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

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Take home message: New-onset dyspnoea is a frequent complaint 4 months after COVID-19 and is generally multifactorial, and the combination of new-onset dyspnoea, fibrotic lesions and DLCO <70%pred is rarely observed.

ABSTRACT

Rationale. The characteristics of patients with respiratory complaints and/or lung radiologic abnormalities after hospitalization for 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 cohort study, 478 hospital survivors were evaluated by telephone 4 months after hospital discharge, and 177 who had been hospitalized 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, 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 *vs.* 61.9±16.6 years), had more severe COVID-19 (ICU admission 56.4% *vs.* 24.5%) and more frequent pulmonary embolism (18.0% *vs.* 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 *vs.* 56±14 years, P=0.03), more frequently managed in ICU (87.9 *vs.* 47.4%, P<0.001), had lower total lung capacity (74.1±13.7 *vs.* 84.9±14.8%pred, P<0.001) and diffusing lung capacity for carbon monoxide (DLCO) (73.3±17.9 *vs.* 89.7±22.8%pred, P<0.001). The combination of new-onset dyspnoea, fibrotic lesions and DLCO <70%pred was observed in 8/478 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 DLCO 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 to 81% of patients [7–13]. However, the characteristics of patients with persistent or residual respiratory complaints after hospitalization 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 hospitalization 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 persistent or residual respiratory complaints after hospitalization 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 function impairment and radiologic abnormalities 4 months after COVID-19 in the COMEBAC study cohort.

MATERIALS & 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 hit 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, hospitalization for greater than 24 hours primarily because of COVID-19, and diagnosis of SARS-CoV-2 infection by reverse transcriptase-polymerase chain reaction (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 hospitalization, 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 CT scan conducted after hospitalization (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 three to four 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 hospitalized for acute COVID-19 were extracted from electronic health records. The patients provided informed consent after ICU hospitalization 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-minute 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 (DLCO) according to the European Respiratory Society/American Thoracic Society (ERS/ATS) guidelines [16]. Forced vital capacity (FVC), forced expiratory volume in 1 second (FEV1), total lung capacity (TLC) and DLCO are expressed as the percentages of predicted values (%pred) using the Global Lung Function Initiative (GLI) 2012 [17] and European Community for Coal and Steel (ECCS) 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 hospitalization, 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 [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 Student's 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 $p < 0.1$ and were clinically important and not collinear (consensus among investigators).

RESULTS

Characteristics of the patients with persistent respiratory symptoms

The flow chart 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 *vs.* 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] *vs.* 8 [4-14] days, P<0.001) and more frequent admission to the ICU (56.4 *vs.* 24.5%, P<0.001). They also more frequently exhibited pulmonary embolism in the acute phase (18.0 *vs.* 6.8%, P<0.001). In the multivariate analysis, only ICU hospitalization 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 hospitalizations 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. Twenty-three patients with new-onset dyspnoea (29.5%) had a Nijmegen questionnaire 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 *vs.* 8.1%, P=0.04) and a lower FVC (85.6±16.3 *vs.* 92.1±16.0%pred, P=0.02) and TLC (80.0±15.2 *vs.* 85.1±15.0%pred, P=0.04) than those without new-onset dyspnoea. No difference was observed in DLCO (85.6±23.7 *vs.* 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 6 (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 hospitalized in the ward for COVID-19 and 78.3% did not show fibrotic lesions on HRCT.

Pulmonary function tests

As shown in the Table 2, the pulmonary volumes (FVC, TLC, FEV1,) were normal in the majority of the 177 patients assessed at the ambulatory care visit but DLCO 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.

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%). Thirty-three 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 *vs.* 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] *vs.* 11 [5-17] days, P<0.001), more frequent admission to the ICU (87.9 *vs.* 47.4%, P<0.001), a longer duration of mechanical ventilation (28 [16-43] *vs.* 18 [10-25] days, P=0.03) and more frequently had acute pulmonary embolism (39.4 *vs.* 11.6%, P<0.001). Associated with the higher frequency of hospitalization in the ICU, patients with fibrotic lesions also had more often received anti-IL6 (36.4% *vs.* 10.2%, P=0.001) and anticoagulants at the therapeutic dose (45.5 *vs.* 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).

