UNIVERSITÉ TOULOUSE III – PAUL SABATIER
FACULTÉS DE MÉDECINE

ANNÉE 2021 2021 TOU3 1771

THÈSE

POUR LE DIPLÔME D'ÉTAT DE DOCTEUR EN MÉDECINE

MÉDECINE SPÉCIALISÉE CLINIQUE

Présentée et soutenue publiquement

par

Thibault VIATGÉ

le 10 Novembre 2021

Moderate to severe SARS-CoV-2 pneumonia: clinical, functional, and imaging outcomes at 4 and 12 months

Directrice de thèse : Dr Elise NOEL-SAVINA

JURY

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AVANT-PROPOS ET REMERCIEMENT

Au Président du Jury,

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SUMMARY

ABBREVIATIONS

6MWT	6-minute walk test
ACE-2	angiotensin-converting enzyme 2
ARDS	acute respiratory distress syndrome
BMI	body mass index
CO/NO	carbon monoxide/nitric oxide
COVID-19	coronavirus disease 19
CPET	cardiopulmonary exercise testing
CT	computed tomography
DAD	diffuse alveolar damage
DLco	diffusing capacity of the lungs for carbon monoxide
HRCT	high-resolution computed tomography
ICU	intensive care unit
ILD	interstitial lung disease
Kco	carbon monoxide transfer coefficient
MERS-CoV	Middle East respiratory syndrome coronavirus
MV	mechanical ventilation
PCR	polymerase chain reaction
SARS-CoV-2	severe acute respiratory syndrome coronavirus 2

SpO2	blood oxygen saturation level
Vc	capillary volume
VTE	venous thromboembolism

ABSTRACT

Introduction: Given the pathophysiology of coronavirus disease 19 (COVID-19), persistent pulmonary abnormalities are expected.

Methods: We conducted a prospective cohort study in severe COVID-19 patients who had oxygen saturation < 94% and were primarily admitted to hospital. We aimed to describe persistent gas exchange abnormalities after 4 and 12 months, defined as decreased diffusing capacity of the lungs for carbon monoxide (DLco) or desaturation on the 6-minute walk test (6MWT), along with associated mechanisms and risk factors.

Results: Among the 72 patients included, 76% required admission to an intensive care unit (ICU), while 68% required invasive mechanical ventilation (MV). 39% developed venous thromboembolism (VTE). 61% were still symptomatic after 4 months, and 31% after 12 months. Functionally, 39% had abnormal carbon monoxide test results or desaturation on the 6MWT at 4 months and 14% at 12 months; significatively associated with initial severity: ARDS, management in ICU and VTE. Restrictive lung disease was observed in 24% of cases, obstructive lung disease in 17%, and respiratory muscle dysfunction in 18%. 44% had interstitial lung disease in high-resolution computed tomography (HRCT) at 4 months and 33% at 12 months associated with ARDS, management in ICU, smoking status, older age, and low BMI (Body Mass Index). Embolic sequelae were rare, however reduced capillary volume (Vc<70%) was the main functional respiratory abnormality (32%).

Conclusion: Among patients with severe COVID-19 pneumonia who were admitted to hospital, 31% were still symptomatic, 14% of patients had persistent functional abnormalities and 33% radiological abnormalities after a year. There was no chronic thrombo-embolic disease. A respiratory check-up after severe COVID-19 pneumonia may be relevant to improve future management of these patients.

1. INTRODUCTION

SARS-CoV-2, or severe acute respiratory syndrome coronavirus 2, is a virus of the coronaviridae family as SARS-CoV and MERS-CoV (Middle East respiratory syndrome-related coronavirus). The viral pneumonia may cause acute respiratory distress syndrome (ARDS) with direct impact on prognosis: 15% of patients with coronavirus disease 19 (COVID-19) are admitted in intensive care unit (ICU), and 5% require mechanical ventilation (MV) [1]. Patients with a severe lung disease receive standard intensive care and corticosteroids [2] based on evidence from the randomized trial RECOVERY [3]. Additionally, Tocilizumab is used in different facilities based on low to moderate-certainty evidence cohort studies which show reduced mortality and mechanical ventilation risk [4].

Concerning pathophysiology of respiratory involvement, ACE-2 (angiotensin-converting enzyme 2) has been identified as functional co-receptor for coronavirus entry in respiratory epithelium, and infection enhancer through its interferon-driven upregulation capacity [5, 6]. This receptor is abundantly expressed in type I and II pneumocytes resulting in viral expansion through epithelial alveolo-capillary interface and potential diffuse alveolar damage (DAD) [7]. ACE-2 is also expressed in macrophages, endothelial, smooth muscle cells and perivascular pericytes causing uncontrolled inflammation, micro-thrombosis, coagulopathy, impaired endothelial regulation of vascular tone, and alveolo-capillary barrier disruption [8–11] (mechanisms illustrated in figure 1 with approval of its author ***Huertas A.*** [8]). In a cohort of 184 critical COVID-19 patients admitted in ICU, 31% developed venous or arterial thrombotic complications, of which 80% involved pulmonary embolism [12, 13].

ARDS corresponding to DAD, damages the alveoli with mechanisms depending on the aetiology and increases the risk of progression to pulmonary fibrosis. ***Meduri et al.*** [14] described fibrotic lesions in the lungs of half of the patients who died from ARDS. It has been reported that post-ARDS fibrotic lesions lead to decreased diffusing capacity of the lungs for

carbon monoxide (DLco) 3 months after extubation; and 80% of patients recovered normal respiratory function within a year [15–17]. Besides parenchymal pulmonary lesions, long-term impact of thromboembolic complications is uncertain.

There are suggested follow-up protocols for patients after COVID-19 pneumonia, particularly towards respiratory function [18, 19]. The implications for lung parenchyma and vascularisation are unclear. *Georges et al.* [18] suggested screening for interstitial and pulmonary vascular disease, mainly if embolism occurred during the acute phase.

This study aims to describe the characteristics of persistent gas exchange abnormalities 4 and 12 months after moderate to severe COVID-19 pneumonia, in patients without prior cardiopulmonary disease.

