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Chest computed tomography and lung function one year following COVID-19 pneumonia

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ABSTRACT

Objectives: To characterise chest CT abnormalities one year following severe-to-critical COVID-19 pneumonia, assess their functional significance and analyse the time-course of CT signs.

Methods: Retrospective observational monocentric study. Chest CT analysis of residual pulmonary opacities in patients having one year follow-up CT (between February 2021 and February 2022) after severe-to-critical COVID-19 pneumonia. Opacities were categorized into fibrotic-like and predominant ground-glass opacities and compared to pulmonary function tests. Sequential analysis of decreasing, stable or increasing signs at 3, 6, 12 and up to 24 months.

Results: One-year pulmonary opacities were present in 46 out of the 66 included patients, and were more frequent in patients admitted as compared to those not admitted to the intensive care unit (38/48, 79% versus 8/18, 44%, p=0.006), with an extent correlated to the length of ICU stay. Pulmonary function tests abnormalities were present in 24/29 patients (82.8%) having fibrotic-like residual opacities versus 6/13 patients (46.1%) having predominant ground-glass opacities (p=0.015). Bronchial distortions decreased in 29% of patients between 6 and 12 months, but CT abnormalities remained mostly stable thereafter in the 16 patients having follow-up CT up to 2 years.

Conclusion: One-year pulmonary opacities are more frequent in patients admitted to ICU as compared to non-ICU patients following severe-to-critical COVID-19 and seem related to the length of ICU stay. Fibrotic-like residual opacities are frequently associated to functional impairment.

Introduction:

The COVID-19 pandemic, caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) has been responsible for more than 700 million cases and 7 million deaths worldwide,[1] mostly related to severe-to-critical forms of pneumonia requiring ventilatory support, which may progress to acute respiratory distress syndrome (ARDS). Whereas such severe forms have become less frequent, due to the broad use of vaccine, improved patient treatment and evolution of the virus itself, long-term complications and persistent lung damage are a cause of concern. As following other type of coronavirus pneumonia, persistent pulmonary opacities alongside lung function alterations may be observed following SARS-CoV-2 pneumonia, remote from the acute phase of infection.[2] The short-term follow-up computed tomography (CT) findings have been extensively described, with more than half of surviving patients having persistent pulmonary abnormalities on chest CT 3 to 6 months following infection in some reports, associated to lung function alteration, affecting mostly the diffusing capacity of the lung for carbon monoxide.[3-6] An advanced age, high body mass index, pre-existing lung disease, severe initial infection and prolonged hospitalization were associated with a higher risk and extent of persistent pulmonary abnormalities.[6,7] These are mostly ground-glass opacities, band-like consolidation and bands, reticular opacities and bronchial distortions, considered "fibrotic-like". However, their long-term evolution remains incompletely understood. Existing studies show significant variability in the percentage and type of persistent chest CT abnormalities at one year,[8-13] with a 38 to 75% rate of persistent opacities in two recent meta-analysis.[12,13] Few studies have described the time-course of CT abnormalities neither the functional significance of different types of persistent opacities.

The aim of this study was to characterise chest CT abnormalities one year following severe-to-critical SARS-CoV-2 pneumonia, alongside pulmonary function tests, comparing patients admitted to the intensive care unit (ICU) to those not requiring ICU admission. Additionally, we sought to identify, through sequential analysis, the CT signs that regress and those that progress during follow-up.

Methods

This single-center retrospective observational study was approved by our institutional review board (Comité d'Ethique de la Recherche en Imagerie Médicale CERIM, ethical approval reference number CRM-2207-281). According to the French law, for this observational study, patients were informed that their data, including their CT scans, were anonymously collected for the study and patients did not object. Adult patients seen at the radiology department of Bichat hospital between February 2021 and February 2022 for a chest CT scan performed around one year after hospitalization for a SARS-CoV-2 pneumonia (named "1-yr FU-CT") were enrolled in the study. These follow-up chest CT scans were all performed 10 to 15 months after initial symptoms. Patients with any intercurrent chest disease at the time of 1-yr FU-CT were excluded.

For each patient, chest CTs performed at the time of diagnosis and 12 months following initial symptoms were analysed. When available, intermediate chest CTs performed at 3 months and 6 months were also analysed in addition to later follow-up CTs, beyond 18 months. All CT examinations comprised 1 mm thick slices volumetrically acquired at full inspiration, without contrast medium, and were reconstructed with a high-spatial frequency algorithm.

