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Original article

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Changes in pulmonary function and patient-reported outcomes during COVID-19 recovery: a longitudinal, prospective cohort study.

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Take home message:

COVID-19 survivors have improvement in pulmonary function at 6 months. However, 83% have abnormal patient-reported outcomes with 42% reporting persistent dyspnea, despite some with normal DLCO. Imaging features at 3 months can help predict DLCO trajectory over time.

ABSTRACT

Objectives

To compare respiratory and patient-reported outcome measures (PROMs) between 3 and 6 months after symptom onset and to identify features that predict these changes.

Methods

This is a consecutive prospective cohort of 73 patients who were hospitalised with COVID-19. We evaluated the changes in pulmonary function tests (PFTs) and PROMs between 3 and 6 months and then investigated the associations between outcomes (change in diffusing capacity for carbon monoxide of the lung (DLCO), dyspnea, and quality of life (QOL)) and clinical and radiological features.

Results

There was improvement in forced vital capacity (FVC), total lung capacity (TLC), and DLCO between 3 and 6 months by 3.25%, 3.82% and 5.69% respectively; however, there was no difference in PROMs. Reticulation and total CT scores were associated with lower DLCO %-predicted at 6 months (coefficients; -8.7 and -5.3 respectively). The association between radiological scores and DLCO were modified by time, with the degree of association between ground glass and DLCO having decreased markedly over time. There was no association between other predictors and change in dyspnea or QOL over time.

Conclusions

There is improvement in pulmonary function measurements between 3 and 6 months after COVID-19 symptom onset; however, PROMs did not improve. A higher reticulation and total CT score are negatively associated with DLCO, but this association is attenuated over time. Lastly, there is a considerable proportion of patients with unexplained dyspnea at 6 months, motivating further research to identify the underlying mechanisms.

INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has resulted in over 2 million deaths globally as of April 2021 [1]. Several follow-up studies have described abnormalities in patient-reported outcome measures (PROMs), pulmonary function tests (PFTs), and chest imaging months after COVID-19 [2-6]. However, it is unclear how these short-term abnormalities change over time and whether long-term patient outcomes can be predicted.

We have previously demonstrated that 50% of patients had dyspnea and impairments in quality of life (QOL) 3 months after symptom onset and that a striking proportion of patients (88%) had abnormalities on imaging, in particular ground glass opacities and reticulation [6]. Similar to other studies, we also showed that the diffusing capacity for carbon monoxide of the lung (DLCO) was the most frequently impaired pulmonary function measurement among COVID-19 survivors [5,7]. A disturbing feature of COVID-19 has been the identification of a subgroup of patients, whose symptoms persist months after initial symptom onset and are seemingly out of proportion to what would be expected based on common investigations (e.g., unexplained dyspnea). In addition to suffering with these abnormalities, patients are burdened by not knowing whether these sequelae will improve. Therefore, being able to understand how outcomes change over time would help inform discussions between clinicians and patients.

In this study, we sought to determine how respiratory symptoms, QOL, and PFTs change over time during COVID-19 recovery and to identify features that predict these changes. We hypothesized that a higher burden of ground glass and/or reticulation on imaging and the

presence of unexplained dyspnea at 3 months post-COVID-19 symptom onset would be associated with greater improvement in respiratory and patient-reported outcomes at 6 months.

METHODS

Study population

This study included a consecutively enrolled prospective cohort of patients hospitalised with COVID-19 in Vancouver, Canada between March and June 2020. Hospitalisation rates in this population are approximately 5% of all patients who tested positive for SARS-CoV-2, of whom 20% required ICU admission (i.e., 1% of all SARS-CoV-2-positive patients) [8]. At discharge, patients admitted to hospital were automatically referred to the Post-COVID-19 Respiratory Clinic (PCRC), which is located at two academic hospitals. Patients were eligible for enrollment if they were hospitalised for COVID-19 (confirmed by positive SARS-CoV-2 PCR), able to complete study questionnaires in English, and were ≥ 18 years of age. There were no exclusion criteria. All patients provided informed written consent (UBC Clinical Research Ethics Board #H20-01239). The 3-month respiratory outcomes and PROMs for this cohort have been previously reported [5,6].

Measurements

Clinical data were obtained from patient surveys and chart reviews. PFTs were conducted in accordance with international guidelines [9-12]. Transthoracic echocardiogram (TTE) was performed according to established guidelines and interpreted by cardiologists with advanced echocardiography training [13,14]. All measurements were collected at both the 3- and 6-month visits (timed from COVID-19 symptom onset), except for the high-resolution computed

tomography (HRCT) of the chest and TTE which were only obtained at 3 months. Time from symptom onset was treated as a categorical variable (i.e., 3 and 6 months).

Two fellowship-trained cardiothoracic radiologists with 12 and 14 years of experience (DM, CH) independently scored the HRCT chests. The HRCT ground glass and reticulation scores were determined using a standardised approach. The lungs were divided into 6 zones and the extent of ground glass and reticulation were scored as a percent of affected lung volume for each zone. The mean of these zones was then used to determine the overall HRCT ground glass and reticulation scores. The total HRCT score was the sum of the overall ground glass and reticulation scores [15,16]. The means of the scores from the two radiologists were used for the study. A 10% threshold was used for the abnormal percentage of lung involvement. This value is double the threshold (5%) used to define interstitial lung abnormalities (ILAs), which are mild interstitial abnormalities in people who have not been diagnosed with an interstitial lung disease [17]. Intraclass correlation coefficient (ICC) was used to determine interobserver agreement between the two radiologists.

