87±0.29
≥0.8 m/s	71/115 (61.7; 53.9-70.4)
<0.8 m/s	44/115 (38.3; 29.6-46.1)
Mean ± SD STS repetitions (repetitions/min) (n=109)	20 ± 7.8
p<2.5	56/109 (51.9; 42.6-60.2)
p(2.5-25%)	39/109 (36.1; 28.7-43.5)
p(25-50%)	9/109 (8.3; 4.6-13.0)
p(50-75%)	3/109 (2.8; 0.0-6.5)
p(75-97.5%)	1/109 (0.9; 0.0-2.8)
Median (IQR) STS SpO_2 nadir (%) (n=109)	96 (93-97)
Desaturation ≥4% (%)	39 (34.5; 26.5-41.6)
Desaturation ≤88% (%)	13 (11.5; 7.1-15.9)

Categorial data are presented as frequency (proportion; 95% confidence interval, continuous data are presented as mean ± SD, median (IQR). 4MGS = 4-metre gait speed, STS = sit-to-stand, SpO_2 = peripheral oxygen saturation, p<2.5 = patients below 2.5th percentile, p(2.5-25%) = patients between 2.5 and 25th percentile, p(25-50%) = patients between 25th and 50th percentile, p(50-75%) = patients between 50th and 75th percentile, p(75-97.5%) = patients between 75th and 97.5 percentile.

All 119 patients underwent chest radiography at follow-up assessment. RALE scores at admission, peak of inpatient clinical illness and follow-up are presented in Figure 4. Only 15 (13%) had evidence of COVID-related lung disease on follow-up radiograph (RALE score >4). 56 patients were invited for follow-up computed tomography and pulmonary angiography (CTPA) based on abnormal chest radiography, persistent respiratory symptoms or exercise desaturation. Of these, 42 scans demonstrated features of COVID-related interstitial lung disease and/or airways disease: 21 revealed ground glass/organising pneumonia (37.5%; 95%CI 26.8-48.2), 9 revealed small airways disease/bronchiectasis (16.1; 8.9-25.0), 5 revealed a combination of interstitial patterns (8.9; 3.6-16.1), 4 had a combination of interstitial and airways changes (7.1; 1.8-14.3), 3 revealed fibrosis/non-specific interstitial pneumonia (5.4; 0.0-12.5). 14 (26.2%; 95% CI 15.1-37.7) CTs were normal or had no abnormality to explain persistent symptoms or desaturation. No pulmonary emboli were identified on CT pulmonary angiography. Presence of COVID-related CT abnormalities were associated with mental health screening questionnaires (PHQ-9 ≥9, GAD-7 ≥9 and/or Trauma Screening Questionnaire ≥6) (χ^2=3.98 p=0.046 95%CI -0.56 to -0.02) but not with any measure of patient-reported or physiological functional impairment (mMRC, PCFS, 4MGS <0.8 m/s or 4% oxygen desaturation during STS testing). Only 21% of patients with abnormal CT findings also had an abnormal follow-up chest radiograph, however 78% of those with ≥4% desaturation during STS also had abnormal CT findings. 33 patients had a normal chest radiograph (RALE score 0-4) and an

abnormal CT, 9 patients had both an abnormal chest radiograph (RALE score >4) and abnormal CT. Amongst those with abnormal CT scans, presence or absence of radiographic abnormalities was not predictive of any patient-reported or physiological outcome measure.

Ordinal logistic regression modelling was performed for the outcomes of return of mMRC to pre-COVID baseline, PCFS score of ≥2, positive mental health screening (PHQ-9 or GAD-7 ≥9 or Trauma Screening Questionnaire ≥6) and physiological functional impairment (4MGS <0.8 m/s, STS repetitions in <2.5 percentile or ≥4% desaturation on STS) (Table 3). Positive associations were found between PCFS score of ≥2, physiological impairment (4MGS <0.8 m/s and STS repetitions in <2.5 percentile) and positive mental health screening. Critical care admission and need for invasive mechanical ventilation were associated with physiological functional impairment. Neither worst inpatient nor follow-up RALE score were associated with any modelled outcome measure.

Discussion

Principal findings

This is the first study to provide holistic characterisation of medium-term sequelae two months following severe COVID-19 pneumonia incorporating clinical, radiological, physiological and psychological outcome measures. At 7-9 weeks following index hospitalisation, chest radiograph was a poor marker of abnormal CT findings and persistent functional disability. 87% of patients had a RALE score of 0-4. 75% of CT scans demonstrated COVID-related interstitial lung disease and/or airways disease however only 21% of patients with abnormal CT findings also had an abnormal follow-up chest radiograph.

The burdens of persistent symptoms, mental health disorders and functional disability 2 months following index hospitalisation were high, with persistent fatigue (68%) and sleep disturbance (57%) more prevalent than respiratory symptoms (breathlessness 32%, cough 7%). Significant depression or anxiety was present in 18% and 22% of patients, respectively, and 25% screened positive for post-traumatic stress disorder. 41% of patients reported persistent limitations in everyday life due to COVID-19 (score ≥2 on the post-COVID functional scale) and mMRC failed to return to pre-COVID baseline in 46%. Face-to-face assessment was invaluable in identifying the high prevalence of objective functional impairment, evident during physiological testing: 4MGS was <0.8 m/s in 38%, in

52% of patients performing the STS, number of repetitions were in the <2.5 percentile for age and sex and 35% desaturated by ≥4% during the STS.

