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.1-3 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.4 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.5 The secondary outcome was the total CT score 12 weeks after symptom onset.6 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 FEV1/FVC <0.70, was present in 11% of patients. Four patients (7%) had SpO2 <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.

Prediction of persistent dyspnoea, lung function deficits and CT abnormalities
Results of the multivariable analysis testing potential predictors of pulmonary outcomes are


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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.

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.1-5 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 have PFT or CT results prior to COVID-19 that would enable longitudinal assessment of impact of COVID-19; however, a

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

<table>
<thead>
<tr>
<th>Model</th>
<th>Outcome (at 12 weeks)</th>
<th>Primary predictor</th>
<th>Unadjusted analysis</th>
<th>Adjusted analysis</th>
<th>Prespecified covariates</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>UCSD*</td>
<td>Days on oxygen supplementation</td>
<td>0.17</td>
<td>0.17 to 0.52</td>
<td>0.35</td>
</tr>
<tr>
<td>2</td>
<td>DLCO %-predicted</td>
<td>Days on oxygen supplementation</td>
<td>-0.49</td>
<td>-0.83 to -0.15</td>
<td>0.01</td>
</tr>
<tr>
<td>3</td>
<td>Total CT score (extent of reticulation+ground glass)†</td>
<td>Days on oxygen supplementation</td>
<td>0.81</td>
<td>0.56 to 1.07</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>4</td>
<td>DLCO %-predicted</td>
<td>UCSD at 12 weeks</td>
<td>-0.46</td>
<td>-0.73 to -0.18</td>
<td>0.002</td>
</tr>
</tbody>
</table>

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 dyspnoea score (n=59) 11 (3–26)

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

FEV1 %-predicted 93±16

FEV1/FVC 0.90±0.13

TLC %-predicted 86±13

RV %-predicted 85±19

DLCO %-predicted 77±16

6min walk test

Baseline SpO2 (%) 98 (96–99)

End of test SpO2 (%) 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. 

† The total ground glass+reticulation score median value is greater than the sum of the individual medians for these variables.
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 post-recovery 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.

Contributors AS and AW are co-first authors and contributed equally to this work. JJ, CC, and CJR are co-senior authors and contributed equally to this work. AS, AW, CC, CJR, and JJ contributed to study design, data analysis, data interpretation and writing of the manuscript. CH and DM provided chest CT interpretations and contributed to data interpretation and writing of the manuscript. All authors read and approved the final version of the manuscript. All authors had full access to the data in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis. 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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Data availability statement The supplementary index provides Table S1 and Figure S1. Relevant raw data available on reasonable request.

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REFERENCES
**Supplement**

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Figure S1. Study cohort flow diagram

85 referrals received within enrolment window

16 excluded
3 deceased
6 declined appointment
7 unable to reach

69 patients assessed in clinic
12 weeks after symptom onset

9 excluded
5 Telehealth appointment only
4 declined consent

60 patients included in analysis
(57 with pulmonary function tests)
Table S1: Baseline characteristics and course in hospital.

<table>
<thead>
<tr>
<th>Characteristics</th>
<th>Values</th>
</tr>
</thead>
<tbody>
<tr>
<td>Subjects</td>
<td>60</td>
</tr>
<tr>
<td>Age, years</td>
<td>67 (54 - 74)</td>
</tr>
<tr>
<td>Male</td>
<td>41 (68%)</td>
</tr>
<tr>
<td>Body mass index, kg/m²</td>
<td>25 (23 - 29)</td>
</tr>
<tr>
<td>Ever smoker</td>
<td>23 (38%)</td>
</tr>
<tr>
<td><strong>Respiratory symptoms on presentation</strong></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>46 (77%)</td>
</tr>
<tr>
<td>Cough</td>
<td>35 (58%)</td>
</tr>
<tr>
<td><strong>Comorbidities</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>21 (35%)</td>
</tr>
<tr>
<td>Diabetes</td>
<td>13 (22%)</td>
</tr>
<tr>
<td>Chronic pulmonary disease*</td>
<td>8 (13%)</td>
</tr>
<tr>
<td>Coronary heart disease</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Malignancy</td>
<td>6 (10%)</td>
</tr>
<tr>
<td>Chronic kidney disease</td>
<td>4 (7%)</td>
</tr>
<tr>
<td><strong>Hospital course</strong></td>
<td></td>
</tr>
<tr>
<td>Hospital length of stay, days</td>
<td>10 (6 - 16)</td>
</tr>
<tr>
<td>Patients requiring oxygen supplementation (n=59)</td>
<td>46 (78%)</td>
</tr>
<tr>
<td>Duration of oxygen supplementation, days (n=56)</td>
<td>9 (4 - 15)</td>
</tr>
<tr>
<td>Need for mechanical ventilation</td>
<td>12 (20%)</td>
</tr>
<tr>
<td>Duration of mechanical ventilation, days</td>
<td>8 (5 - 11)</td>
</tr>
</tbody>
</table>

Data are shown as n (%) or median (IQR).

* Asthma, chronic obstructive pulmonary disease, interstitial lung disease, or previous pulmonary embolism.

# The median duration (IQR) of oxygen supplementation and mechanical ventilation is reported only for those who received this treatment.