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Early View

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Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post infection

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Title: Functional characteristics of patients with SARS-CoV-2 pneumonia at 30 days post infection

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Running title: short-term PFT evaluation after Covid-19 pneumonia

Key words: SARS-CoV2; Vital capacity; TLCO; pneumonia

To the editor:

We read with great interest the series by Mo et al., describing pulmonary function after SARS-CoV-2 in hospitalized patients [1]. The authors describe a significant correlation between TLCO and clinically-defined pneumonia severity.

Lung involvement of various extent has been found in at least 80% of patients on CT in SARS-CoV-2 [2, 3]. Extensive injury to alveolar epithelial cells and endothelial cells, with secondary fibroproliferation is a signature of pulmonary SARS-CoV-2 infection [4] and indicate a potential for chronic vascular and alveolar remodeling leading to lung fibrosis and/or pulmonary hypertension..

We conducted a retrospective study in patients with SARS-CoV-2 pneumonia to assess the pulmonary functional status one month after symptoms onset and correlate lung function alteration with the severity of pneumonia.

Patients under the age of 85 years with confirmed SARS-CoV-2 infection (positive RT-PCR on nasopharyngeal swab) and respiratory symptoms, discharged from Bichat hospital between 03/04/2020 and 04/01/2020, were evaluated with pulmonary function tests (PFT) 30 days after symptom onset [5], as part of routine care. All tests included spirometry, Functional Residual Capacity (FRC), Total Lung Capacity (TLC) and TLCO (single breath real-time CO/NH_4) measurements. FRC was measured by helium dilution (Masterscreen PFT, The Surgical Company, Flaxlanden, France) in non-smokers and by bodyplethysmography (Vyntus Body, The Surgical Company) in smokers. Predicted values from Global Lung Initiative (GLI) were used for FVC and TLCO [6]. A senior radiologist (MPD) reviewed all chest CT and evaluated the extent of pneumonia as absent, mild (<10% of parenchyma involved), moderate (10-24%), wide (25-49%), or severe (≥ 50%), according to European guidelines [7]. For the analysis, we classified patients into three groups according to the extent of pneumonia: none or mild, moderate, and wide-to-severe. For patients with several CT-scans during disease course, we retained the highest extent of parenchymal involvement. We

assessed correlations between PFT values and BMI, and age. Finally, we classified patients in three groups of clinical severity based on oxygen requirement during disease course: none, 0.5-6 L/min, and > 6 L/min/high flow/ invasive ventilation. Comparisons between groups used Mann-Whitney and Kruskal-Wallis tests for continuous variables, and chi-2 or Fischer's exact tests for categorical variables (Prims 8, Graphpad, San Diego, USA). Non-opposition was obtained for all patients, according to French law.

Fifty-six patients were recruited, 5 declined to participate and one had recurrence of symptoms, leading to the assessment of 50 patients. One patient could not perform TLCO and HRCT was not performed in 5 patients. Patients' characteristics and PFT results are described in Table. There was no difference between groups regarding BMI, age, or comorbidities. Prevalence of hypertension and diabetes mellitus was 48% and 16% respectively. At the time of functional assessment, median SpO_2 (room air) was 96%. Among patients without HRCT, 3 had normal PFT, one had restrictive pattern and one had isolated low TLCO. More than half of patients (27/50) had impaired lung function, with a mix of restrictive and low diffusion patterns. We found no difference in FVC, TLC or TLCO (% pred. values) between groups of CT-extent, but a significant difference in the proportion of abnormal values (i.e. restriction and/or altered DLCO) (p=0.0277). Lower TLCO was significantly associated with older age (> 50 years) (p=0.0351), but neither was TLC nor FVC. Finally, FVC, TLC and TLCO were not significantly different between groups of clinical severity (i.e. oxygen requirement).

Overall, our study shows that one month after SARS-CoV-2 infection, a majority of patients have mild alterations of lung function. Unlike Mo et al., we classified patients on chest-CT, which has been shown to have high sensitivity, even in patients with mild symptoms [2, 7], in addition to clinical severity. By contrast to Mo's, our population is comparable to published series, with overweight patients, a predominance of men, and a high prevalence of hypertension. Other strengths are the systematic PFT assessment in patients with initial respiratory symptoms, the use of GLI reference

equations with real-time single breath TLCO measurement, and the CT assessment of the extent of lung involvement during the acute phase.

Noteworthy, we included neither patients with ARDS, since most were still hospitalized at the time of our study, nor patients over 85 years, because of the lack of valuable predicted values. This could lead to underestimation of the percentage of patients with functional impairment. Another limit is the lack of functional data before SARS-CoV-2 but most patients were devoid of known respiratory disease history. We did not systematically perform chest CT at 30 days, due to limited access in the context of epidemic and radiation dose limitation. Of note, in a study by Wang et al., 94% of discharged patients had residual disease on final CT scans although the median illness duration from symptom onset to hospital discharge was 25 days [3], it is thus possible that HRCT in our patients were still abnormal despite normal PFT results. Last, due to the limited number or patients, the absence of approved specific treatment and the retrospective design, we could not assess the effect of treatment on the functional recovery.

