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Short communication

Impaired diffusing capacity for carbon monoxide is common in critically ill Covid-19 patients at four months post-discharge

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ABSTRACT

There is limited knowledge about the long-term effects on pulmonary function of COVID-19 in patients that required intensive care treatment. Spirometry and diffusing capacity for carbon monoxide (DLCO) were measured in 60 subjects at 3-6 months post discharge. Impaired lung function was found in 52% of the subjects, with reduced DLCO as the main finding. The risk increased with age above 60 years, need for mechanical ventilation and longer ICU stay as well as lower levels of C-reactive protein at admission. This suggests the need of follow-up with pulmonary function testing in intensive-care treated patients.

Coronavirus disease 2019 (COVID-19) is known to cause severe disease requiring intensive care in a substantial number of patients and has also been associated with post-acute morbidity, including respiratory symptoms [1]. The most severely affected patients with COVID-19 have been diagnosed with and treated for Acute Respiratory Distress Syndrome (ARDS), which in itself can give residual respiratory physiological impairment[2]. Although there have been follow-up studies of pulmonary function[3–7] there is limited knowledge about the long-term effects of COVID-19 in patients requiring intensive care. Therefore, we studied the prevalence of respiratory impairment as measured by pulmonary function tests (PFT) and associated factors in Intensive Care Unit (ICU)-treated COVID-19 patients 3–6 months after discharge.

The study was approved by the Swedish Ethical Review Authority (EPM-2020-01623 and EPM-2020-0362). A total of 122 COVID-19 patients admitted to the ICU at Uppsala University Hospital between 2020 and 03–13 and 2020-07-02 were included. All included patients had positive nasopharyngeal SARS-CoV-2 RNA PCR, except three that were excluded. At follow-up, 32 patients had died and 27 did not have follow-up PFT as of November 11th, 2020, leaving 60 patients in the present study. At ICU admission all patients had respiratory failure requiring treatment with high flow nasal oxygen, non-invasive or invasive ventilation. A majority of patients met the criteria for at least mild ARDS. All patients received prophylactic dalteparin, initially 100E/kg/day, and later with 200E/kg/day, guided by activated factor X levels.

A total of 60 patients (43 males) aged 27–82 years (mean age 59 years) performed PFT at a mean of 122 days (standard deviation 18 days) after discharge from the ICU. Dynamic spirometry including forced vital capacity (FVC), as well as diffusing capacity for carbon monoxide (DLCO), were performed with the subject in the sitting position and wearing a nose clip using a Jaeger Master Screen PFT (Vyaire, Mettawa, IL, US) according to ATS/ERS standards. PFT results were defined as pathological if below the lower limit of normal (LLN) according to the Global Lung Function Initiative reference values. Comparisons between patients with impaired and normal lung function were tested using Chi-square test for categorical variables and Mann-Whitney rank sum tests for continuous variables. Stata 14.2 (StataCorp, College Station, TX) was used for statistical analyses.

All 60 participants performed DLCO measurements, but three subjects did not perform an acceptable spirometry and therefore FVC could

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not be measured. A total of 31 of 60 (52%) had abnormal lung function values, among them 27 of 31 had reduced DLCO and/or reduced FVC and 4 had isolated FVC-impairment. Average DLCO was 62% of predicted among those with abnormal DLCO, with the lowest of 44% of predicted value.

Patient characteristics are shown in Table 1, divided by DLCO impairment at follow-up. An impaired DLCO was more common among patients older than 60 years and those treated with invasive ventilation. Longer stay in the ICU as well as impaired FVC (<LLN) at follow-up were also associated with impaired DLCO. Level of C-reactive protein (CRP) at admission to the ICU was lower in the group with impaired DLCO and the same was found regarding the lowest values for blood leukocytes and lymphocytes during the ICU-period. No relationship with impaired DLCO was found for D-dimer at admission or for the maximum value during the ICU-period. All these significant relations could be confirmed after further adjusting for age. Regarding FVC at follow-up, only severe ARDS was associated with having FVC < LLN at follow-up in a similar analysis (data not shown). When analysed as a continuous variable, DLCO (%predicted) at follow up was confirmed to significantly related ($p < 0.05$) to all variables that were significantly associated with impaired DLCO in Table 1, with exception for CRP at admission ($p = 0.11$).

The most important finding in the present investigation is that more than half of ICU treated COVID-19 patients have impaired lung function, mainly impaired, DLCO at 4-months follow-up. The prevalence of DLCO impairment is in line with earlier findings after ARDS and after Severe Acute Respiratory Syndrome (SARS)/Middle East Respiratory Syndrome (MERS) [2,8,9]. Studies after COVID-19 with pulmonary PFT at discharge [3], 1 month [4,6] or 2–3 months [5,7] after diagnosis or discharge report residual impairment of primarily DLCO, and secondly FVC. SARS studies suggest that lung function slightly improves from 3 to 6-months follow-up, both with regard to FVC and DLCO [8]. However, in a long-term follow-up of patients with MERS, slightly over one third of the patients had impaired DLCO at 15-years' follow-up[8–10]. Our results differ from the previously published 3-months' follow up results [5] in that we have a higher proportion of lung function impairment and that we found no relationship to D-dimer levels. Both differences might be explained by differences in illness severity between the study populations with regard to need of intensive care treatment and proportion of subjects with elevated D-dimer levels.