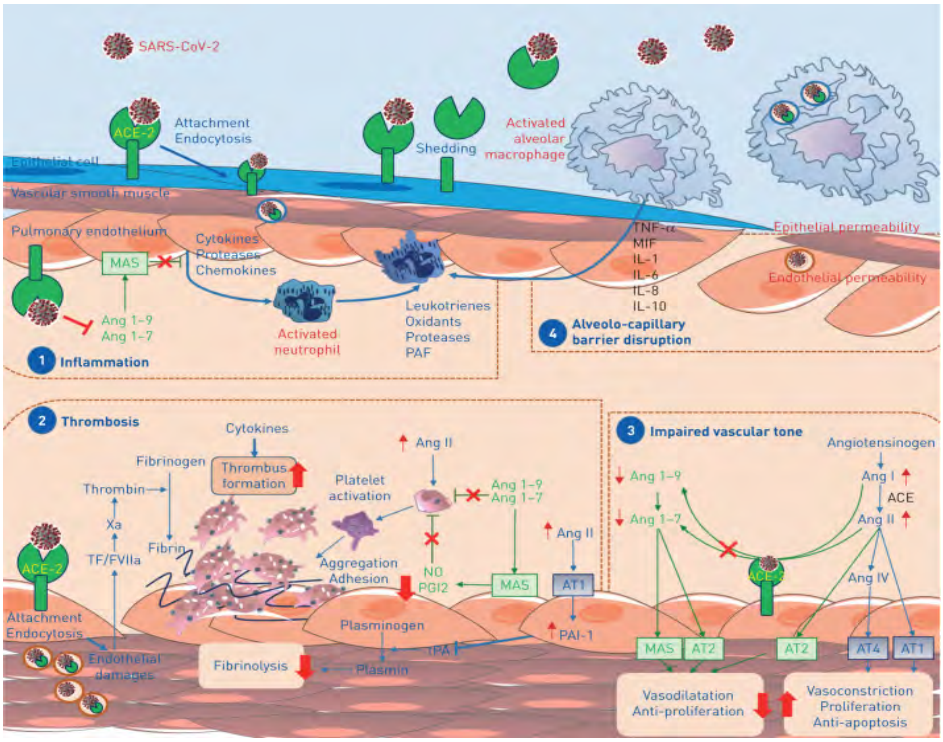


Fig. 1. Mechanisms of endothelial and pulmonary vascular dysfunction - *Huertas A. and al. Endothelial cell dysfunction: a major player in SARS-CoV-2 infection (COVID-19)? Eur Respir J. 2020 Jul 30;56(1):2001634.*

2. MATERIEL AND METHODS

2.1. Study design

This prospective cohort study was conducted in Toulouse University Hospital, France, between April 2020 and April 2021.

The inclusion criteria were COVID-19 pneumonia diagnosed by positive polymerase chain reaction (PCR) assay using a respiratory sample from the saliva, nasopharynx, bronchi, tracheal aspirate or bronchoalveolar lavage. Patients' condition had to require hospitalization, with clinical and radiological lung involvement: blood oxygen saturation level (SpO2) below 94% without respiratory support and chest computed tomography (CT) presenting common features of COVID-19 pneumonia. Patients had to be aged over 18 and to give a written informed consent.

The exclusion criteria were lung disease that was not documented on chest CT, negative COVID-19 PCR, and prior cardiopulmonary disease that could itself provoke abnormal gas exchange.

This study was approved by "Le Comité de Protection des Personnes", the institutional review board of Brest University Hospital as an interventional study involving human subjects that present minimal risks and constraints for patients (RIPH 20.05.07.57618).

2.2. Methods

The primary objective was to describe persistent gas exchange abnormalities after 4 and 12 months, defined by abnormal pulmonary diffusing capacity (DLco < 70%) or oxygen desaturation ≥ 4% during the 6MWT.

The secondary objectives were to identify mechanisms of persistent gas exchange abnormalities and their severity; determine the prevalence of persistent respiratory symptoms; determine the nature of persistent bronchial and ventilatory abnormalities; describe the persistent pulmonary abnormalities on high-resolution computed tomography (HRCT) and lung scintigraphy; compare symptomatic and asymptomatic patients after 4 and 12 months to identify the pathophysiological mechanisms of persistent symptoms; and identify risk factors for persistent respiratory abnormalities among clinical, laboratory and imaging assessments or related to initial patient management.

To determine mechanisms of gas exchange abnormalities, several parameters were analysed: (I) other values from the carbon monoxide/nitric oxide (CO/NO) test (Krogh's diffusion coefficient, capillary volume, and membrane diffusion capacity) to screen for pulmonary capillaries abnormalities; (II) plethysmography and respiratory muscles evaluation (sniff nasal inspiratory pressure, maximal inspiratory pressure); (III) HRCT findings; and (IV) lung scintigraphy findings.

Patients were considered symptomatic if the following criteria were reported:

- dyspnoea on the modified Medical Research Council scale, cough on the Leicester Cough Questionnaire, expectoration, haemoptysis, chest pain, evidence of right ventricular failure, or sleeping disorders,

- or distance covered on the 6-minute walk test (6MWT) < 80% of predicted distance.

Persistent ventilatory or bronchial abnormalities were defined on plethysmography, forced oscillation technique, diaphragmatic examination, or exhaled NO, by:

- obstructive lung disorder (ratio of forced expiratory volume in 1 second to forced vital capacity < 70%),

- restrictive lung disorder (total lung capacity < 80% of predicted value),
- impairment of respiratory muscles consistent with diaphragmatic dysfunction (maximum inspiratory pressure or sniff nasal inspiratory pressure < 60% of predicted value, or vital capacity decrease > 15% when lying down compared to sitting),
- eosinophilic bronchial inflammation (increased fractional exhaled NO),
- suggestive of proximal or distal airway obstruction with a decrease in the impedance measurements on the forced oscillation technique [20].

Interstitial Lung Disease (ILD) is defined as heterogeneous group of non-neoplastic disorders resulting from lung parenchyma damage by varying patterns of inflammation and fibrosis [21]. Radiologic elementary lesions of ILD (ground-glass opacities, alveolar and reticular opacities, micronodules) [22] and bronchiectasis were determined during a multidisciplinary meeting with specialized thoracic radiologists who analysed HRCT. Ventilation/perfusion scintigraphy was also analysed for perfusion defects with normal ventilation.

Check-up was completed with laboratory tests: ionogram, urea, creatinine, clearance of creatinine, liver function test, Nt-proBNP, D-Dimers, cardiolipid antibodies, anti-Beta-2 GP1 antibodies, lupus anticoagulant, complete blood count, CRP, ferritin, CPK, LDH, coagulant test, fibrinogen, SARS-CoV-2 serology, and Beta-HCG in women of childbearing age.

Second-line assessment was left to investigator's decision according to respiratory abnormalities: bronchoalveolar lavage for interstitial disease; thoracic CT angiography, echocardiography, right catheterism, Cardiopulmonary Exercise Testing (CPET) for vascular abnormalities; metacholin testing, diaphragmatic echography in case of respiratory muscles impairment; hyperventilation testing, CPET and echocardiography for dyspnoea of undetermined cause.

Characteristics of symptomatic patients were compared to asymptomatic. Symptoms were correlated to additional examinations findings.

2.3. Statistical analysis

The required sample size was defined according to the expected accuracy in estimating the prevalence of these abnormalities: with at least 60 patients and a prevalence of 50%, the 95% confidence interval (CI) was ± 13% (37%, 63%).

The primary composite endpoint was an adjusted decreased diffusing capacity of the lungs for carbon monoxide (DLco) < 70% of predicted value on the CO test or SpO2 decreased by 4% or more on the 6MWT.

Exchange abnormalities after 4 and 12 months were described by estimating their prevalence and 95% CI. Regarding second endpoints, prevalence of symptoms and pulmonary complications were estimated with 95% CI.

Missing data were described, and aberrant data were screened using logical checks. Patient characteristics at inclusion were described as number and percentage for qualitative variables and as mean, standard deviation, minimum, maximum and quartiles for quantitative variables. The distribution of the potential risk factors at inclusion were described and compared between symptomatic and asymptomatic patients, as well as between patients with and without pulmonary complications. Comparisons were adjusted to the type of variable and conditions under which the tests were applied – *i.e.* chi-squared or Fisher's exact test, and Student's t-test, Wilcoxon-Mann-Whitney test or Kruskal-Wallis test. A multivariate logistic regression model was used to evaluate associations between the risk factors and the two secondary endpoints of being symptomatic and developing respiratory complications.