No difference in the mMRC score or 6MWT distance was observed. Patients with fibrotic lesions had a significantly lower FVC (80.6±20.0 *vs.* 91.5±14.4%pred, P=0.007), TLC (74.1±13.7 *vs.* 84.9±14.8%pred, P<0.001) and DLCO (73.3±17.9 *vs.* 89.7±22.8%pred, P<0.001). The proportion of patients with DLCO under 70%pred was also higher among those with fibrotic lesions (41.4% *vs.* 17.1%, P=0.01). In the multivariate analysis, only hospitalization 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 DLCO under 70%pred was rare, as it was observed in only 8 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 FEV1 (79.3 *vs.* 94.6%pred, P=0.04), FVC (73.9 *vs.* 88.7%pred, P=0.04) and TLC (68.6 *vs.* 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-characterized 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 hospitalization 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 hospitalization [12, 21–25] and approximately 12% in non-hospitalized patients with mild COVID-19 [26]. A recent meta-analysis on 15244 hospitalized during COVID-19 and 9011 non-hospitalized patients found a prevalence of dyspnea at 3 months after COVID-19 of 33.3% in hospitalized patients and of 19.1% in non-hospitalized 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 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 MERS-CoV, which are responsible for epidemics of severe acute respiratory syndrome, showed that approximately 8 to 30% of 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 respiratory complaints”, while others had fibrotic lesions with lower respiratory volumes on pulmonary function tests. Indeed, despite generally normal PFTs 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 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 hospitalization 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 characterization 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 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 [11], 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 do 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 organizing 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 DLCO, functional impairment 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 DLCO <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]. According with that, in a recent study, while there was an improvement in lung function and DLCO between 3 and 6 months after COVID-19, there was no improvement in dyspnea 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 hospitalized patients and 6.7% in non-hospitalized patients [27, 43]. Cough should therefore be included in the respiratory complaints after hospitalization 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 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 [12]. In a recent study comparing symptoms and respiratory assessment between 6 and 12 months

after COVID-19, it was shown on the contrary that dyspnea score slightly worsen between 6 and 12 months and that there was no improvement in DLCO while TLC and lung imaging abnormality gradually recovered [44]. As some studies have shown improvement in both FVC and DLCO and in lung imaging abnormality from 6 months after COVID-19 [42, 45], the precise evolution of respiratory symptoms, 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, 5 had negative SARS-CoV-2 serologic test, 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 hit 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 hospitalization for COVID-19.

In conclusion, persistent respiratory symptoms, especially new-onset dyspnoea and cough, are not rare 4 months after hospitalization for COVID-19. New-onset dyspnoea was rarely associated with severe fibrotic lesions, and the association between new-onset dyspnoea,

fibrotic lesions and low DLCO 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 can lead to 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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EMJ, OM, AB, XJ, TP, LM, AB, SB, SF, AH, MJ, NN, JP, AR, AS, SS, JD, LB, XM, OS, MFB, MH, LS, DM and the COMEBAC Study group contributed substantially to the study design, data analysis and interpretation and read and approved the manuscript. OM and SS reviewed the HRCT images. TP made the statistical analysis. EMJ, LS and DM wrote the manuscript.

