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Lung Function Deficits and Symptom Burden in Survivors of COVID-19 Requiring Mechanical Ventilation

To the Editor:

Recent studies reporting the clinical sequelae of hospitalized patients recovering from coronavirus disease (COVID-19) have included limited data (especially regarding lung function) for survivors who required invasive mechanical ventilation (1–6). As a group who was among the most critically ill and whose recovery may be influenced by the post–intensive care syndrome, we hypothesized that their short-term sequelae would include physiological, radiographic, and exercise impairment as well as high symptom burden.

We conducted an observational study that analyzed clinical data collected prospectively for routine care. Eligible patients were laboratory-confirmed swab positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), mechanically ventilated for a minimum of 72 hours in the Royal Brompton Hospital Adult Intensive Care Units, and discharged to home or a rehabilitation care facility. Admission dates ranged from March 13, 2020, to May 21, 2020, and patients were discharged between March 30, 2020, and July 20, 2020.

Of 52 consecutive patients fulfilling the inclusion criteria, 50 attended a multidisciplinary clinic 6 weeks after discharge. Spirometry, diffusing capacity, and plain chest radiography were performed. Physical functioning and exercise-induced oxygen desaturation were assessed using the 6-minute-step test (6MST) (7). We collected patient self-reported symptoms and information from the following validated questionnaires: Global Rating of Change Questionnaire (range: −5 "very much worse" to +5 "very much better") to assess overall change from discharge, the Medical Research Council (MRC) dyspnea scale to assess respiratory disability, the Numerical Rating Scale (NRS) to assess breathlessness, the Chalder Fatigue Scale (CFS) to assess fatigue, health related quality of life (EQ-5D-5L) to assess health-related quality of life, the Generalized Anxiety Disorder-7 (GAD-7) to assess anxiety, the Patient Health Questionnaire-9 (PHQ-9) to assess depression, the Trauma Screening Questionnaire to assess post-traumatic stress, and the Six-item Cognitive Impairment Test to assess cognition. We used previously defined thresholds for these questionnaires to assess the proportion with significant symptom burden.

Patient demographics and postdischarge clinical outcomes at 6 weeks can be found in Tables 1 and 2. Of note, 80% were male, 84% were of Black Asian Minority Ethnicity, and median (interquartile range) duration of mechanical ventilation was 15.5 (12–20) days and length of hospital stay was 38 (28–51) days. Twenty-four percent of patients received extracorporeal membrane oxygenation (ECMO), while prone positioning was performed in 60% of patients. Intravenous corticosteroids were administered to 34% of patients, and 42% of patients had radiologically confirmed thromboembolic disease during their hospital admission. Follow-up occurred at a mean 44 days after hospital discharge.

Lung function results of 47 patients who completed technically acceptable laboratory testing are presented in Table 2. Abnormal results were defined as below lower limit of normal (standardized residual [SR] threshold of less than −1.645) (8). One hundred percent had abnormally low diffusing capacity of the lung for carbon monoxide (D_{LCO}), 55% low transfer coefficient for carbon monoxide (KCO), 44% low forced vital capacity (FVC), and 28% low forced expiratory volume in 1 second. Length of hospital stay and mechanical ventilation were associated with FVC SR ($r = -0.698$ and -0.492, respectively; both $P < 0.001$) and with D_{LCO} SR ($r = -0.398$ and -0.344; $P = 0.007$ and 0.027, respectively).

Compared with predischarge imaging, follow-up radiography showed improvement in 90% of cases; however, residual radiographic abnormalities were still evident in 64% of cases. Patients with an abnormal chest radiograph had significantly lower mean FVC (SR −1.689 vs. −0.9706; $P = 0.025$), lower mean 6MST (76.5 vs. 128.5; $P = 0.005$), and higher median MRC dyspnea score (3 vs. 2; $P = 0.020$) than those with a normal chest radiograph.