3. RESULTS

3.1. Population characteristics (table 1)

93 patients were selected, of whom 72 were retained for analysis (Figure 2). Their respiratory function was firstly assessed 4.3 months after PCR diagnosis on average.

The population was 76.4% men, and mean age was 60.5 years (±12.8). Their comorbidities were overweight (42.6%), obesity (40%), hypertension (38.5%), diabetes (23%), coronary artery disease (8%) and cancer (12%). 76.1% were admitted to ICU for a mean of 21.1 days, 68.5% required MV for a mean of 19.4 days, and 53.7% were placed in a prone position, with three of those patients receiving only high-flow oxygen (HFO). Before evidence of RECOVERY assay, corticosteroids concerned a total of 36.1% patients with a treatment starting 13 days after diagnosis and for a mean duration of 25 days. 56.9% of patients developed ARDS, and 22.2% post-intensive care tetraparesis. Additionally, 50.7% developed secondary bacterial infection and 31.9% venous thromboembolism (VTE), with 78.3% of those cases involving pulmonary embolism (Table 1).

43 patients (59.7%) presented significative abnormalities at 4 months and pursued a pulmonological follow-up at least for 12 months, 1 was lost to follow-up (Figure 2). The second analyse was assessed 11.5 months after PCR diagnosis on average.

This population was compared between 4 and 12 months. Patients monitored at 12 months were more often admitted in USIR that patients not followed after 4 months (non-significantly: 83.3% versus 65.5%, p=0.08); they were more exposed to non-invasive ventilation (26.8% vs 6.9%, p=0.03), curares (65% vs 25%, p=0.001), mechanical ventilation (69% vs 27.6%, p=0.0006) with a significantly longer mechanical ventilation time (14 ± 14.6 versus 4.3 days ± 9.6, p=0.0003), ventral decubitus (57.1% vs 17.2%, p=0.0008). They presented more complications with significantly more ARDS (p=0.003) (Table 1).

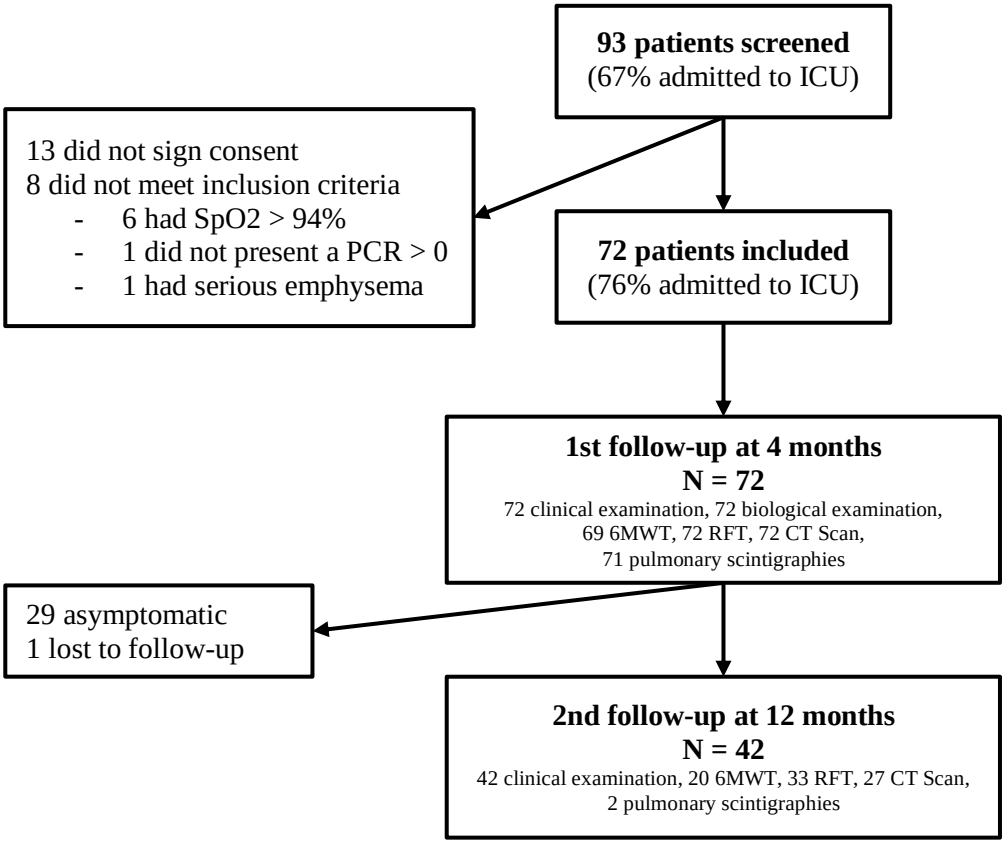


Fig. 2. Study flowchart. ICU: intensive care unit; SpO2: oxygen saturation; PCR: polymerase chain reaction; 6MWT: 6-minute walk test; RFT: respiratory function tests; CT: computed tomography.

TABLE 1 Characteristics on inclusion

	Number of patients (%)	
Characteristics	**1st follow-up**	**2nd follow-up**
	n = 72	**n = 42**
Gender		
Male	55 (76)	31 (74)
Female	17 (24)	11 (26)
Smoking status		
Never smoker	36 (56)	18 (45)
Former smoker	21 (32)	5 (13)
Current smoker	8 (12)	17 (42)
Acute phase management		
Intensive care unit	54 (76)	35 (83)
Intensive care unit admission		
PaO2/FiO2 (mmHg/FiO2)	109 [88; 148]	/
HFO	18 (34)	12 (29)
Non-invasive ventilation	13 (24)	11 (27)
Mechanical ventilation	37 (68)	29 (69)
Use of curare	33 (65)	26 (65)
Prone positioning	29 (54)	24 (57)
ECMO	3 (6)	3 (7)
Extrarenal purification	4 (7)	3 (7)
Drug therapies		
Corticosteroids	26 (36)	18 (43)
Antibiotics	68 (94)	/
Curative anticoagulation	27 (37)	18 (43)
Complications		
Bacterial pneumonia	36 (51)	23 (55)
Venous thromboembolism	23 (32)	17 (41)
Pulmonary embolism	18 (25)	13 (31)
ARDS	41 (57)	30 (71)
Post-intensive care tetraparesis	16 (22)	12 (29)
Baseline CT abnormalities		
Mild (<10%)	6 (9)	3 (8)
Moderate (10-25%)	16 (25)	8 (20)
Extensive (25-50%)	20 (31)	11 (28)
Severe (50-75%)	17 (26)	12 (31)
Critical (>75%)	6 (9)	5 (13)

PaO2/FiO2: ratio of arterial oxygen partial pressure to fractional inspired oxygen; HFO: high-flow oxygen; ECMO: extracorporeal membrane oxygenation; ARDS: acute respiratory distress syndrome.

3.2. Symptoms and respiratory function (table 2 & 3)

The 4-month clinical and paraclinical check-up presented normal results in 30.6% of patients, whereas 10% exhibited deconditioning; 44.4% had interstitial lung disease (ILD), with architectural distortion in 56% of those cases; 6% had venous thromboembolic disease; 7% had bronchial hyper-reactivity; and 7% diaphragmatic muscle dysfunction (Figure 3).

