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Original Research

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ABSTRACT

Introduction: Lung function in survivors of SARS-Co-V2 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 radiological severity and steroid use during acute phase.

Results: 137 patients (69 men, median age 59 (Q1 50; Q3 68), BMI 27.5 kg/m^2 (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 ($p =$

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0.0003) compared to patients with ≤10%. There was no difference in PFT and residual CT lesions between patients who received steroids and those who did not.
Conclusion: The majority of patients have altered PFT at three months, even in patients with mild initial disease, with significantly lower function in patients with residual CT lesions. Steroids do not seem to modify functional and radiological recovery. Long-term follow-up is needed.

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 fibrinous 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 have 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 Salpétrière 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/ECCS 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 Salpétrière), 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.

Table 1
Patients' characteristics. Results are presented as median (Q1; Q3) for continuous variables or n (%) for categorical variables.

	All n = 137
Age	59 (50; 68)
Male	69 (51)
BMI (kg/m^2)	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 Airwaw Pressure (CPAP)	9 (6.6)
Non invasive ventilation	1 (0.7)
Invasive ventilation	44 (32.1)
Steroids	39 (29)

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 ($p = 0.0126$),

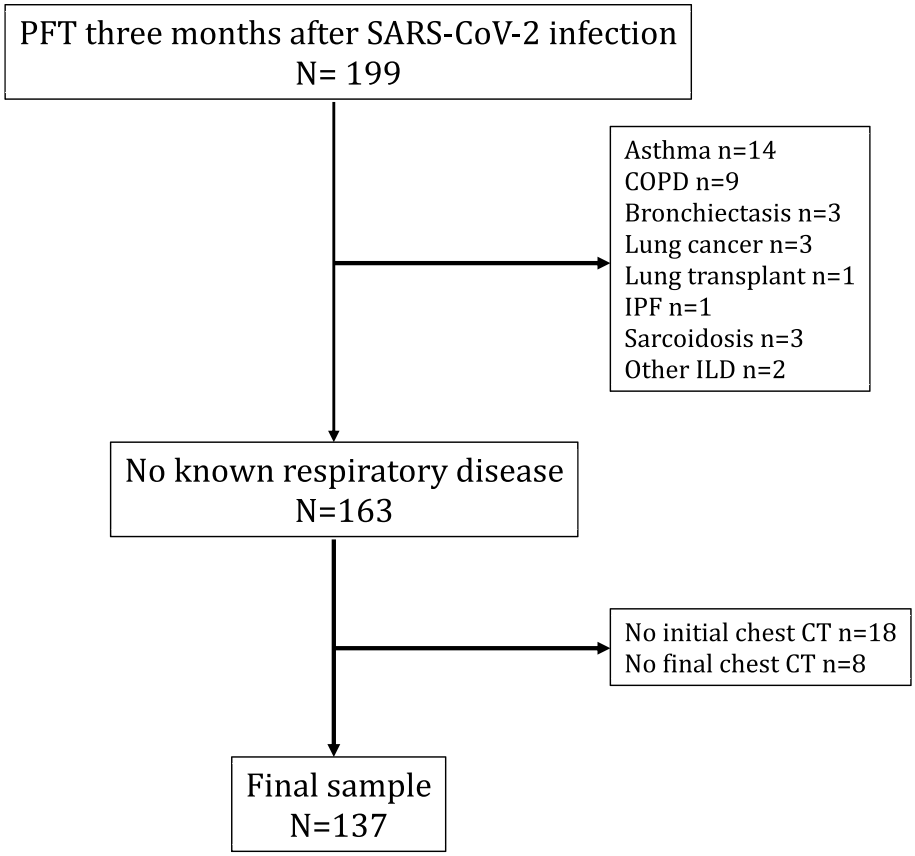

Fig. 1. Study flow chart.

Table 2
Pulmonary function at three months. Results are presented as % predicted values (except for FEV1/FVC), median (Q1;Q3). *:p < 0.05 compared to patients without ground glass opacities (GGO). &: p < 0.05 compared to patients without reticulations. §:p < 0.05 compared to patients without fibrosis.

