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ORIGINAL ARTICLE

Lung function at 1-year follow-up in patients with persistent dyspnea after mild COVID-19 – comparisons with moderate and critical COVID-19

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ABSTRACT

Aim: To assess lung function in patients with persistent dyspnea 1 year after mild coronavirus disease 2019 (COVID-19) and compare with those hospitalized with moderate or critical COVID-19.

Methods: Adults with confirmed severe acute respiratory syndrome coronavirus-2 infection with mild COVID-19 and persistent dyspnea (n = 18) or with moderate (n = 34) or critical COVID-19 (n = 19) were followed up 11–13 months after initial infection. Inclusion criteria were age < 65 years, no smoking history, and no preexisting respiratory diseases. Sociodemographic and clinical data were collected, and patients underwent spirometry and measurement of diffusing capacity for carbon monoxide (D_{LCO}).

Results: The non-hospitalized patients were significantly younger and more often female compared with those in the moderate and critical groups (P = 0.002 and P < 0.001, respectively). No significant differences in comorbidities or body mass index (BMI) were noted between severity groups. An obstructive spirometry pattern (ratio of forced expiratory volume during the first exhalation second to forced vital capacity under the lower limit of normal (LLN)) was found in 5.6, 5.9, and 5.3% of patients in the mild, moderate, and critical groups, respectively (P = 0.995). Abnormal D_{LCO} (< LLN) rates were seen in 5.6, 16.7, and 47.4% in the mild, moderate, and critical groups, respectively (P = 0.018). D_{LCO}, expressed as a z-score, was significantly lower in the critical group compared with the mild group after adjustment for age, sex, and BMI.

Conclusion: Only a few subjects with mild COVID-19 and persistent dyspnea had abnormal lung function 1 year after initial infection, assessed based on spirometry and D_{LCO} measurements. An obstructive spirometry pattern at 1-year follow-up was uncommon even in patients with moderate or critical COVID-19. Impaired D_{LCO} was more common in patients with critical COVID-19.

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Lung function; diffusing capacity for carbon monoxide; COVID-19; severity

Introduction

Concerns have arisen regarding prolonged post-acute complications, notably respiratory manifestations, in individuals recovering from coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) (1, 2). A meta-analysis indicated that a year after discharge, the most common sequela was abnormal pulmonary function (3), particularly reduced diffusing capacity for carbon monoxide (D_{LCO}) (4, 5). Previous studies have suggested that a more severe initial disease increases the risk of reduced D_{LCO} (6, 7). Existing studies on non-hospitalized patients after mild initial disease have revealed little impact on lung function following COVID-19 (6–10). However, additional research is needed to validate these findings, as the available studies are few. In addition, the numbers of patients included are small, persistent symptoms are not accounted for, and there is limited information about smoking habits and comorbidities. Furthermore, the focus on potential impaired lung function in subjects recovering from mild COVID-19 is important, given that they make up the majority of COVID-19 cases, with a significant portion experiencing persistent dyspnea (3, 11). Recent studies have highlighted the correlation between impaired lung function and reduction of health-related quality of life, as well as diminished physical and cognitive abilities (12, 13).

The aim of this study was to evaluate lung function in patients with persistent dyspnea 1 year after mild COVID-19, in comparison with patients after moderate or critical COVID-19.

Materials and methods

Study design

This cross-sectional exploratory study involved three distinct cohorts of adult patients enrolled 11–13 months after an initial

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SARS-CoV-2 infection. They were categorized based on COVID-19 severity at onset and required level of care: mild (non-hospitalized), moderate (hospitalized), and critical (hospitalized in an intensive care unit (ICU)). Each patient had COVID-19 confirmed through a positive reverse transcriptase polymerase chain reaction SARS-CoV-2 test performed at the Uppsala University Hospital in Sweden on a sample obtained using a nasopharyngeal swab. The mild and moderate groups were both part of the longitudinal project called 'COMBAT post COVID', which is investigating the long-term consequences of COVID-19 and has been described previously (14–16). The critical group was part of the longitudinal project called the 'FUP-COVID study' (17). All patients underwent a lung function assessment at the Department of Respiratory, Allergy, and Sleep Research at Uppsala University Hospital. Inclusion criteria were age 18–64 years, no smoking history, and no known pulmonary disease before contracting COVID-19.