CT analysis was performed by one thoracic radiologist (MPD, 23 years of experience in chest diseases) blindly to the clinical severity of the patients at admission or during hospitalization. The visual extent of disease was semi-quantitatively categorized in less than 10%, 5-25%, 25-50% 50-75% and more than 75% of the total lungs volume. Bronchial distortions were graded from 0 to 3 per lobe, with the final grade being the sum of the grades of each lobe (maximum grade, 15). One-year pulmonary opacities were categorized into fibrotic-like or predominantly ground-glass opacities (GGO). The fibrotic-like pattern was defined by the association of reticular opacities and bronchial distortions, associated or not to GGO and honeycombing. The predominant GGO pattern was defined by GGO as the main finding, associated or not with mild parenchymal bands. The fibrotic-like pattern was described further, when appropriate, as showing non-specific interstitial pneumonia (NSIP)-like, usual interstitial pneumonia (UIP)-like or post-acute respiratory distress syndrome (ARDS)-like features. NSIP-like features were defined as basal predominant GGO with bronchial distortions and superimposed reticular opacities, with subpleural sparing or a peribronchovascular distribution, that could suggest non-specific interstitial pneumonia.[14] UIP-like features were defined as subpleural, basal predominant, reticular opacities with peripheral bronchiectasis, with or without honeycombing.[15] Post-ARDS-like features were defined as upper lobe and anterior predominant signs of fibrosis associating bronchial distortions, reticular and band-like opacities.[16]

Elementary signs were analysed side-by-side between successive follow-up CT scans for any decrease, stability or increase.

Additionally, demographic characteristics, comorbidities and pulmonary function test (PFT), including the diffusing capacity for carbon monoxide (DLCO) and the total lung capacity (TLC), closest to the 1-yr FU-CT were collected. PFTs were considered abnormal if the DLCO or the TLC were inferior to the lower limit of the Global Lung function Initiative (GLI) reference equations.[17] Any admission to the ICU and the number of days spent in ICU, the occurrence of ARDS[18] were also collected.

STATISTICAL ANALYSIS

Categorical variables were described as numbers and percentages and continuous variables as median and interquartile range (IQR). The $\chi 2$ test of independence was used to test the distribution of categorical variables and linear regression was used to model a continuous dependent variable adjusted on obesity, smoking, history of hypertension, immunosuppression, respiratory comorbidities and diabetes. Analyses were performed using STATA 15.1 (Statacorp College Station, Texas,

USA). The conventional level of statistical significance of 0.05 was used for all analyses.

Results

A total of 66 patients were included, 48 of whom were admitted to the ICU (21 with ARDS, 27 without) and 18 were admitted to hospital for oxygen supplementation (Table 1). The median [IQR] length of stay in ICU was 19 [7-37] days. Patients were predominantly men (50/66, 76%), with a median age of 62 [52-71] years. Most patients (56/66, 85%) had at least one comorbidity including obesity (30/66, 45%), hypertension (34/66, 51%), diabetes (18/66, 27%), immunosuppression (15/66, 23%) and chronic respiratory disease (16/66, 24%), with no significant difference between the three groups of patients. Four patients had a known pre-existing interstitial lung disease, including three with sarcoidosis (two patients without and one with ICU stay) and one with Sjögren syndrome (having ARDS). Two thirds of the patients (43/66, 66%) were non-smokers. The median interval time between 1-yr FU-CT and initial symptoms was 13.2 [12-14.4] months.