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FIGURE LEGENDS

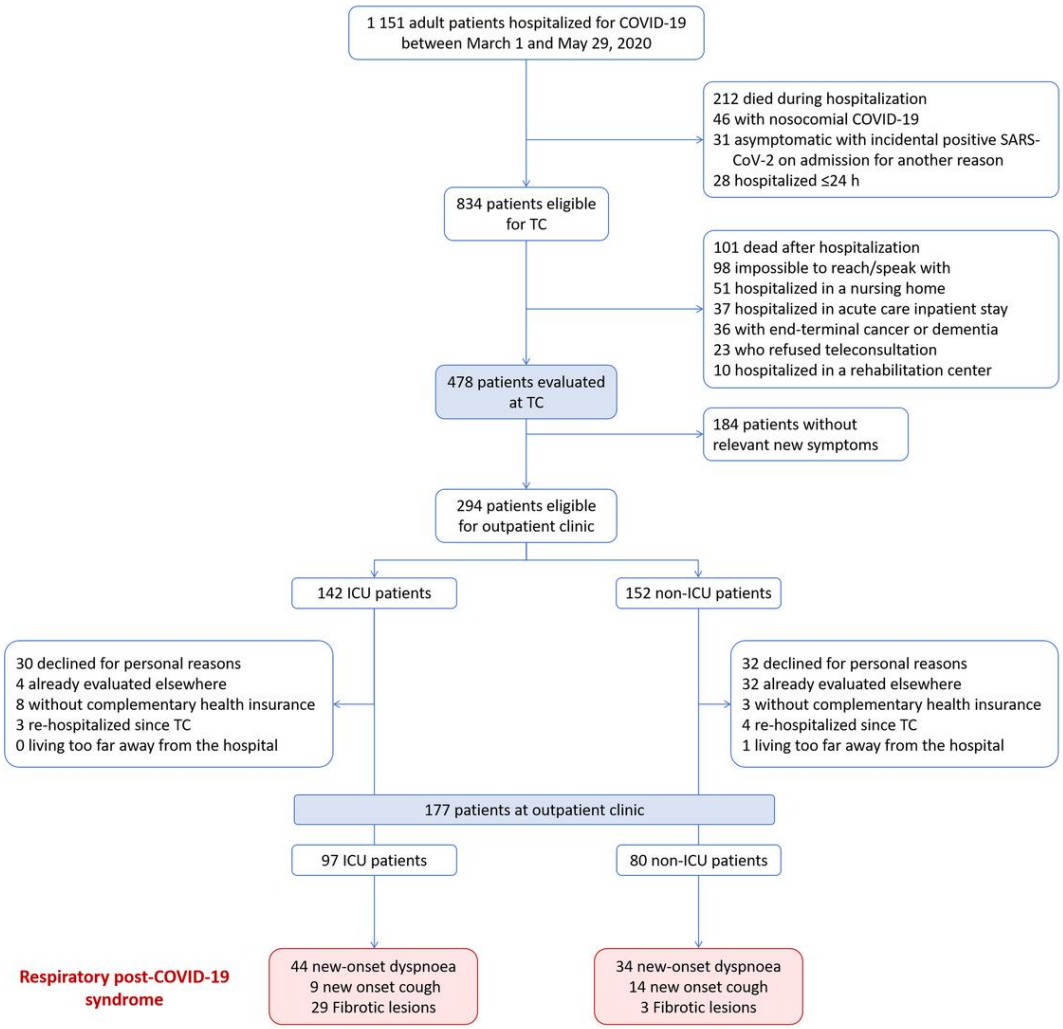

Figure 1. Flow chart of the study

ICU: intensive care unit; TC: telephone consultation

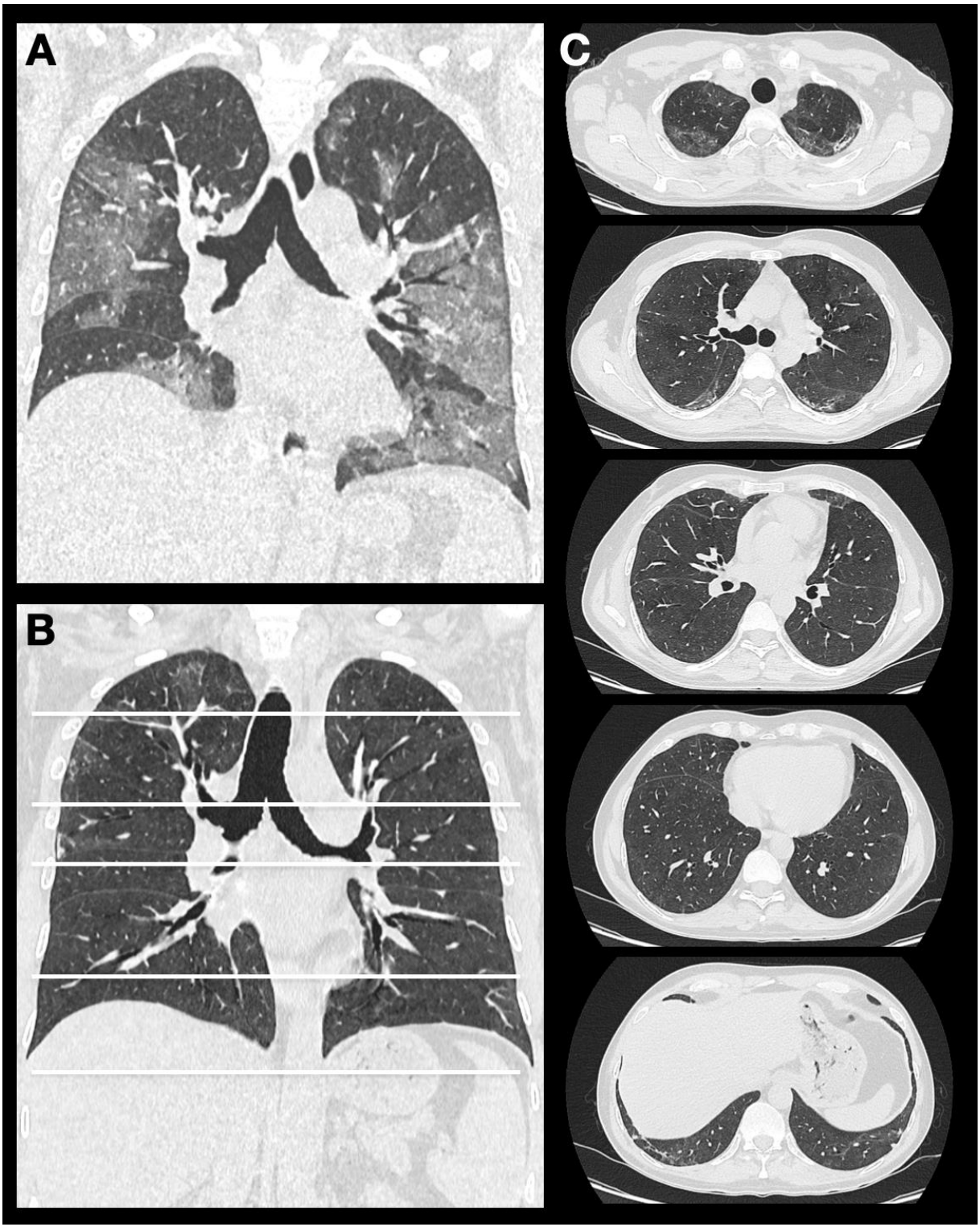
A
B
C

Figure 2. HRCT image of the chest in a patient with mild fibrotic lung lesions 4 months after hospitalization for 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.