The study received approval from the Swedish Ethical Review Authority (Dnr: 2020–05707, Dnr: 2021-01891, Dnr 2020-02697 with changes: 2020-03629, 2020-05758, 2021-02205, 2022-01115-02), and all participants provided written informed consent. The study adhered to the principles of the Declaration of Helsinki.

Cohorts

A total of 566 patients were diagnosed with mild COVID-19 between March and December 2020 at the emergency department at Uppsala University Hospital. Twelve months after the initial infection, they received a questionnaire by email though REDcap or by post to their home address (16). The questionnaire covered sociodemographic information and persistent symptoms. Among the 336 (59% of 566) respondents, 47% reported persistent symptoms, with 41 individuals reporting dyspnea (16). Of those experiencing dyspnea, 28 met the inclusion criteria for this study (age under 65 years, never smokers, no doctor's diagnosis of pulmonary disease before COVID-19). Ultimately, 18 patients participated in the COVID-19 follow-up visit 13 months post-infection.

A total of 152 patients were hospitalized with moderate COVID-19 at the Department of Infectious Diseases between April and July 2020. They were later contacted by telephone and 57 (38%) chose to participate in a COVID-19 follow-up visit 11–13 months after the initial infection. Thirty-four met the inclusion criteria for this study.

A total of 122 patients with critical COVID-19 were admitted to the Uppsala University Hospital ICU between March and June 2020 (17). Initially, 60 patients underwent a follow-up lung function test 4 months after the infection. Of the 122 individuals, 32 (26%) patients had passed away before follow-up, and 27 did not agree to participate in the study. At 11–13 months after the infection, 40 patients were followed up with regard to lung function. Nineteen of them met the inclusion criteria for this study.

Pulmonary function

Each subject underwent dynamic spirometry and D_{LCO} measurements, performed using a Jaeger MasterScreen PFT (Vyaire, Mettawa, IL, US). In dynamic spirometry, the following parameters were assessed: forced expiratory volume during the first exhalation second (FEV_1), forced vital capacity (FVC), and ratio of FEV_1 to FVC. At least three acceptable and reproducible maneuvers were performed to measure all lung function parameters. Additionally, D_{LCO} was assessed. Pulmonary function tests adhered to the American Thoracic Society/European Respiratory Society guidelines (18). Determinations of FEV_1, FVC, FEV_1/FVC, and D_{LCO} under the lower limit of normal (< LLN) were based on *z*-score < –1.645, using the reference values of the Global Lung Function Initiative (19). Abnormal D_{LCO} was defined as D_{LCO}< LLN, and obstructive spirometry pattern was defined as FEV_1/FVC< LLN.

Covariables

This study included data on age, sex, and body mass index (BMI) measured at the time of the lung function test, as well as pre-existing comorbidities diagnosed by a doctor before COVID-19, such as heart diseases, malignancies, diabetes mellitus, and depression/anxiety. For hospitalized and critically ill COVID-19 patients, data on the number of days in hospital (including at an ICU) and the use of corticosteroid treatment during admission were collected. Additionally, data on infection severity at onset were collected. Severity was measured on the World Health Organization scale of 0–10, where 0 is uninfected and 10 is dead (20).

Statistical analysis

Basic characteristics of the included patients after mild, moderate, and critical COVID-19 are presented as means with standard deviation (SDs) for continuous variables or as absolute values and percentages for categorical variables. The differences between the three severity groups were assessed using the Kruskal-Wallis test for continuous variables and the chi-square test (or Fisher's exact test) for categorical variables. The multiple linear regression (adjusted for age, sex, and BMI) was performed to assess differences in D_{LCO}, expressed as *z*-scores, between all three groups. A logistic regression (adjusted for age, sex, and BMI) was used to determine the association between DLCO<LLN and COVID-19 severity at onset (critical vs mild-moderate), with results expressed as odds ratios (ORs) with 95% confidence intervals (CIs). The statistical analysis was performed using STATA version SE 17 (StataCorp, College Station, TX, USA).