Table 1. Initial CT findings, one year follow-up CT and lung function

	All N=66		ICU and ARDS (N=21)		ICU without ARDS (N=27)		Hospitalization without ICU (N=18)		*P-value*
	Initial CT	**1-yr FU-CT**	**Initial CT**	**1-yr FU-CT**	**Initial CT**	**1-yr FU CT**	**Initial CT**	**1-yr FU CT**	
Pattern of residual opacities									0.027* 0.024** 0.172***
Normal or subnormal		20 (30.3)		5 (23.8)		5 (18.5)		10 (55.6)	
Fibrotic-like		29 (43.9)		12 (57.1)		12 (44.4)		5 (27.8)	
NSIP-like		10		4		4		2	
UIP-like		4		1		3		0	
Post-ARDS-like		7		5		2		0	
Predominant GGO		17 (25.8)		4 (19.1)		10 (37)		3 (16.7)	
Elementary signs	N=64	N=66	N=20	N=21	N=26	N=27	N=18	N=18	
GGO	63 (98.4)	40 (60.6)	19 (95)	14 (66.7)	26 (100)	19 (70.4)	18 (100)	7 (38.9)	0.001* <0.001** 0.027***
Consolidation	47 (73.4)	1 (1.5)	17 (85)	0 (0)	21 (80.8)	1 (3.7)	9 (50)	0 (0)	0.480* 0.537** 0.491***
Band-like consolidation	41 (64)	4 (6)	11 (55)	3 (14.3)	18 (69.2)	0 (0)	12 (66.7)	1 (5.5)	0.466* 0.878** 0.239***
Irregular lines	12 (18,7)	38 (57.6)	4 (20)	16 (76.2)	2 (7.7)	14 (51.8)	6 (33.3)	8 (44.4)	0.028* 0.177** 0.008***
Reticular opacities	5 (7.8)	31 (47)	0 (0)	12 (57.1)	1 (3.8)	13 (48.1)	4 (22.2)	6 (33.3)	0.709* 0.580** 0.428***
Bronchial distortion	27 (42.2)	35 (53)	7 (35)	14 (66.7)	10 (38.5)	14 (51.8)	10 (55.5)	7 (38.9)	0.195* 0.280** 0.077***
Honeycombing	0 (0)	2 (3)	0 (0)	2 (9.5)	0 (0)	0 (0)	0 (0)	0 (0)	0.110* 0.379** 0.036***
Visual extent									0.03* 0.007** 0.304***
0	0 (0)	6 (9.1)	0 (0)	0 (0)	0 (0)	1 (3.7)	0 (0)	5 (28.8)	
<10%	3 (4.7)	26 (39.4)	0 (0)	9 (42.9)	0 (0)	9 (33.3)	3 (16.7)	8 (44.4)	
10-25%	12 (18.8)	23 (34.9)	2 (10)	8 (38.1)	4 (15.4)	10 (37)	6 (33.3)	5 (27.8)	
25-50%	27 (42.2)	8 (12.1)	9 (45)	2 (9.5)	10 (38.5)	6 (22.2)	8 (44.4)	0 (0)	
50-75%	20 (31.3)	3 (4.6)	7 (35)	2 (9.5)	12 (46.2)	1 (3.7)	1 (5.6)	0 (0)	
>75%	2 (3.1)	0 (0)	2 (10)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	
1-yr PFT results		N=55		N=20		N=20		N=15	
Abnormal PFT results §		33 (60) #		11 (55)		16 (80)		6 (40)	0.048* 0.064** 0.877***
DLCO<lower limit CPT<lower limit		33 (60) 18 (32.7)		11 (55) 9 (45)		16 (80) 7 (35)		6 (40) 2 (13.3)	

Data are presented as numbers with percentages in parentheses. *p* values for the 1-yr FU-CT: *global *p* value between the three groups of patients; ***p* value comparing ICU and non ICU patients; ****p* value comparing ICU patients with and without ARDS.
§Global Lung function Initiative (GLI) reference equations used to define the lower limit of the diffusing capacity for carbon monoxide (DLCO) and total lung capacity (TLC)
#2 patients having DLCO (diffusing capacity for carbon monoxide) below the lower limit, however unchanged as compared to pre-Covid-19 PFT were categorized in "Normal PFT

One-year pulmonary opacities were present in 46/66 patients (69.7%), mostly of GGO type (40/66, 60.6%), irregular lines (38/66, 57.6%) and reticular opacities (31/66, 47%). Bronchial distortions were present in 35/66 patients (53%) and honeycombing was very rare (2 patients having ICU stay and ARDS). One-year pulmonary opacities occurred more frequently in ICU patients (38/48, 79%) as compared to other patients (8/18, 44%), p=0.006. They were more extensive in ICU patients (p=0.007) and their extent correlated with the length of ICU stay (regression coefficient β=9.39, p=0.006). Pulmonary opacities on initial CT were also more extensive in ICU as compared to non-ICU patients (p=0.002). One-year PFTs were available in 55 patients (83.3%) and were abnormal in 33 of these (60%), all having alteration of the DLCO, and 18 patients (32.7%) having also a restrictive pattern. Similarly to CT findings, abnormal PFTs tended to be more frequent in ICU patients (27/40, 67.5%) than in those not requiring ICU (6/15, 40%), p=0.064. In contrast, among ICU patients, there was no difference in the proportion and extent of residual opacities, nor in the proportion of abnormal PFT between patients with and without ARDS, except for irregular lines and honeycombing, more frequent in patients having ARDS (p=0.008 and p=0.036, respectively). The proportion of fibrotic-like and predominant GGO among residual opacities did not differ between the 3 groups of patients nor between ICU and non-ICU patients, fibrotic-like opacities encompassing 63% of residual opacities for the all population, showing NSIP-like features in one third of cases (10/29, 34%). PFT abnormalities were more frequent in patients with fibrotic-like opacities than in those with predominant GGO (24/29 patients, 82.8% versus 6/13 patients, 46.1%; p=0.015). All patients without residual opacities at 1-yr FU-CT had normal PFT, except one heavy smoker with low DLCO and one obese patient with both low DLCO and TLC. Conversely, 31/43 patients (72%) having residual opacities and available functional data at one year, had functional alterations.