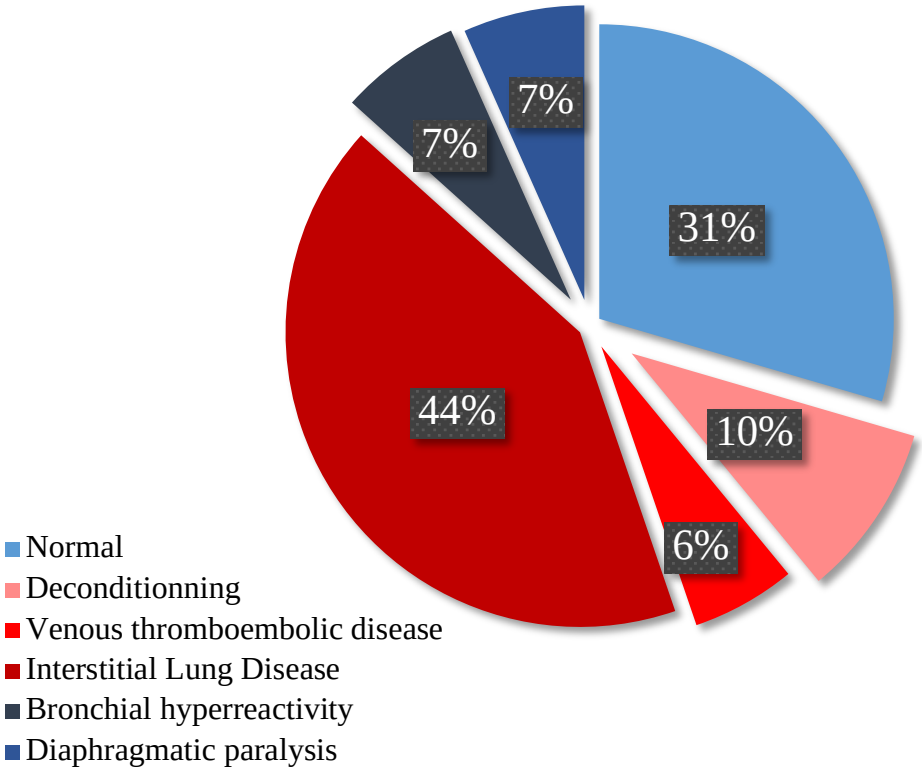


Fig. 3. Respiratory impairment 4 months after moderate to severe SARS-CoV-2 infection

61.4% of the patients declared symptoms. Although they varied, most (44.4%) had dyspnoea, of whom 10.3% were 3 to 4 on the mMRC scale, 30.6% had asthenia and 16.7% coughing (Table 2).

Regarding the primary endpoint, 39.1% had abnormal CO test results or desaturation on the 6MWT. A total of 26.4% had abnormal gas exchange function on the CO/NO test, with a median pulmonary capillary blood volume (Vc) of 77% [58 ; 91] of predicted value and 31.9% of Vc < 70% which was the most frequent abnormal finding. Carbon monoxide transfer

coefficient (Kco) was normal in all cases with a median of 105% [96 ; 116]. 23.6% had restrictive lung disorders and 16.7% obstructive disorders, with 40% partially reversible. Mean fractional exhaled NO was 16.1 parts per billion. Furthermore, 18.1% had respiratory muscle dysfunction (Table 2), leading to diagnose 7% of diaphragmatic paralysis. It was mostly linked to neuromuscular abnormalities acquired in ICU, but in one case the multidisciplinary diagnosis was a Parsonage-Turner syndrome.

Tab. 2. First respiratory follow-up at 4 months (n = 72)

	Number of patients (%)
Primary endpoint – DLco <70% or SpO2 decreased by 4% or more on the 6MWT	27 (39)
Clinical examination	
Symptoms	43 (61)
Dyspnoea	32 (44)
mMRC 0-2	28 (88)
mMRC 3-4	4 (12)
Asthenia	22 (31)
Cough	12 (17)
Thoracic pain	5 (7)
Pulmonary function testing	
Decrease of >4% in SpO2 on the 6MWT	15 (22)
Corrected DLco <70%	18 (25)
Corrected DLco <80%	32 (45)
KCO <70%	0
VC <70%	22 (32)
Dm <70%	3 (4)
TLC <80%	20 (28)
FEV1 <80%	9 (12)
FEV1/FVC <70%	12 (17)
Impaired respiratory muscles	13 (18)
6MWT % pred	92.6 [79-108]
TLC % pred	88.4 [79-99.5]
RV % pred	88.4[73-108]
KCO % pred	106.2[97-115]
DLCO % pred	83.7[67-98]
Vc % pred	75.7[62-89]
Dm % pred	111.8[89-131]
FEV 1% pred	97.9[87-106]
FVC % pred	94.6[83-104]
Pi % pred	103.3[82-127]
SNIP % pred	94[65-96]
Lung scintigraphy	
Perfusion defect	4 (6)
Chest computed tomography	
Normal	22 (31)
Interstitial lung disease	32 (44)
Bronchial dilation	18 (25)

DLco: diffusing capacity of the lungs for carbon monoxide; SpO2: Blood oxygen saturation level; 6MWT: 6-minute walk test; mMRC: modified Medical Research Council scale; KCO: carbon monoxide transfer coefficient; Vc: pulmonary capillary blood volume; Dm: membrane conductance; TLC: total lung capacity; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.

Second follow-up concerned 42 patients whom 76.1% were symptomatic and 57% dyspnoeic after 4 months; at 12 months symptoms and dyspnoea decrease to 52% (Figure 4 & Table 3).

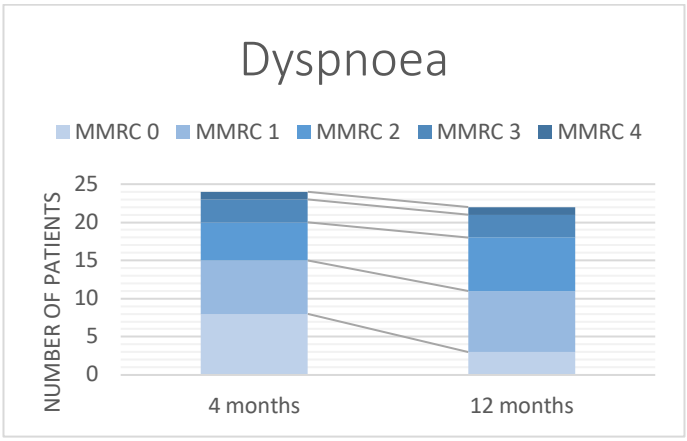


Fig. 4. Dyspnoea improvement after 4 and 12 months

At 12 months, dyspnoea was linked to persistent Interstitial Lung Disease in 57.1%; bronchial hyperreactivity in 9.6%; deconditioning in 9.6%; cardiovascular cause in 9.6%; hyperventilation syndrome in 9.6%; and long COVID with normal respiratory, cardiovascular, and neurologic check-up in 4.7% (Figure 5).

