Received: 19 March 2021 | Revised: 30 April 2021 | Accepted: 11 May 2021

DOI: 10.1111/eci.13603

RESEARCH LETTER

WILEY

Respiratory follow-up after hospitalization for COVID-19: Who and when?

1 | INTRODUCTION

Despite more than 148 million infected people, coronavirus disease 2019 (COVID-19) respiratory intermediate- and long-term survivors' outcome remains largely unknown. Lungs are the main COVID-19 target organ, and 5%-10% patients progress to critical disease including acute respiratory distress syndrome (ARDS).[1] Pulmonary function tests (PFTs) performed at discharge from hospital showed that >80% of patients with severe COVID-19 had lung function impairment.[2] Observational studies in coronavirus-infected patients (SARS-CoV-1 in 2003 or Middle East respiratory syndrome (MERS) in 2012) suggested that functional limitations due to pulmonary fibrosis and other patterns of lung damage may persist after severe acute respiratory syndrome (SARS).[3-5] A recent publication reported persistent respiratory abnormalities four months after severe/critical COVID-19.[6] Currently, results of pulmonary assessment beyond 4 months are not available. The main objective of this study was to identify the patients who will benefit from a first respiratory assessment and determine when and how to evaluate them. Indeed, several follow-up strategies have been proposed but no consensus exists, mainly because of the lack of clinical, radiological and functional middle-term data.[7-9]

2 | METHODS

2.1 | Patients

The Respiratory Care Department of Strasbourg University Hospital, France, participated in COVID-19 patient care during the first outbreak of the pandemic in France (March-April 2020). A respiratory follow-up comprising PFT, chest computerized tomography (CT) scan, 6-minutes walking distance test (6-MWD) and a respiratory consultation was offered to these patients, at 3 months and, if abnormal, also at 6 months after hospital discharge. From June to December 2020, 81 patients participated in this monitoring. Written consent was obtained from patients during hospitalization, and this study was submitted for approbation to the Institutional Review Board of the French Learned Society for Respiratory Medicine (CEPRO 2021-013).

2.2 | Statistical analysis

Data were analysed according to the severity of COVID-19 during hospitalization, as defined by the World Health Organization (WHO), and patients were stratified into three groups : mild-to-moderate disease, severe disease and critical disease.[10] Descriptive data are presented as frequencies and percentages for categorical variables and median and interquartile ranges for continuous variables. Comparisons between the three groups were conducted using the chi-squared test for percentages and the t test for continuous variables. $P < .05$ was considered statistically significant. Reporting of the study conforms to broad EQUATOR guidelines.[11]

3 | RESULTS

Seventy-three per cent were male, and median age was 61 years (interquartile range [IQR], 51-68). Eighteen patients (22%) had a history of pulmonary disease (13 asthma and 5 chronic obstructive pulmonary disease). Thirty-three patients (including 29 critical patients) spent a > 4-week period in a rehabilitation unit after hospitalization. Clinical characteristics and comorbidities of patients are summarized in Table 1.

As defined by the WHO, patients were stratified into 3 groups: mild-to-moderate disease (n = 21), severe disease (n = 15) and critical disease (n = 45) [10] (Figure 1). Few patients (n = 16, 20%) complained of dyspnoea at 3 months, regardless of COVID-19 severity (19% of patients of the mild-to-moderate group, 20% of the severe group and 20% of the critical disease group, $P = .98$). No patient required oxygen therapy during the study period, and transcutaneous pulsed oxygen saturation (SpO_2) was 97% at 3 months (97%-98%) with no difference between the 3 groups of patients ($P = .90$). 6-MWD was normal or slightly decreased. SpO_2 at the end of test did not differ according to disease severity ($P = .34$) and was 96% (94%-97%) at 3 months. Regarding

TABLE 1 Demographics characteristics and comorbidities of the 81 patients. As defined by the World Health Organization, patients with COVID-19 were stratified in 3 groups: mild-to-moderate disease (n = 21), severe disease (n = 15) and critical disease (n = 45)

