A prospective study of 12-week respiratory outcomes in COVID-19-related hospitalisations

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ABSTRACT

The long-term respiratory morbidity of COVID-19 remains unclear. We describe the clinical, radiological and pulmonary function abnormalities that persist in previously hospitalised patients assessed 12 weeks after COVID-19 symptom onset, and identify clinical predictors of respiratory outcomes. At least one pulmonary function variable was abnormal in 58% of patients and 88% had abnormal imaging on chest CT. There was strong association between days on oxygen supplementation during the acute phase of COVID-19 and both DLCO-% (diffusion capacity of the lung for carbon monoxide) predicted and total CT score. These findings highlight the need to develop treatment strategies and the importance of long-term respiratory follow-up after hospitalisation for COVID-19.

INTRODUCTION

Despite the explosion of peer-reviewed literature on COVID-19, few studies describe the long-term health outcomes in COVID-19 survivors.[1–5] Understanding long-term respiratory outcomes, and in particular the clinical predictors of poor respiratory outcomes, will direct evidence-based management of post-COVID respiratory care, resource allocation and health system planning. This is a critical knowledge gap in the subgroup of patients hospitalised with more severe forms of COVID-19 respiratory illness. In this report, we describe the clinical features, pulmonary function abnormalities and radiological outcomes in patients assessed 12 weeks after symptom onset in a prospective cohort of patients hospitalised for COVID-19 in Vancouver, Canada. We also examine clinical predictors of persistent dyspnoea, reduced lung function, and radiological abnormalities.

METHODS

This is a prospective consecutive cohort of adults with COVID-19 hospitalised from March to May 2020 with laboratory-confirmed SARS-CoV-2 infection. Patients were assessed 12 weeks following symptom onset (permitted range 8–12 weeks) and underwent a standardised set of questionnaires and investigations. Investigations included detailed pulmonary function testing (PFT), 6 min walk test (6MWT) and high-resolution CT of the chest.[6] PFT variables with values <80% predicted were considered abnormal.

The co-primary outcomes were dyspnoea and diffusion capacity of the lung for carbon monoxide (DLCO), each measured 12 weeks after symptom onset.[7] The secondary outcome was the total CT score 12 weeks after symptom onset.[8] We used days on oxygen supplementation as a proxy for disease severity. Associations of this predictor variable with primary and secondary outcomes were determined using multivariable linear regression models. We constructed four models that would support risk stratification of patients at discharge and at follow-up. Models 1–3 tested association between duration of oxygen supplementation with UCSD dyspnoea score, DLCO and total CT score respectively, with model 1 also adjusted for body mass index (BMI) given the high risk of BMI confounding associations with dyspnoea. Model 4 aimed to determine whether UCSD dyspnoea score at follow-up could help inform decisions on further investigations. Variables adjusted for in each model are presented in table 1. A two-sided p value <0.05 was considered to be statistically significant.

RESULTS

Enrolment is shown in online supplemental figure S1, with demographics and baseline characteristics in online supplemental table S1 for the 60 included patients. Median age was 67 years (IQR 54–74) and 68% were male. Dyspnoea was the most common symptom at presentation to hospital (77% of patients).

PFT abnormalities at follow up

Mean duration from symptom onset to follow-up assessment was 11.7 weeks. Symptoms and lung function at follow-up are provided in table 2 and figure 1. A minority of patients reported dyspnoea and cough. At least one PFT variable was abnormal in 58% of patients. An abnormal DLCO was present in 52% of patients, with 45% of these patients also having an abnormal total lung capacity indicating a concurrent restrictive ventilatory deficit. Airflow obstruction, defined as FEV_1/FVC <0.70, was present in 11% of patients. Four patients (7%) had SpO_2 ≤88% at the end of a 6MWT, and all of these had an abnormal DLCO.

The majority of patients (55%) had >10% of lung volume affected by either ground glass or reticulation. These patients accounted for a predominant proportion of total patients who warranted mechanical ventilation (67%) and oxygen supplementation (65%). Ground glass abnormality was more common than reticulation (figure 1), with 83% of patients having ground glass, 65% reticulation and only 12% with neither imaging abnormality.