Results

Patient characteristics

A total of 71 adult patients – all of whom were never smokers, had no prior pre-existing diagnosis of respiratory disease before COVID-19, and were < 65 years old – underwent a lung function assessment at 11–13 months after COVID-19 (see flowchart in Figure 1).

The characteristics of the three groups are presented in Table 1. Patients in the mild group were significantly younger

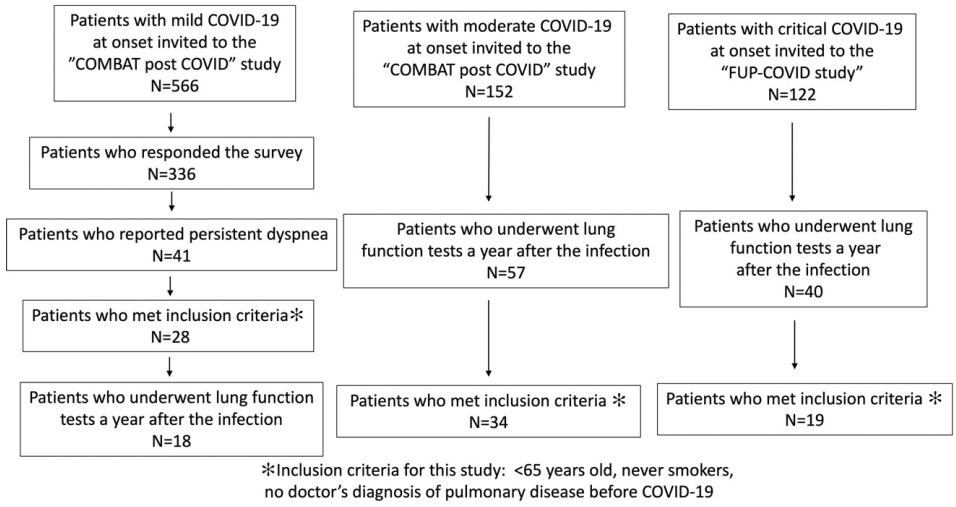

Figure 1. Flowchart of the included study patients.

and more often female than those in the moderate and critical groups. The most common comorbidity was hypertension in the moderate and critical groups, whereas depression/anxiety was more prevalent in those with mild disease. Nearly half of the patients in the moderate and critical groups had obesity (BMI ≥ 30 kg/m^2) at the time of lung function assessment. No study subjects were classified as underweight (< 18.5 kg/m^2). All patients who had moderate COVID-19 with a hospital stay longer than 2 days received corticosteroid treatment during hospitalization. Patients in the critical group spent an average of 8.5 (SD: 5.39) days in the ICU.

Lung function outcomes

Pulmonary function tests were conducted 11–13 months after initial infection. All patients underwent a complete dynamic spirometry. For unknown reasons, three subjects did not undergo D_{LCO} measurements. An obstructive spirometry pattern (FEV_1/FVC < LLN) was observed in only 5–6% of study patients in each severity group (see Table 2 and Figure 2). Abnormal D_{LCO} was observed in 5.6, 16.7, and 47.4% of patients in the mild, moderate, and critical groups, respectively.

Beta coefficients with 95% CIs for the dependent variable D_{LCO} *z*-score were adjusted for age, sex, and BMI, the independent variables (see Table 3). The logistic regression adjusted for age, sex, and BMI showed that critical COVID-19 at onset (vs. mild-moderate) related to a higher likelihood of having D_{LCO} < LLN (OR with 95% CI: 5.18 (1.76–15.27) after adjustment for age, sex, and BMI; OR in crude analysis with 95% CI: 4.43 (1.63–12.03)).