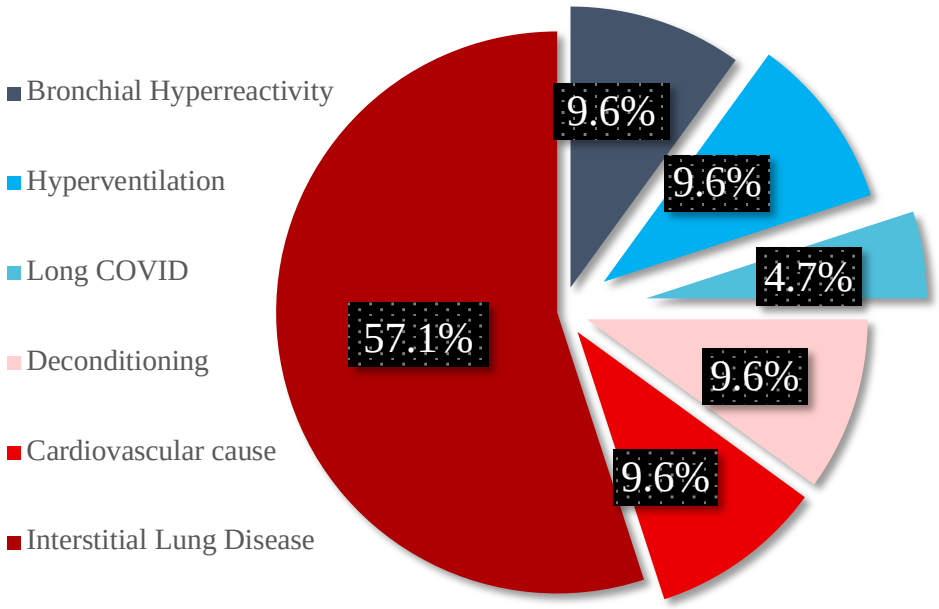


Fig. 5. Dyspnoea assessment 12 months after severe SARS-CoV-2 infection

Concerning primary endpoint, 52.4% presented a DLco <70% or desaturation on 6MWT at 4 months, then 23.8% at 12 months (Table 3). We observed an improvement of respiratory function exploration with 25% of desaturation on 6MWT and a mean perimeter of 103.75% at 12 months whereas 45% of desaturation and a mean perimeter of 92.4% at 4 months; 38.8% DLco <70 and a mean DLco of 76.05% at 12 months whereas 61.1% DLco <70% and a mean DLco of 69.27% at 4 months; a mean FVC of 94.8% at 12 months whereas 86.9% at 4 months (Figure 6).

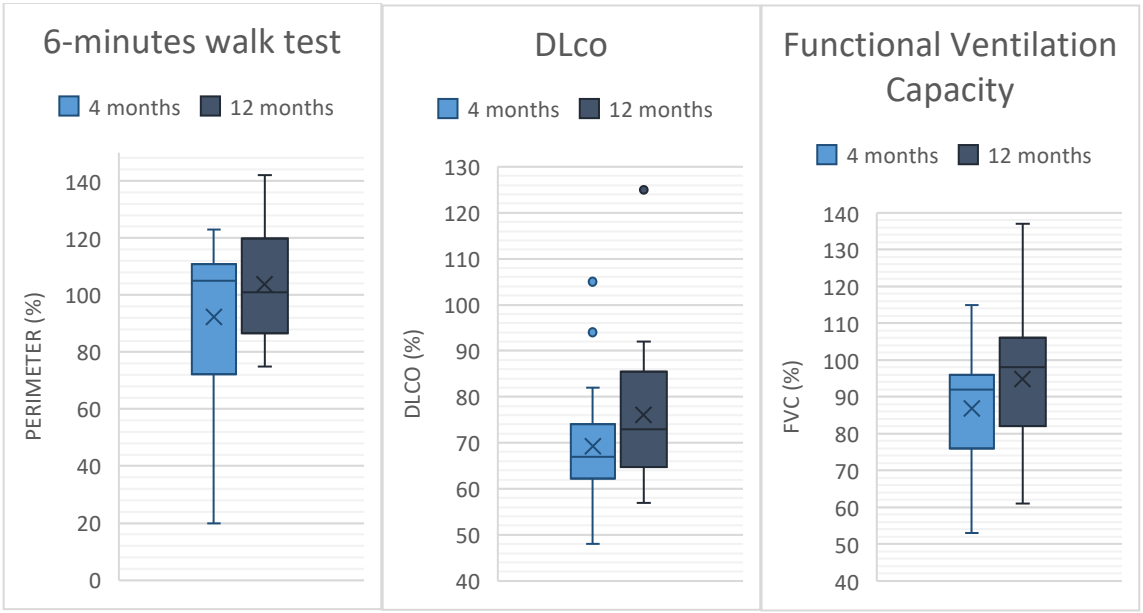


Fig. 6. Respiratory function exploration after 4 and 12 months

Tab. 3. Second respiratory follow-up (n = 42)

	4 months	12 months
Primary endpoint – DLco <70% or SpO2 decreased by 4% or more on the 6MWT	22(52)	10 (24)
Clinical examination (n = 42)		
Symptoms	32 (76)	22 (52)
Dyspnoea	24 (57)	22 (52)
mMRC 0-2	20 (48)	18 (43)
mMRC 3-4	4 (10)	4 (10)
Asthenia	16 (38)	5 (12)
Cough	6 (14)	2 (5)
Thoracic pain	4 (10)	2 (5)
6-minutes walk test (n = 20)		
SpO2 decreased by 4% or more	9 (45)	5 (25)
Perimeter % pred	105 [72.25 ; 110.75]	101 [86.5 ; 119.75]
CO test (n = 18)		
Corrected DLco <70%	11 (61)	7 (39)
Corrected DLco <80%	15 (83)	13 (72)
KCO <70%	0	0
DLCO % pred	67 [62.25 ; 74]	73 [64.75 ; 85.5]
Plesthysmo- or spirography (n = 33)		
FVC <80%	9 (27)	6 (18)
FEV1 <80%	7 (21)	5 (15)
FEV1/FVC <70%	5 (15)	2 (6)
FVC % pred	92 [86 ; 96]	98 [82 ; 106]
Lung scintigraphy (n = 2)		
Perfusion defect	2 (100)	0
Chest computed tomography (n = 27)		
Pathologic	27 (100)	24 (89)
Ground glass opacities	19 (70)	13 (48)
Reticulation	21 (78)	15 (56)
Consolidation	3 (11)	1 (4)
Bronchial dilation	16 (59)	12 (44)

DLco: diffusing capacity of the lungs for carbon monoxide; SpO2: Blood oxygen saturation level; 6MWT: 6-minute walk test; mMRC: modified Medical Research Council scale; KCO: carbon monoxide transfer coefficient; FEV1: forced expiratory volume in 1 second; FVC: forced vital capacity.

3.3. Chest imaging (table 2 & 3)

Only four patients (5.5%) displayed residual defects on ventilation/perfusion scintigraphy at 4 months (Table 2). The four patients were asymptomatic or had normal scintigraphy after three months of anticoagulation (Table 3).

At first follow-up, 31% of HRCT were normal, 46% presented ground-glass opacities, 25% of reticular opacities, 6% of alveolar opacities, 7% of micronodules, 23% of bronchiectasis and no honeycombing. After multidisciplinary meeting, it was concluded that 44.4% of patients had persistent ILD at 4 months, of whom 56% had architectural distortion. This distortion was peripheral in 55.5% of cases, central in 33.3%, and mixed in 11%, and affected a mean of 3 lobes (1–6), the lingula being the most frequently involved (67%).

During second follow-up, 27 chest CT, considered as significatively pathologic, were reassessed: 89% were still pathologic at 12 months while three presented no more elementary lesion. Ground glass opacities decreased from 70% to 48%; reticulation from 78% to 56%, alveolar opacities from 11% to 4% and bronchial distortion from 59% to 44% (Table 3 & Figure 6). There were no more micronodules at 12 months.