Total	Mild-to-moderate disease (n = 81)	Severe disease (n = 21)	Critical disease (n = 15)	*P* (n = 45)
Clinical characteristics				
Male (n/%)	59 (73%)	14 (67%)	12 (80%)	33 (73%) .67
Age (years)	61 (51-68)	58 (50-67)	63 (56-68)	63 (50-71) .39
BMI (Kg/m2)	28.3 (26.1-30.3)	28.7 (26.4-30.2)	30.1(27.7-31.8)	28 (25.8-30.3) .42
Main comorbidities				
Arterial hypertension (n/%)	42 (52%)	8 (38%)[a]	10 (66%)[a]	24 (53%)[a] .23
Diabetes (n/%)	24 (30%)	6 (28%)[a]	7 (47%)[a]	11 (24%)[a] .26
Chronic heart failure (n/%)	1 (1%)	0	1 (7%)	0 .11
Former or active smokers (n/%)	20 (25%)	5 (24%)[a]	6 (40%)[a]	9 (20%)[a] .29
Sleep apnoea syndrome (n/%)	16 (20%)	3 (14%)[a]	2 (13%)[a]	11 (24%)[a] .49
Underlying comorbid respiratory disease				
All causes	18 (22%)	9 (43%)[a]	4 (27%)[a]	5 (11%)[a] .01
COPD (n/%)	5 (6%)	3 (14%)[a]	1 (7%)[a]	1 (2%)[a] .16
Asthma (n/%)	13 (16%)	6 (29%)[a]	3 (20%)[a]	4 (9%)[a] .11
Interstitial lung disease (N/%)	0	0	0	0 _

Note: Quantitative variables are presented as median and interquartile range.

Abbreviations: BMI, body mass index (calculated as weight in kilograms divided by height in metres squared); COPD, chronic obstructive respiratory disease; COVID-19, coronavirus disease 2019.

[a]Percentages of patients stratified according to the group of severity.

PFT, patients with critical disease had lower diffusion capacity for carbon monoxide (DLCO) ($P = .005$) and total lung capacity (TLC) ($P = .006$) compared with the other patients, at 3 and 6 months (Figure 1). TLC and DLCO were measured at 6 months in patients with impaired PFT values at 3 months and showed no significant variation with time. Approximately 66% of patients with mild-to-moderate and severe disease had normal chest CT scan at 3 months, whereas persistent lung infiltrates—mostly peripheral ground-glass opacities—were observed in 71% of patients with critical disease (Figure 1). Extension of lung abnormalities remained below 25% of total surface of the parenchyma in all patients with mild-to-moderate or severe disease and in 84% of patients with critical disease. Between 3 and 6 months, lung infiltrates diminished in extension and density in the 3 groups, but reticulations and bronchiectasis, mostly minor, developed in 50% of patients with critical disease.

Only 11% of our patients with critical COVID-19 form (5 among 45) had a history of pulmonary disease (COPD or asthma), a value consistent with that of previous studies. Fifty per cent of patients with underlying comorbid respiratory disease (9 among 18) developed mild-to-moderate COVID-19 (Table 1). Concerning respiratory follow-up, 8 out of the 18 patients with a history of pulmonary disease had persistent lung infiltrates on chest CT scan at 3 months and only one had severe parenchymal abnormalities. Six of these patients were followed up at 6 months: only two had persistent but minor parenchymal abnormalities on chest CT scan. Regarding PFT, 6 patients had bronchial obstruction with forced expiratory volume in one second (FEV1) <80%. No patients had severe bronchial obstruction (FEV1 < 50%). Considering the observed clinical and radiological respiratory improvement, this bronchial obstruction was likely associated with the history of COPD. Median of DLCO was 75% in these patients and similar to patients without comorbid lung disease ($P = .41$).