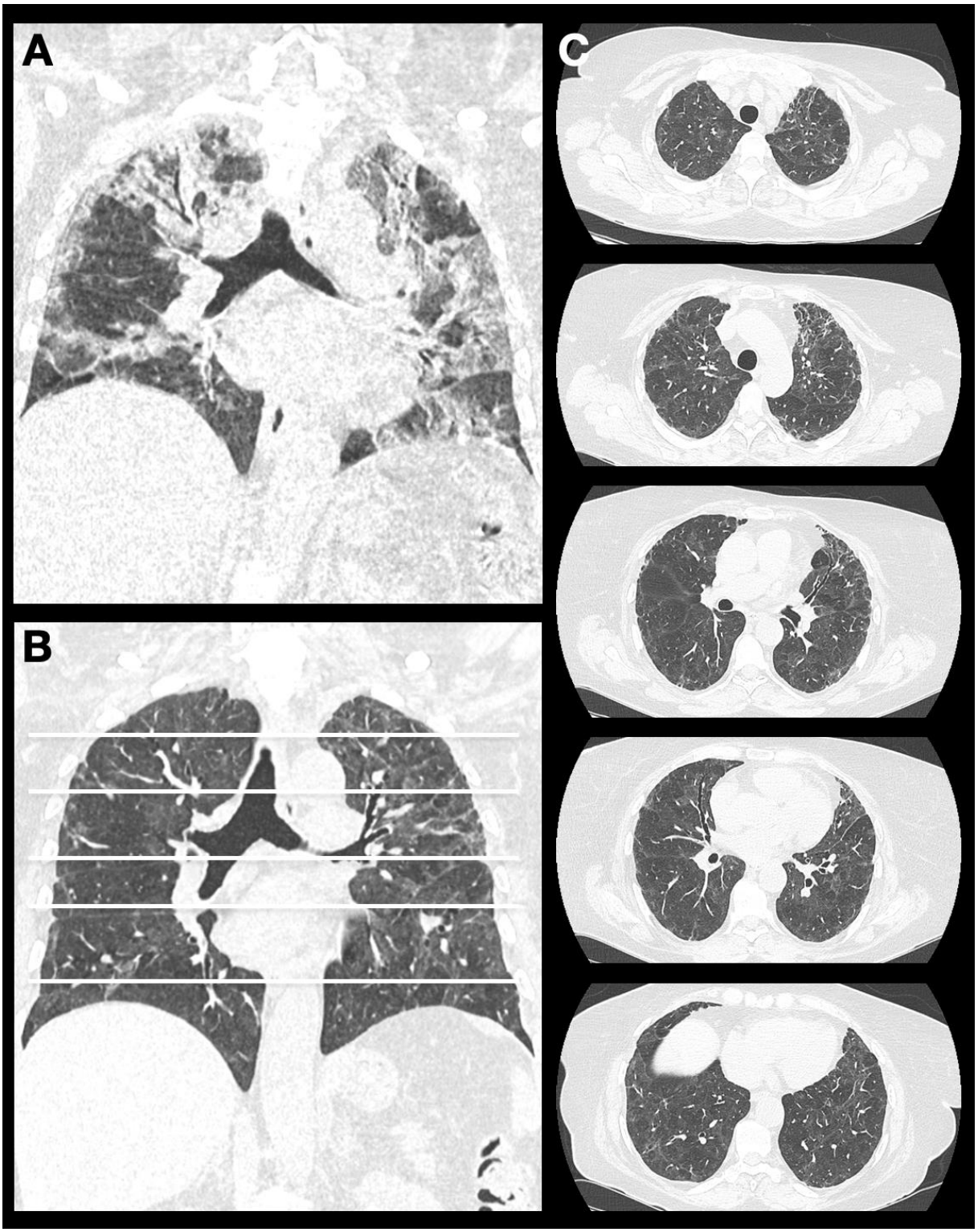
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Figure 3. HRCT image of the chest in a patient with severe fibrotic lung lesions 4 months after hospitalization for COVID-19 compared with that during acute COVID-19.

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.