Comparison with other studies

The baseline characteristics and inpatient clinical course of this cohort are highly consistent with national data for COVID-19 critical care admissions with regards to age, sex, BMI, PaO_2:FiO_2 severity, proportion requiring invasive mechanical ventilation and duration of ICU admission [24]. The higher proportion of patients from ethnic minority background is consistent with the local population served by our hospital. Data from 20,133 patients hospitalised with COVID-19 in the UK between February and April 2020 demonstrated a 26% inpatient mortality, comparable to the 27% inpatient mortality observed in this cohort [25]. Characteristics of this cohort are also consistent with previous studies that have identified risk factors for severe COVID-19 illness, including male sex and obesity, severe hypoxaemic respiratory failure requiring intensive respiratory support and high rates of abnormal admission investigations, including lymphopenia, thrombocytopenia, and elevated CRP, d-dimer and ferritin [2, 26]. High rates of inpatient complications attributable to COVID-19 were observed, comparable to published data, including venous thromboembolism, acute kidney injury, deranged liver function and delirium [2, 27, 28]. Follow-up patients were younger with fewer co-morbidities than the total cohort surviving to discharge, likely representing the characteristics of COVID-19 survivors, since these have been identified as risk factors for inpatient mortality in retrospective analyses [29, 30].

Few data are available on medium- and long-term effects of COVID-19 following hospital discharge. Our population characteristics are consistent with an Italian post-COVID clinic cohort who had comparable quality of life impairment and persistent symptoms, although these patients were seen sooner following hospital discharge (36±13days compared to 61 (51-67) days) [31]. Compared to studies evaluating radiological sequelae of MERS-CoV, the proportion of patients with chest x-ray resolution was much larger in our cohort (87% measured 76 (71-83) days from admission, compared to 64% measured at 32-230 days) [32]. Data on post-COVID CT findings are currently limited to within 3 weeks of symptom onset and indicate rapid evolution from unilateral multifocal ground-glass opacities to bilateral diffuse involvement to early reductions in ground-glass opacities by week 2 [33]. This is the first study to report CT outcomes post-discharge. We did not perform CT scans

indiscriminately and would therefore anticipate that this selection would lead to overrepresentation of interstitial abnormalities. Conversely, interstitial changes were less common in our cohort compared to patients with previous SARS, in whom 15 (62%) of 24 patients exhibited fibrotic changes on CT [5]. 15-year longitudinal data from SARS patients demonstrates resolution or stability of ground-glass changes with corresponding stability of total lung capacity and carbon monoxide diffusing capacity on lung function testing [34]. The long-term clinical implications and prognosis of COVID-related interstitial changes identified in the post-acute phase of illness remains unknown, and labelling these abnormalities as lung fibrosis appears premature, particularly given the lack of association between presence of CT abnormalities and any measure of patient-reported or physiological functional impairment in this cohort.

Prevalence of persistent and burdensome physical symptoms, patient-reported and physiological functional impairment and psychological sequelae was high in our cohort, and critical care admission and need for invasive mechanical ventilation were both associated with patient-reported and objective functional impairment. This is consistent with medium- and long-term data from acute respiratory distress syndrome and SARS survivors, in whom impaired quality of life and functional disability (measured using the 36-Item Short Form Survey and 6-minute walk test) were present at 3, 6 and 12 months following index hospitalisation [4, 7]. The burdens of patient-reported and physiological outcomes were high despite radiographic resolution occurring in the majority. Reasons for this remain speculative and may relate to our early assessment of patients with severe disease 61 (51-67) days post-discharge. Long-term data on post-COVID symptoms and functional outcomes are awaited. Clinically significant depression or anxiety were present in 18% and 22% of our cohort, respectively, and 25% screened positive for post-traumatic stress disorder, consistent with published data (31% depression, 42% anxiety and 28% PTSD 1 month post-discharge) [35].

Implications for clinical practice

Persistent symptoms of fatigue and sleep disturbance following severe COVID-19 pneumonia have implications for productivity, physical activity and mental health, reflected in the high rates of positive screening tests for anxiety, depression and PTSD observed in this cohort. Whilst causative mechanisms for adverse mental health outcomes following COVID-19 infection have not been

established, mental distress at the population level has increased in excess of anticipated trajectories during the COVID-19 pandemic [9]. ICU-acquired weakness is a major contributor to adverse long-term physical and psychological sequelae of critical illness [6] and likely applicable to COVID-19-survivors, particularly since conventional methods of rehabilitation and exercise have been limited [36]. It has also been speculated that biological pathophysiological mechanisms, relating to cerebral vascular inflammation and thrombosis, survivor guilt and isolation in COVID-19 survivors may also contribute to adverse mental health outcomes in this cohort [28, 35].

Chest radiography 12 weeks post-discharge is advocated by current guidelines to evaluate recovery, with face-to-face clinical assessment recommended only in those with abnormal radiographs or those who experienced severe illness [11]. However, the majority (87%) of radiographs performed at follow-up demonstrated recovery (RALE score <5) despite the high prevalence of adverse patient-reported and/or physiological outcomes. The clinical implications of post-COVID interstitial changes identified on CT remain unclear. Of note, parenchymal abnormalities in SARS survivors demonstrated recovery and stability in the 2 years following infection [34]. We strongly encourage integrated holistic assessment of COVID-19 survivors using both radiological and clinical reviews, which may be conducted face-to-face or virtually depending on healthcare resources and patient preference.