PROMs were assessed using standardised questionnaires completed by patients [18]. Participants completed the following validated questionnaires at each study visit: University of California San Diego Shortness of Breath Questionnaire (UCSD), Cough Visual Analogue Scale (Cough VAS), Patient Health Questionnaire-9 (PHQ-9), Pittsburgh Sleep Quality Index (PSQI), and 5-level EQ-5D (EQ-5D) [19-25]. PSQI and PHQ-9 provide assessment of sleep and depression respectively. A global PSQI score > 5 indicates poor sleep and PHQ-9 ≥5 suggests the presence of a mood disorder. Cough VAS was utilized for cough assessment [23,24]. A value greater than

or equal to 17mm was considered abnormal [25]. The EQ-5D is a generic preference-based instrument that measures QOL in five dimensions. The EQ-5D score is then converted to a health utility index which typically ranges between 0 to 1, with 1 representing perfect health and 0 representing death. The EQ-5D also includes a visual analogue scale (VAS), where patients rate their current health from 0 to 100, with a higher value indicating better health [20]. The health utility index and EQ VAS values were compared to the mean Canadian population norm, which is 0.931 and 77.1 respectively for people in the 65 to 74 years age group. [20]. The UCSD questionnaire was used to grade severity of dyspnea and ranges from 0 to 120 [22]. Dyspnea is considered present when the UCSD is > 5, with a higher score representing worse dyspnea [26]. To illustrate clinically meaningful dyspnea, a UCSD score > 10 was used to define the presence of dyspnea.

Previous studies have described correlations between physiologic parameters and dyspnea [22]. For example, in patients with COVID-19, dyspnea and DLCO %-predicted were negatively correlated [27]. Based on this, we defined unexplained dyspnea as the presence of dyspnea (UCSD dyspnea score >10) in an individual with a normal DLCO (≥80 %-predicted).

Outcomes

The primary outcome was the change in DLCO %-predicted between 3 and 6 months after COVID-19 symptom onset, while the secondary outcomes were change in QOL (EQ-5D utility) and dyspnea (UCSD) at these same times. These outcomes were pre-determined based on our previous studies demonstrating that these variables were frequently abnormal 3 months after symptom onset [5,6].

Statistical analyses

We constructed seven models to address our prespecified hypotheses and support risk prediction during COVID-19 recovery. Models 1a-c tested the association between ground glass and/or reticulation scores with change in DLCO over time, with a goal to determine whether imaging at 3 months would predict subsequent change in physiologic parameters at 6 months. Models 2a and 2b investigated the association between ground glass at 3 months with change in dyspnea (UCSD score) and QOL (EQ-5D utility) from 3 to 6 months. Models 3a-b tested association between the presence of unexplained dyspnea at 3 months with changes in dyspnea and QOL from 3 to 6 months.

Linear mixed effects models were used to explore changes in outcomes over time and were adjusted for age, sex, and smoking pack-years. The models included a random intercept and random slope to account for the variability between patients that is not accounted for by the included covariates. Interaction terms were included since the primary predictor variables may have a different effect on the outcome depending on time from symptom onset.

Normally distributed continuous variables were expressed as means ± standard deviation (SD); non-normally distributed variables were expressed as median (interquartile range). A paired student's t-test or Wilcoxon signed rank test was used to compare measurements between 3 and 6 months. A two-sided p-value < 0.05 was considered statistically significant. Statistical analyses were performed using SPSS (version 22.0; SPSS, Chicago, IL) and R (version 3.6.3).

RESULTS

Baseline characteristics

A total of 73 patients admitted between March and June 2020 were included in this study as outlined in **Figure 1**. The demographics and baseline characteristics are displayed in **Table 1**. The median duration from symptom onset was 13 weeks (IQR 11-14) and 27 weeks (IQR 24-30) for the 3- and 6-month visits, respectively. The median age was 65 years (IQR 53-72). The majority of the cohort was male (60%) and approximately one-third had a history of smoking (32%). There were 64% of patients with dyspnea (UCSD dyspnea score >5) and 42% with more severe dyspnea (UCSD dyspnea score > 10). TTE was performed in 72 patients at the 3-month visit; median left ventricular (LV) systolic function (LV ejection fraction 60% [IQR 60 – 65]) and median estimated pulmonary artery systolic pressure (PASP) (27mmHg [IQR 23 – 30]) were normal.

Unexplained dyspnea (i.e., UCSD score >10 and DLCO ≥80%-predicted) was present in a similar proportion of patients at 3 and 6 months (14% and 19%), with median UCSD scores of 25 (IQR 14-26) and 31 (IQR 17-40), respectively (**Table 1).** Among patients with unexplained dyspnea, reduced QOL was present in 70% and 92% of patients with at 3 and 6 months, respectively. The most common abnormal PROMs were reduced QOL (92%) and poor sleep (69%). Characteristics of patients with and without dyspnea (UCSD >10), irrespective of DLCO, are provided in **Table S1**. Patients with dyspnea had greater impairments in physiologic measurements and PROMs compared to patients without dyspnea.

