Persistent disabilities 28 months after COVID-19 hospitalisation, a prospective cohort study

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Shareable abstract (@ERSpublications)
At 28 months after hospitalisation for COVID-19, almost all patients recovered normal PFTs and chest CT scans, but many still endured disabilities (55.7%), in particular, fatigue (31.5%), dyspnoea (29.8%) and neuropsychological symptoms (17.7%) https://bit.ly/3Bq8ewQ

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Abstract

Background Limited data are available on long-term respiratory disabilities in patients following acute COVID-19.

Patients and methods This prospective, monocentric, observational cohort study included patients admitted to our hospital with acute COVID-19 between 12 March and 24 April 2020. Clinical, functional and radiological data were collected up to 28 months after hospital discharge.

Results Among 715 patients hospitalised for COVID-19, 493 (69.0%) were discharged alive. We could access complete medical records for 268 out of 493 patients (54.4%); 138 out of 268 (51.5%) exhibited persistent respiratory symptoms and agreed with the data collection and follow-up. Patients were predominantly male (64.5%), with a mean±SD age of 58.9±15.3 years. At the last follow-up, the leading symptoms were asthenia (31.5%), dyspnoea (29.8%) and neuropsychological symptoms (17.7%). Lung function improved up to the last visit. Mean diffusing capacity of the lung for carbon monoxide (D_{LCO}) was 77.8% of predicted value, total lung capacity (TLC) was 83.5% and O_2 desaturation during exercise (O_2 desaturation) was 2.3%. While D_{LCO} improved over the entire period, TLC improved in the early phase and O_2 desaturation in the late phase. Except for those with lung comorbidities, only one patient presented with minor functional and chest radiological alterations at 28 months.

Conclusion Patients with acute COVID-19 discharged alive showed improved clinical symptoms, lung function parameters and radiological signs up to 28 months post-infection. Persistent symptoms consisted mainly of asthenia and dyspnoea, with lung function returning to normal. One patient without prior respiratory issues exhibited moderate pulmonary fibrosis.

Introduction

On 11 March 2020, the World Health Organisation (WHO) declared severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) infection, also known as coronavirus infectious disease-19 (COVID-19), a pandemic. According to the WHO, as of December 2023, ∼7 million deaths have occurred worldwide from COVID-19 [1].

Respiratory symptoms are often present in the early stages of COVID-19 [2]. Most patients have a benign evolution, while others, particularly older adults and those with underlying medical conditions, develop acute respiratory distress syndrome, which may require high-flow oxygen therapy or invasive mechanical ventilation, with persistently high mortality rates [3]. During consecutive waves of the COVID-19 pandemic, cumulative clinical experience and emerging evidence helped to improve management strategies and lower mortality rates.

In the aftermath of the pandemic first waves, attention has been drawn to the long-term symptoms and physical and/or psychological sequelae after COVID-19, referred to by the WHO as "post-COVID-19 condition", also known as "post-acute sequelae of COVID-19" or "long COVID" [4]. Long-term recovery of pulmonary function remains a matter of concern. Early reports showed persistent abnormal lung function parameters 30 days after symptom onset, marked mainly by a restrictive ventilatory defect and low diffusing capacity, which correlate with clinical severity and extent of chest computed tomography (CT) changes at diagnosis [5]. Subsequent studies reported similar results further from hospital discharge at 1 month [6, 7], 3 months [8] and 6 months [9]. Several longitudinal follow-up studies assessing the evolution of symptoms in COVID-19 survivors over 1 year after hospital discharge have been published [10–12]. Given the prevalence of persistent symptoms even at 1-year follow-up, longer follow-up studies are needed.

We describe the results of a prospective, monocentric, observational cohort study conducted over a 28-month period to analyse evolution in the clinical symptoms, pulmonary function and radiological findings in COVID-19 survivors. Our main objective was to assess persistent clinical symptoms and functional abnormalities after acute COVID-19.

Methods

Study design

This was a prospective, longitudinal, observational cohort study of data collected in our hospital following a cohort of patients with COVID-19 over 28 months.

The aim of the current study was to collect clinical, biological and radiological features of patients with COVID-19 discharged alive, and to document medical outcomes at sequential follow-up times up to 28 months post-infection.

