Respiratory symptoms and radiological findings in post-acute COVID-19 syndrome

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Shareable abstract (@ERSpublications)
New-onset dyspnoea is a frequent complaint 4 months after #COVID19 and is generally multifactorial, and the combination of new-onset dyspnoea, fibrotic lesions and D_{LCO} <70% pred is rarely observed https://bit.ly/3q4hyyM

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Abstract

Rationale The characteristics of patients with respiratory complaints and/or lung radiologic abnormalities after hospitalisation for coronavirus disease 2019 (COVID-19) are unknown. The objectives were to determine their characteristics and the relationships between dyspnoea, radiologic abnormalities and functional impairment.

Methods In the COMEBAC (Consultation Multi-Expertise de Bicêtre Après COVID-19) cohort study, 478 hospital survivors were evaluated by telephone 4 months after hospital discharge, and 177 who had been hospitalised in an intensive care unit (ICU) or presented relevant symptoms underwent an ambulatory evaluation. New-onset dyspnoea and cough were evaluated, and the results of pulmonary function tests and high-resolution computed tomography of the chest were collected.

Results Among the 478 patients, 78 (16.3%) reported new-onset dyspnoea, and 23 (4.8%) new-onset cough. The patients with new-onset dyspnoea were younger (56.1±12.3 *versus* 61.9±16.6 years), had more severe COVID-19 (ICU admission 56.4% *versus* 24.5%) and more frequent pulmonary embolism (18.0% *versus* 6.8%) (all p⩽0.001) than patients without dyspnoea. Among the patients reassessed at the ambulatory care visit, the prevalence of fibrotic lung lesions was 19.3%, with extent <25% in 97% of the patients. The patients with fibrotic lesions were older (61±11 *versus* 56±14 years, p=0.03), more frequently managed in an ICU (87.9 *versus* 47.4%, p<0.001), had lower total lung capacity (74.1±13.7 *versus* 84.9±14.8% pred, p<0.001) and diffusing capacity of the lung for carbon monoxide (D_{LCO}) (73.3±17.9 *versus* 89.7±22.8% pred, p<0.001). The combination of new-onset dyspnoea, fibrotic lesions and D_{LCO} <70% pred was observed in eight out of 478 patients.

Conclusions New-onset dyspnoea and mild fibrotic lesions were frequent at 4 months, but the association of new-onset dyspnoea, fibrotic lesions and low D_{LCO} was rare.

Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has provoked an ongoing global pandemic of coronavirus disease 2019 (COVID-19), which has affected more than 240 million individuals to date [1]. There are multiple respiratory symptoms associated with COVID-19, ranging from mild upper respiratory tract symptoms to severe acute respiratory distress syndrome [2–5]. There is also growing evidence that some patients have long-term effects of COVID-19 that can affect multiple organ systems. These effects have been grouped as "post-acute COVID-19 syndrome", defined by persistent symptoms and/or delayed or long-term complications of SARS-CoV-2 infection beyond 4 weeks from the onset of symptoms [6]. As part of post-acute COVID-19 syndrome, the persistence of respiratory symptoms seems to be common, affecting 15–81% of patients [7–13]. However, the characteristics of patients with persistent or residual respiratory complaints after hospitalisation for COVID-19 remain poorly described and understood. Recently, the Consultation Multi-Expertise de Bicêtre Après COVID-19 (COMEBAC) cohort study reported the outcomes of 478 patients 4 months after hospitalisation for COVID-19 [14]. Half of the patients reported at least one symptom that did not exist before the disease. High-resolution computed tomography (HRCT) of the chest frequently revealed persistent lung abnormalities, including fibrotic lung lesions, in a minority of patients [14].

The aims of this study were to determine: 1) the prevalence of persistent respiratory symptoms or residual respiratory complaints after hospitalisation for COVID-19; 2) the characteristics of patients with persistent respiratory symptoms; 3) the prevalence of fibrotic lung lesions; 4) the characteristics of patients with fibrotic lung lesions; and 5) the relationships between respiratory complaints, respiratory functional impairment and radiologic abnormalities 4 months after COVID-19 in the COMEBAC study cohort.

Materials and methods

Patients

The COMEBAC cohort study (NCT04704388) prospectively included adult patients admitted to the Bicêtre Hospital (Paris-Saclay University hospitals – Assistance Publique – Hôpitaux de Paris) for COVID-19 during the first wave of the pandemic in France [14]. There were two levels of enrolment in the study.

First, patients who met the following inclusion and exclusion criteria were screened for a telephone consultation. The inclusion criteria were as follows: survival 4 months after hospital discharge or after intensive care unit (ICU) discharge for patients who had been admitted to an ICU, age older than 18 years, hospitalisation for greater than 24 h primarily because of COVID-19, and diagnosis of SARS-CoV-2 infection by reverse transcriptase PCR (RT-PCR), by typical HRCT of the chest associated with clinical features, or by both. The exclusion criteria were as follows: death within 4 months after discharge, persistent hospitalisation, end-stage cancer, dementia, nosocomial COVID-19 infection, and incidental positive SARS-CoV-2 RT-PCR result during a hospital stay for a different medical indication.

Second, all the ICU patients and those who were symptomatic at the telephone consultation were invited for further evaluation in the ambulatory care setting. Symptomatic patients were defined as those reporting symptoms (except for anosmia) at the telephone interview, those with persistent creatinine-level elevation, and those with persistent abnormalities on a lung computed tomography (CT) scan conducted after hospitalisation (including any residual ground-glass opacities, bronchial or bronchioloalveolar abnormalities, lung consolidations, or interstitial thickening). "New-onset dyspnoea or cough" was defined as the presence of symptoms that did not exist before COVID-19 or as the worsening of pre-existing symptoms.

The telephone consultation was made 3–4 months after hospital discharge by a medical officer with a questionnaire focused on the general medical condition and symptoms (supplemental methods). The characteristics of the patients who were hospitalised for acute COVID-19 were extracted from electronic health records. The patients provided informed consent after ICU hospitalisation or at the beginning of the telephone consultation and before the ambulatory care setting. The Ethics Committee of the French Intensive Care Society (CE20-56) approved this study.

Respiratory assessment during the ambulatory care visit

Respiratory assessment

The functional impact of dyspnoea was evaluated using the modified Medical Research Council (mMRC) scale (Table E1). A non-encouraged 6-min walk test (6MWT) was performed according to current

recommendations [15]. The patients completed standard pulmonary function tests (PFTs) with spirometry, whole-body plethysmography and single-breath diffusing lung capacity for carbon monoxide (D_{LCO}) according to the European Respiratory Society/American Thoracic Society guidelines [16]. Forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), total lung capacity (TLC) and D_{LCO} are expressed as the percentages of predicted values (% pred) using the Global Lung Function Initiative 2012 [17] and European Community for Coal and Steel 1993 equations [18, 19]. The Nijmegen questionnaire (Table E2) was given, and the patients were considered to have "functional respiratory complaints" when the Nijmegen questionnaire score was >22/64 [20].