The median percentage of lung affected by ground glass and reticulation on 3-month HRCT was less than 10% in these patients. There was excellent inter-observer agreement between the two radiologists with ICCs of 93%, 75% and 87% for ground glass, reticulation and total CT score respectively.

Change in pulmonary function over time

Changes in pulmonary outcomes from 3 to 6 months after symptom onset are shown in **Table 2 and Figure 2**. There was improvement in FVC (mean difference, 3.25%; 95% CI: 1.31, 5.19; p=0.001), TLC (mean difference, 3.82%; 95% CI: 2.16, 5.49; p<0.001), and DLCO (mean difference, 5.69%; 95% CI: 3.56, 7.82; p<0.001) between 3 and 6 months. There was a significant decline in FEV_1/FVC ratio (mean difference, -2.86%; 95% CI: -4.45, -1.26; p=0.001), which was consistent with less ventilatory restriction over time. The proportion of patients with an abnormal DLCO (< 80 %-predicted) decreased from 59% at 3 months to 46% at 6 months (p<0.001). There was no difference in the proportion of patients requiring mechanical ventilation during their acute COVID-19 illness between those with normal versus abnormal DLCO at 6 months (21% and 25%, respectively).

Change in PROMs over time

The change in PROMs from 3 to 6 months after symptom onset is shown in **Table 2 and Figure 2.** At 6 months, 84% of patients had at least one abnormal PROM. QOL was the most common abnormality at 6 months, with 70% of the cohort having an EQ-5D utility (preference value that patients attach to their overall health status) worse than the population norm [20,28]. There was no change in QOL based on the EQ-5D utility; however, there was an improvement in median

EQ-5D VAS from 3 to 6 months (median difference, 6.32; 95% CI: 5.00, 9.50, p<0.001). There was no change in mood or sleep. Despite the improvement in PFT values, there was no significant change in median cough or dyspnea scores, with at least one of these symptoms present in 45% of patients at 6 months.

Predictors of change

Change in PROMs

There were 26 patients (36%) with ground glass opacities involving more than 10% of the lung on HRCT. Among these 26 patients, 9 (35%) had dyspnea and 18 (69%) had an EQ-5D utility worse than the population norm at 6 months. The extent of ground glass present at 3-months was not associated with change in dyspnea or QOL and time did not significantly modify these associations **(Table 3, models 2a-b)**. Furthermore, there was no association between the presence of unexplained dyspnea at 3-months and change in dyspnea or QOL over time **(Table 3, models 3a-b).**

Change in DLCO %-predicted

Reticulation and total HRCT score at 3 months were each associated with the change in DLCO from 3 to 6 months (decrease of 8.7%-predicted per unit increase in reticulation score; decrease of 5.3%-predicted per unit increase in total HRCT score **[Table 3, models 1a-c]**). There was no association between 3-month ground glass and change in DLCO. However, time significantly modified the association between 3-month ground glass and DLCO and also, with marginal significance, the association between 3-month reticulation and DLCO (p=0.05) and between 3-

month total CT score and DLCO (p=0.07). The slope of the relationship between each of these initial radiographic abnormalities and DLCO decreased from 3 months to 6 months **(Figure 3)**.

DISCUSSION

This study demonstrates that there is improvement in most pulmonary function measurements between 3 and 6 months after symptom onset for patients hospitalised with COVID-19. However, improvement was less frequent for PROMs, with QOL (based on EQ-5D VAS) being the only PROM that significantly improved between 3 and 6 months. There was no significant change in dyspnea or cough over time and nearly half of patients continued to experience these symptoms at 6 months. Importantly, 19% of patients with dyspnea at 6 months had normal DLCO %-predicted, highlighting the need to identify the underlying cause of this burdensome symptom that is frequently not explained by gas exchange abnormalities.

Our findings show that DLCO improves with time after COVID-19. However, 3-month CT scores, particularly the ground glass component, were less associated with DLCO at the later assessment. Reticulation is indicative of pulmonary fibrosis that is not reversible and implies permanent physiologic impairments, which may explain why the temporal change in association of DLCO with ground glass was greater than with reticulation. The presence of early ground glass thus appears to leave potential for reversible disease (physiologic recovery over time). However, generalizability of this welcome finding is limited by the fact that the extent of ground glass was mild for the majority of patients in this cohort and that a 3-month time interval may be too short to see larger changes. Furthermore, it is not clear that ground glass is the only or predominant factor that influences DLCO trajectory in COVID-19 survivors. Previous studies

have described the presence of distinct pulmonary vascular changes during acute COVID-19, which could impact change in DLCO over time [29,30]. That said, in our cohort, echocardiograms showed normal LV systolic function and estimated pulmonary artery systolic pressure. Longitudinal follow-up with blood biomarkers, further imaging including ventilation perfusion scans, and pulmonary function tests will provide important insight into the possible correlation between pulmonary vascular sequelae and physiologic outcomes after COVID-19.