In-person medical visits and all laboratory and radiographical investigations were performed at the attending physicians' demand when deemed clinically necessary.

The study report follows the recommendations of the STROBE (STrengthening the Reporting of OBservational studies in Epidemiology) guidelines for cohort study [13] (see supplementary material).

Ethical considerations

This study was conducted in accordance with ethical guidelines. According to French regulations, we obtained non-opposition from all the patients. Patient confidentiality and privacy were strictly maintained throughout the research process.

Study participants and setting

Adult patients with suspected COVID-19 who were admitted to our hospital (European Georges-Pompidou Hospital, Paris, France) between 12 March and 24 April 2020, and tested positive for COVID-19 by reverse transcriptase-polymerase chain reaction (RT-PCR) on a nasopharyngeal swab, were eligible. The collection of data at baseline, the clinical, biological and radiological characteristics of patients with COVID-19 at presentation, were obtained from the SARCODO study cohort (NCT04624997), which investigated coagulation and endothelium activity profiles. The study population consisted of all patients discharged alive who did not oppose the data collection and follow-up.

Study procedures

Baseline and follow-up data were collected *via* face-to-face medical visits, telephone interviews and standardised reviews of medical records. At hospital admission, patients underwent physical examination, blood sample analysis, RT-PCR on a nasopharyngeal swab and chest CT scans when available.

1 month after discharge, all patients were invited to a follow-up visit, including clinical assessment with a lung specialist (S. Günther and B. Renaud), pulmonary function tests (PFTs) and chest CT scan. Based on persistent disabling symptoms or PFT abnormalities, further visits were offered, and PFTs and chest CT were performed at 3, 6, 12 and 28 months.

At 28 months, all patients were interviewed by telephone to record persistent clinical symptoms, emerging medical events and disabilities using a standardised questionnaire. Additional face-to-face medical visits, PFTs and chest CT scans were offered when clinically appropriate.

For patients lost to follow-up, three attempts were made to establish contact either by telephone or through their primary care physician.

Pulmonary function tests

PFTs included spirometry, functional residual capacity (FRC), total lung capacity (TLC) and diffusing capacity for carbon monoxide (D_{LCO}) by single-breath real-time CO/NH_4 measurements. FRC was measured by body plethysmography (Vyntus Body, Duomed, Flaxlanden, France). For forced vital capacity and D_{LCO}, the predicted values were used according to the Global Lung Function Initiative (GLI) [14, 15]. A 6-min walk test (6MWT) was performed according to American Thoracic Society/European Respiratory Society recommendations, with peripheral oxygen saturation (S_{pO_2}) measured by pulse oximetry on the index finger. Dyspnoea was assessed after the 6MWT using the Borg scale (post-6MWT Borg scale). The results were expressed as distance covered and corresponding percentages of predicted values calculated using the method of Enright and Sherrill [15]. D_{LCO} <75% and TLC ⩽80% of the predicted values were considered as abnormal. Regarding 6MWT interpretation, a decrease in S_{pO_2} of at least 4% during exercise was considered as abnormal.

Imaging by chest CT scan

All low-dose chest CT scans were performed on the same multi-row system (Somatom Definition Edge, Siemens) with a collimation of 128×0.6 mm (reconstruction in 1.5 mm in mediastinal setting and in 1 mm in lung setting), and a 280-ms gantry rotation time. The chest CT scans were obtained in a craniocaudal direction from the lung apices to the bases in a single breath-hold at maximum inspiration without ECG gating, and interpreted by the same two radiologists (G. Reverdito and E. Mousseaux), as previously mentioned [16]. Based on body size, the tube voltage was selected (100–120 kVp) by an automated tube voltage selection associated with 40–80 mA. Lung injury in patients with COVID-19 pneumonia was assessed in each lobe by looking for either ground glass opacities (GGO), consolidation (homogeneous opacification with obscuration of the underlying vasculature) or both. Additional chest CT characteristics were assessed including ⩾10 mm lymphadenopathy, nodules, pleural effusions and airway abnormalities.