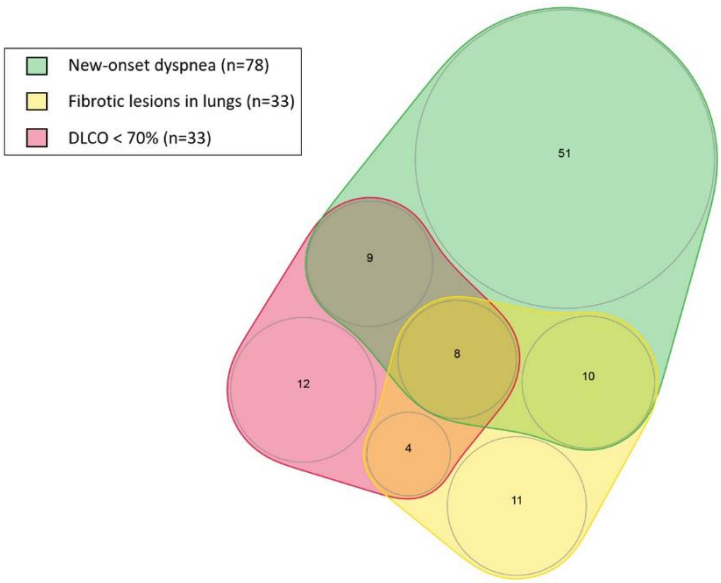

Figure 4. Distribution of patients evaluated at ambulatory care visits according to new-onset dyspnoea, fibrotic lung lesions on HRCT and decreased DLCO <70%

DLCO: diffusing lung capacity for carbon monoxide; HRCT: high-resolution computed tomography

Table 1. Baseline and hospitalization 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
Hospitalization characteristics					
Total duration of hospitalization, days	478	9 [4-15]	13 [7-23]	8 [4-14]	<0.001
Hospitalization 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 hospitalization	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 hospitalization					
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 [IQR], 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; HIV: human immunodeficiency virus; ICU: intensive care unit; IL-1: interleukin-1; IL-6: interleukin 6

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-Minute 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					
FEV1, %pred	157	90.8 ±17.8	87.8 ±16.5	93.3 ±18.5	0.06
FEV1/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
DLCO, %pred	152	86.7 ±22.7	85.6 ±23.7	87.7 ±22.1	0.57
DLCO < 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 [IQR], mean±SD, or number and frequency. The P-values refer to a comparison between patients with and without new-onset dyspnoea.
DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: 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

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%)

Table 4. Baseline and hospitalization 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
Hospitalization characteristics					
Total duration of hospitalization, days	170	13 [6-25]	27 [15-44]	11 [5-17]	<0.001
Hospitalization 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 hospitalization	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 hospitalization					
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 [IQR], 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; HIV: human immunodeficiency virus; ICU: intensive care unit; IL-1: interleukin-1; IL-6: interleukin 6

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-Minute 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					
FEV1, %pred	151	90.9 ±18.0	86.2 ±20.0	92.1 ±17.3	0.14
FEV1/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
DLCO, %pred	146	86.5 ±22.8	73.3 ±17.9	89.7 ±22.8	<0.001
DLCO < 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 [IQR], mean±SD, or number and frequency. The P-values refer to a comparison between patients with and without fibrotic lesions.
DLCO: diffusing capacity of the lungs for carbon monoxide; FEV1: 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

ONLINE SUPPLEMENTAL MATERIAL

Title: Respiratory symptoms and radiologic findings in post-acute COVID-19 syndrome

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Supplemental methods

List of symptoms evaluated at telephone consultation

General signs
→ Anorexia
→ Fatigue
→ New hospitalization
→ Weight loss

Respiratory signs
→ New-onset dyspnoea
→ Chest discomfort, chest pain
→ New-onset cough
→ Abnormal lung CT-scan since discharge

Neurologic signs
→ Headache
→ Paresthesia
→ Anosmia
→ Limb palsy

Cognitive signs
→ Memory losses
→ Slowness for reasoning, activity planification or problem solving
→ Concentration, attention difficulties

Questionnaire administered during telephone consultation

Consent

Date of the teleconsultation: [date]
Consultant name: [Consultant name]
Patient identity: [First name] [Last name], [Date of birth], [Calculated age] years
Was admitted in the following departments: [admission department]
My name is [Consultant name] and I work at Bicêtre hospital. You were admitted in [admission department] for COVID-19 three months ago.
We call you today to organize your follow-up.
If you agree, I will ask you some questions that will be used to orientate your needs of medical follow-up specific to your COVID-19 infection.
May I continue this interview? [YES / NO]
If no, why? [text]
Is-it the patient him/herself? [YES / NO]
If not, who is the respondent [First name] [Last name], [phone number] and relationship to the patient [Spouse, Children, Sibling, Neighbor/Friend, Care giver]