Discussion

The primary finding of this exploratory study was that subjects experiencing persistent dyspnea after mild initial COVID-19 have normal lung function 1 year after infection, assessed based on dynamic spirometry and D_{LCO}. Overall, 5.6% of patients experiencing persistent dyspnea after mild COVID-19 had abnormal D_{LCO}, compared with 16.7 and 47.4% of patients after moderate and critical COVID-19, respectively. Additionally, we showed that only 5–6% of study subjects in each severity group had abnormal dynamic spirometry parameters a year after COVID-19.

To our knowledge, there are no previous studies of lung function results in non-hospitalized COVID-19 patients with persistent dyspnea at 1 year post-infection. A previous Swedish study that followed up both hospitalized and non-hospitalized patients at 3–6 months after initial infection found that breathlessness reported as a modified Medical Research Council (MRC) dyspnea score was associated with impaired D_{LCO}. However, in that study, only a few non-hospitalized patients had impaired D_{LCO} (<5%), whereas breathlessness was reported in 27% of non-hospitalized patients (6). In *a cross-sectional study from Denmark, there was no significant difference between reported MRC dyspnea scores 3 months after non-hospitalized and hospitalized COVID-19, and scores were not associated with* impaired D_{LCO} (8). A low prevalence of abnormal D_{LCO} (<80% of predicted value) was found in subjects 1 year after mild COVID-19 according to a meta-analysis (21). However, no information on persistent symptoms was available in the meta-analysis.

The etiology of dyspnea following mild COVID-19 remains unclear, and exclusion of impaired pulmonary lung function is important, as demonstrated in our study. Various pathophysiological mechanisms for dyspnea after COVID-19 have been proposed, encompassing venous thromboembolic disease, deconditioning, cardiac dysfunction, dysfunctional breathing, hypothyroidism, other endocrine dysfunction, depression-/anxiety-related causes, and chronic fatigue syndrome (7, 10, 22). It is essential to acknowledge that these potential causes of dyspnea cannot be definitively ruled out in the patients included in our study, as it focused only on pulmonary outcomes.

In alignment with several previous studies, we observed that patients with more severe COVID-19 exhibited an increased burden of reduced D_{LCO} (6, 7, 23, 24). Various pathophysiological mechanisms contributing to impaired D_{LCO} in COVID-19 have been

Table 1. Sociodemographic and clinical characteristics of the study population.

Characteristics of the study population	Total ($n = 71$)				Mild ($n = 18$)				Moderate ($n = 34$)				Critical ($n = 19$)				P*
	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%	
Age in years, mean (SD)	53.2	7.8			47.2	8.7			55.2	6.7			55.1	6.2			0.002
Sex (female), n (%)			30	42.9			15	83.3			10	29.41			5	26.3	< 0.001
Comorbidity, n (%)																	
Hypertension			27	38.0			3	16.7			16	47.1			8	42.1	0.091
Other heart disease			3	4.2			0				2	5.9			1	5.3	0.584
Diabetes mellitus type 2			14	19.7			2	11.1			8	23.5			4	21.1	0.556
Malignancy			1	1.4			0				1	2.9			0	0	0.576
Depression/anxiety			13	18.3			4	22.2			8	23.5			1	5.3	0.227
Height (cm), mean (SD)	173.8	10.1			169.8	8.3			174.4	10.2			176.6	10.9			0.068
Weight (kg), mean (SD)	89.9	19.7			82.0	23.4			91.82	17.3			93.9	18.8			0.060
BMI (kg/m^2), mean (SD)	29.7	5.7			28.3	7.2			30.1	5.0			30.0	5.4			0.207
BMI groups, n (%)																	
Normal 18.5–24.9 kg/m^2			14	19.7			6	33.3			5	14.7			3	15.8	0.243
Overweight 25–29.9 kg/m^2			27	38.0			7	38.9			13	38.2			7	36.8	0.691
Obesity ≥ 30 kg/m^2			30	42.3			5	27.8			16	47.1			9	47.4	0.355
Treatment with corticosteroids during admission, n (%)			27	38.0			0	0			26	76.5			0	0	< 0.001
Severity scale, n (%)																	
1			18	25.4			18	100			0	0			0	0	< 0.001
2			0	0			0	0			0	0			0	0	
3			5	7.0			0	0			5	14.7			0	0	
4			1	1.4			0	0			1	2.9			0	0	
5			7	9.7			0	0			7	206			0	0	
6			31	43.7			0	0			20	58.8			11	57.9	
7			1	1.4			0	0			1	2.9			0	0	
8			7	9.9			0	0			0	0			7	36.8	
9			1	1.4			0	0			0	0			1	5.3	
Days in hospital, total, mean (SD)	11.5	12.6			0	0			7.4	7.4			29.7	1.5			< 0.001
Remaining dyspnea at follow-up, n (%)			45	63.4			18	100			27	79.4			Not assessed		< 0.001