4 | DISCUSSION

To summarize, we found that:

1) most patients did not complain of dyspnoea 3 months after COVID-19 onset even in the critical disease group and demonstrated normal or only slightly decreased 6-MWD,

81 patients

MILD to MODERATE disease (n = 21)

- No severe pneumonia including SpO2 > 90% on room air and
- Chest CT scan lesions < 50% of the total parenchyma

	3 months	6 months (n = 12/21)
6-MWD (meters)	452 (395-548)	527 (497-572)
Pulmonary function testing		
DLCO %	86 (79-96)	93 (87-101)
TLC %	109 (101-113)	109 (98-112)
Chest CT-scan		
Pulmonary infiltrates (n/%)	9/ 43%	4 / 33%
Ground glass infiltrates (n/%)	5 / 24%	2 / 17%
Bronchiectasies (n/%)	1 / 5%	0
Linear densities (n/%)	0	2 / 17%
Honeycombing (n/%)	0	0

SEVERE disease (n = 15)

- Clinical signs of severe pneumonia + one of the following
  - SpO2 < 90% on room air
  - Respiratory rate > 30 breaths/min
  - Severe respiratory distress
- Chest CT scan infiltrates > 50% of the total parenchyma

	3 months	6 months (n = 3/15)
6-MWD (meters)	480 (405-525)	&
Pulmonary function testing		
DLCO %	85 (71-92)	&
TLC %	95 (77-103)	&
Chest CT-scan		
Pulmonary infiltrates (n/%)	5 / 33%	&
Ground glass infiltrates (n/%)	3 / 20%	&
Bronchiectasies (n/%)	2 / 13%	&
Linear densities (n/%)	4 / 27%	&
Honeycombing (n/%)	0	&

CRITICAL disease (n = 45)

- Acute respiratory distress syndrome
- Sepsis
- ICU hospitalization

	3 months	6 months (n = 29/45)
6-MWD (meters)	435 (381-480)	484 (440-568)
Pulmonary function testing		
DLCO %	71 (57-82)**	74 (66-77)**
TLC %	90 (75-95)**	87 (70-94)**
Chest CT-scan		
Pulmonary infiltrates (n/%)	32 / 71%**	18 / 62%
Ground glass infiltrates (n/%)	29 / 64%***	16 / 55%
Bronchiectasies (n/%)	16 / 35%**	15 / 50%**
Linear densities (n/%)	19 / 42%***	14 / 48%*
Honeycombing (n/%)	1 / 2%	1 / 3%

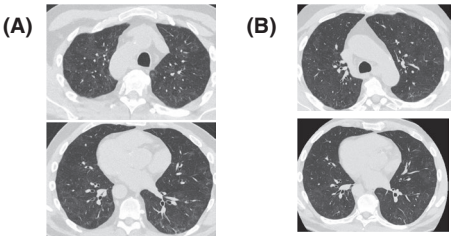

FIGURE 1 Pulmonary function test (PFT) (diffusion capacity for carbon monoxide [DLCO] and total lung capacity [TLC]) and chest CT scan results of the 81 patients. As defined by the World Health Organization, patients with COVID-19 were stratified in 3 groups: mild-to-moderate disease (n = 21), severe disease (n = 15) and critical disease (n = 45). Patients with abnormal CT scan or PFT at 3 months were re-evaluated at 6 months. &: only 3 patients were re-evaluated, precluding any conclusion about this group. Quantitative variables are presented as median and interquartile range, or number of patients (%). *$P < .05$, **$P < .01$ and ***$P < .001$: comparison between the groups of patients at 3 and 6 months. At 6 months, only 2 groups were compared (mild-to-moderate versus critical disease). A and B. Example of persistent lung opacities—mostly peripheral ground-glass opacities—on chest CT performed at 3 (A) and 6 months (B) after critical COVID-19, in a 60-year-old man. At 6 months, lung infiltrates diminished in extension and density with minimal signs of fibrosis

2) TLC and DLCO were moderately decreased at 3 and 6 months and almost only in patients with critical disease and.

3) >50% of patients had persistent chest CT abnormalities at 6 months in the critical disease group, albeit remaining limited to less than 25% of the total lung parenchyma in 84% of them.