Has the patient died since discharge? [YES / NO]
If yes, where has the patient died? [Home, Rehabilitation facility, Retirement home, Other hospital inpatient, Other]
[date of death] and [cause of death]

General inquiry
Do you speak French? [YES / NO]
If not, what language do you speak? [Text]
If not, can someone of your household assist you for the teleconsultation? [YES / NO]
If not, can someone of your household assist you for the day hospital? [YES / NO]
Do you have an insurance? [YES / NO]
On the [date of discharge], you were discharged from Bicêtre hospital. Where did you go? [Home, Rehabilitation facility, Retirement home, Other hospital, Other].
When did you get home? [date]
Are you working at the moment? [YES / NO]
If yes, since when? [date]
What do you do? [Text]
Did you have a significant medical event since your discharge? [YES / NO]
If yes, what was it? [text] When was it? [date]
If yes, were you admitted in a hospital for this event? [YES / NO]
If yes, did you consult a physician? [YES / NO]
If yes, whom? [Text]
If yes, did you do any laboratory or radiologic examination? [YES / NO]
Did you modify your usual treatment since discharge? [YES / NO]
Where do you live now? [Home, Relative, Rehabilitation facility, Retirement home, Other]
Were you living there prior to your hospitalization for COVID19? [YES / NO]
If yes, where were you living prior to your hospitalization for COVID19? [Home, Relative, Rehabilitation facility, Retirement home, Other]
How much did you weigh before your admission? [text]
How much did you weigh when you were discharged? [Text]
How much do you currently weigh? [Text]
Do you have a new and persistent anorexia since your hospitalization?
[YES / NO]
Do you have a new and persistent fatigue since your hospitalization? [YES / NO]

Respiratory symptoms
In his/her chart, is the patient known to have had a pulmonary embolism during his stay? [YES / NO]
Do you feel abnormally breathless at rest or when active? [YES / NO]
If yes, did you feel the same prior to your hospitalization? [YES / NO]
Do you feel heaviness, pain or chest discomfort at rest or when active? [YES / NO]
If yes, did you feel the same prior to your hospitalization? [YES / NO]
Do you cough every day? [YES / NO]
If yes, was it the same prior to your hospitalization? [YES / NO]
Did you do a chest CT scan since your discharge as it may have been prescribed at your discharge? [YES / NO]
If yes, when [date]?

What was the result? [Normal/Abnormal]
Do you have a CD with the images? [YES / NO]

Neurological symptoms
In his/her chart, is the patient known to have had an abnormal brain MRI during his stay? [YES / NO]
In his/her chart, is the patient known to have had an abnormal brain EEG during his stay? [YES / NO]
Do you have a new and persistent anosmia since your hospitalization? [YES / NO]
Do you have new and persistent headaches since your hospitalization? [YES / NO]
If yes, on a scale from 1 to 10, 0 being no pain at all and 10 being the worst you could imagine, how much would you rate your headaches related pain? [1-10]
What medication do you take for your headaches? [Text]
Do you have new and persistent paresthesia since your hospitalization? [YES / NO]
Do you have new and persistent burn-like or electric-like pain since your hospitalization? [YES / NO]
Do you have new and persistent loss of function of one of your limbs since your hospitalization? [YES / NO]

Cognitive disorder screening (Q3PC)
During the last 2 weeks, and significantly more than previously, do you:
- Have memory losses (for eg., Missed an appointment, forgotten a recent event, or misplaced a daily object)?
[Rarely: less than once a week; Sometimes: once a week; Often: Several times a week but not every day; Very often: Almost all the time]
- Feel like you were slower for reasoning, activity planification or problem solving?
[Rarely: less than once a week; Sometimes: once a week; Often: Several times a week but not every day; Very often: Almost all the time]
- Experience difficulties to concentrate or muster your attention (for eg., follow a conversation, read the paper or follow a tv program)?
[Rarely: less than once a week; Sometimes: once a week; Often: Several times a week but not every day; Very often: Almost all the time]

Elderly
Regarding corporeal hygiene, do you have:
- [Total autonomy / Partial help / Dependent]
- Deterioration since the hospitalization for COVID19: [YES / NO]

Regarding dressing, do you have:
- [Total autonomy for clothes choice and dressing / Autonomy for clothes choice and dressing, but requires help for / Dependent]
- Deterioration since the hospitalization for COVID19: [YES / NO]

Regarding bathroom use, do you have:
- [Total autonomy for undressing and dressing / Requires help for undressing or dressing / Dependent]
- Deterioration since the hospitalization for COVID19: [YES / NO]

Regarding locomotion, do you have:
- [Total autonomy / Partial help / Bedridden]
- Deterioration since the hospitalization for COVID19: [YES / NO]