HRCT of the chest

HRCT of the chest was performed in patients assessed at the ambulatory care visit. Two radiologists (OM and SS) who were blinded to the clinical evaluation reviewed the HRCT images and reached a consensus regarding any disagreements. The presence and extension of consolidations, ground-glass opacities, crazy paving, reticulations, fibrosis and emphysema were assessed. The diagnosis of fibrotic lung lesions was based on the presence of traction bronchiectasis or on the association of interface signs with reticulations.

Cardiac assessment

All the patients who were admitted to the ICU, those who developed pulmonary embolism during hospitalisation, and those with cardiac symptoms on examination at the outpatient clinic were evaluated with transthoracic echocardiography.

Statistical analysis

Study data were collected and managed with Research Electronic Data Capture tools hosted at Assistance Publique Hôpitaux de Paris (AP-HP). Analysis was performed with the R statistical package version 4.0.1 (R Foundation for Statistical Computing). We report continuous variables as either the mean±SD or median (interquartile range, IQR) as appropriate and categorical variables as the number and frequency (percentage of group). Comparisons between patients with and without new-onset dyspnoea and patients with and without fibrotic lesions in lungs were performed using the t-test for normally distributed quantitative variables and the Mann–Whitney test for non-normally distributed quantitative variables. Pearson's chi-squared test or Fisher's exact test, as appropriate, was used to compare discrete variables between two groups. Differences were considered significant when the p-value was less than 0.05. We performed multivariate analysis for new-onset dyspnoea among the population who had the telephone consultation and for lung fibrotic lesions among the population who came to the ambulatory care visit. For the multivariate analysis, we focused on variables that in the univariate analysis had a p-value <0.1 and were clinically important and not collinear (consensus among investigators).

Results

Characteristics of the patients with persistent respiratory symptoms

The flowchart of the study is presented in figure 1. Of the 478 patients evaluated by telephone, COVID-19 was diagnosed with RT-PCR in 415 patients (86.8%) and by an association of typical clinical signs and HRCT of the chest in 63 patients (13.2%). To ensure accurate diagnosis, a serological test was performed in the 177 patients who were evaluated at the outpatient clinic, and 172 of 177 patients (97.2%) tested positive. During the telephone consultation, 78 patients among 478 reported new-onset dyspnoea, and 23 reported new-onset cough, corresponding to a minimal prevalence of new-onset dyspnoea and cough of 16.3% and 4.8%, respectively. Compared to patients without new-onset dyspnoea, the patients with new-onset dyspnoea at the telephone consultation were younger (56.1±12.3 *versus* 61.9±16.6 years, p=0.001), but there was no difference in the body mass index or the frequencies of diabetes and hypertension (table 1); these patients also experienced more severe initial episodes of COVID-19, with a longer duration of hospital stay (13 (7–23) *versus* 8 (4–14) days, p<0.001) and more frequent admission to the ICU (56.4 *versus* 24.5%, p<0.001). They also more frequently exhibited pulmonary embolism in the acute phase (18.0 *versus* 6.8%, p<0.001). In the multivariate analysis, only ICU hospitalisation and an episode of pulmonary embolism were significatively associated with new-onset dyspnoea (Table E3).

In all, 177 patients who still had symptoms and/or had been admitted to the ICU during the acute phase were reassessed at the outpatient clinic after a median time of 125 (107–144]) days (table 2). As reported in table 1 of the COMEBAC cohort study article [14], patients reassessed at the ambulatory care visit were comparable to patients who had only a telephone consultation, except for a more severe initial COVID-19 with more hospitalisations in ICU. Among these patients, 78 (44.1%) had new-onset dyspnoea. The mMRC score was higher in the patients with new-onset dyspnoea than in those without, although 28.2% of the patients with new-onset dyspnoea were classified as mMRC 0, as they declared new-onset dyspnoea only for strenuous exercise. 23 patients with new-onset dyspnoea (29.5%) had a Nijmegen questionnaire

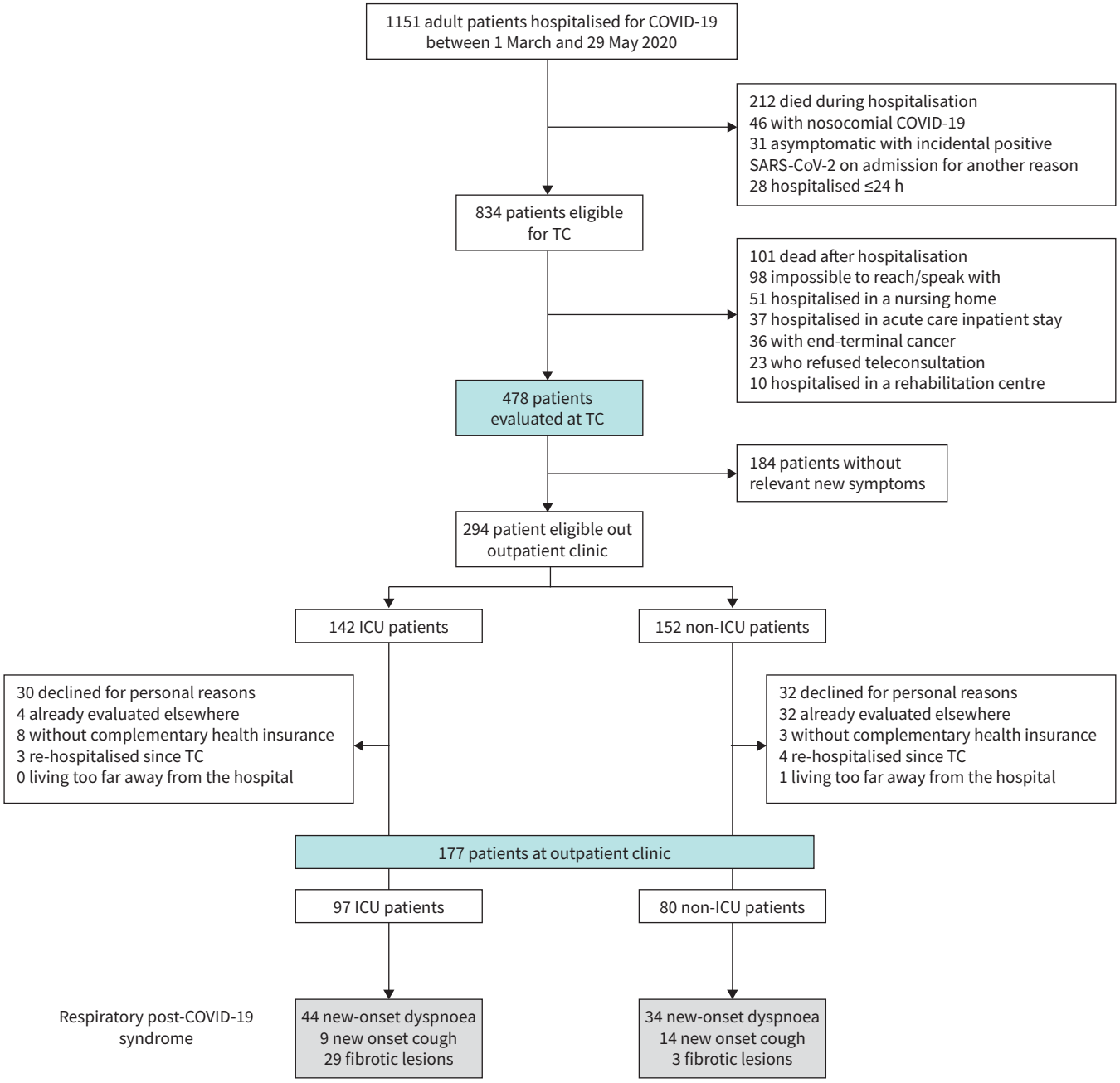

FIGURE 1 Flow chart of the study. COVID-19: coronavirus disease 2019; ICU: intensive care unit; SARS-CoV-2: severe acute respiratory syndrome coronavirus 2; TC: telephone consultation.