Dyspnea is one of the most common persistent symptoms experienced by patients during COVID-19 recovery, but its underlying cause remains elusive. In a longitudinal study with 2469 patients hospitalised with COVID-19, dyspnea (modified Medical Research Council [mMRC] ≥ 1) was present in approximately 25% of patients 6 months after symptom onset [31]. In our study, the proportion of patients with clinically meaningful dyspnea (UCSD > 10) was 42% at 6 months. The difference in these proportions highlights the importance of careful selection of symptom questionnaires. The UCSD ranges between 0 and 120 which offers increased granularity when investigating severity or causes of dyspnea compared to the mMRC which ranges between 0 and 4 [22,32,33]. The UCSD also has high test-retest reliability (i.e., consistently reproduces the same result over multiple visits when other variables remain the same), making it suitable for longitudinal studies [34].

There is growing awareness of a group of patients with persistent unexplained dyspnea following COVID-19. In our cohort, unexplained dyspnea was present in 14% of the cohort at 3 months and 19% at 6 months. Our initial impression was that patients with unexplained dyspnea would demonstrate improvement in dyspnea and quality of life over time given they may be more

impaired at baseline with greater room for improvement. However, these associations were not seen in our study. Patients with unexplained dyspnea represent a unique cohort with distinct outcomes. Further research into the respiratory and non-respiratory causes of unexplained dyspnea and prognosis is greatly needed.

Quality of life (based on EQ-5D VAS) significantly improved with time and was comparable to the population norm by 6 months. This is a reassuring finding, as over 50% of patients reported abnormal QOL 3 months after symptom onset [6]. To our knowledge, there are no studies that have investigated predictors of QOL in COVID-19 survivors at 6 months. Huang and colleagues describe greater frequency of QOL impairments among patients warranting ventilation support during their acute illness; however, the association of QOL with imaging and clinical symptoms has not been investigated [31]. Our study shows that the severity of ground glass and presence of unexplained dyspnea were not associated with change in QOL. However, QOL is not just determined by a person's health status, but is also influenced by other important parameters such as psychosocial features and socioeconomic status. As such, our models may not have been comprehensive enough to identify predictors of change in QOL.

This study has several other limitations. Our sample size is modest, though our cohort has the advantage of being consecutively enrolled and well characterized, with standardised data collection and follow-up protocols all rigorously applied. Furthermore, our study is limited to a small proportion of patients who were hospitalised for COVID-19 and cannot be generalized to patients who were asymptomatic or treated as outpatients. Furthermore, the lack of PROMs and pulmonary function tests at baseline in these patients (preceding COVID-19) limits our ability to

attribute these outcomes to COVID-19, although our longitudinal data partly addresses this. For example, if variables improved over time, then this would increase our confidence that the abnormalities were more likely attributable to recent COVID-19. Lastly, the definition of unexplained dyspnea was synthesized for the purposes of this study and has not been validated. It remains possible that results could vary based on the instruments and the physiologic and clinical variables (e.g., anemia, deconditioning or cardiovascular comorbidites) used to characterize and define unexplained dyspnea. In our cohort, only one patient had anemia in the unexplained dyspnea group and their DLCO adjusted for hemoglobin remained greater than 80%-predicted. There were also no differences in echocardiogram parameters between the groups, making cardiovascular abnormalities an unlikely source of unexplained dyspnea. Further research is needed to better understand the cause of persistent symptoms after COVID-19.

CONCLUSION

The majority of patients discharged from hospital have residual symptoms, pulmonary function impairments, and imaging abnormalities 3 months after COVID-19. Although physiologic impairments improve over the subsequent 3 months, a similar improvement in patient-reported outcomes is not seen. Dyspnea is one of the most persistent symptoms, despite a considerable proportion of these patients having normal PFTs. Further studies to determine the underlying causes and predictors of dyspnea are needed in order to guide effective management for the staggering number of COVID-19 survivors worldwide.

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Table 1: Clinical characteristics and pulmonary function tests of patients hospitalised with COVID-19, 6 months after symptom onset. Patients with dyspnea (n=31) have been categorized into those with unexplained dyspnea (i.e., UCSD >10 with DLCO ≥ 80%-predicted) and those with dyspnea (i.e., UCSD >10 with DLCO < 80%-predicted). There were 3 patients who did not have DLCO measurements and could not be categorized. Echocardiogram data is from 3 months after symptom onset. Data are shown as mean ± SD or median (IQR). *Asthma (n=3), chronic obstructive pulmonary disease (n=4), interstitial lung disease (n=2), or previous pulmonary embolism (n=1).

Abbreviations: DLCO= diffusing capacity of the lung for carbon monoxide; EQ-5D = EuroQol-5 Dimension; FEV1= forced expiratory volume in one second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; PASP = Pulmonary Artery Systolic Pressure; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburgh Sleep Quality Index; RV= residual volume; TLC=total lung capacity; UCSD = University of California, San Diego shortness of breath questionnaire; VAS = visual analogue scale.

