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Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: The post Covid M3 study

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Original Research

Residual ground glass opacities three months after Covid-19 pneumonia correlate to alteration of respiratory function: The post Covid M3 study

Introduction: Lung function in survivors of SARS-CoV-2 pneumonia is poorly known, but concern over the possibility of sequelae exists.
Methods: Retrospective study on survivors with confirmed infection and pneumonia on chest-CT. Correlations between PFT and residual radiologic anomalies at three months taking into account initial clinical and radiologic severity and steroid use during acute phase.
Results: 137 patients (69 men, median age 59 (Q1 50; Q3 68), BMI 27.5 kg/m² (25.1; 31.7)) were assessed. Only 32.9% had normal PFT, 75 had altered DLCO. Median (Q1; Q3) values were: VC 79 (66; 92) % pred, FEV1 81 (68; 89), TLC 78 (67; 85), DLCO 60 (44; 72), and KCO 89 (77; 105). Ground glass opacities (GGO) were present in 103 patients (75%), reticulations in 42 (30%), and fibrosis in 18 (13%). There were significantly lower FEV1 (p = 0.0089), FVC (p = 0.0010), TLC (p < 0.0001) and DLCO (p < 0.0001) for patients with GGO, lower TLC (p = 0.0913) and DLCO (p = 0.0181) between patients with reticulations and lower FVC (p = 0.0618), TLC (p = 0.0742) DLCO (p = 0.002) and KCO (p = 0.0114) between patients with fibrosis. Patients with initial ≥50% lung involvement had significantly lower FEV1 (p = 0.0019), FVC (p = 0.0033), TLC (p = 0.0028) and DLCO (p = 0.0033).

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ABSTRACT

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1. Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection has affected more than 100 millions of people worldwide and is responsible for at least 880 000 deaths [1]. At the acute phase, disease can range from asymptomatic to extremely severe with acute respiratory distress syndrome (ARDS). Few data exist regarding at-distance follow-up and the high number of affected people raises the possibility of millions of people with coronavirus disease 2019 (COVID-19)-related sequelae.

In a retrospective study conducted in China, 79.3% of 145 patients with confirmed SARS-CoV-2 infection showed bilateral pneumonia, 18.6% showed unilateral pneumonia, 61.4% showed ground-glass opacity, and only 2.1% showed no abnormal chest CT result [2]. Radiologic and post mortem studies of patients show that lung injury in severe SARS-CoV-2 infection is not a classic diffuse alveolar damage for patients with ARDS but rather an acute fibrous and organizing pneumonia (AFOP) characterized by an extensive intra-alveolar fibrin deposition called fibrin «balls», rather than hyaline membranes, and that many patients present with secondary consolidation of lesions, resembling organizing pneumonia [3,4].

Extensive injury of alveolar epithelial cells and endothelial cells, with secondary fibroproliferation is a signature of pulmonary SARS-CoV-2 infection and indicate a potential for chronic vascular and alveolar remodeling leading to lung fibrosis and/or pulmonary hypertension.

In survivors of SARS-CoV ARDS, mean lung volumes and spirometric measurements were nearly normal by 6 months, and there was no significant difference in pulmonary function measurement at 12 months between those who had required mechanical ventilation and those who had not, except for a lower diffusion capacity [5,6]. However, the number of affected patients worldwide was lower, with younger age and less comorbidities compared to SARS-CoV-2 patients. Our previous work on short term respiratory follow-up one month after symptom onset showed that more than half of the patients had altered respiratory function, emphasising the need for longer term follow-up [7]. We found no correlation between respiratory function one month after the infection and radiological severity. At an earlier time point, Mo et al. [8] found no correlation between lung function at time of discharge and clinical severity. Still, due to the early timing of functional evaluation, there were few severe patients (i.e requiring invasive ventilation) in both these studies. In the prospective study by Shah et al., more than half of the patients had abnormal PFT at 12 weeks, but only hospitalised patients were included [9]. In addition, in a recent study in the Netherlands, 71% of patients complained of residual dyspnoea at three months after COVID, but no functional data were given [10]. We aimed to assess the natural history of functional recovery after SARS-CoV-2 pneumonia. Thus, we assessed the pulmonary functional status three months after symptoms onset in patients with SARS-CoV-2 pneumonia and studied correlations between lung function alterations and radiological status, taking into account the initial clinical and radiological severity of pneumonia.