The battery of outcome measures implemented in this study is impractical for routine clinical use. Focussed patient interview is an appropriate substitute for questionnaires, utilising the data presented and we recommend routine application of functional exercise testing. The 4MGS and 1-minute STS are reliable and validated methods of assessing exercise performance, are predictive of health-related quality of life and correlate with other tests of functional capacity, including the incremental shuttle walk and 6-minute walk tests [21, 37, 38]. These self-paced tests were quick to perform, required simple instructions to the patients and minimal space, equipment and training and were completed in the majority of cases with no adverse events. Importantly, they provided valuable clinical information regarding oxygen desaturation and exercise limitation which was not obtained from other sources, thus identifying a cohort of patients requiring CT evaluation and who may benefit from pulmonary rehabilitation or advised on graded and paced return to usual activities, although current facilities and evidence in this context remains unestablished [39, 40].

Strengths and limitations

We rapidly designed a pragmatic clinical service to prospectively collect comprehensive data on physical and psychological recovery from severe COVID-19 at a time when sequelae of the acute illness were unknown and healthcare resources were severely strained. We conducted systematic face-to-face assessments which enabled collection of a wealth of clinical, radiological, patient-reported and physiological data in a short period, with all outcome measures contributing to clinical decision making.

This study has some limitations. Firstly, it was not possible to perform lung function testing in serial patients due to decontamination procedures required following this aerosol generating procedure, limiting conclusions that can be drawn regarding respiratory sequelae of the disease [41]. Secondly, conventional field walking tests to evaluate exercise capacity (6-minute walk test (6MWT), incremental shuttle walk test (ISWT)) were impractical in the clinic setting. However, the 4MGS and STS are reliable, validated and pragmatic methods of assessing exercise performance that correlate with the 6MWT and ISWT, breathlessness and health-related quality of life [21, 37, 38]. Thirdly, given the ambiguity in current guidance we devised our own definition of "severe" COVID-19 pneumonia in order to assess patients at highest risk of complications and to rationalise resources, given the large number of COVID-19 admissions. This approach may have missed some patients with persistent symptoms or functional disability, however those recovering from mild to moderate disease are now being invited to attend post-COVID clinic and we plan to report their outcomes in due course. Finally, these data were collected from a single, urban teaching centre which limits the generalisability of our results. However, this dataset is sufficiently large to provide reasonable estimates of post-COVID sequelae whilst results of multicentre studies are awaited.

Conclusion

We have demonstrated that the burden of persistent symptoms, functional limitation and adverse mental health outcomes 2 months after severe COVID-19 pneumonia is high. Physiological impairments frequently persist despite apparent resolution of infiltrates on follow-up chest radiography. Routinely offering face-to-face post-COVID follow-up assessment permitted inclusion of self-paced "bedside" physiological tests, which provided valuable clinical information on functional

disability warranting further investigation that could not have been obtained from questionnaires or telephone consultations. With confirmed cases of COVID-19 continuing to rise worldwide, we recommend prompt face-to-face or virtual clinical assessment of COVID-19 pneumonia survivors to facilitate early recognition and management of physical and psychological sequelae in this vulnerable cohort.

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Contributors: Study conception and design: CJ, MDW, FP. Acquisition, analysis, or interpretation of data: RFD, FP, MW, JP, SN, L-JS, RM, TP, DW, WM, PM, KL, AH, RL, JG, SB, AM, IP, CJJ. Drafting of the manuscript: RFD, JP, SN, CJ. Critical revision of the manuscript for important intellectual content: RFD, FP, MW, JP, SN, L-JS, RM, TP, DW, WM, PM, KL, AH, RL, JG, SB, AM, IP, CJJ. Statistical analysis: RFD, SM, CJ. Study supervision: CJ, JP, SB. CJ and RFD are the guarantors of the study. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