Features	Overall Cohort (n=73)	Patients with dyspnea at 6 months		p-value
		Unexplained dyspnea (n=13)	Dyspnea (n=15)	
Demographics				
Age	65 (53-72)	49 (34-67)	66 (59-76)	**0.02**
Male sex, n (%)	44 (60)	4 (31)	9 (60)	0.12
Ever smoker, n (%)	23 (32)	2 (15)	8 (53)	0.06
Comorbidities, n (%)				
Hypertension	27 (37)	5 (39)	8 (53)	0.43
Diabetes	19 (26)	3 (23)	5 (33)	0.69
Chronic pulmonary disease*	10 (14)	0	4 (27)	0.10
Coronary heart disease	7 (10)	0	3 (20)	0.23
Malignancy	8 (11)	1 (8)	1 (7)	1.00
Chronic kidney disease	6 (8)	1 (8)	2 (13)	1.00
Respiratory symptoms				
UCSD dyspnea score	9 (3-31)	31 (17-40)	35 (23-46)	0.27
Cough VAS, mm	20 (10-37)	10 (9-10)	30 (16-44)	0.07
Patient-reported outcome measures				
EQ-5D health utility	0.9 (0.8-0.9)	0.83 (0.77-0.87)	0.83 (0.76-0.87)	0.79
EQ-5D VAS	80 (75-90)	75 (70-90)	75 (65-85)	0.50
PSQI	5 (2-9) *(n=72)*	9 (6-12) *(n=12)*	7 (5-9)	0.28
PHQ-9	1 (0-6)	6 (2-10)	5 (1-7)	0.39
Pulmonary function tests				
FEV_1 %-predicted	91 ± 15 *(n=72)*	88 ± 14	83 ± 14	0.31
FVC %-predicted	93 ± 16	93 ± 11	81 ± 15	**0.03**

	(n=72)			
FEV_1/FVC %	84 ± 12 *(n=72)*	84 ± 13	84 ± 11	0.88
TLC %-predicted	87 ± 13 *(n=64)*	86 ± 11 *(n=12)*	77 ± 13 *(n=14)*	0.09
DLCO %-predicted	79 ± 18 *(n= 70)*	88 ± 9	63 ± 14	**<0.001**
Transthoracic Echocardiogram *(n=72)*				
LVEF (%)	60 (60 – 65)	60 (60-64)	65 (60-65)	0.29
PASP (mmHg)	27 (23 – 30)	19 (23-34)	27 (23-30)	0.77

Table 2. Respiratory symptoms, patient-reported outcome measures, and pulmonary function at 3 and 6 months after COVID-19 symptom onset. Data for 3- and 6-months are shown as mean ± SD or median (IQR). A paired student's t-test or Wilcoxon signed rank test were used to compare values between 3 and 6 months. *Abbreviations: DLCO= diffusing capacity of the lung for carbon monoxide; EQ-5D = EuroQol- 5 Dimension; FEV1= forced expiratory volume in one second; FVC = forced vital capacity; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburgh Sleep Quality Index; TLC=total lung capacity; UCSD = University of California, San Diego shortness of breath questionnaire; VAS = visual analogue scale.*

	3 months	**6 months**	**Mean or median difference**	**95% CI**	**p-value**
Respiratory Symptoms					
UCSD dyspnea score	11 (3 – 26)	9 (3 – 31)	-1.0	-4.0, 2.0	0.53
Cough VAS	28 (8 – 60)	20 (10 – 35)	-4.6	-18.7, 8.4	0.41
Patient-reported outcome measures					
PHQ-9	2 (1 – 6)	1 (0 – 6)	0.5	0, 1.5	0.16
PSQI	5 (3 – 8)	5 (2 – 9)	0	-1.0, 1.5	0.81
EQ-5D utility	0.87 (0.79 – 0.95)	0.90 (0.81 – 0.95)	-0.022	-0.1, 0.003	0.12
EQ-5D VAS	75 (68 – 90)	80 (75 – 90)	6.3	5.0, 9.5	**<0.001**
Pulmonary function, %-predicted					
FEV_1	89 ± 16	91 ± 16	1.3	-0.8, 3.4	0.21
FVC	90 ± 17	93 ± 17	3.3	1.3, 5.2	**0.001**
FEV_1/FVC	87 ± 12	84 ± 12	-2.9	-4.5, -1.3	**0.001**
TLC	83 ± 14	87 ± 13	3.8	2.2, 5.5	**<0.001**
DLCO	74 ± 17	80 ± 17	5.7	3.6, 7.8	**<0.001**

Table 3: Predictors of change in respiratory outcomes and QOL between 3 and 6 months after COVID-19 symptom onset. Time was categorized as 3 months (reference) and 6 months from symptom onset. Ground glass, reticulation, and total CT scores were continuous variables that were log-transformed to make them normally distributed and to meet model assumptions. Unexplained dyspnea at 3 months (defined as the presence of a UCSD dyspnea score > 10 with DLCO %-predicted ≥ 80%) was categorical (present or absent). Time was included as an interaction term to evaluate whether time modified the effect of the primary predictor on the outcome. The primary predictor variables are denoted in bold. *Example of Model 1a interpretation:* The coefficient of -2.2 for ground glass score indicates that each 1% increase in ground glass score is associated with a 2.2% decrease in DLCO %-predicted. This association is modified by time. At 6 months, for each 1% increase in ground glass, the coefficient will increase by 1.4 (0.8+0.6), which means there will be a 0.8% (-2.2+1.4) decrease in DLCO %-predicted at 6 months compared to a 2.2% decrease at 3 months. *Abbreviations: CI = confidence intervals; DLCO= diffusing capacity of the lung for carbon monoxide; UCSD = University of California, San Diego shortness of breath questionnaire.*

