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Original article

Mid-term pulmonary sequelae after hospitalisation for COVID-19: The French SISCOVID cohort

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ABSTRACT

Background: Even though COVID-19 clinical features, pathogenesis, complications, and therapeutic options have been largely described in the literature, long-term consequences in patients remain poorly known.

Methods: The French, multicentre, non-interventional SISCOVID study evaluated lung impairment three (M3) and six months (M6) after hospital discharge in patients recovered from COVID-19. Evaluation was based on clinical examination, pulmonary function tests, and chest computed tomography (CT-scan).

Results: Of the 320 included patients (mean age: 61 years; men: 64.1%), 205 had had a severe form of COVID-19, being hospitalised in an intensive care unit (ICU), and requiring high flow nasal cannula, non-invasive ventilation, or invasive mechanical ventilation. At M6, 54.1% of included patients had persistent dyspnoea (mMRC score ≥ 1), 20.1% severe impairment in gas diffusing capacity ($DL_{CO} < 60\%$ pred.), 21.6% restrictive ventilatory pattern (total lung capacity $< 80\%$ pred.), and 40% a fibrotic-like pattern at CT-scan. Fibrotic-like pattern and restrictive ventilatory pattern were significantly more frequent in patients recovered from severe than non-severe COVID-19. Improved functional and radiological outcomes were observed between M3 and M6. At M6, age was an independent risk factor for severe DL_{CO} impairment and fibrotic-like pattern and severe COVID-19 form was independent risk factor for restrictive ventilatory profile and fibrotic-like pattern. **Conclusion:** Six months after discharge, patients hospitalised for COVID-19, especially those recovered from a severe form of COVID-19, frequently presented persistent dyspnoea, lung function impairment, and persistent fibrotic-like pattern, confirming the need for long-term post-discharge follow-up in these patients and for further studies to better understand long-term COVID-19 lung impairment.

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Introduction

By the end of 2019, COVID-19 pandemic, an infectious disease caused by a newly discovered coronavirus (SARS-CoV-2), became the most urgent global healthcare issue, with dramatic consequences. As

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of 21 February 2022, over 425 million cases and 5.8 million deaths were confirmed [1].

Early epidemiological reports showed that, following infection, most people experienced mild illness without complications, but some patients required hospitalisation for pneumonia with rapid onset of severe respiratory failure, and 6 to 8% of patients developed an acute respiratory distress syndrome [2,3]. Currently, it is estimated that among patients who develop symptoms following infection, about 80% recover from the disease without needing hospital treatment, 15% become seriously ill and require oxygen, and 5% become critically ill and need intensive care [1].

Even though clinical features, pathogenesis, and complications of COVID-19 as well as therapeutic options for COVID-19 patients have been largely described in the literature, the long-term consequences of COVID-19 remain poorly known. A recent meta-analysis identified decline in carbon monoxide diffusing capacity (DL_{CO}) whose prevalence was 27%, and reduced exercise capacity as most common long-term complications in survivors of severe acute respiratory syndrome (SARS) or Middle East respiratory syndrome (MERS), two infectious diseases caused by coronaviruses (SARS-CoV and MERS-CoV, respectively) [4]. In SARS survivors, the presence of pulmonary fibrosis was correlated with disease severity [5]. A fibrosis radiological pattern could persist in approximately one third of patients through three to six months [6,7].

The recent Swiss COVID-19 lung study showed significant persistent functional and radiological abnormalities four months after severe acute SARS-CoV-2 infection in 113 survivors who had experienced mild to moderate (N=47) or severe to critical (N=66) COVID-19 according to the World Health Organization severity classification. According to the authors, persistent functional and radiological abnormalities were potentially due to small-airway impairment and parenchymal lung disease [8]. A second and larger cohort study showed that the more severe the respiratory failure was during the hospital stay, the more severe the pulmonary diffusion capacities and the abnormal chest imaging manifestations in COVID-19 survivors were six months after the acute disease [9]. Finally, a recent meta-analysis suggested that about half of the patients recovered from COVID-19 had residual abnormalities on CT-scan and at pulmonary function tests three months after hospital discharge [10].

France was one of the first European countries affected by the SARS-CoV-2 pandemic, the first case being diagnosed on 24 January 2020. One year later the French national health system is still under tremendous pressure, having to deal with patients ill following SARS-CoV-2 infection but also COVID-19 survivors presenting with chronic complications of the disease. In this context, the French-speaking Respiratory Medicine Society (SPLF) has published a guide for the management of patients who experienced pneumonia following SARS-CoV-2 infection and could develop respiratory sequelae [11].

This multicentre observational study (SISCOVID trial) was designed to assess functional and radiological impairment six months after discharge in patients hospitalized for COVID-19. The pulmonary sequelae were evaluated according to the severity of the initial infectious disease. By complementing the current available data, our results are expected to improve the understanding of the heterogeneous evolution of the disease and thus better adapt the proposals for long-term management of patients with an initial serious or critical COVID-19.