The lack of dyspnoea and the good performance at the 6-MWD surprised us, especially since a previous study showed that severe/critical COVID-19 was associated with reduced 6-MWD and exercise-induced oxygen desaturation at 4 months.[6] Two-third of our patients with critical COVID-19 were hospitalized for >4 weeks in a rehabilitation unit after hospitalization. As pulmonary rehabilitation is established as a key management strategy in a large number of chronic respiratory diseases, it may explain optimization of exercise capacity and absence of breathlessness in most of these patients at 3 to 6 months.

These preliminary data support the need to assess respiratory outcomes of the most severe patients after COVID-19, that is patients with critical disease /ARDS. Recently, Guler et al reported that DLCO measured at 4 months was the strongest independent factor associated with previous severe/critical disease in a multivariable model.[6] In our study, DLCO was also significantly reduced almost only in the most severe patients. As a result, and as in SARS-CoV-1 or MERS survivors, DLCO seems to be the more relevant functional parameter to evaluate respiratory function after COVID-19.[12] Furthermore, similar to ARDS induced by causes other than COVID-19, critical disease patients had more lung infiltrates on chest CT than the others. Infiltrates were mainly ground-glass opacities, with a common subpleural and basal location and linear densities that lessened between 3 and 6 months. Bronchiectasis, mostly minor, were present in 50% of the critical patients at 6 months, as previously described.[12,13] These radiological and respiratory functional abnormalities might represent residual damage after ARDS or might be COVID-19 sequelae per se. Let us note that previous studies on SARS have demonstrated persistence of impaired PFT 2 years after the disease onset.[12]

According to our data, respiratory evaluation at 3 months seems to be premature if patients do not complain of respiratory symptoms. Scheduling evaluation at 6 months appears more appropriate. Less severe patients' follow-up should be discussed on a case-by-case basis and scheduled in patients

who complain of persistent dyspnoea or other respiratory symptoms. Moreover, in our series, clinical, functional and radiological additional respiratory impairment at 6 months is uncommon in patients with a history of pulmonary disease.

In any event, the prevalence and severity of pulmonary sequelae after severe forms of COVID-19 being unknown, a long-term respiratory monitoring of patients with intermediate-term functional or chest CT impairment, is warranted. Indeed, the course of such abnormalities remains to be described, and pulmonary function impairments are known to be associated with a significant reduction in health-related quality of life.[14] Such follow-up will help to understand the natural course of disease and—if any—to identify patients who may develop pulmonary fibrosis and who could be enrolled in clinical trials assessing antifibrotic or immune-modulating drugs.[15]

To conclude, evaluating respiratory function and imaging before 6 months after COVID-19 onset seems to be premature, because most abnormalities improved between 3 and 6 months even in patients with critical disease. A systematic respiratory follow-up of patients without critical disease does not seem relevant and must be discussed on a case-by-case basis. However, since potential sequelae are still to be described, longer follow-up of patients who present persistent respiratory symptoms, impaired PFT or lung abnormalities on CT is required.

KEYWORDS

COVID-19, respiratory function, respiratory outcome, respiratory sequelae

ACKNOWLEDGEMENTS

We acknowledge all the medical and paramedical team of the Chest Diseases Department and the Department of Physiology and Functional Exploration for their help in this follow-up.

CONFLICT OF INTEREST

All authors except Frédéric De Blay have no conflict of interest. Pr De Blay perceived financial supports from Aimmune, Stallergènes Greer, Mundipharma, Novartis, Regeneron, DVB, Sanofi, ALK, Boehringer and AstraZeneca, outside the submitted work.

AUTHOR CONTRIBUTIONS

MR, MC, WO, IE, CP and EC contributed to the medical follow-up of the patients and collected the data. MR and AC analysed the data and wrote the manuscript. AL and MO contributed to the chest CT scans and analysed and reviewed the manuscript. All authors reviewed and edited the manuscript and contributed to the discussion, were the guarantor of this work and, as such, had full access to all the data in the study and had taken responsibility for the integrity of the data and the accuracy of the data analysis.

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Written consent was obtained from patients during hospitalization, which articulated that they had no objections to the use of their clinical or paraclinical data. This study was submitted for approbation to the Institutional Review Board of the French Learned Society for Respiratory Medicine.