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Figure 1

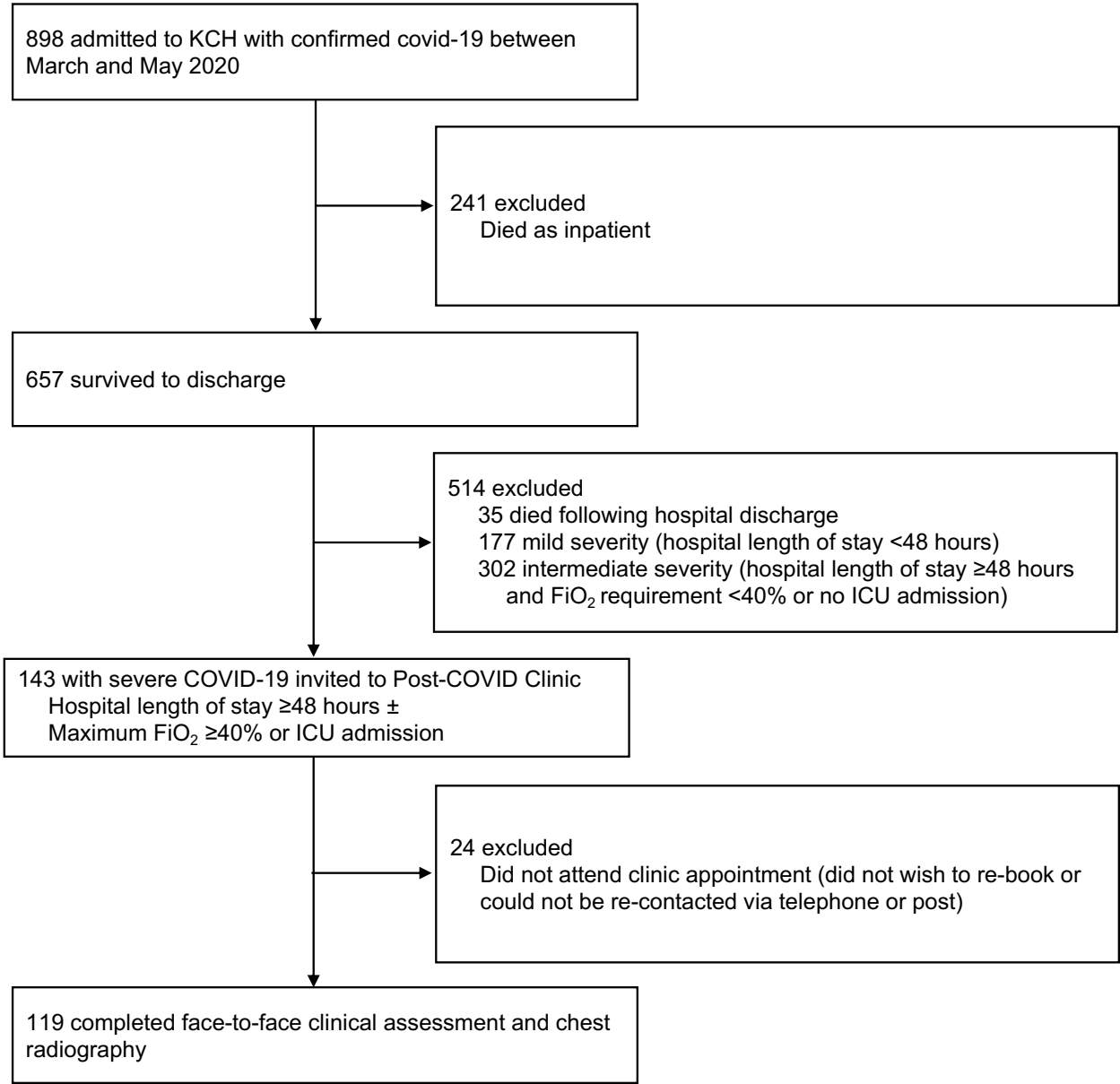

898 admitted to KCH with confirmed covid-19 between March and May 2020
241 excluded
Died as inpatient
657 survived to discharge
514 excluded
35 died following hospital discharge
177 mild severity (hospital length of stay <48 hours)
302 intermediate severity (hospital length of stay ≥48 hours and FiO_2 requirement <40% or no ICU admission)
143 with severe COVID-19 invited to Post-COVID Clinic
Hospital length of stay ≥48 hours ±
Maximum FiO_2 ≥40% or ICU admission
24 excluded
Did not attend clinic appointment (did not wish to re-book or could not be re-contacted via telephone or post)
119 completed face-to-face clinical assessment and chest radiography

Figure 2 Relationship between mMRC breathlessness scores and time from hospital discharge

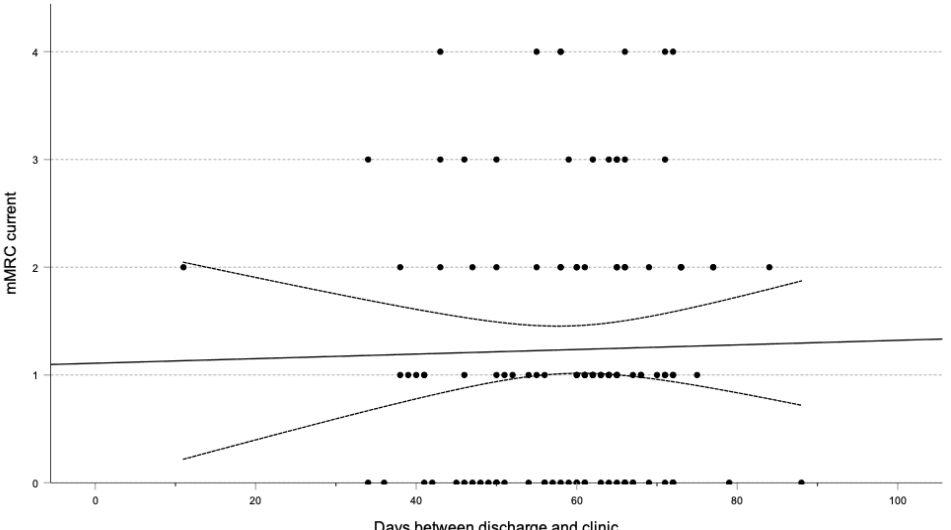
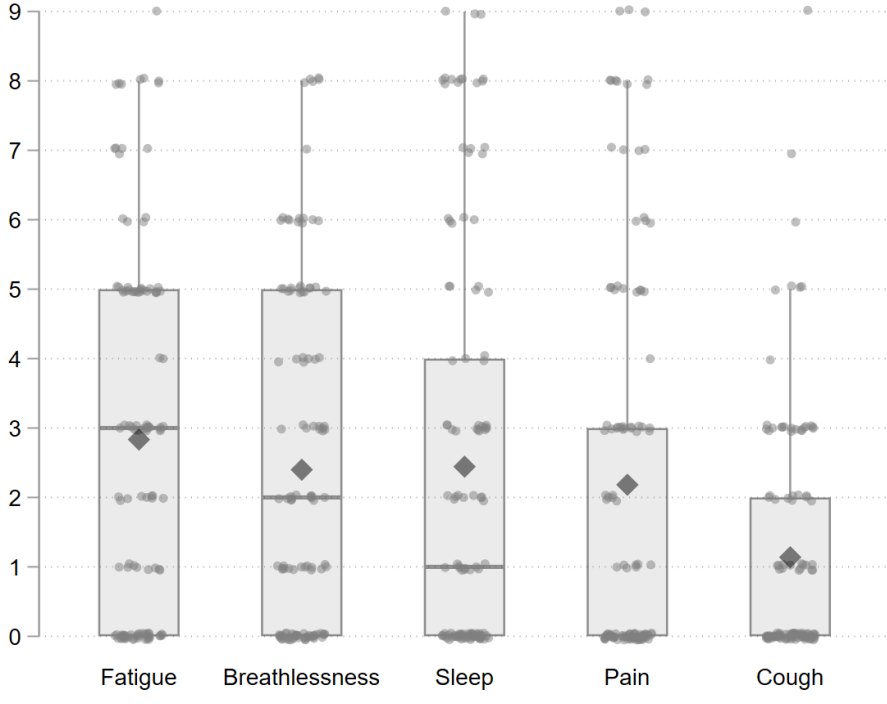