*Statistical test: Kruskal-Wallis test for analysis of continuous variables and chi-square test for analysis of categorical variables between the three groups. Significance was set at $P < 0.05$. BMI = body mass index, SD = standard deviation.

Table 2. Lung function parameters in the three severity groups 11–13 months after initial COVID-19.

Characteristics of the study population	Total ($n = 71$)				Mild ($n = 18$)				Moderate ($n = 34$)				Critical ($n = 19$)				P*
	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%	Mean	SD	n	%	
FVC, L (SD)	4.10	1.05			3.74	0.84			4.24	1.04			4.21	1.20			0.092
FVC, % predicted (SD)	99.37	14.30			98.89	12.65			101.31	14.73			96.36	15.15			0.239
FVC < LLN, n (%)			4	5.63			1	5.56			2	5.88			1	5.26	0.995
FEV_1, L (SD)	3.27	0.81			3.05	0.61			3.36	0.84			3.33	0.92			0.223
FEV_1, % predicted (SD)	99.68	13.79			99.74	11.50			101.34	15.02			96.65	13.65			0.134
FEV_1<LLN, n (%)			3	4.23			0	0			2	5.88			1	5.26	0.584
FEV_1/FVC (SD)	0.79	0.05			0.78	0.07			0.78	0.07			0.80	0.05			0.539
FEV_1/FVC< LLN, n (%)			4	5.63			1	5.56			2	5.88			1	5.26	0.995
D_{LCO}, mmol/min/kPa (SD)	7.87	1.95			7.36	1.46			8.71	2.06**			7.02	1.70			0.013
D_{LCO}, % predicted (SD)	92.22	17.92			94.10	11.72			100.65	18.34**			77.12	11.96			< 0.001
D_{LCO}< LLN, n (%)			15	22.39			1	5.56			5	16.67**			9	47.37	0.018

FVC = forced vital capacity; FEV_1 = forced expiratory volume in the first exhalation second; D_{LCO} = diffusion capacity for carbon monoxide; LLN = lower limit of normal. *Statistical test: Kruskal-Wallis test for analysis of continuous variables and chi-square test for analysis of categorical variables across the three groups. Significance was set at $P < 0.05$. **Missing variables: D_{LCO} measurements were missing in four patients from the moderate group.

Figure 2. Boxplot of differences between D_{LCO} *z*-scores across severity groups. The center line in each box represents the 50th percentile (median) of the D_{LCO} *z*-score. The bottom of each box represents the 25th percentile of the D_{LCO} *z*-score and the top of each box represents the 75th percentile. The interquartile range is the difference between the 75th and 25th quartiles. The bottom whisker is equal to the 25th percentile minus 1.5 times the interquartile range. The upper whisker is equal to the 75th percentile plus 1.5 times the interquartile range.

Table 3. Results from unadjusted and adjusted (for age, sex and BMI) linear regression models for D_{LCO}, expressed as *z*-scores, in relation to severity group (mild as reference group).

Characteristics of the study population	Beta coefficients with 95% CI (not adjusted)	P	Beta coefficients with 95% CI (adjusted)	P
Severity				
Mild	Reference		Reference	
Moderate	0.37 (–0.24 to 0.97)	0.23	0.48 (–0.24 to 1.19)	0.24
Critical	–1.20 (–1.87 to –0.53)	0.001	-1.13 (–1.90 to –0.36)	0.005

suggested. These include a hyperinflammatory state with disturbed coagulation that leads to disseminated pulmonary microthrombi causing a mismatch between pulmonary ventilation and perfusion (25, 26). Additionally, it has been proposed that SARS-CoV-2 may induce aberrant alveolar wound healing, loss of pulmonary vascular bed, or both, leading to gas exchange abnormalities (27). Moreover, previous studies in patients after critical disease have suggested that subsequent reduction of D_{LCO} can be attributed to ventilatory-induced lung injury (28).