No significant differences in lung function parameters or proportion with abnormal chest radiograph were observed at 6 weeks

Table 1. Patient demographics and hospital admission details

Baseline Demographics	Patients (*n* = 50)
Age, median (IQR), yr	54.50 (44.25–59.00)
Sex, male:female, %	80:20
Ethnicity, % Black, Asian, Minority Ethnic	84
Ethnicity, % Asian	52
Body mass index, kg/m^2	29.78 (5.59)
Smoking status, % current or past history	28
Diabetes mellitus, %	22
Hypertension, %	34
Asthma/COPD, %	10
Receiving immunosuppression, %	2
Hospital Admission	
Overall duration, median (IQR), d	38 (21.25–50.25)
Duration of mechanical ventilation, median (IQR), d	15.50 (12.00–20.00)
Extracorporeal membrane oxygenation, %	24
Prone positioning, %	60
Intravenous steroids, %	34
Tracheostomy, %	54
Radiologically confirmed pulmonary embolism, %	32
Radiologically confirmed deep vein thrombosis, %	22

Definition of abbreviations: COPD = chronic obstructive pulmonary disease; COVID-19 = coronavirus disease; IQR = interquartile range. Baseline demographics and summary of hospital admission for patients admitted with severe COVID-19 requiring mechanical ventilation at the Royal Brompton Hospital.

Table 2. Summary of lung function parameters, functional assessment, self-reported symptoms, and proportion of patients reaching case threshold for patient-reported outcome measures

Patient-reported Outcome Measures and Lung Function Parameters (*n* = 47)	Patients
FEV_1, L	2.52 (0.77)
FEV_1, % predicted	82.54 (19.22)
FEV_1, standardized residuals	−0.97 (0.96)
FVC, L	2.86 (0.91)
FVC, % predicted	77.23 (16.10)
FVC, standardized residuals	−1.43 (1.07)
FEV_1/FVC ratio	0.88 (0.05)
D_{LCO}, mmol/min/kPa	4.88 (1.71)
D_{LCO}, % predicted	51.32 (13.06)
D_{LCO}, standardized residuals	−3.28 (0.86)
K_{CO}, mmol/min/kPa	1.28 (0.24)
K_{CO}, % predicted	75.70 (14.05)
K_{CO}, standardized residuals	−1.72 (1.18)
Functional Assessment (*n* = 45)	
6-minute-step test, steps	85.5 (38.6)
Oxygen saturations nadir, %	93.93 (3.48)
Proportion with significant exercise-induced oxygen desaturation, %	9
Patient-reported Outcomes (*n* = 50), %	
Proportion GRCQ ⩾3	80
Proportion MRC ⩾3	46
Proportion NRS ⩾4	34
Chalder fatigue proportion with ⩾4 items	72
Proportion GAD-7 ⩾8	30
Proportion PHQ-9 ⩾10	26
Proportion TSQ ⩾6	14
Self-reported Symptoms, %	
Fatigue	84
Breathlessness	80
Cough	20
Muscle weakness	70
Joint pain	54
Fever	0
Hemoptysis	0
Loss of sense or smell	16
Low mood	10
Anxiety	14
Insomnia	20

Definition of abbreviations: D_{LCO} = diffusing capacity of the lung for carbon monoxide; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GAD-7 = Generalized Anxiety Disorder Questionnaire; GRCQ = Global Rating of Change Questionnaire; K_{CO} = transfer coefficient for carbon monoxide; MRC = Medical Research Council dyspnea scale; NRS = Breathlessness Numerical Rating Scale; PHQ-9 = Patient Health Questionnaire-9; TSQ = Trauma Screening Questionnaire.
For lung function parameters and functional assessment outcome, data are expressed as mean (standard deviation) unless otherwise stated. For patient-reported outcomes and self-reported symptoms, data are expressed as the proportion of patients reaching the case threshold.

after discharge between those who did or did not receive ECMO or between those with or without secondary bacterial pneumonia. Radiologically confirmed pulmonary embolism was associated with reduced mean FVC SR (−1.908 vs. −1.175; $P = 0.022$) and D_{LCO} SR (−3.654 vs. −3.077; $P = 0.029$) compared with those without pulmonary embolism.

6MST was completed in 45 patients. Mean (standard deviation) 6MST was 86 (39) steps with four patients (9%) showing significant exercise-induced oxygen desaturation (fall ⩾4% to a nadir below 90%). Based on data from healthy individuals (7), 98% of our cohort had a 6MST below the 95% confidence interval.

Eighty percent of patients reported at least good recovery (Global Rating of Change Questionnaire ⩾3) from hospital discharge, with 16% and 10% returning to work and driving, respectively. The most frequent self-reported symptoms were fatigue (84%), dyspnea (80%), muscle weakness (70%), joint pain (especially shoulder) (54%), and cough (20%). Thirty-four percent screened positive for burdensome breathlessness (NRS ⩾4), 46% for significant respiratory disability (MRC ⩾3), 72% for fatigue (CFS ⩾4 items), 30% for anxiety (GAD-7 ⩾8), 26% for depression (PHQ-9 ⩾10), and 14% for post-traumatic stress (TSC ⩾6), and 66% reported at least a moderate problem in one or more EQ-5D-5L dimensions. All had a normal Six-item Cognitive Impairment Test score.