Figure 3 Box plots of persistent symptoms and mental health and neurocognitive outcomes. Plots in (A) illustrates numerical rating scores for fatigue, breathlessness, sleep, pain and cough. Plots in (B) depict scores for the PHQ-9 (Patient Health Questionnaire-9 for depression), GAD-7 (Generalised Anxiety Disorder assessment), Trauma Screening Questionnaire and 6-CIT (6-Item Cognitive Impairment Test).

(A)



(B)

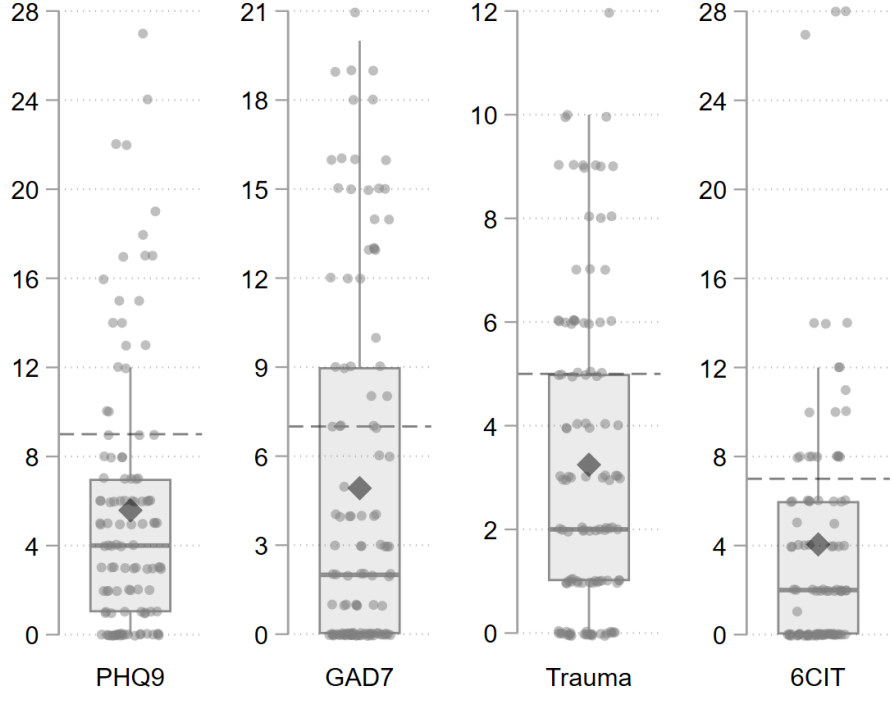
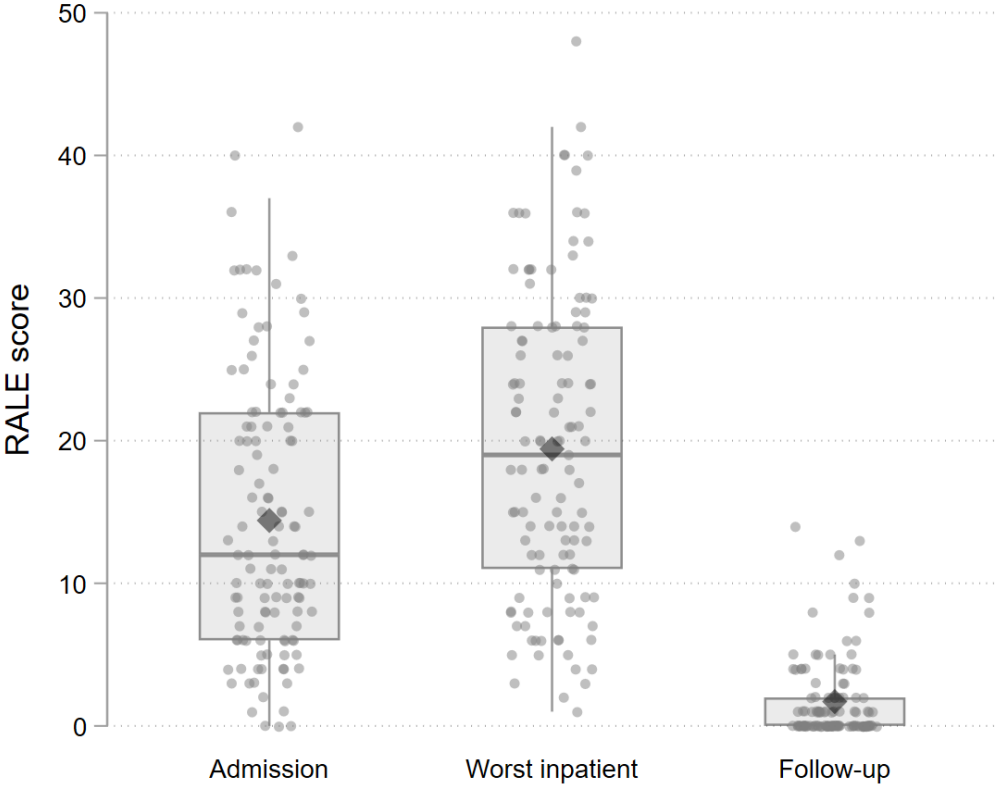