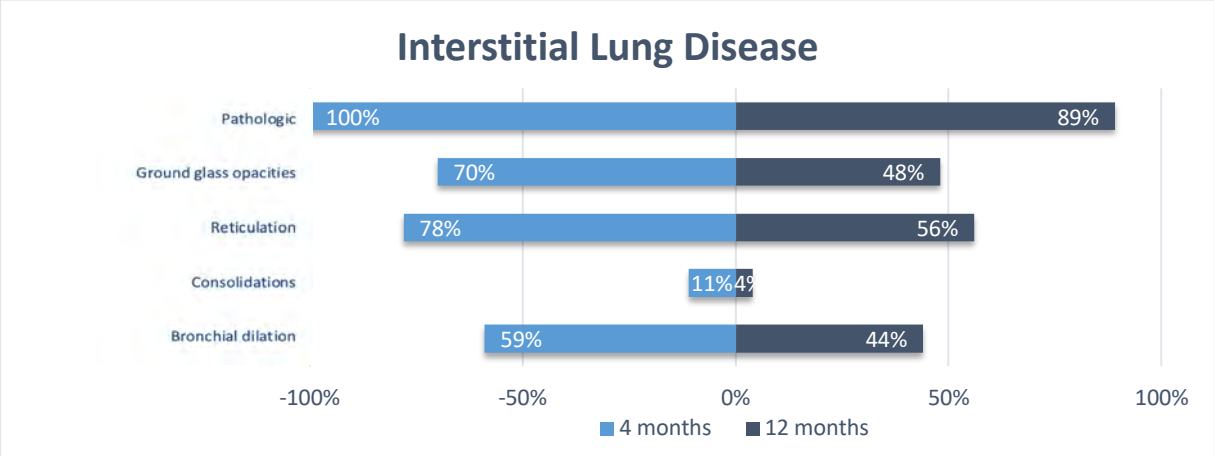


Fig. 6. Assessment of 27 pathologic chest computed tomographies between 4 and 12 months

3.4. Factors associated with gas exchange abnormalities

Admission to ICU, MV, its duration, and prone position were associated with abnormal gas exchange at 4 months, as were complications like VTE, ARDS and tetraparesis. Patients presenting abnormal gas exchange tended to have received corticosteroids later, specifically 15.3 days versus 10 days after PCR diagnosis. Initial CT severity was also associated with abnormal gas exchange (p=0.01) (Table 4).

Persistence of gas exchange impairment after 12 months was significantly associated with smoking status, ARDS during acute phase with MV and its duration.

3.5. Factors associated with persistent interstitial lung disease

Most patients with ILD at 4 months have been admitted to ICU (93.8% versus 6.3%, p=0.001) and treated with MV, HFO and prone position. They also had significantly more complications including VTE, ARDS and tetraparesis; an older age (64.5 versus 55.3 years old, p=0.02) and lower BMI (Body mass index) (26.7 versus 30.6, p=0.002) (Table 4). It seems that persistence of ILD was influenced by time delays from diagnosis to steroids onset: begun 15.3 days after PCR diagnosis in patients with ILD, while 8.6 days in those who did not (non-significant result, p=0.0726). However, patients with ILD were not more symptomatic nor dyspnoeic than others.

Patients presenting ILD with distortion seemed to have displayed more severe forms than those without, required MV and drug curare more frequently, developed more VTE. They might have received less corticosteroid medication than ILD patients without distortion (50% vs 57.1%, non-significant result).

During 2nd follow-up, ILD persistence was significantly associated with ARDS, its management with mechanical ventilation and MV duration (14 days versus 8, p=0.001), an older age (65.8 years old versus 58.1, p=0.04), and lower BMI (26.9 versus 29.6, non-significant p=0.05) (Table 5).

Tab. 4. Risk factors for respiratory abnormalities and persistent interstitial lung disease after 4 months

	Primary endpoint – DLco <70% or oxygen desaturation on the 6MWT			Secondary endpoint – persistent ILD		
	No (n = 42)	**Yes (n = 27)**	**p-value**	**No (n = 42)**	**Yes (n = 27)**	**p-value**
Age	59 [50;68]	62 [54;72]	0.44	58 [48;66]	64 [54;74]	0.02†
BMI	29 [26;32]	28 [25;31]	0.19	30 [27;34]	27 [23;29]	0.002‡
Smoking status						
Never smoker	21 (58)	13 (50)		21 (58)	15 (52)	
Former smoker	1 (3)	6 (23)	0.05	2 (6)	6 (21)	0.22
Current smoker	14 (39)	7 (27)		13 (36)	8 (27)	
Intensive care unit admission						
HFO						
No	33 (80)	16 (61)	0.0882	33 (85)	19 (61)	0.0266*
Yes	8 (20)	10 (39)		6 (15)	12 (39)	
Non-invasive ventilation						
No	38 (93)	16 (62)	0.0017*	35 (90)	22 (71)	0.0448*
Yes	3 (7)	10 (38)		4 (10)	9 (29)	
Mechanical ventilation						
No	26 (63)	5 (18)	0.0003*	25 (64)	9 (28)	0.0025*
Yes	13 (37)	22 (82)		14 (36)	23 (72)	
Prone positioning						
No	30 (73)	9 (33)	0.0012*	32 (82)	10 (31)	0.0*
Yes	11 (27)	18 (67)		7 (18)	22 (69)	
MV duration	0 [0;9]	13 [0;25]	0.0003‡	0 [0;9]	13 [0;27]	0.0004‡
Complications and severity						
VTE						
No	33 (79)	13 (48)	0.0089*	35 (87)	14 (44)	0.0001*
Yes	7 (17)	14 (52)		5 (13)	18 (56)	
ARDS						
No	24 (57)	4 (15)	0.0005*	24 (60)	7 (22)	0.0012*
Yes	18 (43)	23 (85)		16 (40)	25 (78)	
Tetraparesis						
No	38 (91)	15 (56)	0.0008*	38 (95)	18 (56)	0.0001*
Yes	4 (9)	12 (44)		2 (5)	14 (44)	
Baseline CT abnormalities						
Mild <10%	5 (13)	0		5 (14)	1 (3)	
Moderate 10-25%	12 (30)	4 (17)		11 (31)	5 (17)	
Extensive 25-50%	14 (35)	5 (22)	0.0166§	11 (31)	9 (31)	0.2566
Severe 50-75%	8 (20)	9 (39)		7 (19)	10 (35)	
Critical >75%	1 (2)	5 (22)		2 (5)	4 (14)	

*: p-value <0.05 (Chi-2); §: p-value < 0.05 (Exact); †: p-value <0.05 (Student); ‡ p-value < 0.05 (Wilcoxon/Mann-Whitney). BMI: body mass index; DLco: diffusing capacity of the lungs for carbon monoxide; 6MWT: 6-minute walk test; ILD: interstitial lung disease; HFO: high-flow oxygen; VTE: venous thromboembolism; ARDS: acute respiratory distress syndrome; CT: computed tomography.