1 shows a correlation matrix heatmap demonstrating the strength and direction of relationship between lung function tests, 6MST, and patient-reported outcomes. FVC SR correlated significantly with MRC ($r = -0.330$; $P = 0.023$), 6MST ($r = 0.439$; $P = 0.028$), and lowest oxygen saturations during exercise ($r = 0.496$; $P = 0.011$) but not with other patient-reported outcomes. D_{LCO} correlated significantly with MRC ($r = -0.298$; $P = 0.050$); 6MST ($r = 0.457$; $P = 0.033$) and lowest oxygen saturations during exercise ($r = 0.398$; $P = 0.015$).

Health-related quality of life, as measured by the EQ-5D-5L Utility Score and Visual Analog Score, showed moderate to strong correlations with respiratory symptoms (MRC, NRS), psychological outcomes (GAD-7, PHQ-9, Trauma Screening Questionnaire), and CFS (Figure 1).

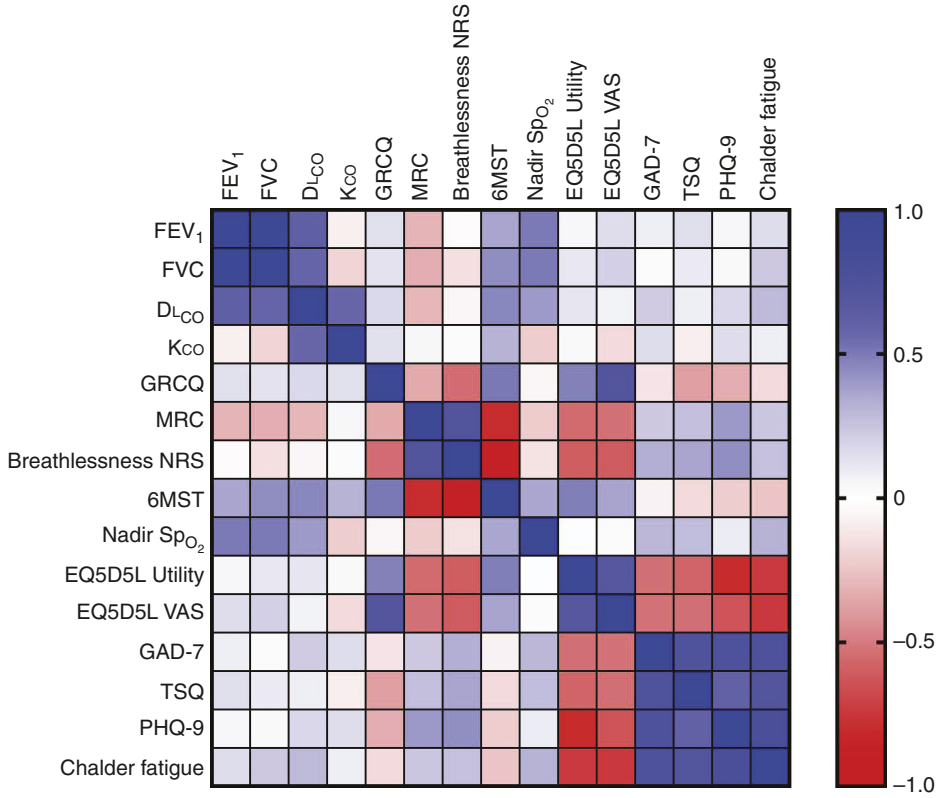

Figure 1. Correlation matrix heatmap showing strength and direction of relationship between lung function tests and patient-reported outcomes. Lung function parameters were normalized to standardized residuals. 6MST = 6-minute-step test; Breathlessness NRS = "Worst" breathlessness in last 24 hours Numerical Rating Scale; Chalder fatigue = Chalder Fatigue Scale; D_{LCO} = diffusing capacity of the lung for carbon monoxide; EQ5D5L = 5-level ED-5D version; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; GAD-7 = General Anxiety Disorder-7; GRCQ = Global Rating of Change Questionnaire; K_{CO} = transfer coefficient for carbon monoxide; MRC = Medical Research Council dyspnea scale; Nadir Sp_{O_2} = lowest oxygen saturations as measured by pulse oximetry during exercise test; PHQ-9 = Patient Health Questionnaire-9; TSQ = Trauma Screening Questionnaire; VAS = visual analogue scale.