Regarding continence, do you have:
- [Continent / Occasional incontinence / Incontinent]
- Deterioration since the hospitalization for COVID19: [YES / NO]

Regarding meals, do you:
- [Eats alone/ Requires help for service, cutting the meat or peeling a fruit/ Dependent]
- Deterioration since the hospitalization for COVID19: [YES / NO]

Does the patient have 3 or more deterioration in the score? [YES / NO]
Do you have any helping at home? [YES / NO]
Did you fell since your hospitalization? [YES / NO]
If yes, how many times? [Number]
If more than twice, are you under a physiotherapist care? [YES / NO]
Has the patient lost more than 5kg since discharge? [YES / NO]
Did the patient report an altered general state with association of asthenia, anorexia and weight loss? [YES / NO]

Nephrology
Do you have a known renal disease (e.g., renal transplant recipient, on hemodialysis or any renal chronic condition)? [YES / NO]
In his/her chart, what is the patient's last known creatinine level and glomerular filtration rate before discharge? [Text]

Ethics
We would like to inform you that your personal data, recorded during this teleconsultation may be used for medical research under the responsibility of the *Assistance publique-hôpitaux de Paris*. You can refuse now, or any time by contacting us, your primary doctor at the hospital or the data protection officer at the hospital.
Information was given and the patient did not express refusal: [YES / NO]

Table E1. Modified Medical Research Council (mMRC) dyspnoea scale

Grade	Description of breathlessness
0	I only get breathless with strenuous exercise
1	I get short of breath when hurrying on level ground or walking up a slight hill
2	On level ground, I walk slower than people of the same age because of breathlessness, or have to stop for breath when walking at my own pace
3	I stop for breath after walking about 100 yards or after a few minutes on level ground
4	I am too breathless to leave the house or I am breathless when dressing

Table E2. Nijmegen questionnaire

How often do you suffer from the symptoms listed? Please score each item from 0 to 4:
0: never; 1: rarely; 2: sometimes; 3: often; 4: very often

SYMPTOMS	SCORE (from 0 to 4)
Chest pain	
Feeling tense	
Blurred vision	
Dizzy spells	
To be confused, losing touch with environment	
Accelerated or deepened breathing	
Shortness of breath	
Constricted chest	
Bloated abdominal sensation	
Unable to breathe deeply	
Tingling around the mouth	
Cold hands or feet	
Palpitations	
Anxiety	
Total score	**/64**

A score > 22 suggests respiratory functional complaints.

Table E3. Multivariate analysis for the comparisons of patients with and without new-onset dyspnea.

	Estimate	95% CI low	95% CI high	Pr (>|z|)
Age	0.98	0.96	1.00	0.082
Chronic heart disease	0.27	0.04	1.01	0.098
Chronic kidney disease	0.17	0.01	0.86	0.093
Hospitalization in ICU	3.9	2.2	6.98	<0.001
Pulmonary embolism	2.48	1.12	5.35	0.022

CI : confidence interval ; ICU: intensive care unit ;

Table E4. Multivariate analysis for the comparisons of patients with and without lung fibrotic lesions

	Estimate	95% CI low	95% CI high	Pr (>|z|)
Age	1.04	0.99	1.09	0.114
Hospitalization in ICU	18.57	5.02	102.29	<0.001
Pulmonary embolism	6.56	2.26	21.02	0.001

CI : confidence interval ; ICU: intensive care unit ;

Table E5. Baseline and hospitalization characteristics of the patients who had fibrotic lesions at the ambulatory care visit according to the presence of dyspnoea

	Available data	All patients (33)	Patients with fibrotic lesions and new-onset dyspnoea (18)	Patients with fibrotic lesions without new-onset dyspnoea (15)	P-value
			Demographic data		
Age, years	33	61.2±10.9	59.1±8.3	63.6±13.4	0.27
Women	33	9 (27.3%)	6 (33.3%)	3 (20.0%)	0.46
Body mass index, kg/m^2	31	28.2±4.9	26.6±4.2	29.8±5.2	0.07
			Smoking		
No (< 5 pack-years)	31	22 (71.0%)	14 (82.4%)	8 (57.1%)	
Former (≥ 5 pack-years)	31	5 (16.1%)	2 (11.8%)	3 (21.4%)	0.29
Active	31	4 (12.9%)	1 (5.9%)	3 (21.4%)	
			***Pre-COVID-19* Comorbidities**		
Respiratory disease					
- **COPD**	33	1 (3.0%)	0 (0%)	1 (6.7%)	0.46
- **Other than COPD**	33	5 (15.2%)	1 (5.6%)	4 (26.7%)	0.15
Hypertension	33	12 (36.4%)	6 (33.3%)	6 (40.0%)	0.97
Chronic heart disease	33	3 (9.1%)	1 (5.6%)	2 (13.3%)	0.58
Diabetes	33	7 (21.2%)	4 (22.2%)	3 (20.0%)	1
Chronic kidney disease	33	1 (3.0%)	0 (0%)	1 (6.7%)	0.46
Declared psychiatric disorder	33	5 (15.2%)	3 (16.7%)	2 (13.3%)	1
Neurodegenerative disorder	33	2 (1.2%)	0 (0%)	2 (1.5%)	1
Alcohol misuse	31	1 (3.2%)	1 (5.9%)	0 (0%)	1
Active cancer	33	1 (3.0%)	1 (5.6%)	0 (0%)	0.48
Other immunosuppression	33	1 (3.0%)	1 (5.6%)	0 (0%)	1