Methods

Study design

This French, multicentre, observational cohort study was conducted in 12 French non-academic hospitals (Mulhouse, Orleans, Colmar, La Roche-sur-Yon, Bayonne, Montfermeil, Douai, Le Mans, Dunkerque, Soissons, Libourne, and Chambéry).

The trial protocol was approved by a French institutional review board (code 20-GMSA-01) and was registered at ClinicalTrials.gov (registration number: NCT04505631). Non-opposition was obtained from all patients before inclusion.

Population

All adult patients hospitalised for COVID-19 between 1 March 2020 and 30 June 2020 were considered for eligibility provided they had no history of pre-existent chronic pulmonary disease: i.e., chronic obstructive pulmonary disease (COPD) with forced expiratory volume (FEV1) <50%, pulmonary fibrosis with DL_{CO} <60%, or respiratory failure requiring supplemental oxygen. Patients without dyspnoea, auscultation abnormalities, chest X-ray infiltrates, and/or oxygen saturation $\leq 94\%$ at inclusion visit and patients under legal protection were not included. Any patient who expressed opposition later in the study was excluded.

Included patients were stratified according to initial COVID-19 severity: the 'Severe COVID-19' group included all patients who required high flow nasal cannula (HFNC), non-invasive ventilation (NIV), or invasive mechanical ventilation (IMV), and were hospitalised in an intensive care unit (ICU), and the 'Non-severe COVID-19' group included all patients hospitalised in a conventional ward and requiring standard oxygen therapy. For feasibility reasons we could not include all the patients hospitalized in our centers and we decided to assess the follow-up at 3 and 6 months only for symptomatic patients after hospital discharge.

Follow-up

Patients were included during the first consultation for follow-up in the pulmonology ward, which was routinely performed between two and four months after hospital discharge (by convention on Month 3, M3). Second visit occurred five to seven months after hospital discharge (by convention Month 6, M6). At each visit, complementary medical examinations were performed according to French follow-up guideline [11]. As the study was non-interventional, these examinations were performed at the discretion of the attending physician in accordance with local practices, and none of these examinations were mandatory for inclusion or follow-up continuation.

Outcomes

The main outcomes of this study were the description of clinical status, pulmonary function, and radiological findings six months after hospitalisation for COVID-19. Secondary outcomes included assessment of the same parameters stratified according to COVID-19 severity and their evolution between M3 and M6.

Data sources

Medical history (comorbidities, usual treatments) before hospital admission for COVID-19 and history of COVID-19 (in-hospital care included) were retrieved from medical records. The McCabe score was used as a marker of comorbidity [12].

The following prospective data were recorded at each follow-up visit: physical examination, score on the modified Medical Research Council (mMRC) dyspnoea scale, and results of complementary examinations. Pulmonary function tests, DL_{CO} measurement, 6-minute walk test (6MWT), arterial blood gas (ABG) test, and respiratory muscle tests were performed using standard protocols [13–17]. Respiratory muscle tests allowed the estimation of muscle strength via maximal static inspiratory (MIP) and expiratory (MEP) pressures. Low-dose CT scans were performed at each visit for radiological evaluation of sequelae.

Radiological evaluation

The CT scans were constructed with 1-mm slice thickness. The images were stored in the local picture archiving and communication system (PACS). Two readers, blinded to the clinical status, performed a consensus review of all CT scans. The presence of the following chest CT patterns was assessed: alveolar consolidation, ground-glass opacities, mosaic attenuation pattern, subpleural reticulations, honeycombing, traction bronchiectasis, and distribution of damages among pulmonary lobes. Fibrotic-like pattern was defined by the presence of traction bronchiectasis together with subpleural reticulations, and/or honeycombing [18]. Disease extent was estimated using the method proposed by Francone et al. [19] which rates the involvement of each lobe on a five-point scale (0: 0%; 1: <5%; 2: 5-25%; 3: 26-50%; 4: 51-75%; 5: >75%). The CT total score which is the sum of scores for each lobe ranged from 0 to 25.

Statistical analysis

Data quality controls and data management were performed in a reproducible way. Analyses were mainly descriptive, using mean and standard deviation (SD) or median and interquartile range (IQR) for quantitative variables, according to their distribution, and count and proportion (%) for categorical variables.

Univariate analyses, mainly between the two groups of patients defined on the severity of the acute disease, used parametric t-test or non-parametric Wilcoxon test for quantitative variables with normal or non-normal distribution (graphically assessed), respectively, and chi-square test with Yates' continuity correction for categorical variables.

Multivariate logistic regression model was used to assess the independent relationship between three respiratory outcomes and some relevant possible risk factors according to already published studies: age, gender, body mass index (BMI), smoking habits, history of diabetes and/or arterial hypertension, chronic kidney disease, mild to moderate COPD, COVID-19 severity, and C-reactive protein level [8,20]. The three respiratory outcomes were: (1) severe decrease in DL_{CO} defined as DL_{CO} <60% of the predicted value (pred.), restrictive ventilatory pattern defined by total lung capacity (TLC) <80% pred., and fibrotic-like pattern at CT scan. Odds ratios were reported with their 95% confidence interval.