DATA AVAILABILITY STATEMENT

The data sets used and/or analysed during the current study are available from the corresponding author on reasonable request.

Marianne Riou[1,2,3]
Christophe MarcoT[3]
Walid Oulehri[2,4]
Irina Enache[1,2]
Cristina Pistea[1]
Eva Chatron[3]
Aissam Labani[5]
Bernard Geny[1,2]
Mickael Ohana[5]
Frederic De Blay[2,3]
Romain Kessler[3,6]
Anne Charloux[1,2]

[1]*Department of Physiology and Functional Exploration, University Hospital of Strasbourg, Strasbourg CEDEX, France*
[2]*Translational Medicine Federation of Strasbourg (FMTS), Faculty of Medicine, Team 3072 'Mitochondria, Oxidative Stress and Muscle Protection', University of Strasbourg, Strasbourg, France*
[3]*Chest diseases department, University Hospital of Strasbourg, Strasbourg CEDEX, France*
[4]*Department of Anesthesiology and Surgical Critical Care, University Hospital of Strasbourg, Strasbourg CEDEX, France*
[5]*Department of Radiology B, University Hospital of Strasbourg, Strasbourg CEDEX, France*
[6]*INSERM-UNISTRA, UMR 1260 'Regenerative NanoMedicine', University of Strasbourg, Strasbourg CEDEX, France*

Correspondence
Marianne Riou, Physiology and Functional Exploration Service, University Hospital of Strasbourg, 1 Place de l'hôpital 67091 Strasbourg CEDEX, France.
Email: marianne.riou@chru-strasbourg.fr

ORCID

Marianne Riou https://orcid.org/0000-0001-6807-8582

REFERENCES

1. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
2. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J*. 2020;55(6):2001217.
3. Chang Y-C, Yu C-J, Chang S-C, et al. Pulmonary sequelae in convalescent patients after severe acute respiratory syndrome: evaluation with thin-section CT. *Radiology*. 2005;236(3):1067-1075.
4. Ketai L, Paul NS, Wong KT. Radiology of severe acute respiratory syndrome (SARS): the emerging pathologic-radiologic correlates of an emerging disease. *J Thorac Imaging*. 2006;21(4):276-283.
5. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: A systematic review and meta-analysis. *J Rehabil Med*. 2020;52(5):jrm00063.
6. Guler SA, Ebner L, Beigelman C, et al. Pulmonary function and radiological features four months after COVID-19: first results from the national prospective observational Swiss COVID-19 lung study. *Eur Respir J*. 2021;57(4):2003690
7. Balachandar V, Mahalaxmi I, Subramaniam M, et al. Follow-up studies in COVID-19 recovered patients–is it mandatory? *Sci Total Environ*. 2020;10(729):139021.
8. George PM, Barratt SL, Condliffe R, et al. Respiratory follow-up of patients with COVID-19 pneumonia. *Thorax*. 2020;75(11):1009-1016.
9. Raghu G, Wilson KC. COVID-19 interstitial pneumonia: monitoring the clinical course in survivors. *Lancet Respir Med*. 2020;8(9):839-842.
10. https://www.who.int/publications/i/item/clinical-management-of-covid-19
11. Simera I, Moher D, Hoey J, Schulz KF, Altman DG. A catalogue of reporting guidelines for health research. *Eur J Clin Invest*. 2010;40(1):35-53.
12. Ngai JC, Ko FW, Ng SS, To K-W, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*. 2010;15(3):543-550.
13. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128(4):2247-2261.
14. Schelling G, Stoll C, Vogelmeier C, et al. Pulmonary function and health-related quality of life in a sample of long-term survivors of the acute respiratory distress syndrome. *Intensive Care Med*. 2000;26(9):1304-1311.
15. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: the potential role for antifibrotic therapy. *Lancet Respir Med*. 2020;8(8):807-815.

How to cite this article: Riou M, MarcoT C, Oulehri W, et al. Respiratory follow-up after hospitalization for COVID-19: Who and when?. *Eur J Clin Invest*. 2021;51:e13603. https://doi.org/10.1111/eci.13603