Figure 4 Radiographic Assessment of Lung Oedema scores at admission, worst during hospitalisation and follow-up.



Chest radiography is a poor predictor of respiratory symptoms and functional impairment in survivors of severe COVID-19 pneumonia

Supplementary material

Methods

Table S1 Assessment of clinical, radiological, patient-reported and physiological COVID-19 sequelae

	Tool	Highest score	Cut off score	Time to complete
Clinical outcomes				
COVID-19 complications, healthcare utilisation	Electronic medical records, patient interview, physical examination	-	-	15 minutes
Radiological outcomes				
Chest radiograph resolution	Radiographic Assessment of Lung Oedema (RALE) score	48	Lung infiltrates absent/minimal defined as 0-4	1 minute
Thoracic computed tomography	Multidisciplinary team discussion	-	-	
Patient-reported outcomes				
Breathlessness, cough, fatigue, pain, sleep	Numerical Rating Scale	10	≥1 present ≥4 burdensome	<1 minute each
Breathlessness-related functional disability	Modified MRC Dyspnoea Scale	5	>1	1 minute
Disease-specific functional impairment	Post-COVID Functional Scale	4	≥2	1 minute
Depression	PHQ-9	27	>9	<3 minutes
Anxiety	GAD-7	21	>9	2-5 minutes
Post-Traumatic Stress Disorder	Trauma Screening Questionnaire	10	≥6	3 minutes
Cognitive impairment	6-Item Cognitive Impairment Test	28	≥8	5 minutes
Physiological outcomes				
Resting vital observations	Temperature, heart rate, oxygen saturation, blood pressure	-	-	2 minutes
Functional exercise performance	4-minute gait speed 1-minute sit-to-stand	-	<0.8m/s <2.5 percentile Desaturation ≥4%	3-5 minutes each

Persistent breathlessness, cough, fatigue, pain and sleep disturbance were measured using the 11-point Numerical Rating Score (NRS) [1-4]. For each symptom, patients selected an integer between zero (not present) and 10 (unbearable) that best reflected the intensity of the symptom in the preceding 24 hours. Symptoms were categorised as being present (score of ≥1) and burdensome (score of ≥4). Current and pre-COVID functional impairment was quantified using the 5-point modified Medical Research Council (mMRC) Dyspnoea Scale [5]. The 16-point Nijmegen Questionnaire was used to screen for hyperventilation syndrome and dysfunctional breathing (cut off score of 23) [6].

Anxiety and depression screening was performed using the PHQ-9 and GAD-7 questionnaires, in which patients score 7 and 9 questions respectively between zero (not at all) to three ("nearly every day") using a cut-off score of >9 [7, 8]. The Trauma Screening Questionnaire was used to screen for post-traumatic stress disorder (PTSD), with patients asked to review 10 items and endorse those experienced at least twice in the preceding two weeks, using a cut off score of ≥6 [9]. The 6-Item Cognitive Impairment Test (6CIT) was used to screen for cognitive impairment [10]. The recently designed Post-COVID Functional Scale (PCFS) is a five-point scale used to reflect functional limitations during COVID-19 recovery and intended for use at 4-8 weeks and 6 months post-discharge [11].

Functional disability was objectively assessed using the 4-metre gait speed (4MGS) and 1-minute sit-to-stand (STS) test. Patients wore surgical masks continuously whilst on hospital premises, including during 4MGS and STS testing, thereby minimising aerosolisation of respiratory droplets. For the 4MGS, patients were timed whilst walking along an unobstructed 4-metre path at their usual speed, with their usual walking aids or oxygen if applicable, recording the fastest of two efforts and stratifying speeds as normal (≥0.8m/s) or slow (<0.8m/s). The 4MGS is a reliable and validated method of assessing exercise performance and frailty, and correlates with other tests of functional capacity, such as the incremental shuttle walk test, breathlessness and health-related quality of life (HRQoL) [12, 13]. For the STS, following a demonstration by the healthcare professional, patients were instructed to perform self-paced repetitions of sitting and standing from a chair for 1-minute. The number of repetitions, oxygen saturation and heart rate were recorded at baseline, end-exercise and during recovery, with repetitions categorised according to their percentile for age and sex [14]. The STS is a simple and highly reproducible measurement that correlates closely with other tests of functional capacity, including the 6-minute walk test (6MWT), and is predictive of mortality and HRQoL [15, 16]. Lung function testing was limited to urgent cases due to decontamination procedures required following this aerosol generating procedure [17].