Scores

The Charlson Comorbidity Index (CCI) was used to assess the extent of comorbid conditions encompassing 17 categories. A score of zero indicates the absence of comorbidities, while a higher score correlates with a greater predicted mortality rate [17]. The 4C mortality score was also assessed, which is an externally validated score developed by the ISARIC 4C consortium (International Severe Acute Respiratory and Emerging Infection Consortium). This tool stratifies the risk of in-hospital mortality in patients with COVID-19 from low to very high risk [18], and has been recently recommended for clinical application [19].

Data collection

The following data were collected at baseline: demographic data (age, sex); morphological variables (height, weight); comorbid conditions (cardiovascular, bronchopulmonary, metabolic, renal, hepatic and oncological); symptoms (dyspnoea, cough, asthenia, myalgia, arthralgia, anosmia, ageusia, myalgia, headache and diarrhoea); and physical examination findings (body temperature, blood pressure, heart and respiratory rate, pulse oximetry). Blood tests included haematology (red blood cell count, haematocrit, white blood cell count and formula, haemoglobin) and chemistry (sodium, potassium, glucose, albumin, creatinine, troponin, D-dimer and C-reactive protein).

Persistent clinical symptoms and disabilities, re-infection with SARS-CoV-2 and immunisation against SARS-CoV-2 were recorded using a standardised questionnaire administered at 1, 3, 6, 12 and 28 months.

Statistical analyses

Quantitative variables are summarised as mean±SD or median and interquartile range (IQR), while qualitative variables are presented as number and percentage. Expected values were determined for respiratory function tests, accounting for age, body weight, height, sex and race/ethnicity, and the measured values were standardised as a percentage of the corresponding expected values. Data collected at baseline and at 1, 3 and 28 months of follow-up are summarised using descriptive statistics. Missing values exceeding 5% of the study population, as displayed in table 1, were not supplemented using any imputation method.

We conducted comparisons of patients' characteristics at baseline and last follow-up based on the performance of clinically indicated PFTs, utilising Pearson's chi-squared test for categorical variables, and employing either the t-test or the Kruskal–Wallis non-parametric test for numerical variables where applicable.

The changes in standardised TLC, D_{LCO} and O_2 desaturation levels during the 6MWT at 1, 3 and 28 months were evaluated using repeated-measures analysis of variance. In addition, a random intercept ordered logistic regression model was employed for longitudinal data, with the "post 6MWT Borg scale" as the dependent variable and "Time (1, 3 and 28 months)" as the independent variable. Multiple pairwise comparisons were adjusted using Bonferroni corrections. A significance level of 5% ($p<0.05$) was adopted. All analyses were performed using Stata 18.0 (StataCorp, College Station, TX, USA).

Results

Study participants

In total, 715 patients were admitted to our hospital during the study period, among whom 493 were discharged alive (69.0%). The investigators could access and review 268 out of 493 (54.4%) complete patients' medical records. Of these, 138 out of 268 (51.5%) with persistent respiratory symptoms did not oppose the data collection and follow-up, forming the study population (figure 1). The patients had a mean ±SD age of 58.9±15.3 years, 89 (64.5%) were male and 28 (20.3%) were obese (body mass index >30 $kg \cdot m^{-2}$) (table 1). 110 patients (41.3%) had comorbidities (table 1), including hypertension (44 out of 110; 40.0%), diabetes mellitus (26 out of 110; 23.6%), cardiovascular diseases (23 out of 110; 20.9%), and cancer or haematological neoplasms (17 out of 110; 15.5%). 10 of 138 patients (7.3%) had a previous history of venous thromboembolism.

COVID-19-related symptoms at admission

On admission, fever (81.2%), cough (79.0%), dyspnoea (70.3%) and asthenia (65.2%) were the most common symptoms. 72 out of 138 patients (52.2%) had at least four COVID-19 symptoms. Low pulse oximetry <90% was observed in 17.4% of patients and mean arterial pressure <65 mmHg in 2.2%. Elevated C-reactive protein (>50 $mg \cdot L^{-1}$) was seen in 66.7%, positive D-dimer in 77.4% and lymphocyte count <1 $G \cdot L^{-1}$ in 51.5% of patients (table 1).

39 patients (28.3%) required admission to the intensive care unit (ICU), with a higher proportion of males compared to females (34.8% *versus* 16.3%, respectively). Among these, 14 of 39 (35.9%) underwent invasive mechanical ventilation. Median length of stay in the ICU was 5.5 days (4–15).