Table 1 Predictors of dyspnoea severity, abnormal DLCO and CT abnormalities 12 weeks after symptom onset

			Unadjusted analysis			Adjusted analysis			
Model	Outcome (at 12 weeks)	Primary predictor	Coefficient	95% CI	P value	Coefficient	95% CI	P value	Prespecified covariates
1	UCSD*	Days on oxygen supplementation	0.17	−0.19 to 0.52	0.35	0.19	−0.17 to 0.55	0.29	Sex, age, BMI
2	DLCO %-predicted	Days on oxygen supplementation	−0.49	−0.83 to −0.15	0.01	−0.44	−0.77 to −0.11	0.01	Sex, age
3	Total CT score (extent of reticulation+ground glass)†	Days on oxygen supplementation	0.81	0.56 to 1.07	<0.001	0.77	0.52 to 1.02	<0.001	Sex, age
4	DLCO %-predicted	UCSD at 12 weeks	−0.46	−0.73 to −0.18	0.002	−0.39	−0.65 to −0.13	0.005	Sex, age, days on oxygen

Models 1–3 test the association of the outcome variable with the primary predictor variables that were available at the time of hospital discharge. Model 4 tests the association of the outcome variable with data that were available postdischarge in outpatient setting.
*UCSD: higher score represents worse dyspnoea (range 0–120).
†HRCT scores were determined by separating each lung into three zones and determining the per cent of lung affected by either ground glass or reticulation. The average scores from the six zones were then used to determine the total reticulation and ground glass scores for each patient, with the sum of these used to determine the total HRCT score.
BMI, body mass index; DLCO, diffusion capacity of the lung for carbon monoxide; HRCT, high-resolution CT; UCSD, University of California San Diego shortness of breath questionnaire.

Prediction of persistent dyspnoea, lung function deficits and CT abnormalities

Results of the multivariable analysis testing potential predictors of pulmonary outcomes are presented in table 1. The number of days on oxygen supplementation during the acute phase of COVID-19 was not associated with dyspnoea score at follow-up, but was associated with both DLCO %-predicted and total CT score. These findings remained consistent after adjustment for prespecified covariates. Using follow-up dyspnoea score as the primary predictor variable, there was a similarly strong association of dyspnoea severity with DLCO %-predicted.

Table 2 Respiratory outcomes 12 weeks after symptom onset

	Value
Subjects	**60**
Symptoms	
Dyspnoea (present/absent)*	12 (20%)
UCSD dyspnoea score (n=59)	11 (3–26)
Cough (present/absent)	12 (20%)
Cough VAS, mm (n=58)	10 (5–47)
Pulmonary function tests (n=57)	
FVC %-predicted	94±16
FEV_1 %-predicted	93±16
FEV_1/FVC	0.90±0.13
TLC %-predicted	86±13
RV %-predicted	85±19
DLCO %-predicted	77±16
6 min walk test	
Baseline SpO_2 (%)	98 (96–99)
End of test SpO_2 (%)	97 (94–99)
6MWD %-predicted	96±16
6MWD (m)	504±107
High-resolution CT	
Ground glass score	7 (2–16)
Reticulation score	2 (0–8)
Total ground glass+reticulation score†	13 (3–25)

Data are shown as n (%), median (IQR) or mean±SD.
*Dyspnoea was presented as a dichotomous (presence/absent) response, with no specified reference to their symptoms before COVID-19.
†The total ground glass+reticulation score median value is greater than the sum of the individual medians for these variables.
DLCO, diffusion capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in one second; FVC, forced vital capacity; 6MWD, 6-minute walk distance; RV, residual volume; SpO_2, oxygen saturation by pulse oximetry; TLC, total lung capacity; UCSD, University of California San Diego shortness of breath questionnaire; VAS, Visual Analogue Scale.

DISCUSSION

This prospective cohort demonstrates that more than half of people hospitalised for COVID-19 have lung function and chest imaging abnormalities 12 weeks after symptom onset. Abnormal DLCO and ground glass opacity on CT chest were the most frequent abnormalities at follow-up and were associated with duration of oxygen supplementation. Our cohort extends findings of existing studies by confirming that a substantial proportion of patients have lung function and chest imaging abnormalities 12 weeks after symptom onset.[3–5] Extrapolating from the SARS and MERS literature, it is likely that a substantial percentage of these patients will continue to have chronic abnormalities.[9]

There exists a knowledge gap in understanding which patients with COVID-19 are more likely to develop long-term consequences of this disease. We show that duration of oxygen supplementation, a routinely captured clinical datapoint, can be used as a proxy for disease severity and aid prioritisation of investigations on discharge. Based on our data, dyspnoea severity measured 12 weeks after symptom onset may also help guide further testing.