Impaired DLCO related to need of mechanical ventilation and duration in ICU as well as lower CRP upon ICU admission and lower nadir of blood lymphocytes and leukocytes. It can be speculated if these relations might be due to a weaker or delayed inflammatory response to infection, but it cannot be excluded that these subjects might exhibit early respiratory failure because of pre-existing respiratory impairment or sensitivity.

The strengths of our study are the long follow-up time and the largest population of ICU-treated COVID-19-patients followed so far with PFTs. However the sample size could limit the validity and robustness of our findings and they should therefore be interpreted with care regarding risk factors for impaired lung function at follow-up. The absence of previous PFTs for comparison means that pre-existing DLCO impairment cannot be excluded in some of the subjects. Non-participation in this follow-up introduces a selection bias which could be due to physical impairment, suggesting that lung function is this cohort could on average be even worse than we report.

In conclusion, over half of the ICU treated COVID-19 patients in our cohort had impaired lung function at follow-up. The results suggest the need for further follow-up studies with PFT, including DLCO, especially with longer follow-up duration to determine the natural history of pulmonary function impairment in surviving patients and find evidence if lung function is improving over time. More studies are needed on the association of subsequent long-term pulmonary function impairment with the inflammatory and clinical characteristics of the acute COVID-19-disease.

Table 1
Characteristics of study participants, divided by diffusing capacity for carbon monoxide (DLCO) above or below the lower limit of normal (LLN) at follow-up. Continuous variables are presented as median (range), categorical variables as number and percentage of total.

	Normal DLCO	DLCO < LLN	p-value
	N = 33	N = 27	
Age <60 years	23 (70%)	10 (37%)	0.01
Male gender	25 (76%)	18 (67%)	0.44
Smoking status			
Never smoked	25 (76%)	21 (78%)	0.63
Current smoker	1 (3%)	2 (7%)	
Ex-smoker	7 (21%)	4 (15%)	
BMI			
20–25 kg/m^2	3 (10%)	6 (23%)	0.54
25–30 kg/m^2	13 (43%)	11 (42%)	
30–35 kg/m^2	8 (27%)	6 (23%)	
>35 kg/m^2	6 (20%)	3 (12%)	
Time to follow up	125 (116–130)	117 (105–127)	0.11
Severe ARDS	9 (27%)	13 (48%)	0.10
Invasive ventilation	13 (39%)	19 (70%)	0.02
Days in ICU	7 (4–11)	11 (6–16)	0.02
Highest SOFA score	6 (5–9)	8 (6–9)	0.14
Previous lung disease			
No lung disease	23 (70%)	21 (78%)	0.07
Asthma	9 (27%)	2 (7%)	
COPD	0 (0%)	3 (11%)	
Unspecified	1 (3%)	1 (4%)	
Treatment with anticoagulants or platelet inhibitors	0 (0%)	6 (22%)	0.004
Treatment with dexametasone during COVID-19	3 (9%)	3 (11%)	0.80
CRP at admission	213 (139–262)	151 (74–196)	0.01
Max D-dimer	1.85 (1.3–4.1)	3.4 (1.9–7.2)	0.09
Lowest blood lymphocytes	0.9 (0.7–1)	0.7 (0.5–0.9)	0.046
Lowest blood leukocytes	6.4 (5.4–8.2)	5.4 (4.1–6.8)	0.03
FVC < LLN at follow-up	4 (13%)	9 (36%)	0.04

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CRediT authorship contribution statement

Ekbom E: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. **Frithiof R:** Funding acquisition, Conceptualization, Supervision, Project administration, Resources, Methodology Investigation, Writing – review & editing. **Emilsson Öi:** Methodology, Writing – review & editing. **Larson Im:** Investigation, Writing – review & editing. **Lipcsey M:** Supervision, Project administration, Resources, Funding acquisition, Conceptualization, Methodology, Investigation, Writing – review & editing. **Rubertsson S:** Writing – review & editing. **Wallin E:** Investigation, Writing – review & editing. **Janson C:** Supervision, Writing – review & editing. **Hultström M:** Funding acquisition, Conceptualization, Supervision, Project administration, Resources, Investigation, Methodology, Writing – review & editing. **Malinovschi A:** Supervision, Project administration, Resources, Funding acquisition, Conceptualization, Methodology, Writing – review & editing.

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