Model	Outcome	Predictor (at 3 months)	Coefficient	95%CI	P-value	Prespecified covariates
1a	DLCO %-predicted	**Ground glass score**	-2.2	-5.9, 1.4	0.23	Sex, age, smoking pack-years
		Time	0.8	-0.5, 2.0	0.21	
		Ground glass score*Time	0.6	0.05, 1.2	**0.03**	
1b	DLCO %-predicted	**Reticulation score**	-8.7	-12.1, -5.4	**<0.001**	Sex, age, smoking pack-years
		Time	1.2	0.1, 2.2	**0.03**	
		Reticulation score*Time	0.6	-0.01, 1.25	0.05	
1c	DLCO %-predicted	**Total CT score**	-5.3	-8.7, -1.8	**0.003**	Sex, age, smoking pack-years
		Time	0.8	-0.5, 2.2	0.23	
		Total CT score*Time	0.5	-0.04, 1.05	0.07	
2a	UCSD	**Ground glass score**	0.8	-3.4, 5.0	0.69	Sex, age, smoking pack-years
		Time	-0.2	-2.9, 2.5	0.88	
		Ground glass score*Time	-0.1	-1.4, 1.1	0.87	
2b	QOL	**Ground glass score**	-0.003	-0.05, 0.04	0.89	Sex, age, smoking pack-years
		Time	-0.003	-0.02, 0.02	0.77	
		Ground glass score*Time	0.01	-0.002, 0.02	0.15	
3a	UCSD	**Unexplained dyspnea**	5.16	-7.95, 18.3	0.43	Sex, age, smoking pack-years
		Time	-0.45	-1.98, 1.08	0.56	
		Unexplained dyspnea*Time	1.01	-2.98, 5.01	0.61	
3b	QOL	**Unexplained Dyspnea**	0.01	-0.11, 0.13	0.88	Sex, age,

		Time	0.01	-0.001, 0.02	0.07	smoking pack-years
		Unexplained Dyspnea*Time	-0.01	-0.04, 0.01	0.33	