score of >22 and were considered to have "functional respiratory complaints". Fibrotic lesions on HRCT were present in 18 (23.1%) patients with new-onset dyspnoea. Among the patients assessed at the ambulatory care visit, those with new-onset dyspnoea more often had new-onset cough (19.2 *versus* 8.1%, p=0.04) and a lower FVC (85.6±16.3 *versus* 92.1±16.0% pred, p =0.02) and TLC (80.0±15.2 *versus* 85.1 ±15.0% pred, p=0.04) than those without new-onset dyspnoea. No difference was observed in D_{LCO} (85.6 ±23.7 *versus* 87.7±22.1% pred, p=0.57) (table 2). Echocardiography was performed in 40 patients with new-onset dyspnoea and revealed a mild decrease in left ventricular systolic function (ejection fraction 40–49%) in six (15%) patients, no signs of pulmonary hypertension and no significant difference compared with patients without new-onset dyspnoea (table 2). Among the 177 patients reassessed at the outpatient clinic, 23 (13.0%) had new-onset cough. The majority of these 23 patients (60.9%) had been hospitalised in the ward for COVID-19 and 78.3% did not show fibrotic lesions on HRCT.

TABLE 1 Baseline and hospitalisation characteristics of patients who were evaluated by telephone 4 months after hospital discharge according to the presence of new-onset dyspnoea

	Available data	All patients (478)	Patients with new-onset dyspnoea (78)	Patients without new-onset dyspnoea (400)	p-value
Demographic data					
Age, years	478	61.0±16.1	56.1±12.3	61.9±16.6	0.001
Women	478	201 (42.1%)	30 (38.5%)	171 (42.8%)	0.56
Body mass index, kg·m^{-2}	351	28.8±5.6	29.0±5.1	28.8±5.8	0.69
Smoking					
No (<5 pack-years)	452	343 (75.9%)	60 (81.1%)	283 (74.9%)	
Former (⩾5 pack-years)	452	83 (18.4%)	11 (14.9%)	72 (19.0%)	0.63
Active	452	26 (5.8%)	3 (4.1%)	23 (6.1%)	
Pre-COVID-19 comorbidities					
Respiratory disease					
COPD	478	17 (3.6%)	2 (2.6%)	15 (3.8%)	1
Other than COPD	478	75 (15.7%)	12 (15.4%)	63 (15.8%)	1
Hypertension	478	225 (47.1%)	30 (38.5%)	195 (48.8%)	0.12
Chronic heart disease	478	77 (16.1%)	4 (5.1%)	73 (18.2%)	0.007
Diabetes	478	128 (26.8%)	24 (30.8%)	104 (26.0%)	0.47
Chronic kidney disease	478	51 (10.7%)	2 (2.6%)	49 (12.2%)	0.02
Declared psychiatric disorder	478	42 (8.8%)	5 (6.4%)	37 (9.3%)	0.55
Neurodegenerative disorder	478	34 (7.1%)	0 (0%)	34 (8.5%)	0.02
Alcohol misuse	450	21 (4.7%)	3 (4.1%)	18 (4.8%)	1
Active cancer	478	18 (3.8%)	2 (2.6%)	16 (4.0%)	0.75
Other immunosuppression	478	18 (3.8%)	2 (2.6%)	16 (4.0%)	0.75
Long-term dialysis	478	17 (3.6%)	0 (0%)	17 (4.3%)	0.09
HIV infection	478	12 (2.5%)	1 (1.3%)	11 (2.8%)	0.7
Solid organ transplantation	478	9 (1.9%)	1 (1.3%)	8 (2.0%)	1
Liver disease	478	7 (1.5%)	2 (2.6%)	5 (1.3%)	0.32
Pregnancy	478	5 (1.1%)	0 (0%)	5 (1.3%)	1
Hospitalisation characteristics					
Total duration of hospitalisation, days	478	9 (4–15)	13 (7–23)	8 (4–14)	<0.001
Hospitalisation in the ICU	478	142 (29.7%)	44 (56.4%)	98 (24.5%)	<0.001
Duration of ICU stay, days	141	9 (4–19)	9 (4–21)	9 (4–19)	0.73
High flow oxygen	142	62 (43.7%)	20 (45.5%)	42 (42.9%)	0.92
Intubation during hospitalisation	142	73 (51.4%)	25 (56.8%)	48 (49.0%)	0.50
Duration of intubation, days	73	18 (11–32)	24 (12–38)	16 (11–27)	0.21
Pulmonary embolism	430	39 (9.1%)	14 (18.0%)	25 (6.8%)	<0.001
Active anticoagulation (at the full therapeutic dose)	478	75 (15.7%)	30 (38.5%)	45 (11.2%)	<0.001
Specific treatments during hospitalisation					
Azithromycin	478	120 (25.1%)	28 (35.9%)	92 (23.0%)	0.02
Anti-IL-6	478	37 (7.7%)	12 (15.4%)	25 (6.2%)	0.01
Hydroxychloroquine	478	32 (6.7%)	9 (11.5%)	23 (5.8%)	0.10
Corticosteroids	478	24 (5.0%)	1 (1.3%)	2 (5.8%)	0.15
Lopinavir/ritonavir	478	16 (3.4%)	6 (7.7%)	10 (2.5%)	0.03
Anti-IL-1	478	11 (2.3%)	3 (3.9%)	8 (2.0%)	0.40
Remdesivir	478	5 (1.1%)	1 (1.3%)	4 (1.0%)	0.59

Values are expressed as the median (interquartile range), mean±SD, or number and frequency. The p-values refer to a comparison between patients with and without new-onset dyspnoea. COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; ICU: intensive care unit; IL: interleukin.

Pulmonary function tests

As shown in the table 2, the pulmonary volumes (FVC, TLC, FEV_1) were normal in the majority of the 177 patients assessed at the ambulatory care visit but D_{LCO} was decreased in 22% of the patients.

Echocardiography results

Among the 177 patients assessed at the ambulatory care visit, an echocardiography was performed in 83 patients and 12% had a decreased left ventricular ejection fraction but none had echocardiographic signs of pulmonary hypertension.