Missing data could not be considered as missing at random, because of the non-interventional design, and the main purpose of this study was descriptive. That is why no imputation of missing data was used, and, unless otherwise stated, all analyses were performed on complete cases. Rate of missing data was systematically described for each variable.

All data management process and analyses were performed with R software version 3.5.2. Statistic tests were two-sided and a significance level of 0.05 was considered.

Deidentified data and R scripts are available on the study Gitlab repository (<https://gitlab.com/s-degoul/siscovid-study-data-analyses>).

Results

Baseline description

From 11 June 2020 to 22 October 2020, 320 patients were included: 205 patients in the Severe COVID-19 group and 115 in the Non-severe COVID-19 group (Fig. 1). The mean (SD) time from

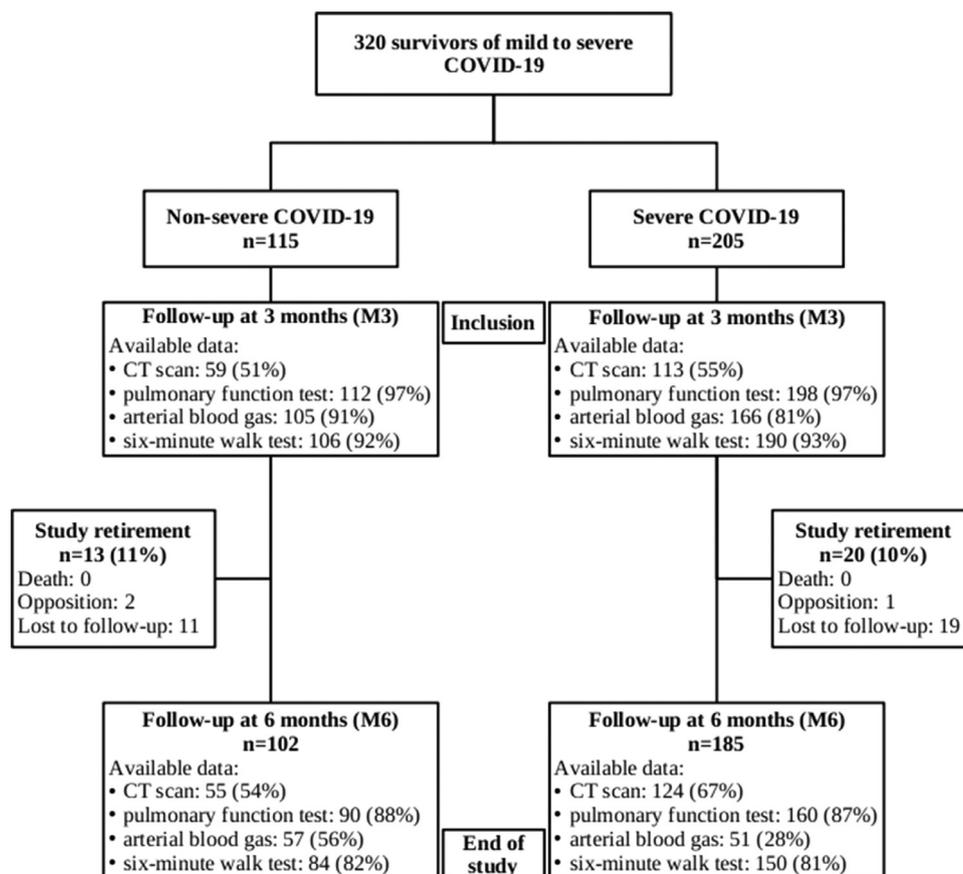


Fig. 1. Flowchart of the study.
CT: computed tomography.

Table 1
Demographic and clinical features during hospitalisation for COVID-19 stratified according to the severity of the initial infectious disease.