To our knowledge, this is the first report of outcomes in a specific cohort of survivors of COVID-19 who received invasive mechanical ventilation during their acute illness. We comprehensively characterized our cohort with lung function evaluation, chest radiography, functional exercise testing, and a broad range of validated symptom questionnaires to assess physical and psychological functioning.

Emerging reports of short-term sequelae in survivors of COVID-19 have focused largely on hospitalized patients who were not mechanically ventilated; for example, recent Italian and UK cohorts included a minimal number of such patients ($n = 7$ and $n = 1$, respectively) (1, 2). Similarly, the few studies that have measured lung function following hospitalization for COVID-19 have either completely excluded or comprised very few individuals who were mechanically ventilated (3, 5, 6).

All patients in our cohort demonstrated evidence of impaired gas transfer 6 weeks after leaving the hospital, 44% of whom had concomitantly decreased FVC. These deficits were far more severe than in previous reports of survivors of COVID-19 (3, 5, 6), reflecting the constitution of our patients who required mechanical ventilation for severe acute respiratory failure, 25% of whom received ECMO. However, lung function deficits in our cohort (measured at 6 wk after discharge) were comparable to those observed in non–COVID-19 acute respiratory distress syndrome (ARDS) at 3 months (9). Further longitudinal studies are required to compare the trajectory of recovery in patients with severe COVID-19 and those with non–COVID-19–related ARDS.

In view of persisting chest radiographic abnormalities, we hypothesize that most of the gas transfer perturbation may be explained by residual parenchymal abnormalities secondary to ARDS and/or post–COVID-19 interstitial lung abnormalities. However, gas transfer deficits were evident despite normal chest radiography in a third of the cohort, suggesting the possibility of perfusion-associated impairment caused by pulmonary angiopathy (10). There were only weak to moderate correlations between lung function and MRC, and there was no significant association between lung function and other patient-reported outcomes, suggesting that extrapulmonary manifestations are important contributors to symptom burden.

Despite 80% and 90% of our cohort reporting interval symptom improvement and showing radiographic improvement, respectively, there remained a high prevalence of lung function deficits, functional impairment, and significant symptomatology. The most prominent symptoms were fatigue and breathlessness, in line with previous reports in COVID-19 (1, 2). Muscle weakness and joint pain were also frequently reported in our cohort, perhaps reflecting the effects of post–intensive care syndrome, as observed in survivors of

non–COVID-19 ARDS (11). Half of our cohort complained of shoulder pain. This warrants further investigation, given that 60% of our cohort underwent prone positioning during their hospital admission.

In summary, we report a high prevalence of lung function and functional impairment as well as substantial symptom burden in survivors of severe COVID-19 requiring mechanical ventilation. Detailed longitudinal studies are required to document the recovery trajectory of this group of individuals. ■

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Telemedicine-enabled, Hotel-based Management of Patients with COVID-19: A Single-Center Feasibility Study

To the Editor:

The dramatic spread of the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) pandemic in the first half of 2020 demanded a significant readjustment of healthcare organization to deal with the massive wave of patients with coronavirus disease (COVID-19) (1, 2). Healthcare resources were exploited not only by patients who were severely ill but also by those who were still contagious after clinical recovery and could not be discharged at home. As such, it became pivotal to develop innovative management strategies to unload hospitals while reducing the risk of SARS-CoV-2 transmission among family members of infected patients who could not ensure effective domiciliary isolation.

Between April and May 2020, a novel framework consisting in a telemedicine-enabled hotel facility was implemented by the Fondazione Policlinico Universitario A. Gemelli IRCCS in Rome, Italy. The scope was to provide adequate isolation for clinically stable patients with COVID-19 while ensuring clinical safety (3). We assessed the feasibility and safety of this management approach.

Consecutive patients with COVID-19 discharged from the emergency care or the COVID-19 units of our hospital were referred to the hospital facility if they were unable to comply with self-isolation measures at home. Eligibility criteria for study participation included a COVID-19 diagnosis (requiring a positive real-time reverse transcriptase–polymerase chain reaction [RT-PCR] nasopharyngeal swab test), self-sufficiency, ability to use a smartphone (as reported by the patient), and persistence of SARS-CoV-2 infection via RT-PCR at the time of hospital discharge. Clinical stability at the time of hospital discharge was also required, as defined by arterial oxygen tension/pressure ⩾60 mm Hg in room air, absence of fever, and no need for intravenous therapies. Institutional