Admission, worst inpatient and follow-up radiographs were graded using the Radiographic Assessment of Lung Oedema (RALE) score [18]. This involves review of consolidation and density of alveolar opacities in lung quadrants and produces a score between zero and 48. The RALE validation study was used to define radiological recovery as scores between 0 and 4 [18]. Patients with

persistent radiological abnormalities, respiratory symptoms or desaturation of ≥4% during the STS underwent thoracic computed tomography (CT).

Results

Table S2 Baseline characteristics of all patients hospitalised with severe COVID-19 pneumonia between 5th March and 28th May 2020, those surviving to discharge and those attending Post-COVID assessment. Analyses represent comparisons between patients surviving to discharge and those attending Post-COVID assessment.

	All admissions (n=898)	**Survived to discharge (n=657)**	**Post-COVID assessment (n=119)**	**Mean difference/ χ^2 (95% CI)**	**p-value**
Age (years)					
Median (IQR)/ Mean± SD	68 (55-81)	64 (52-80)	58.7 ± 14.4	-6.1 (-9.2 to -3.0)	<0.001
18-29	34 (3.8; 2.6-5.0)	33 (5.0; 3.5-6.7)	4 (3.4; 0.8-6.7)		
30-39	42 (4.7; 3.5-5.9)	41 (6.2; 4.5-8.0)	11 (9.2; 5.0-14.3)		
40-49	70 (7.8; 6.2-9.4)	60 (9.1; 7.1-11.2)	13 (10.9; 6.7-15.1)		
50-59	159 (17.7; 15.1-20.4)	132 (20.1; 16.9-23.3)	36 (30.3; 22.7-38.7)	28.6 (0.17-0.29)	<0.001
60-69	168 (18.7; 16.4-21.3)	124 (18.9; 16.2-21.8)	27 (22.7; 16.0-28.6)		
70-79	160 (17.8; 15.6-19.9)	100 (15.2; 12.2-18.0)	18 (15.1; 10.1-21.0)		
80+	265 (29.5; 26.5-32.6)	167 (25.4; 22.1-28.7)	10 (8.4; 5.0-12.6)		
Sex (%)					
Female	385 (42.9; 39.2-46.3)	302 (46.0; 41.9-50.0)	45 (37.8; 29.4-46.2)	3.89 (0.01 to 0.15)	0.049
Male	513 (57.1; 54.1-60.4)	355 (54.0; 50.4-57.7)	74 (62.2; 53.8-70.6)		
Ethnicity (%)†					
BAME (Yes/No)	459/825 (55.6; 52.6-58.8)	329/600 (54.8; 50.8-59.1)	83/119 (69.7; 61.3-78.2)	36.2 (0.17 to 0.32)	<0.001
White	319 (35.5; 32.4-38.5)	224 (34.1; 30.4-37.8)	36 (30.3; 22.6-37.8)		
Black	378 (42.1; 39.1-45.3)	284 (43.2; 39.6-47.3)	52 (43.7; 36.1-51.3)		
Asian	51 (5.7; 4.2-7.0)	34 (5.2; 3.7-6.7)	18 (15.1; 10.1-20.2)	45.6 (0.20 to 0.36)	<0.001
Mixed race	17 (1.9; 1.2-2.6)	12 (1.8; 0.9-2.8)	5 (4.2; 1.7-6.7)		
Other	60 (6.7; 5.2-8.1)	46 (7.0; 5.1-9.0)	8 (6.7; 3.4-10.9)		
Not specified	73 (8.1; 6.5-9.9)	57 (8.7; 6.6-10.6)	0 (0)		
Median (IQR) / Mean±SD Index of multiple deprivation score ‡	29 (20-34) (n=893)	28.5 (20-34) (n=652)	26.6 ± 9.7 (n=115)	-1.0 (-3.0 to 0.92)	0.30
Body Mass Index (kg/m^2)					
Median (IQR)	27.0 (22.7-32.0)	27.7 (23.5-32.8)	30.0 (25.9-35.2)	2.7 (1.0 to 4.3)	0.005
Underweight (<18.5)	42/565 (7.4; 5.7-9.6)	30/482 (6.8; 4.7-9.1)	0/118 (0.0)		
Normal (18.5-24.9)	171/565 (30.3; 27.1-33.3)	125/482 (25.9; 22.3-29.8)	22/118 (18.6; 12.7-24.6)		
Overweight (25-29.9)	165/565 (29.2; 25.4-33.1)	150/482 (31.1; 26.8-35.2)	35/118 (29.7; 22.9-37.3)		
Obese (30-34.9)	104/565 (18.4; 15.6-21.6)	93/482 (19.3; 15.9-22.5)	30/118 (25.4; 19.5-33.1)	24.9 (0.18 to 0.32)	<0.001
Severely obese (35-39.9)	38/565 (6.7; 5.1-8.8)	45/482 (9.3; 6.9-12.0)	20/118 (16.9; 11.0-22.0)		
Morbidly obese (40-49.9)	36/565 (6.4; 4.8-8.1)	32/482 (6.6; 4.7-8.9)	9/118 (7.6; 4.2-11.0)		
Super obese (50+)	9/565 (1.6; 0.9-2.3)	7/482 (1.5; 0.4-2.6)	2/118 (1.7; 0.0-4.2)		
Comorbidities					
Median (IQR) Charlson comorbidity index‡	3 (1-5)	3 (1-5)	2 (1-4)	0.92 (0.44-1.36)	0.001
Any cardiovascular disease	431/659 (65.4; 61.8-68.7)	294/478 (61.5; 57.4-65.8)	57/119 (47.9; 40.3-55.5)	12.4 (0.07 to 0.25)	<0.001
Hypertension	405/651 (62.2; 58.8-65.6)	276/471 (58.6; 54.1-63.5)	54/119 (45.4; 37.8-53.8)	11.5 (0.06 to 0.25)	0.001
Ischaemic heart disease/ Heart failure	190/658 (28.9; 25.1-32.7)	120 /477 (25.2; 21.3-29.0)	8/119 (6.7; 3.4-10.1)	28.6 (0.17 to 0.31)	<0.001
Diabetes	264/655 (40.3; 36.6-44.1)	180/475 (37.9; 33.4-42.3)	41/119 (34.5; 26.4-42.9)	0.80 (0.00 to 0.13)	0.37
Chronic respiratory disease	246/654 (37.6; 33.7-41.3)	165/474 (34.8; 30.8-39.0)	13/119 (10.9; 6.7-16.0)	39.9 (0.22 to 0.36)	<0.001
Malignancy	80/654 (12.2; 9.9-14.5)	53/474 (11.2; 8.4-14.0)	12/119 (10.1; 5.9-14.3)	0.19 (0.00 to 0.10)	0.66
Cerebrovascular disease	153/654 (23.4; 20.5-26.3)	101/464 (21.3; 17.6-24.8)	5/119 (4.2; 1.7-6.7)	27.7 (0.18 to 0.30)	<0.001