TABLE 2 Characteristics of patients evaluated at the ambulatory care visit according to the presence of new-onset dyspnoea

	Available data	All (177)	Patients with new-onset dyspnoea (78)	Patients without new-onset dyspnoea (99)	p-value
Time from hospital discharge to the outpatient clinic, days	177	125 (107–144)	118 (105–140)	126 (108–146)	0.28
Assessment at the ambulatory care visit					
mMRC scale score for dyspnoea	177				<0.0001
0		87 (49.2%)	22 (28.2%)	65 (65.7%)	
1–2		76 (42.9%)	48 (61.5%)	28 (28.3%)	
3–4		14 (7.9%)	8 (10.3%)	6 (6.0%)	
New-onset cough	177	23 (13.0%)	15 (19.2%)	8 (8.1%)	0.04
6-min walk distance, m	161	462 (380–507)	450 (377–495)	474 (384–516)	0.35
Abnormal HRCT of the chest	171	108 (63.2%)	47 (61.0%)	61 (64.9%)	0.72
Reticulations	171	91 (53.2%)	41 (53.2%)	50 (53.2%)	1
Persistent ground-glass opacities	171	72 (42.1%)	36 (46.8%)	36 (38.3%)	0.30
Fibrotic lesions	171	33 (19.3%)	18 (23.1%)	15 (16.0%)	0.28
Pulmonary function tests					
FEV_1, % pred	157	90.8±17.8	87.8±16.5	93.3±18.5	0.06
FEV_1/VC, % pred	157	82.1±7.4	82.3±6.9	82.0±7.9	0.77
VC, % pred	152	89.1±16.4	85.6±16.3	92.1±16.0	0.02
TLC, % pred	149	82.8±15.3	80.0±15.2	85.1±15.0	0.04
D_{LCO}, % pred	152	86.7±22.7	85.6±23.7	87.7±22.1	0.57
D_{LCO}<70%	152	33 (21.7%)	17 (24.6%)	16 (19.3%)	0.55
Nijmegen score>22	168	36 (21.4%)	23 (29.5%)	13 (14.1%)	0.02
LVEF⩽50% on echocardiography	83	10 (12.0%)	6 (15.0%)	4 (9.3%)	0.50

Values are expressed as the median (interquartile range), mean±SD, or number and frequency. The p-values refer to a comparison between patients with and without new-onset dyspnoea. D_{LCO}: diffusing capacity of the lungs for carbon monoxide; FEV_1: forced expiratory volume in the first second of expiration; HRCT: high-resolution computed tomography; LVEF: left ventricular ejection fraction; mMRC: modified Medical Research Council; VC: vital capacity.

Radiologic characteristics on HRCT of the chest

Among the 177 patients assessed at the ambulatory care visit, HRCT of the chest was performed in 171 (96.6%). One or more abnormalities related to COVID-19 were observed in 108 patients (63.2%). The most frequent abnormalities were reticulations (53.2%) and ground-glass opacities (42.1%). 33 patients (19.3%) demonstrated fibrotic lesions (table 3). The extent of lesions was limited to <10% of parenchymal involvement in the majority of the patients with ground-glass opacities (69.4%), consolidations (80.0%) and fibrotic lesions (51.5%). The extent of fibrotic lesions was <25% in 97% of the patients (table 3).

There was no significant difference in radiologic abnormalities (type of lesion and extension) between the patients with and without new-onset dyspnoea (table 2). A typical HRCT image of the chest in a patient with mild fibrotic lesions (<10% parenchymal involvement) is shown in figure 2, and that of a patient with severe fibrotic lesions (>50% parenchymal involvement) is shown in figure 3**,** compared with that for acute COVID-19.

Characteristics of patients with fibrotic lesions on HRCT at 4 months

Of the patients with fibrotic lesions, 18 (54.5%) and 5 (15.1%) had new-onset dyspnoea and cough, respectively, which was not significantly different from patients without fibrotic lesions (58 (42.0%) and 17 (12.3%), respectively, all p>0.05) (table 4). Compared to patients without fibrotic lesions on HRCT, the patients with fibrotic lesions were older (61.2±10.9 *versus* 56.3±13.6 years, p =0.03). There was no significant difference in the sex ratio, BMI, comorbidities or smoking status (table 4). On the other hand, the patients with fibrotic lesions experienced significantly more severe episodes of COVID-19, with a longer duration of hospital stay (27 (15–44) *versus* 11 (5–17) days, p<0.001), more frequent admission to the ICU (87.9 *versus* 47.4%, p<0.001), a longer duration of mechanical ventilation (28 (16–43) *versus* 18 (10–25) days, p=0.03) and more frequently had acute pulmonary embolism (39.4 *versus* 11.6%, p<0.001). Associated with the higher frequency of hospitalisation in the ICU, patients with fibrotic lesions also had more often received anti-interleukin (IL) 6 (36.4% *versus* 10.2%, p=0.001) and anticoagulants at the therapeutic dose (45.5 *versus* 24.8%, p=0.03). Of note, at this period, very few patients (with and without fibrotic lesions) were treated with corticosteroids (9% and 3%, respectively).

TABLE 3 Lung abnormalities on HRCT at the ambulatory care visit (n=171)

Ground-glass opacities	
Ground-glass opacities, n (%)	72 (42.1%)
Extent of ground-glass opacities	
0%	98 (57.3%)
1–10%	50 (29.2%)
11–25%	19 (11.1%)
26–50%	3 (1.8%)
Consolidations	
Consolidations n (%)	10 (5.9%)
Extent of consolidations	
0%	160 (93.6%)
1–10%	8 (4.7%)
11–25%	2 (1.2%)
Reticulations and crazy paving	
Reticulations, n (%)	91 (53.2%)
Crazy paving, n (%)	2 (1.2%)
Fibrotic lesions	
Fibrotic lesions, n (%)	33 (19.3%)
Extent of fibrotic lesions	
0%	138 (80.7)
1–10%	17 (9.9%)
11–25%	13 (7.6%)
26–50%	2 (1.2%)
Other abnormalities	
Emphysema, n (%)	11 (6.4%)
Pleural effusion, n (%)	3 (1.8%)

No difference in the mMRC score or 6MWT distance was observed. Patients with fibrotic lesions had a significantly lower FVC (80.6±20.0 *versus* 91.5±14.4% pred, p=0.007), TLC (74.1±13.7 *versus* 84.9 ±14.8% pred, p<0.001) and D_{LCO} (73.3±17.9 *versus* 89.7±22.8% pred, p<0.001). The proportion of patients with D_{LCO} under 70% pred was also higher among those with fibrotic lesions (41.4% *versus* 17.1%, p=0.01). In the multivariate analysis, only hospitalisation in the ICU and an episode of pulmonary embolism were significantly associated with fibrotic lung lesions (Table E4).