	Total (N=320)	Non-severe COVID-19 (N=115)	Severe COVID-19 (N=205)	p-value	MD (%)
Male, N (%)	205 (64.1)	62 (53.9)	143 (69.8)	0.007	0
Age (year), mean (SD)	61.7 (11.3)	61.8 (12.9)	61.7 (10.3)	0.991	0
BMI (kg/m ²), median [IQR]	28.8 [25.7, 32.7]	28.1 [25.2, 32.4]	29.1 [26.3, 32.9]	0.398	4.7
Active or former smoker, N (%)	127 (41.6)	43 (37.7)	84 (44.0)	0.341	4.7
Hypertension, N (%)	156 (48.8)	49 (42.6)	107 (52.2)	0.126	0
Diabetes, N (%)	67 (20.9)	20 (17.4)	47 (22.9)	0.306	0
Coronary artery disease, N (%)	34 (10.6)	12 (10.4)	22 (10.7)	1.000	0
Mild COPD, N (%)	12 (3.8)	3 (2.6)	9 (4.4)	0.618	0
Chronic kidney disease, N (%)	17 (5.3)	9 (7.8)	8 (3.9)	0.214	0
McCabe score, N (%)				0.052	1.2
- non-fatal	295 (93.4)	111 (96.5)	184 (91.5)		
- ultimately fatal	20 (6.3)	3 (2.6)	17 (8.5)		
- rapidly fatal	1 (0.3)	1 (0.9)	0 (0.0)		
Length of hospital stay (day), median [IQR]	27.0 [13.0, 45.0]	11.0 [7.8, 16.0]	34.0 [25.0, 57.0]	<0.001	5.9
Time from illness onset to admission (day), median (IQR)	7.0 [5.0, 10.0]	8.0 [6.0, 10.8]	7.0 [5.0, 10.0]	0.066	2.8
SARS-CoV-2 positive PCR, N (%)	276 (88.2)	94 (81.7)	182 (91.9)	0.012	2.2
Maximal oxygen flow, N (%)				<0.001	5.3
- ≤5 L/min	100 (33.0)	83 (74.8)	17 (8.9)		
- 5-10 L/min	56 (18.5)	17 (15.3)	39 (20.3)		
- 10-15 L/min	134 (44.2)	9 (8.1)	125 (65.1)		
>15 L/min	13 (4.3)	2 (1.8)	11 (5.7)		
Lymphocyte count (G/L), median [IQR]	0.8 [0.6, 1.1]	0.9 [0.7, 1.2]	0.8 [0.6, 1.0]	0.001	13.4
CRP (mg/L), median [IQR]	121.5 [67.8, 171.2]	79.5 [38.4, 143.2]	137.8 [96.5, 187.2]	<0.001	15.0
D-dimer (μg/dL), median [IQR]	1192.0 [745.5, 2290.0]	1196.0 [719.0, 2171.0]	1187.0 [799.5, 2299.5]	0.858	60.3
Glucocorticoids during acute phase, N (%)	52 (16.5)	13 (11.3)	39 (19.5)	0.084	1.6

Data are presented as N (%), mean (SD), or median [IQR].

BMI: body mass index; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus infectious disease 2019; CRP: C-reactive protein; dL: decilitre; G: Giga; IQR: interquartile range; L: litre; min: minute; MD: missing data; N: number of patients; PCR: polymerase chain reaction; SD: standard deviation.

hospital discharge to follow-up was 98 (19) days for visit 1 at M3 and 194 (17) days for visit 2 at M6. COVID-19 was diagnosed by reverse transcription polymerase chain reaction (RT-PCR) in 276 patients (88.2%) and by the association of specific clinical signs and lung CT scan for the remaining 44 patients (11.8%).

Demographic and clinical features during hospitalisation for COVID-19 and comparison according to COVID-19 severity are presented in Table 1. Patients were mainly male (64.1%), especially those included in the Severe COVID-19 group (69.8% vs 53.9%; $p=0.007$). The mean (SD) age of the study population was 61.7 (11.3) years (range 28-88). 79.3% of patients were overweight or obese (BMI >25 kg/m²). No significant difference was observed between the two groups of patients in smoking history, BMI, and initial clinical symptoms. Hospital stay was significantly longer in patients from the Severe than Non-severe COVID 19 group (median: 34 vs 11 days). During the first wave of COVID-19 pandemic, 52 (16.5%) patients were treated with high dose of glucocorticoids (39 and 13 patients from Severe and Non-severe COVID-19 groups, respectively) and 178 patients required invasive ventilation with a median stay in ICU of 20 days (range: 12-30 days).

Pulmonary function, physical performance, and oxygenation

The self-reported dyspnoea, pulmonary function tests, ABG test, and 6MWT at M6 for the study population, with comparison between patients from Severe and Non-severe COVID-19 groups, are presented in Table 2.

54.1% of patients reported persistent dyspnoea (mMRC score ≥ 1), and 3.9% reported severe persistent dyspnoea (mMRC score ≥ 3). The prevalence and the severity of the dyspnoea was similar in both groups of patients. Restrictive ventilatory pattern was found in 21.6% of patients; it was significantly more frequent in patients from the Severe than Non-severe COVID-19 group (29.1% vs 8%). Impaired DL_{CO} (i.e., DL_{CO} <80% pred.) was found in 68% of patients and severe DL_{CO} impairment (<60% pred.) in 20.1% of patients, without significant difference between the two groups of patients. The partial

pressure of oxygen (PaO₂) was measured by ABG test for 108 patients; 16 (14.8%) had hypoxia (PaO₂ ≤ 70 mmHg): 15 had mild hypoxia (PaO₂=60-70mmHg), and one patient had severe hypoxia (PaO₂ <60 mmHg). At M6, a good exercise performance (476 m, 93% pred.) was observed, but 34.6% of patients showed a persistent and significant desaturation $\geq 4\%$ at 6MWT. Persistent and significant desaturation $\geq 4\%$ at 6MWT was significantly more prevalent in the Severe than Non-severe COVID-19 group (40% vs 25%).

Improved dyspnoea and functional status were observed between the follow-up visits (Fig. 2).