Tab. 5. Risk factors for respiratory abnormalities and persistent interstitial lung disease after 12 months

	Primary endpoint – oxygen desaturation on the 6MWT			Secondary endpoint – persistent ILD		
	No (n = 37)	**Yes (n = 5)**	**p-value**	**No (n = 18)**	**Yes (n = 24)**	**p-value**
Age	60 [54;71]	62 [61;73]	0.44	58 [51;62]	66 [58;74]	0.04‡
BMI	28 [25;31]	27 [25;33]	0.28	28 [26;32]	27 [23;29]	0.05
Smoking status						
Never smoker	17 (48)	1 (20)		8 (44)	10 (45)	
Former smoker	3 (9)	2 (40)	0.04§	2 (12)	3 (14)	0.22
Current smoker	15 (43)	2 (40)		8 (44)	9 (41)	
Intensive care unit admission						
HFO						
No	26 (70)	3 (75)	0.81	15 (83)	14 (61)	0.23
Yes	11 (30)	1 (25)		3 (17)	9 (39)	
Non-invasive ventilation						
No	28 (76)	2 (50)	0.04§	14 (78)	16 (70)	0.08
Yes	9 (24)	2 (50)		4 (22)	7 (30)	
Mechanical ventilation						
No	11 (30)	2 (40)	0.001§	7 (39)	6 (25)	0.002*
Yes	26 (70)	3 (60)		11 (61)	18 (75)	
Prone positioning						
No	16 (43)	2 (40)	0.002§	12 (67)	6 (25)	< 0.0001*
Yes	21 (57)	3 (60)		6 (33)	18 (75)	
MV duration	11 [0;18]	23 [0;53]	0.002‡	8 [0;16]	14 [0;23]	0.001‡
Complications and severity						
VTE						
No	22 (60)	3 (60)	0.16	13 (72)	12 (50)	0.06
Yes	15 (40)	2 (40)		5 (28)	12 (50)	
ARDS						
No	9 (24)	3 (60)	0.003§	7 (39)	5 (21)	0.007*
Yes	28 (76)	2 (40)		11 (61)	19 (79)	
Tetraparesis						
No	29 (78)	1 (20)	0.009§	14 (78)	16 (67)	0.21
Yes	8 (22)	4 (80)		4 (22)	8 (33)	
Baseline CT abnormalities						
Mild <10%	3 (9)	0		2 (12)	1 (5)	
Moderate 10-25%	6 (18)	2 (50)		3 (18)	5 (23)	
Extensive 25-50%	11 (31)	0	0.47	5 (29)	6 (27)	0.76
Severe 50-75%	11 (31)	1 (25)		4 (23)	8 (36)	
Critical >75%	4 (11)	1 (25)		3 (18)	2 (9)	

*: p-value <0.05 (Chi-2); §: p-value < 0.05 (Exact); ‡ p-value < 0.05 (Kruskal-Wallis). BMI: body mass index; DLco: diffusing capacity of the lungs for carbon monoxide; 6MWT: 6-minute walk test; ILD: interstitial lung disease; HFO: high-flow oxygen; VTE: venous thromboembolism; ARDS: acute respiratory distress syndrome; CT: computed tomography.

3.6. Comparison of symptomatic and asymptomatic patients

Persistent symptoms at 4 and 12 months did not significantly correlate with any of the risk factors assessed.

4. DISCUSSION

Four months after a moderate to severe SARS-CoV-2 infection, less than half of the patients had persistent diffusion abnormalities. The main predictive factors for this respiratory impairment were disease severity during initial presentation and VTE occurrence during the acute phase. At 12 months, it concerned only 14% of this cohort, and initial severity was still the main risk factor.

Nearly half of the patients displayed ILD on HRCT at 4 months, of which 12% were reassessed normal after 12 months. Bronchial distortion was frequently observed, even in those who were not treated with MV. Such pulmonary lesions may partly explain why gas exchange abnormalities persisted at 4 and 12 months. The predictive factors were admission to USIR, important respiratory supports as HFO, NIV and MV, complications, lower BMI, and older age according with acute phase severity, patient fragility and major impact of invasive management.

In this cohort of patients infected between March and April 2020, corticosteroids were mostly initiated in severe cases, remote from initial diagnosis. Patients who received corticosteroids earlier tended to present fewer functional and radiographic sequelae at 4 months. Currently, guidance on steroids in COVID-19 pneumonia has been provided by the World Health Organization [23].

A study characterising respiratory function 3 and 6 months after SARS infection [24] revealed that 15% of survivors had reduced surface area for gas exchange, while DLco was significantly lower at 6 months in the subgroup of patients admitted to ICU. Those abnormalities were partly due to the lung injury, since other factors like effort deconditioning and respiratory muscle dysfunction were also involved, as in the present study. In the study by *Luyt et al.* [25] on 1-year sequelae in survivors of H1N1-related ARDS, impaired gas exchange and persistent dyspnoea were found in 64% and 56% of patients who did not require extracorporeal membrane oxygenation. Concerning SARS-CoV-2, the abnormalities described in this cohort are

comparable with those reported in the literature [26–29] (Table 6), in which chest CT sequelae and DLco impairment were significantly associated with severity of acute pneumonia [30, 31].

Tab. 6. Follow-up studies after SARS-CoV-2 pneumonia

Assessment	**3 months**				**4 months**		**12 months**		
Study	***Zhou et al.***	***Wu et al.***	***Zhou et al.***	***Gonzalez J et al.***	***Viatgé et al.***	***Viatgé et al.***	***Wu et al.***	***Zhan Y et al.***	***Viatgé et al.***
Severity	Mild/Moderate	Moderate/Severe	Severe	Severe	Moderate/Severe	Severe	Moderate/Severe	Severe	Severe
Number	51	83	95	62	72	42	83	19	42
Dyspnoea	/	67 (81%)	/	30 (47%)	32 (44%)	24 (57%)	4 (5%)	2 (11%)	22 (48%)
6MWT (m)	/	535 [490 ; 565]	/	400 [362 ; 440]	555 [430 ; 605]	567 [435 ; 604]	615 [583 ; 633]	545 [518 ; 625]	540 [475 ; 683]
Dlco (%)	83 [76 ; 94]	77 [67 ; 87]	80 [72 ; 91]	68±12	83 [67 ; 98]	67 [62 ; 74]	92% [81 ; 99]	82 [73 ; 89]	73 [65 ; 85]
Dlco < 80%	20 (42%)	46 (55%)	40 (47%)	51 (82%)	32 (45)	15 (83%)	27 (33%)	4 (36%)	13 (72%)
FVC (%)	111 [103 ; 124]	92 [81 ; 99]	107 [96 ; 115]	81±17	95 [83 ; 104]	92 [86 ; 96]	98 [89 ; 109]	94 [84 ; 99]	98 [82 ; 106]
FVC < 80%	0	19 (23%)	3 (3.5%)	/	14 (10%)	9 (27%)	9 (11%)	2 (18%)	6 (18%)
ILD	34 (68%)	65 (78%)	74 (85%)	/	32 (44%)	27 (100%)	20 (24%)	10 (53%)	24 (89%)
GGO	30 (60%)	65 (78%)	69 (79%)	34 (60%)	32 (44%)	19 (70%)	19 (23%)	/	13 (48%)
Reticulation	18 (36%)	27 (33%)	10 (11%)	28 (49%)	19 (26%)	21 (78%)	3 (4%)	/	15 (56%)
Consolidations	8 (16%)	/	61 (70%)	9 (16%)	4 (6%)	3 (11%)	/	/	1 (4%)
Bronchiectasis	0	1 (1%)	4 (5)%	41 (72%)	16 (22%)	16 (59%)	1 (1%)	/	12 (44%)

Quantitative variables are described as median [QT 1 ; QT 3] or mean ± SD; qualitative variables are described as n (%) - 6MWT: 6-minute walk test; DLco: diffusing capacity of the lungs for carbon monoxide; FVC: forced vital capacity.