The prospective enrolment of patients enabled us to study the symptoms, pulmonary physiology and imaging abnormalities in a standardised fashion. Despite these strengths, our findings are limited by the small sample size and exclusion of 25 patients who were unable to be assessed or unwilling to participate in the study. A small proportion of patients in our cohort required invasive mechanical ventilation which may result in underestimates of the long-term consequence of COVID-19 compared with more severe cohorts. Multivariable models did not adjust for co-existing medical comorbidities and differences in therapies that can impact estimates of associations, but this is unlikely to impact the value of oxygen supplementation as a predictor of persistent impairment. Lastly, we did not

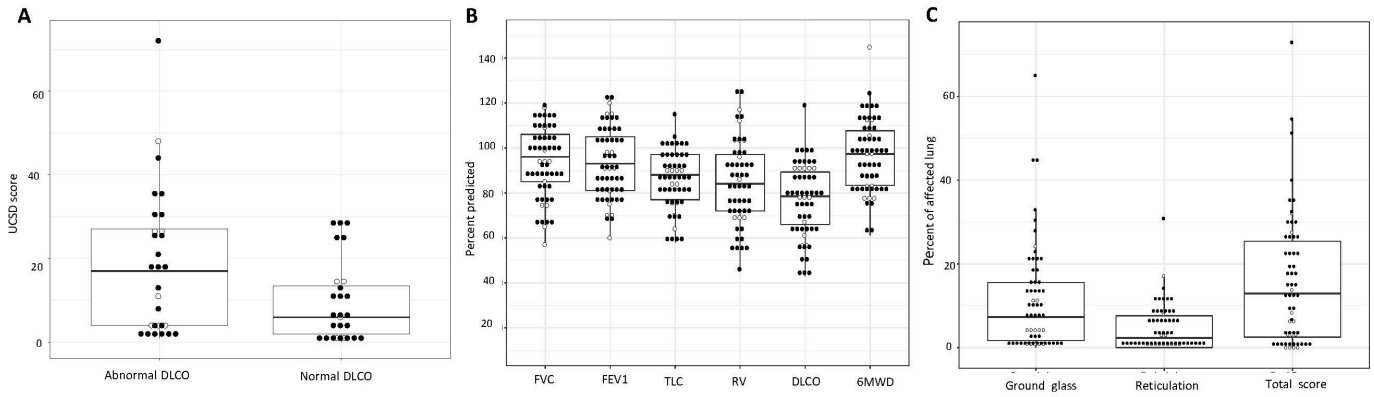

Figure 1 Respiratory outcomes 12 weeks after symptom onset of hospitalised patients with COVID-19. Box plots represent median and IQR for per cent (%)-predicted values. Each circle represents a patient who required (black circle) or did not require (white circle) supplemental oxygen during hospitalisation. (A) UCSD dyspnoea score 12 weeks after symptom onset of COVID-19, stratified by the DLCO %-predicted (DLCO <80% predicted considered abnormal). (B) Pulmonary function measurements and 6 min walk distance 12 weeks after symptom onset of COVID-19. (C) Percentage of lung affected by ground glass and reticulation 12 weeks after symptom onset of COVID-19. The total score is the sum of ground glass and reticulation scores. 6MWD, 6 min walk distance; DLCO, diffusing capacity of the lung for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; RV, residual volume; TLC, total lung capacity; UCSD, University of California San Diego Shortness of Breath Questionnaire.

have PFT or CT results prior to COVID-19 that would enable longitudinal assessment of impact of COVID-19; however, a minority of our patients were ever-smokers or had known pre-existing pulmonary disease.

Our findings identify that even minimally symptomatic people may have objective abnormalities postrecovery from acute COVID-19 and stress the importance of preventative strategies to mitigate spread of COVID-19. We further provide the initial evidence base to direct further studies that will enable prompt and appropriate referrals for investigations and specialty care.

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