Moderate to severe dyspnoea (mMRC score ≥ 2) was more frequent in patients with severe than non-severe DL_{CO} impairment (30.6% vs 16.2%, $p=0.026$) and in patients with than without restrictive ventilatory pattern (30.6% vs 16.2%, $p=0.023$). In logistic regression analysis, severe COVID-19 form and male sex were the independent risk factors associated with restrictive ventilatory pattern at M6 (odds ratio, OR [95% confidence interval, 95%CI]: 5.22 [2.18-14.66]; $p=0.001$ and respectively OR [95%CI]: 2.53 [1.09-6.52]; $p=0.04$). Age (OR [95%CI]: 1.06 [1.02-1.11]; $p=0.004$) and glucocorticoid treatment during the acute phase (OR [95%CI]: 2.47 [1.04-5.72]; $p=0.037$) were associated with severe impairment in DL_{CO}. The results of univariate and multivariate analyses of factors associated with these outcomes (restrictive ventilatory pattern and DL_{CO} impairment) are reported in Tables 3 and 4, respectively.

CT-scan evaluation

Lung CT scan was performed in 179 patients at M6 visit. Lung abnormalities were found in 142 patients (80.2%) (Table 5). The most frequent findings were mosaic attenuation pattern, subpleural reticulations, traction bronchiectasis, and ground-glass opacities. In 87.2% of patients, pulmonary involvement was found bilaterally, with diffuse extent of pulmonary abnormalities. Fibrotic-like pattern was found in 40% of patients; it was significantly more prevalent in the Severe COVID-19 group ($p=0.007$).

Table 2
Lung function outcomes 6 months after discharge stratified according to severity of the initial infectious disease.

	Total (N=320)	Non-severe COVID-19 (N=115)	Severe COVID-19 (N=205)	p-value	MD (%)
Dyspnoea ≥2 mMRC score, N (%)	48 (18.8)	18 (19.8)	30 (18.3)	0.901	20.3
FVC (% pred.), mean (SD)	99.0 (18.8)	101.7 (19.2)	97.4 (18.4)	0.085	21.9
FEV1(% pred.), mean (SD)	98.9 (19.4)	99.1 (20.1)	98.7 (19.1)	0.888	21.9
FEV1/FVC (%), mean (SD)	80.6 (9.2)	77.9 (9.4)	82.1 (8.8)	0.001	22.5
FEV1/FVC <70%, N (%)	18 (7.3)	10 (11.4)	8 (5.0)	0.111	22.5
TLC (% pred.), mean (SD)	94.2 (16.6)	99.8 (15.6)	91.1 (16.4)	<0.001	23.4
TLC <80%, N (%)	53 (21.6)	7 (8.0)	46 (29.1)	<0.001	23.4
MIP (% pred.), mean (SD)	93.5 (39.9)	87.6 (33.8)	96.2 (42.3)	0.183	44.7
MEP (% pred.), mean (SD)	81.5 (33.4)	78.2 (28.9)	83.1 (35.4)	0.365	44.4
DL _{CO} (% pred.), mean (SD)	73.6 (16.4)	74.8 (17.2)	73.0 (15.9)	0.428	23.8
DL _{CO} <60%, N (%)	49 (20.1)	16 (18.2)	33 (21.2)	0.696	23.8
K _{CO} (% pred.), mean (SD)	89.1 (17.8)	86.3 (16.9)	90.6 (18.2)	0.070	25.3
PaO ₂ (mmHg), mean (SD)	84.0 (13.0)	84.2 (13.7)	83.8 (12.3)	0.890	66.2
6MWD (m), mean (SD)	476.0 (112.6)	465.8 (136.0)	481.7 (97.0)	0.302	27.2
SpO ₂ nadir on 6MWT (%), mean (SD)	94.5 [92.0, 96.0]	95.0 [93.0, 97.0]	94.0 [92.0, 96.0]	0.007	26.9
Significant exertional desaturation >4%, N (%)	81 (34.6)	21 (25.0)	60 (40.0)	0.030	26.9

Data are presented as mean (SD) or N (%).
 COVID-19: coronavirus infectious disease 2019; DL_{CO}: diffusing capacity of the lung for carbon monoxide; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity; K_{CO}: carbon monoxide transfer coefficient; m: metre; MD: missing data; MEP: maximum static expiratory pressure; MIP: maximum static inspiratory pressure; mmHg: millimetre of mercury; mMRC: modified Medical Research Council dyspnoea scale; N: number of patients; PaO₂: partial pressure of oxygen; pred: predicted value; SD: standard deviation; SpO₂: arterial oxygen saturation; TLC: total lung capacity; 6MWD: six-minute walk distance; 6MWT: six-minute walk test.

Between the two follow-up visits (Fig. 2), the prevalence of lung damage slightly decreased from 87% to 81% of patients who underwent CT-scan, and 55.1% of patients showed a radiological improvement (decrease in Francone score ≥1), while 6.8% suffered a worsening (increase of Francone score ≥1). The extent of radiological abnormalities was estimated at 20% (median Francone score: 5) at M3 and 12% (median Francone score: 3) at M6, with a significant difference between the two groups of patients at M6 (16% vs 8% for patients from the Severe and Non-severe COVID-19 groups, respectively; p=0.003).