The presence of new-onset dyspnoea, fibrotic lesions and decreased D_{LCO} under 70% pred was rare, as it was observed in only eight patients (4.5% of the population assessed at the ambulatory care visit and 1.6% of the whole population) (figure 4). When we compared patients with fibrotic lesions according to the presence of new-onset dyspnoea, the only differences were lower levels of FEV_1 (79.3 *versus* 94.6% pred, p=0.04), FVC (73.9 *versus* 88.7% pred, p=0.04) and TLC (68.6 *versus* 81.3% pred, p=0.01) in patients with new-onset dyspnoea (Tables E5 and E6).

Discussion

This study investigated the respiratory complications of post-acute COVID-19 syndrome at 4 months in a well-characterised population to define the characteristics of patients with new-onset dyspnoea and the relationships between respiratory symptoms, radiologic abnormalities and functional impairment. New-onset dyspnoea and cough were identified in 16.3% and 4.8% of the COMEBAC population, respectively. The mechanisms identified as possibly related to dyspnoea were multifactorial, with frequent "functional respiratory complaints". Fibrotic lung lesions were often limited and were more frequently observed in patients with the most severe forms of initial COVID-19. Fibrotic lesions had limited consequences on the functional status and were not systematically associated with persistent respiratory symptoms.

This study confirms that new-onset dyspnoea is not rare 4 months after hospitalisation for COVID-19, as it affected at least 16.3% of patients who were discharged alive. This result is in accordance with previous studies in which patients were assessed between 1 and 12 months after COVID-19 and that reported a prevalence of persistent dyspnoea ranging from 15 to 81% after hospitalisation [12, 21–25] and approximately 12% in non-hospitalised patients with mild COVID-19 [26]. A recent meta-analysis on 15244 hospitalised during COVID-19 and 9011 non-hospitalised patients found a prevalence of dyspnoea at 3 months after COVID-19 of 33.3% in hospitalised patients and of 19.1% in non-hospitalised patients [27]. Telephone interviews seem to be an effective approach to detect residual respiratory symptoms requiring complementary investigations at ambulatory care visits. Indeed, with more than 240 million

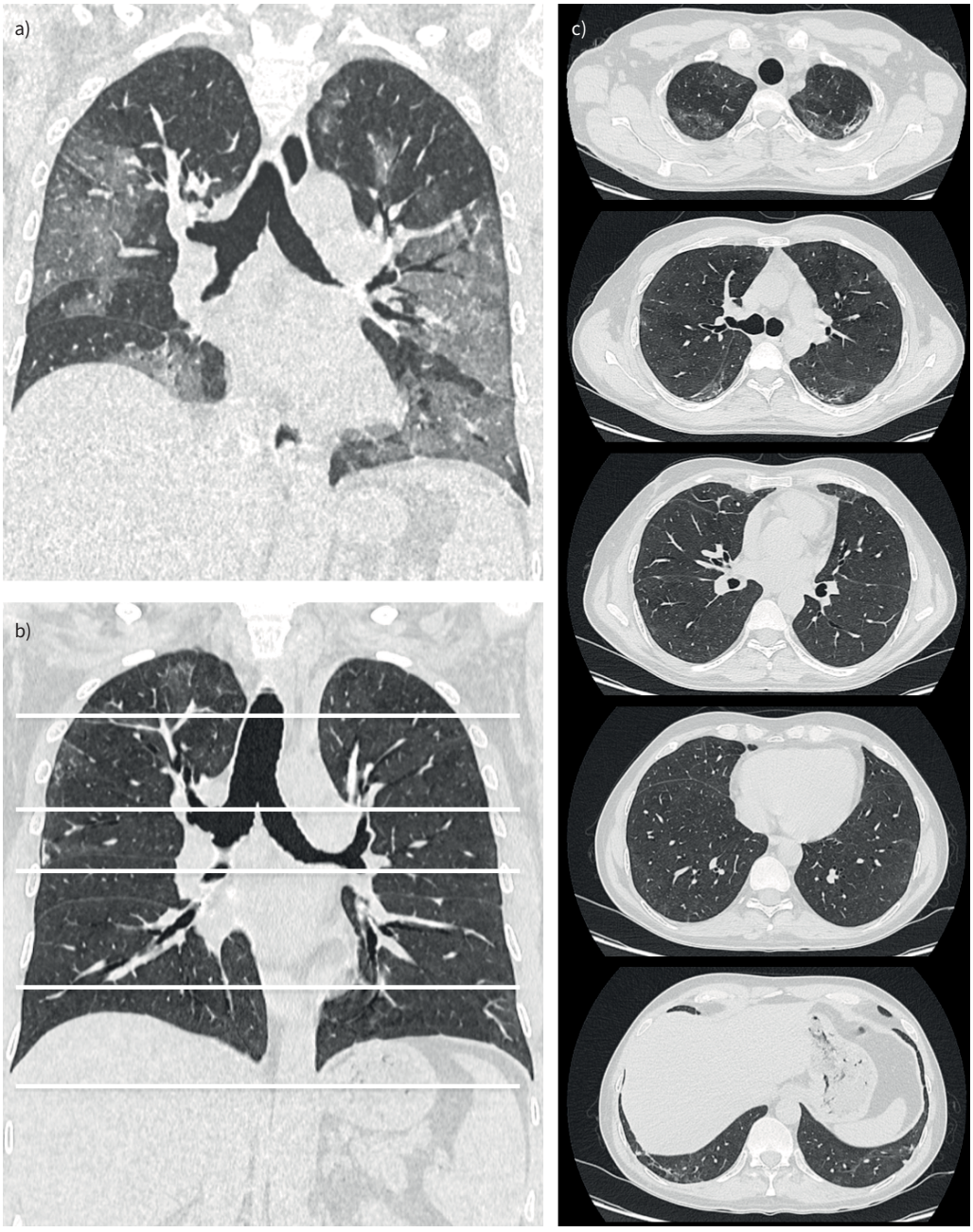

FIGURE 2 High-resolution computed tomography (HRCT) image of the chest in a patient with mild fibrotic lung lesions 4 months after hospitalisation for coronavirus disease 2019 (COVID-19) compared with that during acute COVID-19. Coronal a) multiplanar reconstruction of an HRCT image of the chest during acute COVID-19 with extensive bilateral ground-glass opacities. Coronal b) multiplanar reconstructions and axial sections c) of an HRCT image of the chest from the same patient showing mild fibrotic lung lesions at 4 months, demonstrating small traction bronchiectasis close to the marginal fibrotic sequelae with a sub-pleural predominance.

people infected with COVID-19 worldwide [1], the percentage of patients with new-onset dyspnoea after infection (16%) could have a major impact on public health programmes, potentially affecting nearly 40 million people worldwide.