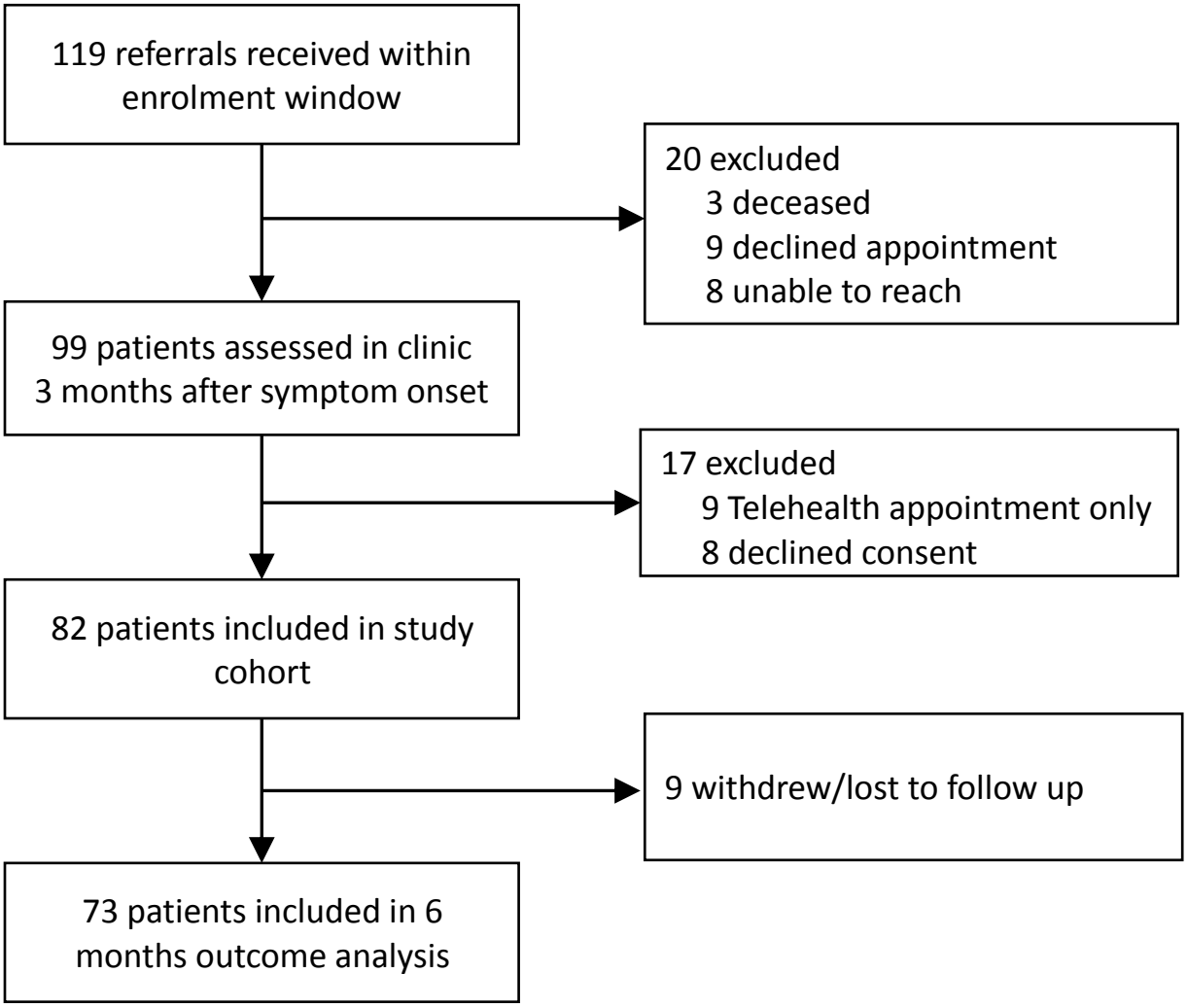

Figure 1. Flow diagram of study enrollment

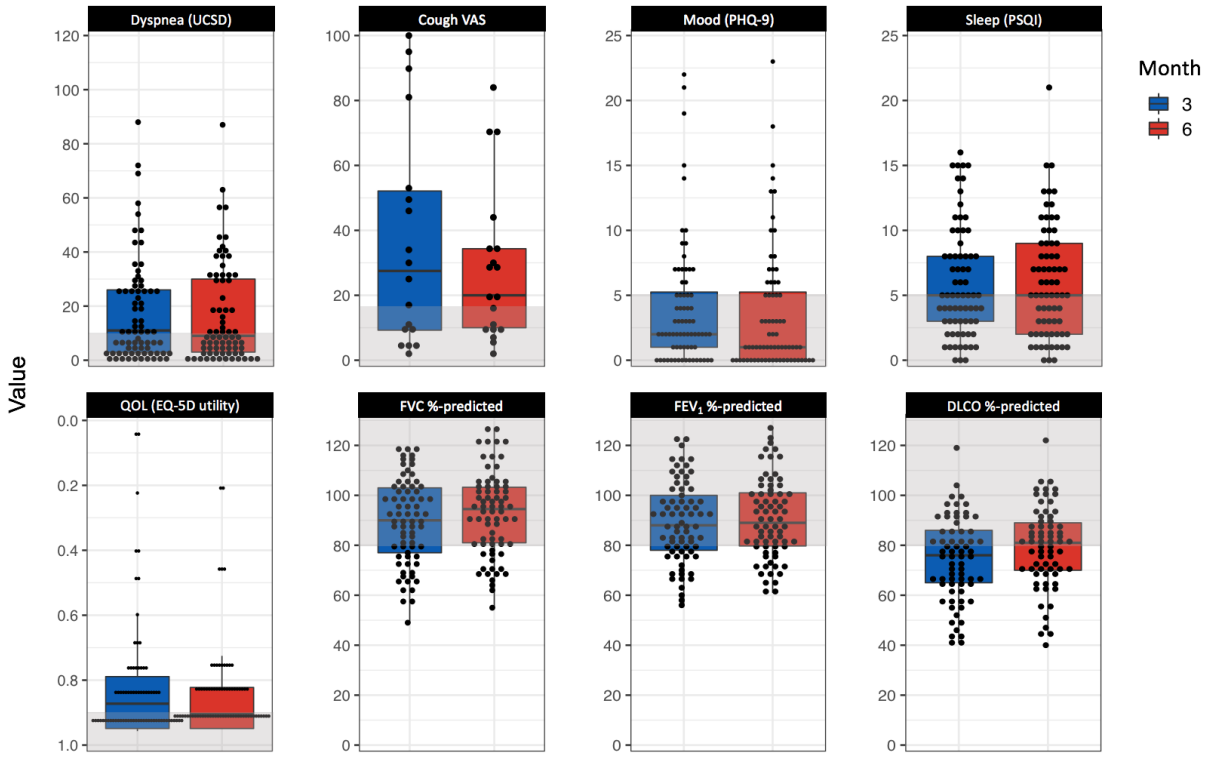

Figure 2. Patient-reported outcomes and pulmonary function measurements at 3 and 6 months after COVID-19 symptom onset. Each circle represents a patient and the box represents the median and interquartile range. The y-axis shows the complete range of possible scores, and areas shaded in grey represent the normal range based on population adjusted norms where available.