2. Methods

All consecutive patients with confirmed SARS-CoV-2 infection (positive RT-PCR on nasopharyngeal swab) and respiratory symptoms, followed at two tertiary hospitals (Bichat hospital or la Pitié Salpêtrière hospital, Paris, France) between 01 feb 2020 and 01 aug 2020, referred for pulmonary function tests (PFT) three months after disease onset, as part of routine care, were eligible. Patients were systematically offered hospital PFT evaluation if they had needed 6 l/min or more oxygen during acute phase, or if they had residual respiratory symptoms at three months. Patients were excluded if they had not performed initial or three-month chest-CT, or if they had previously known respiratory disease, including asthma and COPD. All tests included spirometry, Functional Residual Capacity (FRC), Total Lung Capacity (TLC) and DLCO (single breath) measurement. Six-minute walking test was performed if the patient was able to walk. Predicted values from ERS/ECSS 1993 and lower limits of normal (LLN) were used [11,12].

Three senior radiologist (MPD, SB or AK) reviewed all chest computed tomography (CT) scans performed at three months performed as part of routine care. They assessed the presence of residual ground-glass opacities (GGO, categorized as absent, mild, moderate or severe depending on extent and density), the presence of reticulations and signs suggestive of fibrosis. They also evaluated the extent of pneumonia during initial acute phase as absent, mild (<10% of parenchyma involved), moderate (10–24%), wide (25–49%), severe (50–74%), or very severe (≥75%), according to European guidelines [13].

We assessed correlations between PFT values and three-month chest-CT abnormalities. We also assessed correlations between PFT values and initial pneumonia extent, body mass index (BMI), and age. To assess the effect of steroids during acute infection on functional recovery, we matched patients who had received steroids and those who had not, based on age, BMI and initial radiological severity. Finally, we classified patients in groups of clinical severity based on maximal oxygen requirement during the disease course: none, 0.5–6 L/min, 6–15 L/min, high flow canula with active humidification, non-invasive ventilation (including continuous positive airway pressure), or invasive ventilation.

Comparisons between groups used Mann-Whitney and Kruskal-Wallis (with Dunns’ multiple comparisons tests) 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. The study was approved by the Institutional Review Board of the French learned society for respiratory medicine -Société de Pneumologie de Langue Française (ref 2020–056).

3. Results

3.1. Patients’ characteristics

One hundred and ninety-nine patients had performed PFT at three months, either as outpatients (Bichat), or during post-Covid19 rehabilitation (La Pitié Salpêtrière), among which 36 were excluded because of known previous respiratory condition. Twenty-six patients were excluded because they had performed neither initial chest-CT (n = 18) nor three-month chest-CT (n = 8), leading to a final sample of 137 patients (see Fig. 1 for the study flow-chart). Patients’ characteristics and PFT results are described in Tables 1 and 2 (see Fig. 2). Sixty-eight (49.6%) had hypertension and 38 (27.7%) had diabetes mellitus. There was no difference in PFT results between younger (e.g. < 60 years) and older patients. Obese patients had significantly lower KCO than non-obese patients (p = 0.0057), other PFT values were not significantly different.

Overall, only 45 (32.9%) patients had normal PFT results at three
months, 13 (9.5%) had a restrictive pattern, 39 (28.5%) had restriction and diffusion alteration, and 36 (26.3%) had isolated low diffusion capacity. Obstruction was noted in 7 (5%) patients. Among the 75 patients with altered DLCO (either with or without restriction), alteration was mild (DLCO > 60% of predicted value) for 32 patients (43%), moderate (DLCO 40–60%) for 33 patients (44%), and severe (DLCO <40%) for 10 patients (13%).