We also showed that regardless of initial COVID-19 severity, patients generally had normal dynamic spirometry results at a 1-year follow-up. Our result was in line with those of a recent meta-analysis, where 7.3% of patients after mild-moderate COVID-19 and 5.8% of patients after critical COVID-19 had abnormal FEV_1/FVC (FEV_1/FVC<0.7) at 1-year follow-up (21). Previous studies have concluded that impaired pulmonary function is mainly driven by an abnormal D_{LCO} (24), and that reduction in D_{LCO} is often seen even when no restrictive or obstructive lung function impairment is found (21).

In line with prior reports, our study group with mild COVID-19 mainly comprised females, whereas the group with critical COVID-19 consisted mainly of male patients, typically of higher age (10, 29).

Strengths and limitations

The strength of this study lies in its assessment of lung function outcomes a year after polymerase chain reaction-confirmed COVID-19, with three severity groups included. Notably, there has been only one prior study on lung function in individuals experiencing dyspnea after mild disease, with follow-up of at least 1 year (7). Moreover, our study adds value by distinguishing between two hospitalized groups, with disease of moderate and critical severity, respectively.

There are several limitations in our study. First, the study was conducted at a single medical center and there were limited numbers of study subjects in each severity group. On the other hand, one of the reasons for the small groups was that we excluded patients with smoking history, known diagnosis of respiratory diseases before the COVID-19 infection, or age ≥ 65 years, as we had no lung function measurements from before COVID-19 onset. Smoking is a known cause of reduced diffusing capacity (30). We had to choose an age below 65 years to match the mild cohort, which consisted of healthcare workers in active employment. Furthermore, common lung disease such as chronic obstructive pulmonary disease and asthma would lead to impaired lung function and might have had a higher risk of critical COVID-19 (31). The exclusion of patients with these comorbidities reduces the generalizability of the moderate and critical groups. Further, the selection of persons experiencing dyspnea in the mild group precludes conclusions regarding the frequency of dyspnea as such.

A second weakness of this study was the inclusion of patients from different periods of the pandemic (with different SARS-CoV-2 variants), resulting in variations in the regimen of corticosteroid treatment during hospitalization. The use of corticosteroids was recommended during the second wave of the pandemic (32). In our study, corticosteroids were used to a very small extent in the critical group that contracted COVID-19 in the initial phase of the pandemic. Previous studies have shown that corticosteroid treatment during hospitalization was an independent protective factor for lung function in survivors (32, 33). Therefore, in our study, the use of corticosteroids was potentially a protective factor in the moderate group.

A third weakness of our study was the lack of information on total lung capacity, vaccination status, and details on experiences of dyspnea at 12 months in the critical group. The lack of information on total lung capacity prevents drawing conclusions regarding restrictive lung function impairment, although the normal vital capacity findings make impaired total lung capacity less likely (18). Regarding vaccination status, vaccines were not available at the beginning of the pandemic, when the critical group had COVID-19. However, vaccines might have protected the other two groups of patients from more severe disease.

Conclusions

We found that only few subjects with mild COVID-19 and persistent dyspnea had abnormal lung function 1 year after initial infection, assessed based on spirometry and D_{LCO} measurements. The risk of impaired D_{LCO} increased with disease severity. This study was exploratory, and further research is needed to determine if impaired D_{LCO} after COVID-19 improves over time. It might be also important to investigate if improvement of D_{LCO} can be supported through rehabilitation.

Disclosure statement

The authors report no conflict of interests.

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Informed consent statement

Written informed consent was obtained from all subjects involved in the study.

Data availability statement

The authors declare that they have no relevant or material financial interests that relate to the research described in this paper.

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