Previous data on SARS-CoV and Middle East respiratory syndrome-coronavirus (MERS-CoV), which are responsible for epidemics of severe acute respiratory syndrome, showed that approximately 8–30% of

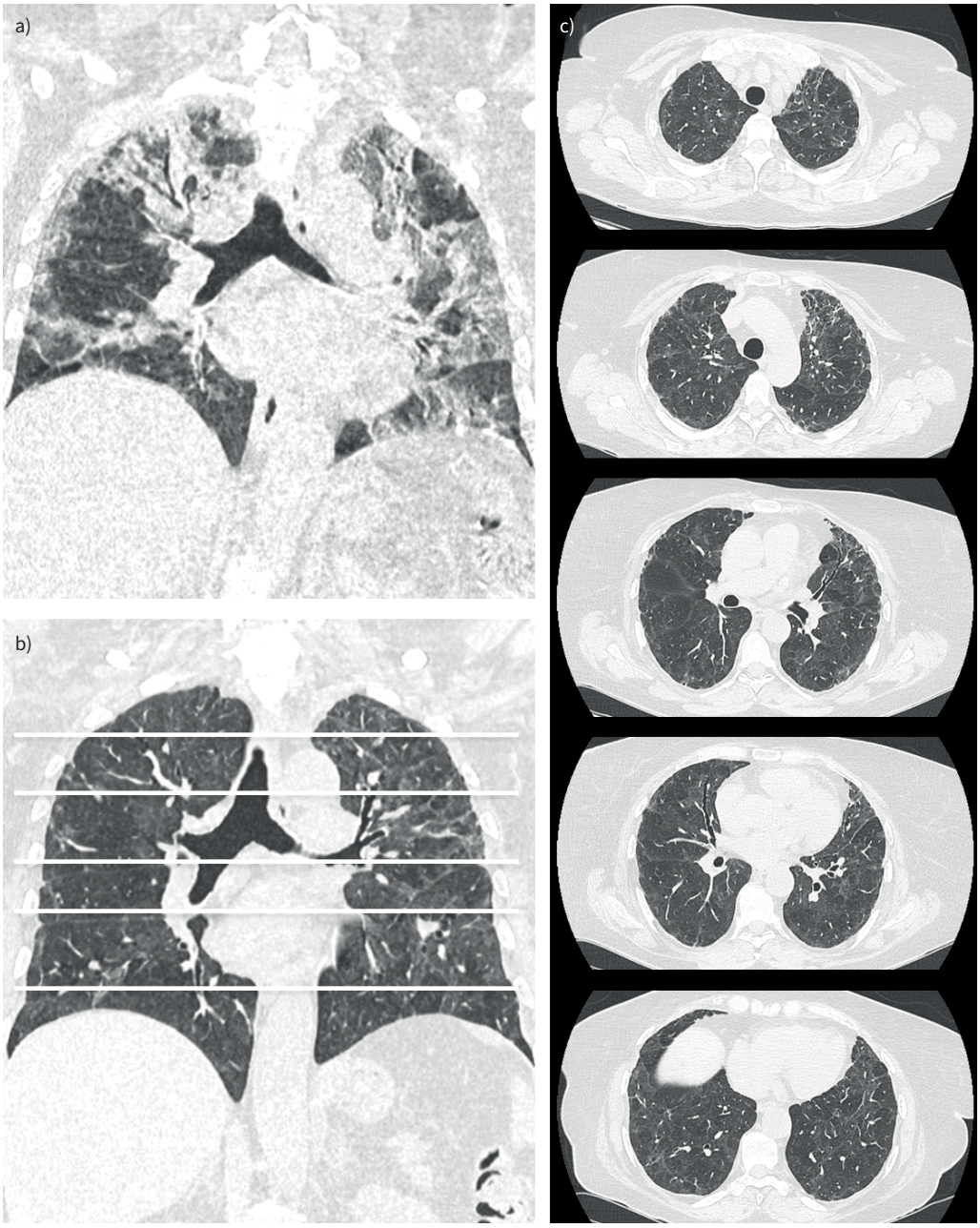

FIGURE 3 High-resolution computed tomography (HRCT) image of the chest in a patient with severe fibrotic lung lesions 4 months after hospitalisation for coronavirus disease 2019 (COVID-19) compared with that during acute COVID-19. Coronal a) multiplanar reconstruction of an HRCT image of the chest during acute COVID-19 with extensive bilateral ground-glass opacities and consolidations. Coronal b) multiplanar reconstructions and axial sections c) of an HRCT image of the chest from the same patient showing severe fibrotic lung lesions at 4 months, demonstrating diffuse traction bronchiectasis and association with ground-glass opacities.

patients developed fibrotic lesions on chest CT within 3 months after discharge [28, 29]. Because SARS-CoV-2 shares many similarities with SARS-CoV and MERS-CoV, with the frequent occurrence of severe pneumoniae or acute respiratory distress syndrome (ARDS), it was feared that the SARS-CoV-2 epidemic could be followed by a significant number of patients with respiratory sequelae leading to serious functional consequences [30]. This study demonstrated that the mechanisms of post-COVID-19 dyspnoea are rather multifactorial and cannot be related only to parenchymal sequelae. In particular, some patients with new-onset dyspnoea had a Nijmegen questionnaire score greater than 22, suggesting "functional

TABLE 4 Baseline and hospitalisation characteristics of patients who were evaluated at ambulatory care visits according to the presence of fibrotic lesions in lungs

	Available data	All (171)	Patients with fibrotic lesions (33)	Patients without fibrotic lesions (138)	p-value
Demographic data					
Age, years	171	57.3±13.2	61.2±10.9	56.3±13.6	0.03
Women	171	65 (38.2%)	3 (9.1%)	56 (40.9%)	0.21
Body mass index, kg·m^{-2}	159	29.1±5.4	28.2±4.9	29.4±5.5	0.24
Smoking					
No (<5 pack-years)	162	125 (77.2%)	22 (71.0%)	103 (78.6%)	
Former (⩾5 pack-years)	162	24 (14.8%)	5 (16.1%)	19 (14.5%)	0.46
Active	162	13 (8.0%)	4 (12.9%)	9 (6.9%)	
Pre-COVID-19 comorbidities					
Respiratory disease					
COPD	170	5 (2.9%)	1 (3.0%)	4 (2.9%)	1
Other than COPD	170	30 (17.6%)	5 (15.2%)	25 (18.2%)	0.87
Hypertension	170	74 (43.5%)	12 (36.4%)	62 (45.3%)	0.47
Chronic heart disease	170	14 (8.2%)	3 (9.1%)	11 (8.0%)	0.74
Diabetes	170	51 (30.0%)	7 (21.2%)	44 (32.1%)	0.31
Chronic kidney disease	170	16 (9.4%)	1 (3.0%)	15 (10.9%)	0.32
Declared psychiatric disorder	170	10 (5.9%)	5 (15.2%)	5 (3.7%)	0.03
Neurodegenerative disorder	170	2 (1.2%)	0 (0%)	2 (1.5%)	1
Alcohol misuse	161	8 (5.0%)	1 (3.2%)	7 (5.4%)	1
Active cancer	170	3 (1.8%)	1 (3.0%)	2 (1.5%)	0.48
Other immunosuppression	170	7 (4.1%)	1 (3.0%)	6 (4.4%)	1.0
Long-term dialysis	170	6 (3.5%)	0 (0%)	6 (4.4%)	0.60
HIV infection	170	2 (1.2%)	0 (0%)	2 (1.5%)	1
Solid organ transplantation	170	4 (2.3%)	0 (0%)	4 (2.9%)	1
Liver disease	170	5 (2.9%)	0 (0%)	5 (3.7%)	0.58
Pregnancy	170	1 (0.6%)	0 (0%)	1 (0.7%)	1
Hospitalisation characteristics					
Total duration of hospitalisation, days	170	13 (6–25)	27 (15–44)	11 (5–17)	<0.001
Hospitalisation in the ICU	170	94 (55.3%)	39 (87.9%)	65 (47.4%)	<0.001
Duration of ICU stay, days	170	9 (4–22)	22 (5–33)	8 (3–14)	0.006
High flow oxygen	170	44 (46.8%)	18 (62.1%)	26 (40%)	0.08
Intubation during hospitalisation	170	49 (52.1%)	18 (62.1%)	31 (47.7%)	0.29
Duration of intubation, days	170	20 (12–34)	28 (16–43)	18 (10–25)	0.03
Pulmonary embolism	171	29 (17.0%)	13 (39.4%)	16 (11.6%)	<0.001
Active anticoagulation (at the full therapeutic dose)	170	49 (28.8%)	15 (45.5%)	34 (24.8%)	0.03
Specific treatments during hospitalisation					
Azithromycin	170	53 (31.2%)	12 (36.4%)	41 (29.9%)	0.61
Anti-IL-6	170	26 (15.3%)	12 (36.4%)	14 (10.2%)	0.001
Hydroxychloroquine	170	18 (10.6%)	5 (15.2%)	13 (9.5%)	0.35
Corticosteroids	170	7 (4.1%)	3 (9.1%)	4 (2.9%)	0.13
Lopinavir/ritonavir	170	7 (4.1%)	2 (6.1%)	5 (3.7%)	0.62
Anti-IL-1	170	8 (4.7%)	3 (9.1%)	5 (3.7%)	0.19
Remdesivir	170	3 (1.8%)	0 (0%)	3 (2.2%)	1