Abbreviations DLCO= diffusing capacity of the lung for carbon monoxide; EQ-5D = EuroQol- 5 Dimension; FEV1= forced expiratory volume in one second; FVC = forced vital capacity; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburgh Sleep Quality Index; RV= residual volume; TLC=total lung capacity; UCSD = University of California, San Diego shortness of breath questionnaire; VAS = visual analogue scale

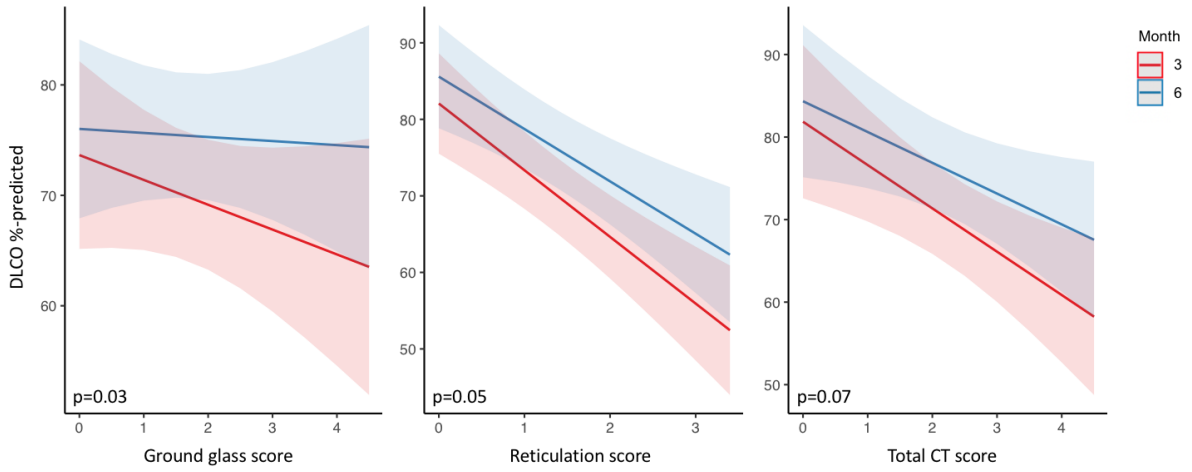

Figure 3. The effect of time on the association between radiologic abnormalities and DLCO at 3 and 6 months after COVID-19 symptom onset. The x-axis represents the log of each radiological score. This figure demonstrates the association between 3-month CT scores (ground glass, reticulation, and total CT scores) and DLCO %-predicted. There is a negative relationship between the radiologic abnormalities and DLCO %-predicted. However, this negative relationship is attenuated over time, as demonstrated by the shallower slopes at 6 months compared to 3 months.

Supplement

Changes in pulmonary function and patient-reported outcomes during COVID-19 recovery: a longitudinal, prospective cohort study.

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Table S1: Clinical characteristics and pulmonary function tests of patients hospitalised with COVID-19, with and without dyspnea 6 months after symptom onset.
Dyspnea was defined as UCSD dyspnea score higher than 10. Echocardiogram data is from 3 months after symptom onset. Data are shown as mean ± SD or median (IQR). *Asthma, chronic obstructive pulmonary disease, interstitial lung disease, or previous pulmonary embolism.

Abbreviations: DLCO= diffusing capacity of the lung for carbon monoxide; EQ-5D = EuroQol-5 Dimension; FEV1= forced expiratory volume in one second; FVC = forced vital capacity; LVEF = left ventricular ejection fraction; PASP = Pulmonary Artery Systolic Pressure; PHQ-9 = Patient Health Questionnaire-9; PSQI = Pittsburgh Sleep Quality Index; RV= residual volume; TLC=total lung capacity; UCSD = University of California, San Diego shortness of breath questionnaire; VAS = visual analogue scale.

Features	Patients without dyspnea (n = 42)	Patients with dyspnea (n = 31)	P value
Demographics			
Age	65 (53 – 72)	65 (49 – 76)	0.7
Male sex, n (%)	29 (69)	15 (48)	0.08
Ever smoker, n (%)	11 (26)	12 (39)	0.26
Comorbidities, n (%)			
Hypertension	13 (31)	14 (45)	0.21
Diabetes	11 (26)	8 (26)	0.97
Chronic pulmonary disease*	4 (10)	5 (16)	0.48
Coronary heart disease	3 (7)	4 (13)	0.45
Malignancy	5 (12)	3 (10)	1.00
Chronic kidney disease	0	6 (19)	**0.004**
Respiratory symptoms			
UCSD dyspnea score	4 (1 – 7)	31 (18 – 41)	**<0.001**
Cough VAS, mm	9 (5 – 40)	28 (13 – 40)	0.06
Patient-reported outcome measures			
EQ-5D health utility	0.91 (0.90 – 0.95)	0.83 (0.76 – 0.87)	**<0.001**
EQ-5D VAS	85 (80 – 95)	75 (65 – 85)	**<0.001**
PSQI	3 (2 – 6)	8 (5 – 11) (n=30)	**<0.001**
PHQ-9	0 (0 – 2)	5 (1 – 7)	**<0.001**
Pulmonary function tests			
FEV_1 %-predicted	95 ± 16	85 ± 14 *(n=30)*	**0.008**
FVC %-predicted	97 ± 17	86 ± 14 *(n=30)*	**0.004**
FEV_1/FVC %	85 ± 11	84 ± 12 *(n=30)*	0.72
TLC %-predicted	90 ± 12	81± 13 *(n=26)*	**0.01**

DLCO %-predicted	84± 16	74 ± 17 *(n=28)*	**0.02**
Transthoracic Echocardiogram *(n=72)*			
LVEF (%)	60 (59 – 65)	60 (60 – 65)	0.88
PASP (mmHg)	27 (22 – 31)	27 (23 – 30)	0.75