Patients presenting a moderate to severe dyspnoea (mMRC score ≥2) at M6 showed a larger extent of radiological abnormalities than patients with mild dyspnoea (median Francone score: 5 vs 3; p=0.007). No significant relation was found between fibrotic-like pattern and dyspnoea or DL_{CO}.

In logistic regression analysis, age (OR [95%CI: 1.06 [1.02, 1.11], p=0.005) and severe COVID-19 form (OR [95%CI: 2.85 [1.21, 7.12], p=0.019) were independent risk factors associated with fibrotic-like pattern at M6 (table 6).

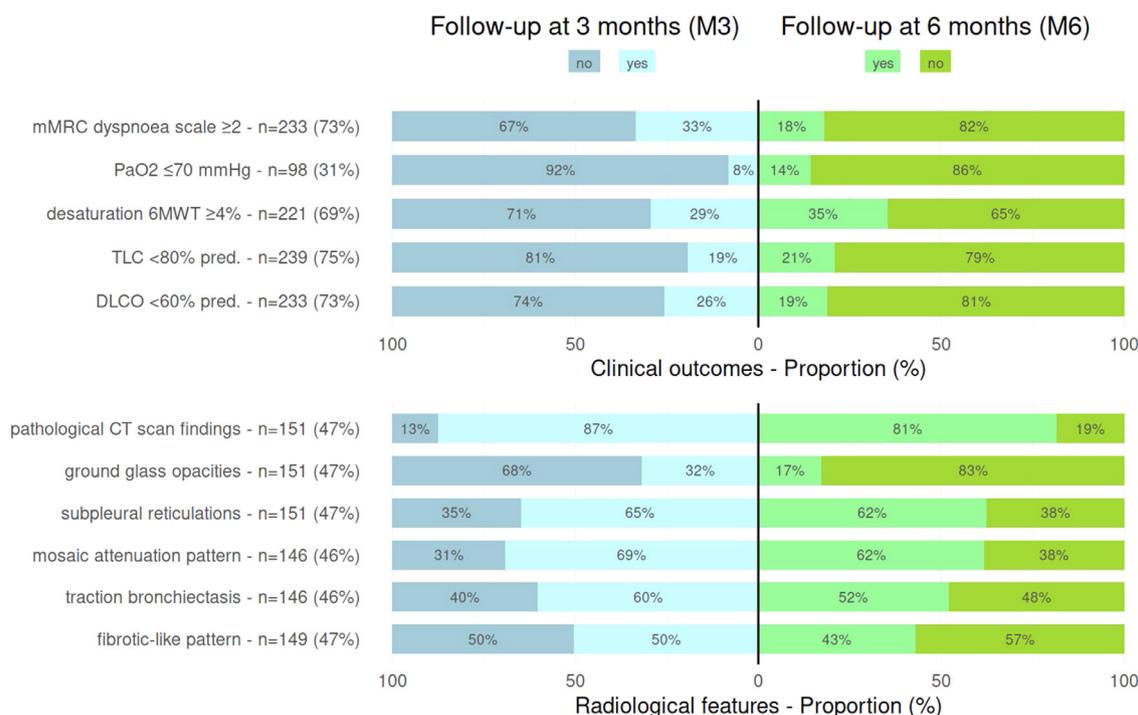


Fig. 2. Comparison of most relevant pathological findings between 3-month and 6-month follow-up visits after COVID-19.

Proportion computed on the whole population, including missing values.
 6MWT: six-minute walk test; CT: computed tomography; DL_{CO}: diffusing capacity of the lung for carbon monoxide; mMRC: modified Medical Research Council dyspnoea scale; NA: not available; PaO₂: partial pressure of oxygen; TLC: total lung capacity.

Table 3

Distribution of independent variables stratified by restrictive ventilatory pattern and results of univariate and multivariate tests at 6 months.

	Total lung capacity ≥80% (N=192)	Total lung capacity <80% (N=53)	p-value (univariate)	OR [95 % CI] (multivariate)	p-value (multivariate)	MD (%)
Male, N (%)	119 (62.0)	45 (84.9)	0.003	2.53 [1.09, 6.52]	0.04	0
Age (year), mean (SD)	62.2 (10.8)	61.1 (11.9)	0.504	0.99 [0.95, 1.02]	0.496	0
BMI (kg/m ²), median [IQR]	29.1 [25.8, 33.1]	28.4 [25.6, 31.4]	0.471	0.96 [0.91, 1.05]	0.218	4.7
Active or former smoker, N (%)	75 (41.0)	21 (40.4)	1.000	0.75 [0.36, 1.51]	0.42	4.7
Hypertension or diabetes, N (%)	105 (54.7)	29 (54.7)	1.000	1.13 [0.54, 2.4]	0.743	0
Chronic kidney disease, N (%)	10 (5.2)	2 (3.8)	0.945	0.86 [0.12, 4]	0.863	0
Severe COVID-19, N (%)	112 (58.3)	46 (86.8)	<0.001	5.22 [2.18, 14.66]	0.001	0
Glucocorticoid treatment, N (%)	26 (13.9)	12 (22.6)	0.185	2.16 [0.88, 5.19]	0.085	1.6

BMI: body mass index; CI: confidence interval; IQR: interquartile range; L: litre; MD: missing data; N: number of patients; OR: odds ratio; SD: standard deviation.
Restrictive ventilatory pattern: total lung capacity <80% pred.