Based on literature data on other viruses and ARDS, *Ojo et al.* [32] suggest that some factors might predict the risk of developing pulmonary fibrosis, including age, duration of ICU hospitalization and MV, smoking, and alcoholism. These parameters were also spotted as risk factors in this cohort, except for alcoholism. Besides post-ARDS sequelae, COVID-19 lung disease patients also display persistent reticulation during HRCT assessment 4 weeks after the onset of symptoms [33] and this pandemic involves more patients than other epidemics: currently 238,460,430 confirmed cases worldwide whom 38,930,639 in Europe. Prevalence of ILD with architectural distortion was substantial in cohort studies and could potentially concern more than 7 million patients worldwide whom 700,000 in Europe. Therefore, prospective studies would be relevant to determine risk and potential treatment of pulmonary fibrosis after SARS-CoV-2 infection such as clinical randomized trial NINTECOR: Nintedanib for the Treatment of SARS-Cov-2 Induced Pulmonary Fibrosis [34]. Neither of prospective studies, including our cohort, present evolutionary process of fibrosis; on the contrary both of them demonstrate clinical or scannographic improvement.

The main functional respiratory abnormality in this study was reduced Vc. However, the reduction was moderate, and not associated with radiographic abnormalities or the persistence of symptoms, including dyspnoea. It may have resulted from capillary inflammation during the acute phase of COVID-19. The reduced DLco with normal Kco would sustain loss of alveolar unit rather than alveolar-capillary damage or microvascular pathology [35].

The current available data about the risk of chronic thromboembolic pulmonary disease following COVID-19 infection are reassuring. *Georges et al.* [18] suggested assessing scintigraphy and echocardiography at 3 months for all patients who develop pulmonary embolism during a SARS-CoV-2 infection. However, it has been reported between 46 and 66% prevalence of persistent pulmonary scintigraphy abnormalities, 3 months after acute idiopathic pulmonary embolism in non-infectious diseases [36, 37], which is higher than the results found in this study. Three patients had scintigraphy defects at 4 months probably due to undiagnosed

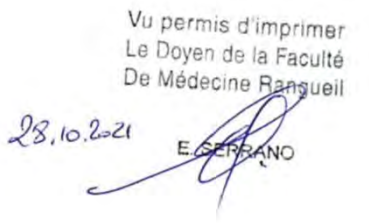
pulmonary embolism during the acute phase or subsequent rehabilitation. After 3 months of anticoagulation, perfusion defects disappeared.

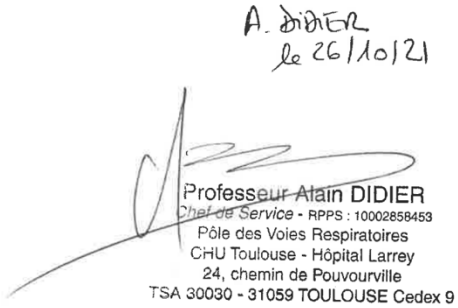
Persistent symptoms at 4 months, particularly dyspnoea and asthenia, were common in this study, as in recent prospective studies [30, 38, 39]. However, no predictive factor was found, not even initial severity or management, implying a multifactorial process. Long COVID is described as persistent fatigue and varied symptoms such as dyspnoea 3 months after onset of symptoms; it seems to concern more likely females, persons with history of anxiety or depression, with various symptoms during acute phase, without any association with initial disease severity [40]. Studies report various incidence from 30 to 90% at 3 months, without complete medical check-up; and only rehabilitation has been found as possibly effective in improving symptoms [41]. In our cohort, patients with persistent dyspnoea benefited to complete check-up; and only 4.7% were linked to long COVID presenting asthenia, dyspnoea, chest pain, no abnormalities in respiratory, neurologic and cardiovascular assessment, and finally benefited from rehabilitation.

This study was limited by its single-centre design. It should be mentioned that transthoracic echocardiography was not systematically performed to assess the risk of pulmonary arterial hypertension: the examination was conducted later if respiratory check-up revealed isolated dyspnoea and/or reduced DLco.

5. CONCLUSION

Among patients with moderate to severe COVID-19 pneumonia, 61% were still symptomatic after 4 months, and 31% after 12 months, but no predicting factor was found. Moreover, persistent functional abnormalities concerned 39% of patients after 4 months, and 14% after 12 months linked to acute phase severity. Interstitial lung disease was detected in 44% of HRCT at 4 months, with only 12% of improvement after 12 months and a substantial part of bronchiectasis. Embolic sequelae were rare, and there was no diagnostic of chronic thrombo-embolic disease. A respiratory check-up after moderate and severe COVID-19 pneumonia may be relevant to improve future management of patients: physical examination, 6MWT, diffusion capacity test and chest CT. Echocardiography and scintigraphy do not appear relevant as first-line exams.





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Moderate to severe SARS-CoV-2 pneumonia: clinical, functional, and imaging outcomes at 4 and 12 months

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LIEU ET DATE DE LA SOUTENANCE : Le 10 Novembre 2021
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RESUMÉ EN ANGLAIS :
This prospective cohort study in severe COVID-19 patients describe persistent gas exchange abnormalities at 4 and 12 months. Among 72 patients included, 76% required admission to an intensive care unit, 68% invasive mechanical ventilation and 39% developed venous thromboembolism. After 12 months, 31% were symptomatic without risk factor identified. 39% had decreased DLco or desaturation on the 6MWT, and 33% presented radiologic abnormalities, significatively associated with a severe initial presentation. There were no residual defects on lung scintigraphy after 12 months. In conclusion, there is no risk of embolic sequelae, but secondary Interstitial Lung Disease and sequelae of invasive management justifying a respiratory check-up after severe COVID-19 pneumonia.

TITRE EN FRANÇAIS : **Pneumonie à SARS-CoV-2 modérée à sévère : évaluation clinique, fonctionnelle, et imagerie à 4 et 12 mois**

RESUMÉ EN FRANÇAIS :
Cette étude de cohorte prospective menée suite à une pneumonie COVID-19 sévère décrit les anomalies persistantes des échanges gazeux à 4 et 12 mois. Parmi 72 patients inclus, 76% ont été admis en soins intensifs ou Réanimation, 68% une ventilation mécanique invasive et 39% ont présenté un épisode thromboembolique. Après 12 mois, 31% étaient symptomatiques sans facteur de risque identifié. 39% présentaient une DLco <70% ou désaturation au test de marche à 12 mois, et 33 % des séquelles radiologiques, significativement associés à une présentation initiale sévère. Il n'y avait pas de défect résiduel en scintigraphie pulmonaire à 12 mois. En conclusion, il n'y a pas de risque de séquelle embolique, mais de Pneumopathie Interstitielle Diffuse secondaire à l'atteinte sévère ou la prise en charge invasive, justifiant un bilan respiratoire dans ces cas de pneumonie sévère à SARS-CoV-2.

DISCIPLINE ADMINISTRATIVE : Médecine spécialisée clinique

MOTS-CLÉS : SARS-CoV-2 ; COVID-19 ; suivi ; séquelles ; embolie pulmonaire ; fibrose pulmonaire

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