Comparing 1-yr FU-CT to the most recent available CT at three (n=20) or six (n=34 patients) months, the extent and density of opacities decreased in half of the patients and remained unchanged in the others (Fig 1). Bronchial distortions and reticular opacities decreased in one third of patients (12/38 and 10/30, respectively), remained unchanged in two thirds of them and increased in only one patient (Fig 2). Between 6 and 12 months, bronchial distortions decreased in 7/24 patients (29%). Chest CT scans performed at 2 years (median time from initial symptoms 24.6 [20.2-26.3] months) was available for 16 patients, showing a fibrotic-like pattern in 11 of these. CT abnormalities remained unchanged in 13 patients, showed minor decrease of GGO in two patients and signs of fibrosis increased in one patient.

Fig 1. Time-course of chest CT features in a 69 year-old patient having critical SARS-CoV-2 pneumonia. *There is gradual improvement of opacities between the time of admission to the intensive care unit (Panel A), 3 months (Panel B) and 12 months (Panel C) later, and a decrease of bronchial distortions between 3 and 12 months. Mild bronchial distortions persist at 12 months, the pattern being categorized as fibrotic-like, and remain unchanged at 24 months (Panel D).*

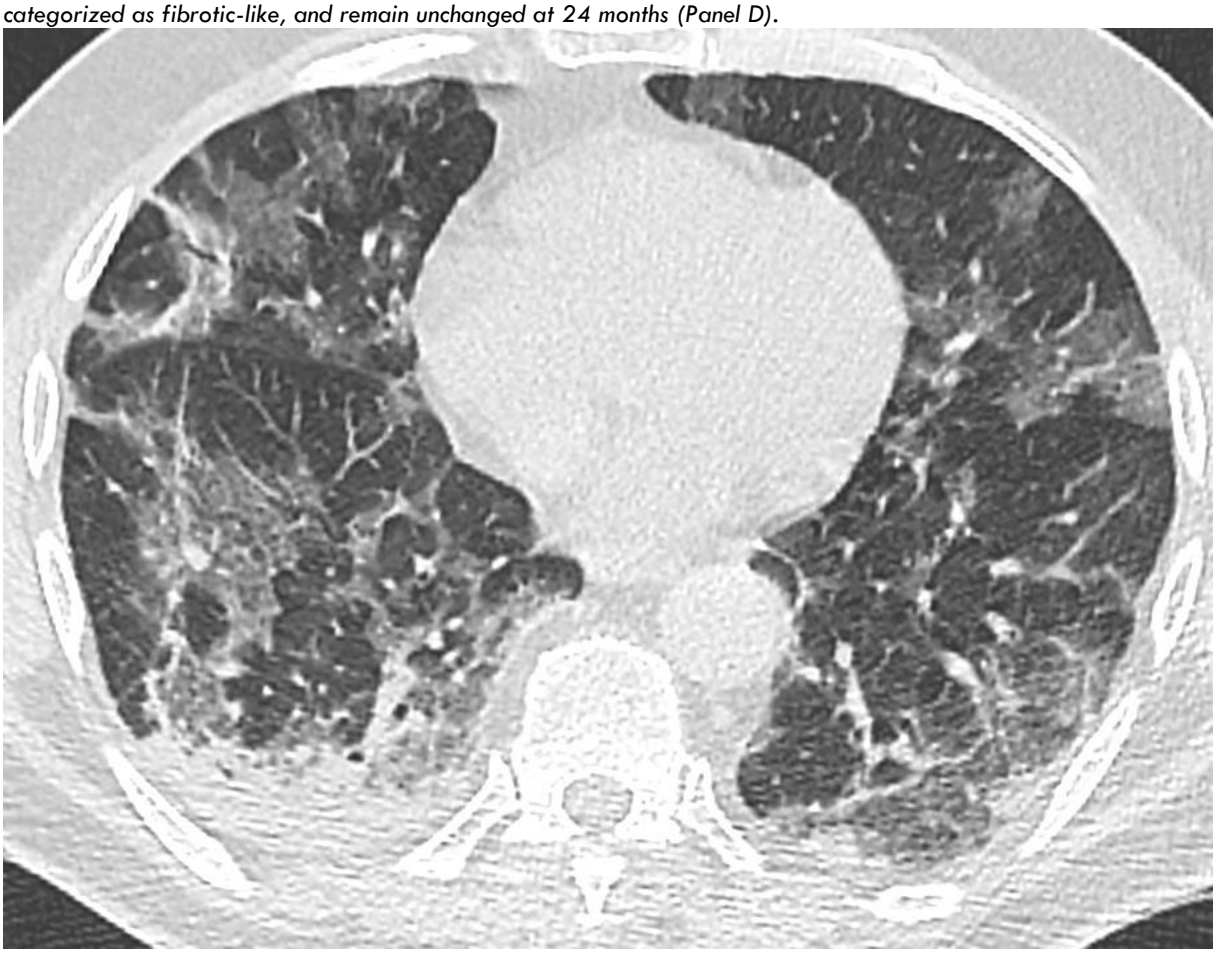


Fig.1A

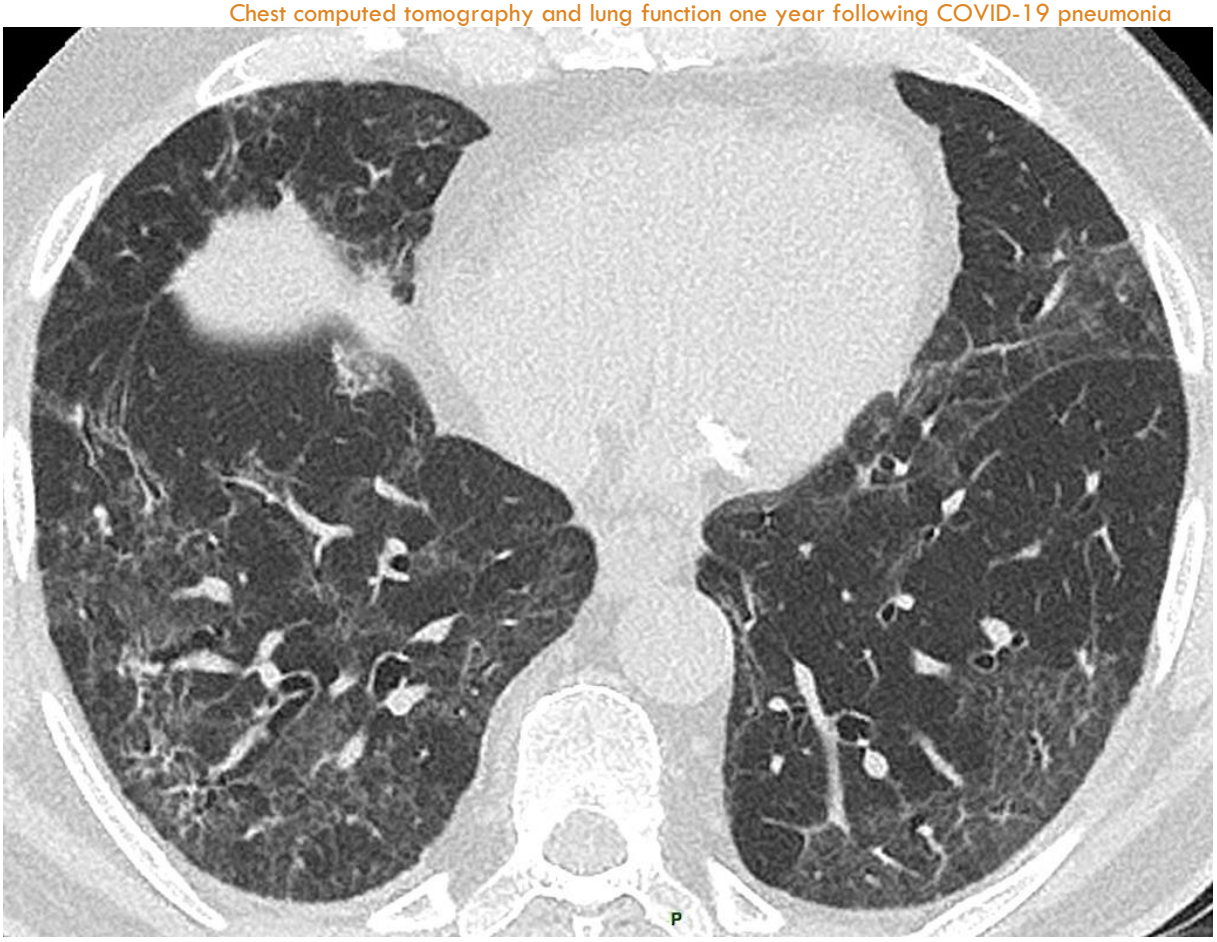


Fig. 1B

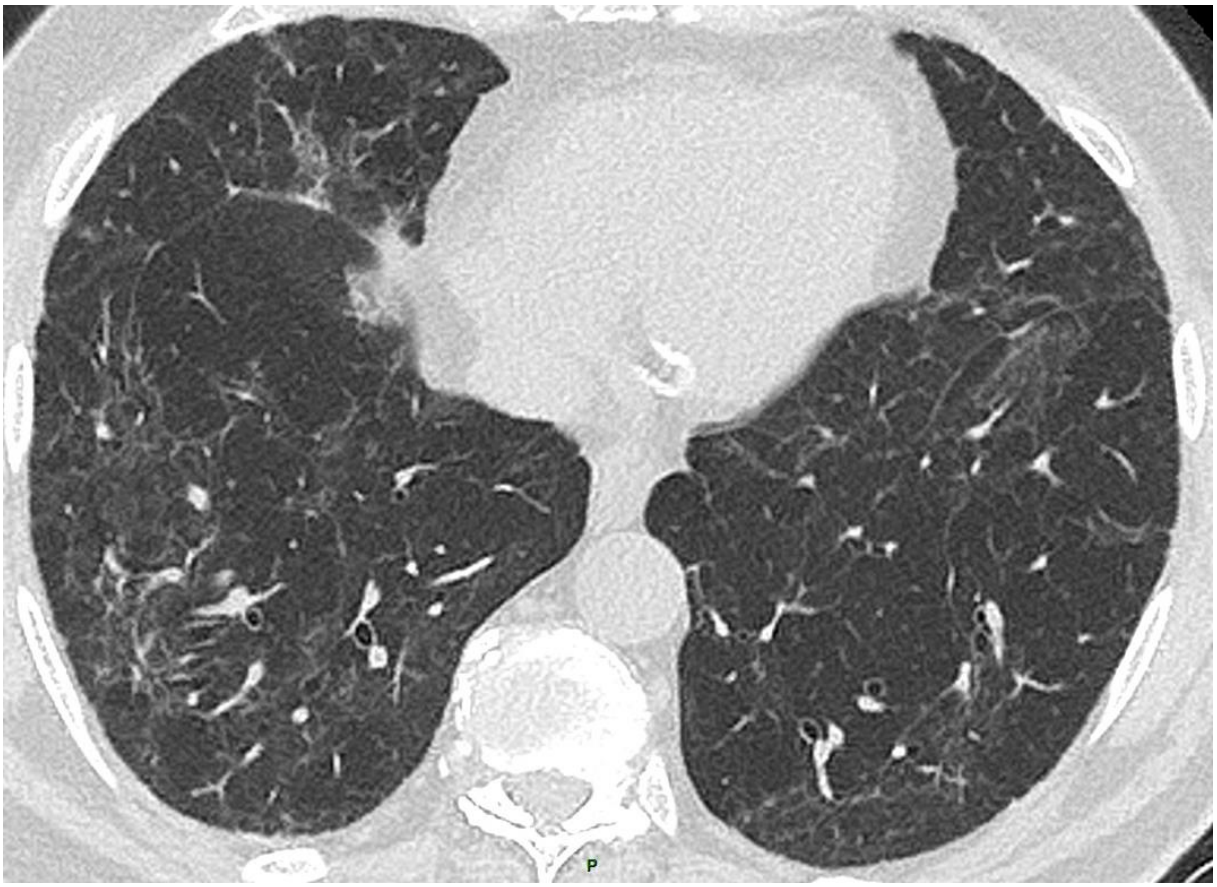


Fig. 1C

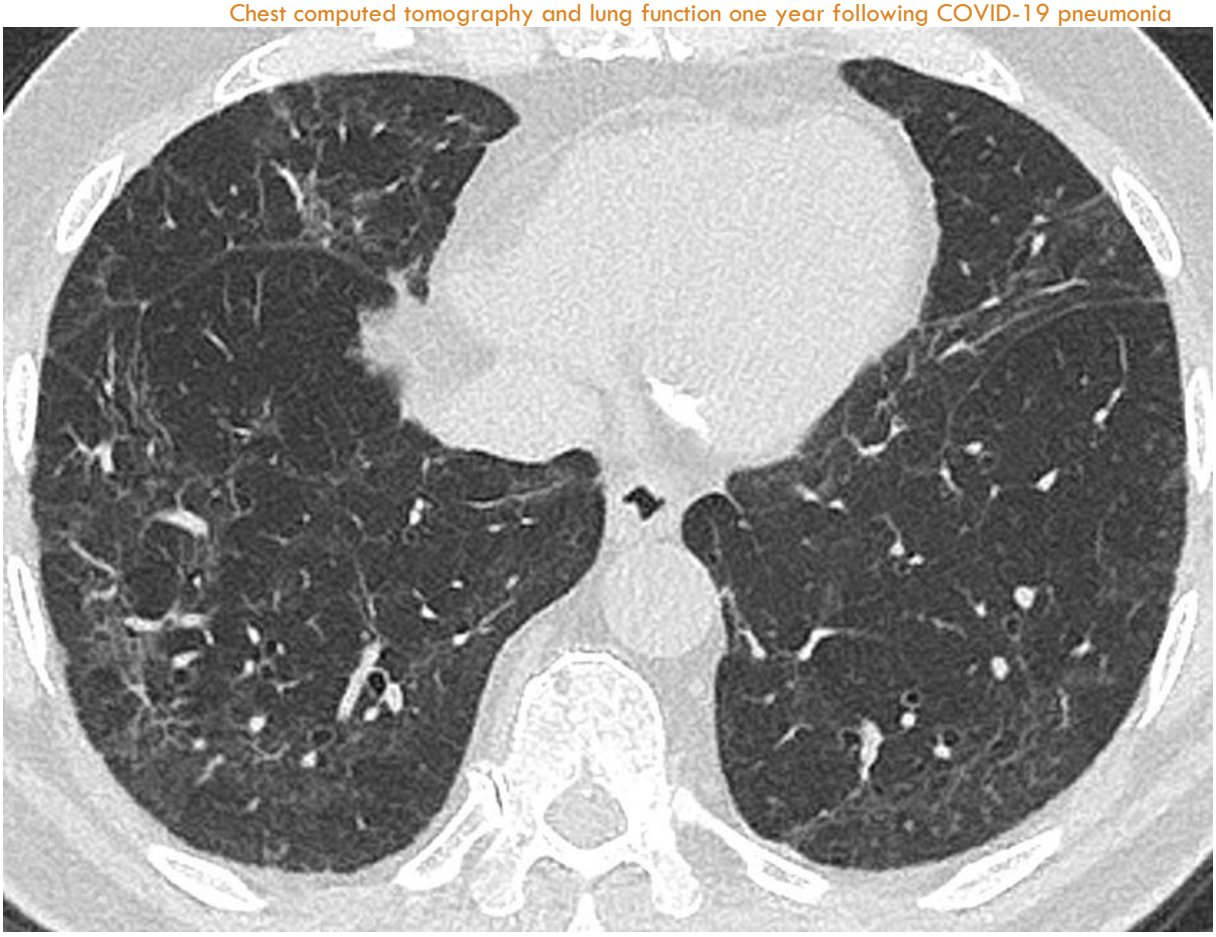
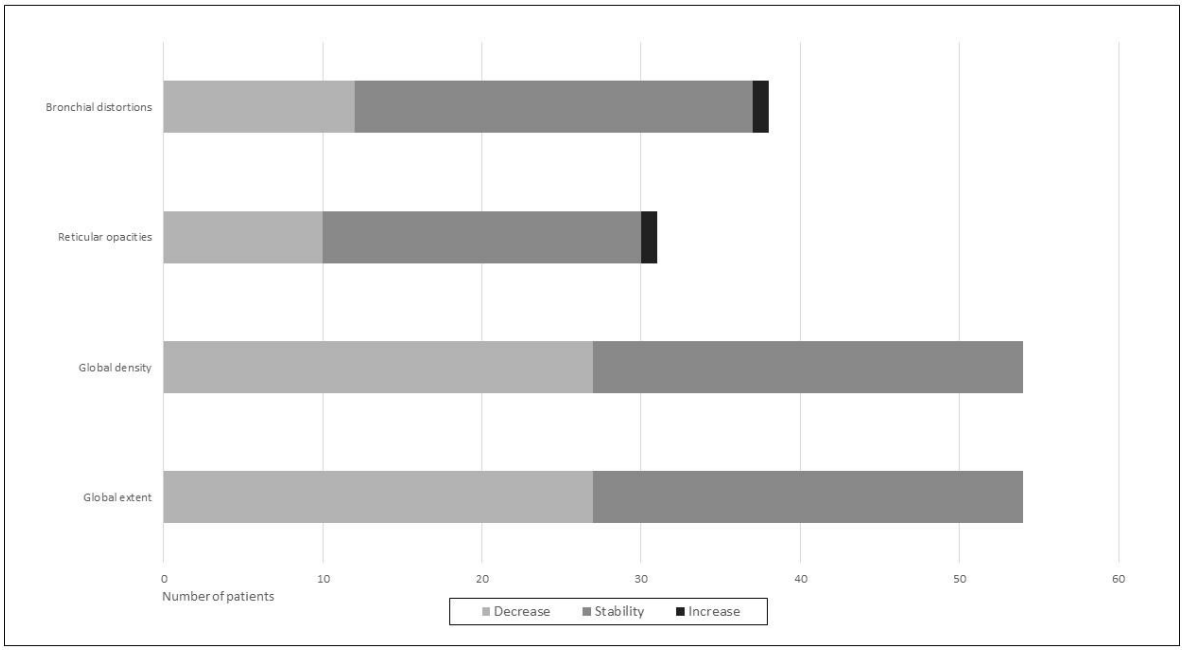