3.2. Correlation between residual CT abnormalities at three months and pulmonary function

Ground glass opacities (GGO) were the most common feature and were present in 103 patients (75%), reticulations were present in 42 (30%), and fibrosis in 18 (13%). Patients with residual GGO had significantly lower FEV1 (p = 0.0089), FVC (p = 0.0010), TLC (p < 0.0001) and DLCO (p < 0.0001), but not FEV1/FVC or KCO. Patients with reticulations had significantly lower TLC (p = 0.0913) and DLCO (p = 0.0181) but not FEV1, FVC, FEV1/FVC or KCO. Finally, patients with fibrosis had significantly lower values for DLCO (p = 0.002) and KCO (p = 0.0114), but not for FEV1, FVC, TLC and FEV1/FVC. Frequency of GGO, reticulations and fibrosis did not differ neither between smokers and non-smokers, nor between men and women. Results are summarized in Table 2.

3.3. Effect of steroids during acute infection on residual CT lesions and PFT

Thirty-nine patients (28.5%) had received oral or IV steroids during acute phase. There was no difference in lung function at three months between patients who had received steroids and those who had not. The proportion of patients with reticulations (p = 0.0383) and fibrosis (p = 0.0298) was significantly higher in patients who received steroids, than in those who did not, while the proportion of patients with residual GGO was similar in the 2 groups. in those who had received steroids. When patients were matched on initial radiological severity, BMI and age, there was no difference between patients who had received steroids and those who had not on reticulations and fibrosis.

3.4. Initial radiological and clinical severity and pulmonary function at three months

Patients with severe-to-extremely severe radiological initial pneumonia (defined as ≥ 50% of lung involvement), had a significantly lower 3 month-FEV1 (p = 0.0135), FVC (p = 0.0392), and DLCO (p = 0.0126),

| Table 1 | Patients’ characteristics. Results are presented as median (Q1; Q3) for continuous variables or n (%) for categorical variables. |
|-----|-----|
| Age | 59 (50; 68) |
| Male | 69 (51) |
| BMI (kg/m²) | 27.5 (25.1; 31.7) |
| Hypertension | 68 (50) |
| Diabetes | 38 (28) |
| Smoking status |  |
| Active | 18 (13) |
| Former | 27 (20) |
| Respiratory support |  |
| None | 13 (9.5) |
| Oxygen 0–6 L/min | 50 (36.5) |
| Oxygen > 6 L/min | 8 (5.8) |
| High flow nasal canula | 12 (8.8) |
| Continuous Positive Airway Pressure (CPAP) | 9 (6.6) |
| Non invasive ventilation | 1 (0.7) |
| Invasive ventilation | 44 (32.1) |
| Steroids | 39 (29) |

Fig. 1. Study flow chart.
compared to patients with none/mild initial pneumonia. Patients who had received invasive ventilation had significantly lower PFT values at three months for FEV1/FVC, TLC and KCO. There was no significant difference in PFT values at three months between patients with moderate or severe initial pneumonia or patients with none/mild pneumonia.

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recommendations is also a strength.

Although retrospective, our study included a high number of patients of different radiological and clinical severity. A limit of our study is that we included 31% of patients who had undergone invasive ventilation. This is higher than expected in a general population of SARS-CoV-2 infected patients, and could have contributed to increase the proportion of abnormal PFT results. We did not classify patients according to unit of admission (ICU or non-ICU), since in the context of the pandemic, many patients with high flow oxygen or CPAP were treated in non-ICU wards. Another limit is the lack of functional data before SARS-CoV-2 pneumonia, but patients with known previous respiratory condition were excluded. Interestingly, in the study by Guler et al. focusing only on hospitalized patients and not assessing the effect of steroids [21]. As for ourselves, we did not assess the effect of other treatments on steroids on the functional recovery since treatment modalities other than respiratory support and steroids are heterogenous.