COVID-19-related symptoms at follow-up

The median follow-up of the study population was 842.5 days (IQR: 828–867), and 124 patients (89.9%) attended the follow-up at 28 months (table 1). During follow-up, five patients (3.6%) died between 377 and 969 days after presentation. COVID-19 was not the cause of death of any of these patients (supplementary table S1). Additionally, nine patients followed up until 12 months declined to participate at the 28-month visit (supplementary table S2).

Among the 124 patients, the most prevalent persistent symptoms were asthenia (31.5%) and dyspnoea (29.8%); 17.7% of patients had neuropsychological symptoms (table 1). Overall, 55.7% of patients experienced at least one symptom at 28 months (table 1). 44 patients presented were diagnosed with an emergent disease during the 28-month follow-up (supplementary table S3). Of those, nine (7.3%) experienced an episode of venous thromboembolism, four (3.2%) at presentation and six (4.8%) during the follow-up.

PFTs were performed in 132 (95.7%) patients at 1 month, 76 (55.1%) at 3 months, 22 (15.9%) at 6 months and 11 (8.0%) at 12 months. Among 124 (89.9%) patients contacted at 28 months, 28 of 124 (22.6%) patients were invited to face-to-face visits and to perform PFT because of ongoing disabling symptoms (supplementary table S4). The most common PFT findings were a restrictive ventilatory pattern (34.9% and 46.4% at 3 and 28 months, respectively), reduced D_{LCO} (55.1% and 42.3%) and O_2 desaturation

TABLE 1 Characteristics of the study population at presentation and according to pulmonary function tests (PFTs) performed at the 28-month follow-up