Fig. 1D

Fig 2. Evolution of CT findings between 3-6 months and 12 months. *The latest available chest CT, between 3 and 6 months following initial symptoms, was compared side-by-side to the chest CT performed at 12 months in 54 patients.*



Discussion

This study emphasizes the functional impact of fibrotic-like opacities observed one year following severe-to-critical COVID-19 and comprising more than half of any persistent opacities in our population. Abnormal PFT were observed in 82.6% of patients having fibrotic-like opacities, almost twice more frequently as compared to patients having predominant GGO. This is in accordance with previous studies having reported an association between fibrotic-like features on CT and functional alterations.[10,19,20] As previously reported,[8] functional alteration involved the diffusing capacity more frequently than the lung volumes, with a restrictive pattern observed twice less frequently than a decrease of DLCO. Contrary to previous studies, who reported no change in fibrotic-like signs between 6 and 12 months, we found they may partially regress during the first year, bronchial distortions having decreased in 29% of patients between 6 and 12 months. Such differences may be explained by our side-by-side comparison of CT scans which could more easily detect subtle changes than a comparison based on fibrotic scores. Beyond 12 months, CT

abnormalities seem to remain mostly stable, even though only a small number of patients had a follow-up CT up to 24 months in our study. This is however in accordance with the recent study of Han et al[16], showing fibrotic-like residual opacities remain stable between 12 and 24 months and are associated with persistent functional impairment. On the contrary, and unlike some previous studies,[5,19,21] we did not observe functional alteration in patients without persistent opacities. This may be explained by our use of the most recent and stringent ATS-ERS standards to define abnormal PFT. We cannot exclude however having underestimated functional alterations in few patients because PFTs were not performed in all patients.

We found any persistent opacities at one year were more frequent in patients having been admitted to the ICU, as compared to non-ICU patients, with an extent of opacities related to the duration of ICU stay. Ventilation induced lung injury is a well described process[22] and this factor could contribute to the presence of persistent opacities in ICU patients, in particular post ARDS fibrosis. Indeed, one quarter of fibrotic-like opacities evoked post ARDS fibrosis, all of them observed in ICU patients and most of them in patients having ARDS. However, surprisingly, no difference was observed in the percentage of fibrotic-like persistent opacities between ICU patients having and those not having ARDS. Of note, fibrotic-like opacities were not restricted to ICU patients, though of limited extent. Persistent fibrotic-like opacities evoked NSIP in one third of the patients, in line with the pathologic study of Ravaglia et al[23] in post COVID pneumonia having described fibrosing NSIP and organising pneumonia in a subset of patients a few months after recovery. In another study, UIP was the most frequent pathologic pattern in patients having persistent interstitial lung disease up to 12 months following initial symptoms of COVID pneumonia, with corresponding chest CT described as GGO and interstitial thickening or peripheral reticulations with bronchiectasis.[24] A minority of patients showed UIP-like CT features in our study but we cannot exclude more patients had underlying pathologic UIP. In the absence of any pathologic data, we can not precisely determine the type of the underlying interstitial lung fibrosis.

The main limitations of our study include its single-center and retrospective design. As all patients having severe-to-critical COVID-19 were not prospectively followed, we cannot provide any prevalence of persistent opacities. The absence of systematic CT follow-up in most previous studies, in addition to various grades of severity of the included patients may explain the wide range of percentages of persistent opacities in the literature. Such selection bias does not however preclude the functional correlation nor the time course analysis of opacities. Another limitation relates to the fact that the scans were read by a single, although experienced, reader.

Conclusion

We found one-year pulmonary opacities were more frequent in patients admitted to ICU as compared to non-ICU patients following severe-to-critical COVID-19 and seemed related to the length of ICU stay. Fibrotic-like residual opacities were frequently associated to functional impairment. We showed that CT abnormalities could decrease, even those suggestive of fibrosis, in one third to half of cases between 3-6 months and one year following infection, whereas CT signs of fibrosis progressed thereafter in a very small number of patients.

Conflicts of interest statement :

Marie-Pierre Debray: personal fees and non-financial support from Boehringer-Ingelheim, GlaxoSmithKline outside the submitted work
Camille Taillé: grants or contracts and personal fees from GlaxoSmithKline, Sanofi, Astrazeneca, personal fees from Novartis, Stallergenes, non financial support from GlaxoSmithKline, Astrazeneca, outside the submitted work
Jade Ghosn: consulting fees from Gilead, ViiV Healthcare, MSD, Astrazeneca, outside the submitted work
Pauline Balagny, Sacha Rosencwajg, Etienne de Montmollin, Lynn Ezzeddine, Christophe Rioux, Catherine Bancal, Antoine Khalil: nothing to disclose

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