Abbreviations: IQR = interquartile range, SD = standard deviation, BAME = Black, Asian, minority ethnic, χ^2 = Chi-square, 95% CI = 95% confidence interval

Table S3 Baseline characteristics and inpatient clinical course of post-COVID patients assessed between 3rd June and 2nd July 2020 compared to those who did not attend their scheduled assessment.

	Attended Post-COVID assessment (n=119)	**Did not attend (n=24)**	**Mean difference/ χ^2 (95% CI)**	**p-value**
Age (years)				
Mean ± SD	58.7 ± 14.4	57.7 ± 18.4	1.02 (-5.90 to 7.95)	0.81
18-29	4 (3.4; 0.8-6.7)	2 (9.1; 0.0-25.0)		
30-39	11 (9.2; 5.0-14.3)	3 (13.6; 0.0-31.6)		
40-49	13 (10.9; 6.7-15.1)	1 (4.7; 0.0-16.7)		
50-59	36 (30.3; 22.7-38.7)	6 (27.3; 8.3-47.6)	2.90 (0.12 to 0.40)	0.82
60-69	27 (22.7; 16.0-28.6)	4 (18.2; 3.7-35.7)		
70-79	18 (15.1; 10.1-21.0)	4 (18.2; 4.0-35.7)		
80+	10 (8.4; 5.0-12.6)	2 (9.1; 0.0-23.5)		
Sex (%)				
Female	45 (37.8; 29.4-46.2)	8 (33.3; 15.4-52.9)	0.17 (-0.14 to 0.20)	0.68
Male	74 (62.2; 53.8-70.6)	16 (66.7; 47.1-84.6)		
Comorbidities				
Cardiovascular disease	63 (52.9; 44.5-61.8)	3 (13.0; 0.0-29.4)	1.08 (-0.10 to 0.29)	0.30
Diabetes	41 (34.5; 26.4-42.9)	6 (26.1; 8.7-45.4)	0.61 (-0.22 to 0.09)	0.44
Obstructive lung disease	13 (10.9; 6.7-16.0)	3 (13.0; 0.0-30.0)	0.09 (-0.13 to 0.21)	0.77
Solid cancer	9 (7.6; 3.3-12.6)	1 (4.3; 0.0-14.3)	0.30 (-0.14 to 0.13)	0.58
Cerebrovascular disease	5 (4.2; 1.7-6.7)	5 (21.7; 5.3-40.0)	9.06 (0.02 to 0.49)	0.003
End stage renal failure	8 (6.7; 3.4-10.1)	2 (8.7; 0.0-21.4)	0.12 (-0.12 to 0.23)	0.74
Immunosuppressed	16 (13.4; 8.4-18.5)	4 (17.4; 3.4-33.3)	0.25 (-0.13 to 0.22)	0.62

Table S4 Additional inpatient complications

	Number (%)
Cardiac	
Fast atrial fibrillation	3 (2.5)
Myocarditis	2 (1.7)
Acutely impaired left ventricular function	2 (1.7)
Respiratory	
Pneumothorax	2 (1.7)
Pneumomediastinum	1 (0.8)
Haematological	
Venous thromboembolism	27 (22.7)
Pulmonary embolism	23 (19.3)
Deep vein thrombosis	6 (5.0)
Endocrine	
Hyperglycaemia	2 (1.7)
Diabetic ketoacidosis	1 (0.8)
New type 1 diabetes	1 (0.8)
Acute hyperthyroidism	1 (0.8)
Neurological	
Delirium	18 (15.1)
Subarachnoid haemorrhage	1 (0.8)
Intraparenchymal haemorrhage	1 (0.8)
Other	
Acute kidney injury	41 (34.5)
Deranged liver function tests	17 (14.3)
Neutropenic sepsis	1 (0.8)
Angioedema	1 (0.8)
Psoas haematoma	1 (0.8)
Sickle crisis requiring exchange transfusion	1 (0.8)
Upper gastrointestinal bleed	1 (0.8)

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