Values are expressed as the median (interquartile range), mean±SD, or number and frequency. The p-values refer to a comparison between patients with and without fibrotic lesions. COPD: chronic obstructive pulmonary disease; COVID-19: coronavirus disease 2019; ICU: intensive care unit; IL: interleukin.

respiratory complaints", while others had fibrotic lesions with lower respiratory volumes on pulmonary function tests. Indeed, despite generally normal PFT results in the whole population, the patients with new-onset dyspnea had lower FCV and TLC, suggesting a possible role for lung sequalae in new-onset dyspnea. It has been suggested that dyspnoea could also be induced by cardiovascular dysfunction or muscular deconditioning independent of respiratory sequelae [9, 13, 31, 32]. However, in our study, left ventricular systolic dysfunction was not overrepresented in patients with new-onset dyspnoea, suggesting that left ventricular systolic dysfunction pre-existed in this at-risk population. The role of thromboembolic events in residual dyspnoea after COVID-19 remains unclear. In the studied population, pulmonary

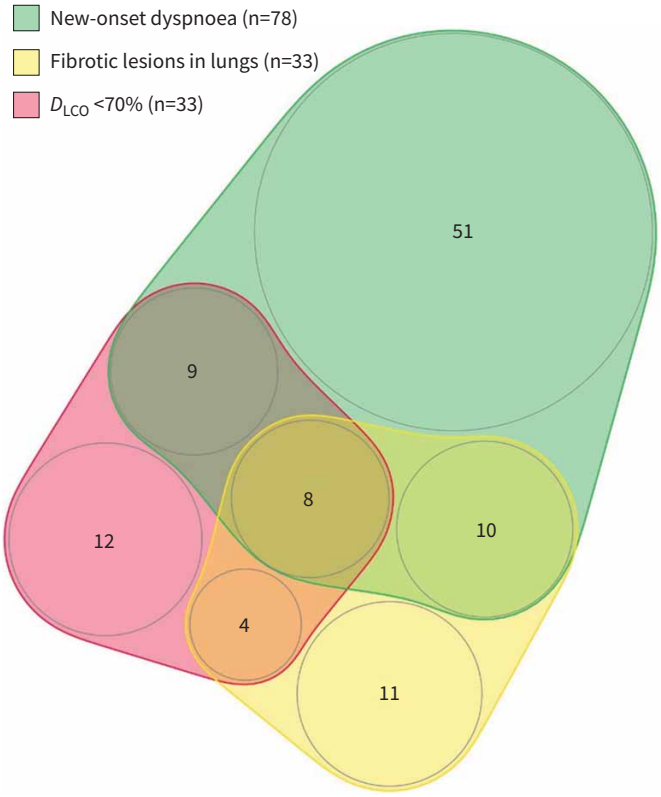

FIGURE 4 Distribution of patients evaluated at ambulatory care visits according to new-onset dyspnoea, fibrotic lung lesions on high-resolution computed tomography and decreased D_{LCO} <70%. D_{LCO}: diffusing capacity of the lung for carbon monoxide.

embolism during acute infection was more frequently observed in patients with new-onset dyspnoea, and this difference remained in multivariate analysis and could suggest the role of pulmonary embolism in residual dyspnoea; however, none of these patients had signs of persistent pulmonary hypertension on echocardiography.

In this cohort, patients with fibrotic lesions experienced significantly more severe episodes of COVID-19, with more frequent hospitalisation in the ICU and a longer duration of intubation. At 4 months, ground-glass opacities were frequently observed (>40%). Even in transient lesions, the long-term evolution of these abnormalities remains an unresolved issue. By contrast, fibrotic lesions were rare, as previously described [33], and usually had limited extension and no functional impact. The precise characterisation and evolving nature (irreversible, progressive or potentially regressive) of these lesions are matters of debate. Fibrotic lesions seem to be generally in the same areas as acute lesions as seen in figures 2 and 3. VAN GASSEL *et al.* [11] reported signs of reticulation, including course fibrous bands either with or without obvious parenchymal distortion, bronchiectasis, and bronchiolectasis, in almost 67% of 95 mechanically ventilated survivors of COVID-19 3 months after hospital discharge, and fibrotic lesions could also have a rapid onset in patients who never required mechanical ventilation [34]. COVID-19 patients with ARDS and diffuse alveolar damage can progress to the fibrosing pattern as seen on *post mortem* analysis [35] even if traction bronchiectasis does not always correlate with the histologic fibrosis pattern [36]. However, histological data on surviving patients with radiological signs of fibrotic lesions in lungs are lacking. It has been suggested that the signs of fibrosis may represent areas of consolidation as in organising pneumonia, which could reverse [37]. This hypothesis is reinforced by studies showing an improvement in residual interstitial lesions, including fibrotic lesions, after corticosteroid therapy or spontaneously [38, 39]. Fibrotic lung lesions were also more frequently associated with episodes of pulmonary embolism during COVID-19, and this difference was still present in multivariate analysis. This could suggest the presence of parenchymal sequelae of pulmonary embolism, such as pulmonary infarcts, intertwined with fibrosing lesions, but there was no evidence of typical pulmonary infarcts on the HRCT images. Even though patients with fibrotic lesions had significantly lower respiratory volumes and D_{LCO}, functional impairment