Altogether, these results plead for systematic assessment of SARS-CoV-2 patients with initial respiratory symptoms and long-term follow-up, ideally with lung volumes assessment and chest-CT scan. When considering the normal KCO and the correlation between 3 month-lung function and chest-CT residual abnormalities, follow-up measurement is not easily available (e.g. private practices, countries with limited resources in PFT). This is in accordance with the position paper by George et al. who propose chest X-ray and CT as screening tools [22]. In the study by Huang et al., at six months, recovery is achieved in less than 80% of patients, raising the possibility of permanent sequelae [23]. Indeed, it is important to assess pulmonary function at early time points to get a better knowledge of the natural history of SARS-CoV-2 recovery, and research on lung function has been granted priority in the last ERS/ATS task force on Covid-19 management [24].

In conclusion, impairment in lung function is common at three months after SARS-CoV-2 pneumonia, even in patients with mild initial disease. Larger studies, involving patients who did not require oxygen and/or hospitalisation, but also other studies involving more patients with ARDS and comparing the evolution of patients under different treatments, are now needed to understand, predict and prevent pulmonary sequelae of COVID-19. The specific effect of steroids on lung function recovery should be assessed in prospective studies with standardized treatment regimen.

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Table 3

| Variable                        | Univariate β coefficient | 95% CI     | p value  | Multivariate β coefficient | 95% CI     | p value  |
|---------------------------------|--------------------------|------------|----------|---------------------------|------------|----------|
| Age                             | 0.06                     | [0.03-0.09] | 0.003*   | 0.07                      | [0.04-0.12] | 0.015*   |
| Sex (female)                    | -0.31                    | [-0.43-0.10]| 0.396    |                           |            |          |
| BMI                             | -0.05                    | [-0.11 - 0.02] | 0.174    |                           |            |          |
| Hypertension                    | 0.07                     | [0.65 - 0.78] | 0.855    |                           |            |          |
| Diabetes                        | 0.08                     | [0.71 - 0.91] | 0.845    |                           |            |          |
| Administration of corticosteroids | 0.48                    | [0.33 - 1.34] | 0.001*   | 1.12                      | [0.39 - 1.94]| 0.004*   |
| Degree of initial lung involvement | 1.24                    | [0.55 - 2.02] |          | 1.29                      | [0.33 - 2.36] | 0.012*   |
| Endotracheal intubation          | 0.85                     | [0.04 - 1.74] |          | 0.048*                    |            |          |

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CRedit authorship contribution statement

Justine Frija-Masson: Conceptualization, Methodology, Formal analysis, Writing – original draft, Writing – review & editing. Marie-Pierre Debray: Investigation, Validation, Writing – review & editing, Methodology, Writing – review & editing, Supervision. Samia Boussoar: Investigation, Validation, Writing – review & editing. Antoine Khalil: Investigation, Validation, Writing – review & editing. Catherine Bancal: Investigation, Resources, Validation, Writing – review & editing. Justina Motiejunaite: Investigation, Resources, Formal analysis. Maria Alejandra Galarza-Jimenez: Investigation, Resources. Dominique Penaud: Investigation, Resources. Pierantonio Laveneziana: Investigation, Resources, Writing – review & editing. Roxane Malrin: Investigation, Resources. Alban Redheuil: Investigation, Writing – review & editing. Victoria Doncic: Investigation, Writing – review & editing. Olivier Lucidarme: Investigation, Writing – review & editing. Camille Taille: Investigation, Resources, Writing – review & editing. Antoine Guerder: Investigation, Resources. Florence Arnould: Investigation, Resources. Emmanuelle Vidal-Petiot: Methodology, Writing – review & editing. Martin Plamant: Data curation, Methodology, Formal analysis. Thomas Simkowksi: Resources, Writing – review & editing. Capucine Morelot-Panzini: Resources, Writing – review & editing. Morgane Faure: Investigation, Resources. Francois-Xavier Lesrue: Resources, Writing – review & editing. Christian Straus: Investigation, Resources, Writing – review & editing. Jesús Gonzalez-Bermejo: Conceptualization, Methodology, Writing – review & editing, Supervision.
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