Long-term dialysis	33	0 (0%)	0 (0%)	0 (0%)	1
HIV infection	33	0 (0%)	0 (0%)	0 (0%)	1
Solid organ transplantation	33	0 (0%)	0 (0%)	0 (0%)	1
Liver disease	33	0 (0%)	0 (0%)	0 (0%)	1
Pregnancy	33	0 (0%)	0 (0%)	0 (0%)	1
Hospitalization characteristics					
Total duration of hospitalization, days	33	34±25	36±29	33±19	0.78
Hospitalization in ICU	33	29 (87.9%)	17 (94.4%)	12 (80.0%)	0.31
Duration of ICU stay, days	29	24±21	25±25	22±15	0.66
High flow oxygen	33	18 (62.1%)	12 (70.6%)	6 (50.0%)	0.08
Intubation during hospitalization	33	18 (62.1%)	12 (70.6%)	6 (50.0%)	0.44
Duration of intubation, days	33	30±17	31±17	28±16	0.73
Pulmonary embolism	33	13 (44.8%)	6 (37.5%)	7 (53.8%)	0.61
Active anticoagulation (at full therapeutic dose)	33	15 (45.5%)	12 (66.7%)	3 (20.0%)	0.02
Specific treatments during hospitalization					
Azithromycin	33	12 (36.4%)	10 (55.6%)	2 (13.3%)	0.03
Tocilizumab (anti-IL-6)	33	12 (36.4%)	6 (33.3%)	6 (40.0%)	0.97
Hydroxychloroquine	33	5 (15.2%)	4 (22.2%)	1 (6.7%)	0.35
Corticosteroids	33	3 (9.1%)	1 (5.6%)	2 (13.3%)	0.58
Lopinavir/ritonavir	33	2 (6.1%)	2 (11.1%)	0 (0%)	0.49
Anakinra (anti-IL-1RA)	33	3 (9.1%)	0 (0%)	3 (20%)	0.08
Remdesivir	33	0 (0%)	0 (0%)	0 (0%)	1

Values are expressed as the mean±SD, or as number and frequency. The P-values refer to a comparison between patients with and without fibrotic lesions

COPD: chronic obstructive pulmonary disease; HIV: human immunodeficiency virus; ICU: intensive care unit

Table E6. Characteristics of the patients with fibrotic lesions at the ambulatory care visit according to the presence of new-onset dyspnoea

	Available data	All patients (33)	Patients with fibrotic lesions with new-onset dyspnoea (18)	Patients with fibrotic lesions without new-onset dyspnoea (15)	P-value
Time from hospital discharge to outpatient clinic, days	33	82±26	82±28	82±26	0.98
Assessment at ambulatory care visit					
mMRC scale score for dyspnoea	33				0.006
- **0**		15 (45.5%)	4 (22.2)	11 (73.3)	
- **1-2**		14 (42.4%)	12 (66.6)	2 (13.3)	
- **3-4**		4 (12.1%)	2 (11.1)	2 (13.4)	
New-onset cough	33	5 (15.6%)	4 (23.5%)	1 (6.7%)	0.34
6-Minute walk test, m	33	451±107	457±74	445±138	0.78
Pulmonary functional tests					
FEV1, %pred	31	86.2±20.0	79.3±14.4	94.6±23.0	0.04
FEV1/VC, %	31	82.3±6.4	82.9±5.8	81.5±7.2	0.55
VC, %pred	31	80.6±20.0	73.9±15.6	88.7±22.2	0.04
TLC, %pred	31	74.1±13.7	68.6±12.0	81.3±12.8	0.01
DLCO, %pred	29	73.3±17.9	71.2±21.1	75.8±13.4	0.48
DLCO < 70%	29	12 (41.4%)	8 (50.0%)	4 (30.8%)	0.51
Nijmegen score > 22	33	2 (6.3%)	2 (11.8%)	0 (0%)	0.49
LVEF ≤ 50% on echocardiography	26	5 (19.2%)	4 (25.0%)	1 (10.0%)	0.62

Values are expressed as the mean±SD, or as number and frequency. The P-values refer to a comparison between patients with and without fibrotic lesions