Table 4Distribution of independent variables stratified by DL_{CO} level and results of univariate and multivariate tests at 6 months.

	DLCO ≥60% (n=195)	DLCO <60% (n=49)	p-value (univariate)	OR [95 % CI] (multivariate)	p-value (multivariate)	MD (%)
Male, N (%)	133 (68.2)	31 (63.3)	0.625	0.77 [0.35, 1.73]	0.524	0
Age, mean (SD), year	60.5 (11.1)	67.6 (9.0)	<0.001	1.06 [1.02, 1.11]	0.004	0
BMI, median [IQR], kg/m ²	29.3 [26.3, 33.0]	27.3 [24.4, 30.4]	0.005	0.96 [0.89, 1.02]	0.18	4.7
Active or former smoker, N (%)	73 (39.5)	24 (49.0)	0.298	1.53 [0.73, 3.23]	0.26	4.7
Hypertension or diabetes, N (%)	105 (53.8)	27 (55.1)	1.000	0.97 [0.46, 2.04]	0.93	0
Chronic kidney disease, N (%)	8 (4.1)	4 (8.2)	0.420	1.21 [0.27, 4.6]	0.785	0
Severe COVID-19, N (%)	123 (63.1)	33 (67.3)	0.696	1.44 [0.68, 3.16]	0.356	0
Glucocorticoid treatment, N (%)	24 (12.6)	14 (29.2)	0.010	2.47 [1.04, 5.72]	0.037	1.6

BMI: body mass index; COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus infectious disease 2019; DLCO: diffusion capacity of the lung for carbon monoxide; IQR: interquartile range; MD: missing data; mL: millilitre; N: number of patients; OR: odds ratio; SD: standard deviation.

Table 5

CT-scan findings at 6 months after discharge stratified by severity of the initial infectious disease.

	Total (N=320)	Non-severe COVID-19 (N=115)	Severe COVID-19 (N=205)	p-value	MD (%)
Abnormal lung CT-scan findings, N (%)	148 (79.6)	37 (64.9)	111 (86.0)	0.002	41.9
Mosaic attenuation, N (%)	111 (61.3)	28 (49.1)	83 (66.9)	0.034	43.4
Subpleural reticulations, N (%)	112 (60.2)	25 (43.9)	87 (67.4)	0.004	41.9
Traction bronchiectasis, N (%)	89 (49.2)	17 (29.8)	72 (58.1)	0.001	43.4
Ground-glass opacities, N (%)	32 (17.2)	5 (8.8)	27 (20.9)	0.070	41.9
Lung involvement - Bilateral, N (%)	129 (87.8)	29 (78.4)	100 (90.9)	0.085	54.1
Fibrotic-like pattern, N (%)	73 (39.9)	14 (24.6)	59 (46.8)	0.007	42.8
Francone severity score, median [IQR]	3.0 [1.0, 5.0]	2.0 [0.0, 5.0]	4.0 [2.0, 5.0]	0.003	43.1

Data are presented as N (%) or median (IQR).

COVID-19: coronavirus infectious disease 2019; CT: computed tomography; IQR: interquartile range; MD: missing data; N: number of patients.

Table 6

Distribution of independent variables among patients with or without CT scan fibrotic-like pattern and results of univariate and multivariate tests.

	Non-fibrotic pattern (N=105)	Fibrotic pattern (N=70)	p-value (univariate)	vOR [95 % CI] (multivariate)	p-value (multivariate)	MD (%)
Male, N (%)	59 (56.2)	54 (77.1)	0.007	1.76 [0.75, 4.26]	0.197	0
Age, mean (SD), year	61.4 (10.6)	64.7 (11.0)	0.044	1.06 [1.02, 1.11]	0.005	0
BMI, median [IQR], kg/m ²	29.4 [25.7, 33.8]	29.0 [26.2, 30.9]	0.130	0.95 [0.88, 1.02]	0.18	4.7
Active or former smoker, N (%)	34 (34.7)	31 (47.7)	0.135	2.04 [0.94, 4.51]	0.073	4.7
Hypertension or diabetes, N (%)	67 (63.8)	37 (52.9)	0.198	0.45 [0.2, 0.97]	0.045	0
Chronic kidney disease, N (%)	10 (9.5)	2 (2.9)	0.160	0.25 [0.03, 1.19]	0.112	0
Severe COVID-19, N (%)	64 (61.0)	57 (81.4)	0.007	2.85 [1.21, 7.12]	0.019	0
Glucocorticoid treatment, N (%)	15 (14.7)	11 (16.2)	0.965	1.32 [0.44, 3.89]	0.612	1.6

BMI: body mass index; COVID-19: coronavirus infectious disease 2019; DLCO: diffusion capacity of the lung for carbon monoxide; IQR: interquartile range; L: litre; MD: missing data; N: number of patients; OR: odds ratio; SD: standard deviation.