	All	GGO		Reticulations		Fibrosis	
	All	No	Yes	No	Yes	No	Yes
VC	79 (66; 92)	100 (86; 118)	85 (72; 100)*	89 (76; 105)	85 (73; 98)	89 (77; 104)	78 (64; 94) §
TLC	78 (67; 85)	104 (86; 117)	83 (73; 95)*	88 (78; 103)	84 (72; 96) &	85 (77; 103)	81 (70; 95) §
DLCO	60 (44; 72)	74 (68; 83)	62 (51; 74)*	68 (59; 79)	62 (50; 71) &	66 (59; 78)	49 (36; 64) §
KCO	89 (77; 105)	91 (82; 104)	89 (77; 101)	90 (81; 102)	89 (72; 103)	90 (81; 104)	74 (63; 92) §
FEV1	81 (68; 89)	94 (83; 114)	85 (75; 98)*	89 (78; 104)	86 (75; 95)	89 (79; 102)	82 (69; 95)
FEV1/ FVC	0.84 (0.75; 0.86)	0.80 (0.76; 0.83)	0.81 (0.76; 0.84)	0.81 (0.75; 0.84)	0.81 (0.76; 0.85)	0.81 (0.75; 0.84)	0.81 (0.77; 0.84)

compared to patients with none/mild initial pneumonia, (defined as < 10% of lung involvement). No difference was found regarding FEV1/FVC, TLC and KCO. There was no significant difference in PFT values at three months between patients with moderate or wide initial pneumonia and patients with none/mild pneumonia.

Patients who had received invasive ventilation had significantly lower PFT values at three months for FEV1 (p = 0.0001), FVC (p = 0.0002), TLC (p = 0.0001), DLCO (p = 0.0049), but not KCO or FEV1/FVC.

We performed a univariate logistic regression in order to predict abnormal pulmonary function at 3 months after the initial SARS-CoV-2 infection. We saw that age, the severity of initial lung involvement as shown by chest CT as well as necessity for endotracheal intubation and invasive ventilation during hospitalisation were predictive of abnormal PFT at 3-month follow-up. Multivariate logistic regression (after adjustment of age, sex and body mass index) confirmed these findings (see Table 3 for *P*-values).

4. Discussion

Our study shows that three months after disease onset of SARS-CoV-2 pneumonia, the majority of the patients have altered lung function. The predominant abnormality is altered diffusion capacity, sometimes without restriction. Residual GGO were present in 75% of patients and significantly associated with a poorer lung function. Steroids during the acute phase had no effect on 3 month-lung function or residual CT-lesions in our cohort. Our population is comparable to published series, with overweight patients, a discrete predominance of men, and a high prevalence of hypertension. To our knowledge, this is the first study to assess the effect of steroids during acute infection on functional and radiological 3 month-recovery.

The finding of abnormal lung function tests in more than 50% of the patients raises concern regarding potential progression towards lung fibrosis, especially given the lung alveolar epithelial cell tropism of the virus [14]. Another important finding of our study, with crucial clinical implications, was the poor correlation between extent of pneumonia on initial CT and PFT findings at three months, except for severe-to-extremely-severe pneumoni. Indeed, abnormal respiratory function tests were observed despite mild initial disease on CT in some patients. Thereby, sequalae of COVID-19 are not easily predictable and further studies are necessary to identify prognostic markers and select patients who require closer follow-up after discharge. In the study by Zhao et al., 16% of the patients had abnormal DLCO at three months, but the study included only 55 patients, with only 4 patients having experienced severe disease. In addition, the population was younger than in our study (mean age 47 years) [15]. Shah et al., included 60 hospitalised patients, with an evaluation ranging from 8 to 12 weeks, with potential selection bias towards abnormal PFT results [9]. The authors do not report fibrosis on CT. Also, in both these studies, the authors reported DLCO <80% as abnormal, and did not use lower limit of normal as recommended [16].

Isolated decreased DCLO in 26.3% of patients may lead to the hypothesis of a persistent vascular damage in line with SARS-CoV-2-induced lung vascular damage at the acute phase [17]. On the contrary, median KCO was normal even in patients with severe-to-extremely-severe radiological pneumonia, indicating that many patients have altered diffusion capacity due to restriction. The normality of KCO is in accordance with reports at one month after symptom onset [8,18] and the low proportion of patients with fibrosis signs at three months. The high proportion of patients who required invasive ventilation in our study could explain this restrictive pattern. It is unlikely that restrictive patterns are explained by neuromuscular abnormalities, since post-ICU NIV was rarely needed in our patients.