TABLE 5 Characteristics of patients evaluated at the ambulatory care visit according to the presence of fibrotic lesions in lungs

	Available data	All (171)	Patients with fibrotic lesions (33)	Patients without fibrotic lesions (138)	p-value
Time from hospital discharge to the outpatient clinic, days	171	122 (106–143)	109 (94–125)	127 (109–146)	0.004
Assessment at the ambulatory care visit					
New-onset dyspnoea	171	76 (44.4%)	18 (54.5%)	58 (42.0%)	0.28
mMRC scale score for dyspnoea	171				0.65
0		83 (48.5%)	15 (45.5%)	68 (49.3%)	
1–2		74 (43.3%)	14 (42.4%)	60 (43.5%)	
3–4		14 (8.2%)	4 (12.1%)	10 (7.2%)	
New-onset cough	171	22 (13.3%)	5 (15.1%)	17 (12.3%)	0.77
6-min walk distance, m	155	459 (378–504)	486 (401–510)	454 (375–498)	0.24
Abnormal HRCT of the chest	171	108 (63.5%)	33 (100%)	75 (54.5%)	<0.001
Reticulations	171	91 (53.5%)	31 (93.9%)	60 (43.5%)	<0.001
Persistent ground-glass opacities	171	72 (42.1%)	22 (66.6%)	50 (36.2%)	0.03
Pulmonary function tests					
FEV_1, % pred	151	90.9±18.0	86.2±20.0	92.1±17.3	0.14
FEV_1/VC, %	151	82.0±7.5	82.3±6.3	82.0±7.8	0.82
VC, % pred	146	89.2±16.3	80.6±20.0	91.5±14.4	0.007
TLC, % pred	143	82.6±15.2	74.1±13.7	84.9±14.8	<0.001
D_{LCO}, % pred	146	86.5±22.8	73.3±17.9	89.7±22.8	<0.001
D_{LCO}<70%	146	32 (21.9%)	12 (41.4%)	20 (17.1%)	0.01
Nijmegen score>22	162	35 (21.6%)	2 (6.3%)	33 (25.4%)	0.03
LVEF⩽50% on echocardiography	80	10 (12.5%)	5 (19.2%)	5 (9.3%)	0.28

Values are expressed as the median (interquartile range), mean±SD, or number and frequency. The p-values refer to a comparison between patients with and without fibrotic lesions. D_{LCO}: diffusing capacity of the lungs for carbon monoxide; FEV_1: forced expiratory volume in the first second of expiration; HRCT: high-resolution computed tomography; LVEF: left ventricular ejection fraction; mMRC: modified Medical Research Council; VC: vital capacity.

was usually mild and was not associated with a poor impact on the mMRC scale. Indeed, the presence of new-onset dyspnoea, fibrotic lesions and decreased D_{LCO} <70% was found in only 1.6% of the whole population. While other studies have reported that lung radiologic abnormalities are correlated with poor pulmonary function and lung diffusion disorder [8, 10, 40], no study has demonstrated a clear association with dyspnoea or limited effort capacity [7–11, 25, 41]. In accordance with that, in a recent study, while there was an improvement in lung function and D_{LCO} between 3 and 6 months after COVID-19, there was no improvement in dyspnoea and quality of life [42].

Interestingly, 13.0% of the patients investigated at outpatient clinics and 4.8% of the whole population had new-onset cough. This finding is in agreement with studies showing that cough can persist for weeks or months after SARS-CoV-2 infection with a prevalence in a recent meta-analysis of 10.4% in hospitalised patients and 6.7% in non-hospitalised patients [27, 43]. Cough should therefore be included in the respiratory complaints after hospitalisation for COVID-19 and does not seem to be associated with lung sequelae, as cough appeared to be similarly distributed in patients with or without lung fibrosis.

Even if long-term studies are still needed to determine whether respiratory symptoms and radiologic lesions could resolve or worsen over time, the first 1-year follow-up studies after COVID-19 have recently been published and allow us to better understand the evolution of respiratory symptoms and sequelae of COVID-19 at a distance from the acute episode. Wu *et al.* [12] were the first to show that among 83 patients reassessed 1 year after severe COVID-19 who did not require mechanical ventilation, dyspnoea scores and exercise capacity improved over time but that a subgroup had persistent physiological and radiographic changes. In a recent study comparing symptoms and respiratory assessment between 6 and 12 months after COVID-19, it was shown on the contrary that dyspnoea score slightly worsen between 6 and 12 months and that there was no improvement in D_{LCO} while TLC and lung imaging abnormality gradually recovered [44]. As some studies have shown improvement in both FVC and D_{LCO} and in lung imaging abnormality from 6 months after COVID-19 [42, 45], the precise evolution of respiratory symptoms and of functional and radiological lung damage remains to be described and specified in long-term prospective follow-up studies.

This prospective study has some limitations. First, there was a selection bias for the comparison of the results of PFTs and lung CT scans between patients with and without new-onset dyspnoea, given that patients who were evaluated at ambulatory care visits were selected on the basis of the initial severity of the episode (ICU stay) or the presence of persistent symptoms. This bias was alleviated by comparing the characteristics of patients with and without new-onset dyspnoea among the entire cohort who was consulted *via* telephone. Second, of the 177 patients reassessed at the ambulatory care visit, five had negative SARS-CoV-2 serologic tests, and we cannot rule out that some patients included in the study did not in fact have COVID-19 initially. Moreover, the design of this study did not allow us to assess the prevalence of respiratory symptoms in outpatients. Additionally, this study was conducted during the first wave of the pandemic and, at that time, the use of corticosteroids and anti-IL6 was limited. We cannot evaluate the impact of anti-inflammatory treatments and new variants on the occurrence of persistent or residual respiratory complaints after hospitalisation for COVID-19.

In conclusion, persistent respiratory symptoms, especially new-onset dyspnoea and cough, are not rare 4 months after hospitalisation for COVID-19. New-onset dyspnoea was rarely associated with severe fibrotic lesions, and the association between new-onset dyspnoea, fibrotic lesions and low D_{LCO} was rare. There was no difference in echocardiographic results according to the presence of a new-onset dyspnoea either. Radiologically persistent lesions were mainly associated with the initial severity of COVID-19 but had mild functional consequences. Therefore, new-onset dyspnoea is the direct consequence of neither fibrotic lesions nor cardiologic sequalae but may be a multifactorial consequence of lung sequalae, vascular sequalae of pulmonary embolism, dysfunctional breathing, muscular deconditioning and probably other unknown causes, and the importance of each of these causes may be different in each patient. Due to the large number of COVID-19 patients worldwide, the long-term respiratory complications of COVID-19 could lead to the major use of health resources. Physicians should be aware of this condition and of the mechanisms that could lead to persistent dyspnoea in these patients to propose individual management adapted to each condition. Further long-term studies are needed to determine the evolution of respiratory symptoms and radiologic lesions over time.

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