Discussion

Previous studies revealed a high rate of functional and radiological abnormalities in the first months after hospitalisation for COVID-19. These abnormalities were considered mild to moderate which often

improved over time. However, most reports enrolled only a small contingent of critical COVID-19 patients, ranging between 14.5% and 29.4% of their study population [20–22]. In our six-month follow-up prospective cohort of 320 survivors after critical COVID-19, 64% of them received IMV or HFNC oxygen therapy.

More than half of all included patients had persistent dyspnoea on exertion (mMRC ≥ 1), 20.1% had reduced DL_{CO} <60% pred. and 21.6% of them showed restrictive ventilatory pattern at six-month follow-up. The lack of difference in terms of respiratory muscle strength, according to MIP and MEP, suggested a lung parenchymal issue rather than a respiratory muscle impairment.

The multivariate analysis identified age and glucocorticoid treatment during the acute phase as risk factor for DL_{CO} <60% pred. and severe COVID-19 pattern and male sex as risk factors for restrictive ventilatory pattern at six months of follow-up. The surprisingly effect of glucocorticoid treatment could be explained by an indication bias. During the first wave of COVID-19 epidemics in France, the glucocorticoid treatment was used only for a minority of patients (16.5% of the study population), presenting a severe form of COVID-19 in 75% of cases (table 1).

In our study, severe impairment of DL_{CO} and restrictive ventilatory pattern were accompanied by a non-negligible prevalence of persistent exertional desaturation. This observation is in accordance with SARS studies which revealed abnormal gas exchange as the most relevant residual finding [6,23]. In contrast to our findings, Tori Vingeland Lerum et al. showed a mild respiratory impairment at three months of follow-up, probably due to a small proportion of patients with severe form of COVID-19 [22].

We found a high prevalence of significant dyspnoea (18.8% of patients showed dyspnoea mMRC scale ≥ 2) six months after hospital discharge. However, a significant improvement of self-reported dyspnoea was observed during the follow-up, which may indicate that a proportion of severe COVID-19 patients continue to improve months after hospitalisation.

About 40% of patients showed a fibrotic-like pattern. The multivariate analysis identified age and severe COVID-19 form as risk factors for fibrotic-like pattern at six months of follow-up. This result is comparable with a recent study by Xiaoyu Han et al. which showed fibrotic-like changes in older patients with more severe disease during the acute phase [18]. Similarly to a previous study [8], we observed a high incidence of persistent mosaic attenuation on CT scan at six months which could be explained by small-airway component. However, our analysis showed an improvement of radiological abnormalities between the follow-up evaluations.

The patients with more severe respiratory failure during the acute phase of COVID-19 showed more frequently restrictive ventilatory pattern or fibrotic-like pattern at follow-up. Similarly, Sabina A. Guler et al. showed a negative correlation between the duration of mechanical ventilation during the acute phase and pulmonary function at 4-month follow-up [8]. This might be explained by a prolonged pulmonary inflammation after severe COVID-19 or related to ventilatory induced lung-injury as described in patients who survived after acute respiratory distress syndrome [24].

We found a significant relation between dyspnoea, functional status, and radiological impairment at six months of follow-up, but it is still unknown if the lung abnormalities are permanent, progressive, or reversible, and therefore we believe that patients with severe COVID-19 require longer and closer follow-up than other patients admitted to hospital for COVID-19.

The strength of our study is the multicentre prospective design, which allows the generalisability of the study results to all COVID-19 adult patients discharged from non-academic hospitals. However, we encountered several limitations. Initial pulmonary function tests and imaging were not available and therefore a pre-existing lung disease cannot be completely ruled out, which could predispose to a poorer pulmonary function at follow-up. However, we excluded patients with history of moderate to severe COPD, pulmonary fibrosis, or chronic pulmonary fibrosis. We did not use routinely contrast agent for the CT-scan evaluation and therefore occult pulmonary embolism could not be ruled out. Another limitation of this study is its non-interventional design, which is responsible for the rate of missing

data and could lead to attrition bias, since patients with less severe clinical status and COVID-19 history were less likely to attend the six-month follow-up visit and to have invasive complementary examinations such as ABG test.

Conclusion

In our six-month follow-up French cohort post moderate-to-severe COVID-19, 40% of patients developed fibrotic-like opacities, 20% showed a restrictive ventilatory pattern and severely impaired DL_{CO}, and 35% desaturated at 6MWT, confirming the need for long-term post-discharge follow-up in these patients and for further studies to better understand long-term COVID-19 lung impairment. The risk factor associated to severely impaired DL_{CO} and fibrotic-like pattern at follow-up was age. Male patients who survived from a severe form of COVID-19 have an increased risk of developing a restrictive ventilatory pattern at six months, highlighting the importance of their systemic follow-up.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Take home message

The French SISCOVID study reports lung sequelae in COVID patients 6 months after hospital discharge: 40% had fibrotic-like opacities; 20% severely reduced gas diffusing capacity and restrictive ventilatory pattern; 35% desaturation during 6-min walk test.

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