Recent data suggest that high-flow nasal canula with humidified oxygen and CPAP are beneficial to severe SARS-CoV-2 patients, limiting the need to intubate patients [19,20]. Due to the limited number of patients in our study who had received CPAP and high-flow nasal canula, we were not able to assess the effect of these treatment on pulmonary function recovery compared to invasive ventilation.

We do not find a significant difference in lung function and residual chest-CT abnormalities between patients who received or not steroids. This could be because of a lack of effect, but also of a lack of power. Indeed, we included all patients who had been evaluated with PFT and chest-CT at our centers, but due to the retrospective design of the study, we did not include a sample calculation. Also, since our patients were treated during the first epidemic wave in France, there were no national guidelines on steroid prescription. Thus, patients with equal clinical severity might have been treated differently, i.e. with or without steroids, but also with different regimens (dexamethasone, methylprednisolone or prednisolone). This renders the comparison between patients difficult and pleads for a prospective study.

Strengths of our study are the systematic 3-months-PFT assessment in patients with initial severe disease or residual respiratory symptoms, inclusion of patients of all ages and disease severity including patients who did not require hospitalisation, systematic CT assessment of the extent of lung involvement during the acute phase. The use of lower limit of normal for PFT interpretation according to international

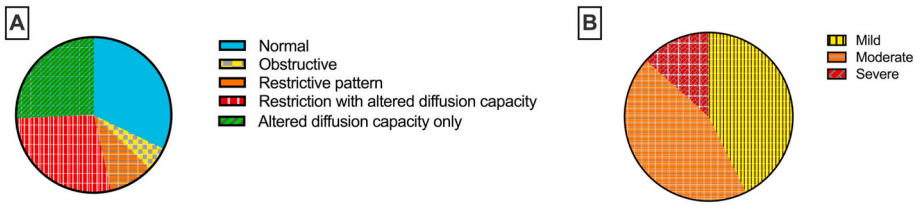

Fig. 2. Interpretation of pulmonary function test at three months in all patients (panel A) and severity of diffusion capacity alteration (according to ERS standards [16]) in patients with altered DLCO, with or without restriction.

Table 3
Univariate and multivariate logistic regression for pathologic pulmonary function tests at 3 months after Covid-19 diagnosis.

Variable	Univariate			Multivariate		
	β coefficient	95% CI	p value	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	[-1.03– 0.40]	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]	0.259			
Degree of initial lung involvement	1.24	[0.55–2.02]	0.001*	1.12	[0.39–1.94]	0.004*
Endotracheal intubation	0.85	[0.04–1.74]	0.048*	1.29	[0.33–2.36]	0.012*

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 pandemics, 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 on survivors at 4 months, chronic respiratory conditions did not account for a significant difference in PFT results, but again the study focused only on hospitalised patients and did not assess the effect of steroids [21]. As for ourselves, we did not assess the effect of other treatments than 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 could be limited to spirometry combined with chest CT when DLCO 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, impairement 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.

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 Boussouar:** 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. **Hélène Benzaquen:** Investigation, Resources. **Dominique Penaud:** Investigation, Resources. **Pierantonio Laveneziana:** Investigation, Resources, Writing – review & editing. **Roxane Malrin:** Investigation, Resources. **Alban Redheuil:** Investigation, Writing – review & editing. **Victoria Donciu:** Investigation, Writing – review & editing. **Olivier Lucidarme:** Investigation, Writing – review & editing. **Camille Taillé:** Investigation, Resources, Writing – review & editing. **Antoine Guerder:** Investigation, Resources. **Florence Arnoult:** Investigation, Resources. **Emmanuelle Vidal-Petiot:** Methodology, Writing – review & editing. **Martin Flamant:** Data curation, Methodology, Formal analysis. **Thomas Similowski:** Resources, Writing – review & editing. **Capucine Morelot-Panzini:** Resources, Writing – review & editing. **Morgane Faure:** Investigation, Resources. **François-Xavier Lescure:** Resources, Writing – review & editing. **Christian Straus:** Investigation, Resources, Writing – review & editing. **Jésus Gonzalez-Bermejo:** Conceptualization, Methodology, Writing – review & editing, Supervision.

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