Abnormal lung function tests in more than 50% of the patients raise concern regarding potential progression towards lung fibrosis especially taking into account the lung alveolar epithelial cell tropism [8]. In addition isolated decreased TCLO in 13/50 (26%) of them may also lead to the hypothesis of a vascular damage according to SARS-CoV-2-induced lung vascular damage [9]. The pathogenicity of SARS-CoV-2 pneumonia to date is still debated, with some post mortem biopsies showing acute fibrinous and organizing pneumonia (AFOP) rather than diffuse alveolar damage [10], rending functional evolution of patients difficult to predict. The poor correlation between extent of pneumonia on CT and PFT findings renders difficult the a priori evaluation of prognosis, with patients presenting abnormal results despite mild disease on CT. Altogether these results plead for systematic functional assessment of SARS-CoV-2 patients with initial respiratory symptoms and long-term follow-up with HRCT and PFT. Larger studies, involving older patients and comparing the evolution of patients under different treatments, are also needed.

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Table : patients characteristics. Unless specified, results are presented as median (Q1;Q3). Extent of pneumonia on CT was defined as absent, mild (<10%), moderate (10-24%) or wide-to-severe (≥ 25%)[7]. *: p<0.05

	All n=50	No CT n=5	None/Mild n=12	Moderate n=17	Severe n=16
Age	54 (46;62)	30 (30;46)	55 (46;63)	53 (47;56)	58 (49;67)
Male sex, n (%)	28 (56)	2 (40)	4 (33)	9 (53)	13 (81)
BMI (kg/m^2)	27.0 (24.6;32.5)	24.0 (21.0;25.0)	28.5 (25.0;34.0)	28.0 (24.5;31.0)	27.0 (25.8;31.5)
Respiratory Comorbidities					
Emphysema	2 (4)	0 (0)	1 (8)	1 (6)	0 (0)
Asthma	2 (4)	0 (0)	2 (17)	0 (0)	0 (0)
Sarcoidosis	1 (2)	0 (0)	1 (8)	0 (0)	0 (0)
Smoking history					
Active, n (%)	5 (10)	0 (0)	1 (8)	3 (18)	1 (6)
Former, n (%)	9 (18)	0 (0)	2 (17)	3 (18)	4 (25)
Care modality					
Out-patient, n (%)	9 (18)	4 (80)	4 (33)	1 (6)	0 (0)
Infectious diseases ward, n (%)	33 (66)	1 (20)	8 (66)	15 (88)	9 (56)
ICU, n (%)	7 (14)	0 (0)	0 (0)	1 (6)	7 (44)
Respiratory support					
None, n (%)	20 (40)	5 (100)	9 (75)	6 (6)	0 (0)
Oxygen 0-6 L/min, n (%)	24 (48)	0 (0)	3 (25)	11 (65)	10 (63)
Oxygen ≥12 L/min, n (%)	1 (2)	0 (0)	0 (0)	0 (0)	1 (6)

High flow oxygen, n (%)	4 (8)	0 (0)	0 (0)	0 (0)	4 (25)
Invasive ventilation, n (%)	1 (2)	0 (0)	0 (0)	0 (0)	1 (6)
FVC (% pred)	93 (85;99)	101 (93;102)	93.5 (88;97)	87 (85;101)	90 (81;96)
TLC (% pred)	91.5 (81;103)	104 (102;120)	97.5 (91;103)	91 (81;101)	82.5 (77;92)
TLCO (% pred)	80 (70;92)	90 (81;91)	87 (73;92)	81 (72;93)	71 (57;78)
KCO (% pred)	94 (78;108)	96 (76;99)	99 (77;108)	101 (89;111)	90 (84;95)
FEV1 (% pred)	93 (83;100)	104 (93;111)	92 (85;96)	91 (82;97)	92 (85;104)
FEV1/FVC	0.81 (0.75;0.87)	0.85 (0.84;0.87)	0.78 (0.74;0.84)	0.79 (0.77;0.87)	0.84 (0.75;0.88)
PFT interpretation					
Normal, n (%)	24 (48)	3 (60)	8 (66)*	9 (53)*	3 (19)*
Restrictive pattern, n (%)	4 (8)	1 (20)	0 (0)	3 (18)	2 (13)
Restriction with altered diffusion capacity, n (%)	9 (18)	0 (0)	0 (0)	2 (12)	6 (38)
Altered diffusion capacity only, n (%)	13 (26)	1 (20)	4 (33)	3 (18)	5 (31)

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