Characteristic	All patients	Patients followed up to 28 months	Face-to-face visit at 28 months[#]		p-value[#]
			No	Yes	
Patients n	138	124	96	28	
Demographic and morphological characteristics					
Sex, male	89 (64.5)	77 (62.1)	58 (60.4)	19 (67.9)	0.475
Age years	58.9±15.3	58.6±14.9	59.5±14.9	55.7±14.9	0.231
Age range, years					
<50	40 (29.0)	36 (29.0)	25 (26.0)	11 (39.3)	0.635
50–59	30 (21.7)	27 (21.8)	22 (22.9)	5 (17.9)	
60–69	32 (23.2)	29 (23.4)	22 (22.9)	7 (25.0)	
70–79	23 (16.7)	21 (16.9)	18 (10.7)	3 (10.7)	
⩾80	13 (9.4)	11 (8.9)	9 (9.4)	2 (7.1)	
Body mass index $kg \cdot m^{-2}$	26.8±4.6	27.0±4.7	27.1±4.6	26.5±5.0	0.553
At presentation					
Charlson Comorbidity Index					0.180
Score 0	28 (20.3)	25 (20.2)	16 (16.7)	9 (32.1)	
Score 1–3	71 (51.5)	65 (59.4)	55 (57.3)	10 (35.7)	
Score 4–5	24 (17.4)	24 (19.4)	18 (18.8)	6 (21.4)	
Score 6–9	15 (10.9)	10 (8.1)	7 (7.3)	3 (10.7)	
Symptoms					
Fever[¶]	112 (81.2)	103 (83.1)	78 (81.3)	25 (89.3)	0.319
Asthenia	90 (65.2)	79 (63.7)	60 (62.9)	19 (67.9)	0.604
Dyspnoea	97 (70.3)	88 (71.0)	65 (67.7)	23 (82.1)	0.139
Cough	109 (79.0)	98 (79.0)	76 (79.2)	22 (78.6)	0.946
Myalgia or arthralgia	46 (33.3)	40 (32.3)	33 (34.4)	7 (25.0)	0.350
Ageusia/anosmia	40 (29.0)	37 (29.8)	32 (33.3)	5 (17.9)	0.115
Headache	36 (26.1)	35 (28.2)	28 (29.2)	7 (25.0)	0.666
Any symptom[§]	135 (97.8)	121 (97.6)	93 (96.9)	28 (100.0)	0.344
Number of symptoms	4 (3–5)[§]	4 (3–5)	4 (3–5)	4 (3–4.5)	0.771
Physical examination findings					
Body temperature °C	37.9 (37.2–38.5)	38.0 (37.2–38.6)	38.0 (37.2–38.6)	38.0 (37.2–38.4)	0.812
Pulse oximetry %	94 (91–97)	94 (91–96)	94 (91–97)	93 (91–96)	0.885
Respiratory rate $breaths \cdot min^{-1}$	20 (17.5–25)	20 (17.5–25)	20 (16–24)	22 (18–25)	0.240
Heart rate $beats \cdot min^{-1}$	90 (80–103)	90 (81–103.5)	90 (81–104)	92 (82.5–102)	0.827
Mean blood pressure mmHg	95 (86–102)	96 (87–103)	96 (87–104)	92.5 (85–101.5)	0.431
Laboratory findings					
Natraemia $mmol \cdot L^{-1}$	137 (135–139)	137 (135–139)	137 (137–139)	137.5 (134.5–139)	0.959
Creatinine $\mu mol \cdot L^{-1}$	73 (60–92)	72 (60–89)	71.5 (59–89)	74 (63–89.5)	0.393
Blood glucose $mmol \cdot dL^{-1}$	6.0 (5.3–7.5)	6.0 (5.3–7.5)	6.0 (5.3–7.4)	6.0 (5.5–7.5)	0.999
C-reactive protein $mg \cdot L^{-1}$	74.0 (33.8–133.3)	83.5 (35.0–139.2)	79.0 (35.0–132.6)	97.8 (41.5–176.5)	0.490
Troponin ⩾19.8 $ng \cdot L^{-1}$	7.1 (4.5–12.0)	7.0 (4.5–11.0)	7.0 (4.5–11)	7.4 (4.1–12.6)	0.846
D-dimer $\mu g \cdot L^{-1}$[f]	918 (628–1355)	918 (636–1404)	936 (638.5–1410.5)	902 (525–1310)	0.742
Haemoglobin $g \cdot dL^{-1}$	13.8 (12.5–15.0)	13.8 (12.5–15.0)	13.9 (12.7–15.0)	13.8 (12.1–15.1)	0.816
Haematocrit %	39.5 (36.7–42.6)	39.5 (36.9–42.7)	39.4 (37–42.4)	39.8 (35.0–43.3)	0.777
Platelets $G \cdot L^{-1}$	198 (147.5–247.5)	203 (149–255)	205 (149–262)	168 (148.5–232.5)	0.406
White blood cells $G \cdot L^{-1}$	6.1 (4.5–7.2)	6.1 (4.5–7.4)	6.1 (4.4–7.9)	6.2 (4.9–6.8)	0.640
Neutrophils $G \cdot L^{-1}$	4.2 (2.9–5.6)	4.5 (3.1–5.8)	4.4 (2.9–5.9)	4.5 (3.8–5.6)	0.538
Lymphocytes $G \cdot L^{-1}$	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.0 (0.7–1.3)	1.1 (0.7–1.5)	0.410
Radiographic findings					
Chest CT scan	126 (91.3)	112 (90.3)	89 (92.7)	23 (82.1)	0.096
Chest CT scan findings suggesting COVID-19[ff]	117 (92.1)	104 (92.0)	84 (93.3)	20 (87.0)	0.385
Alveolar consolidation	89 (64.5)	77 (62.1)	59 (61.5)	18 (64.3)	0.270
Ground glass opacities	112 (96.7)	100 (97.1)	80 (96.4)	20 (100.0)	0.761
Severity of chest CT findings					0.149
<10% extension	26 (22.4)	20 (19.2)	15 (17.8)	5 (25.0)	
⩾10% and <25%	53 (45.7)	48 (46.2)	41 (48.8)	7 (35.0)	
⩾25% and <50%	34 (29.3)	33 (31.7)	26 (31.0)	7 (35.0)	
⩾50%	3 (2.6)	3 (2.9)	2 (2.4)	1 (5.0)	

Continued

TABLE 1 Continued

Characteristic	All patients	Patients followed up to 28 months	Face-to-face visit at 28 months[#]		p-value[#]
			No	Yes	
4C mortality score					0.860
Low risk (1.2–1.7%)	22 (15.9)	19 (15.3)	14 (14.6)	5 (17.9)	
Intermediate risk (9.1–9.9%)	61 (44.2)	55 (44.4)	43 (44.8)	12 (42.9)	
High risk (31.4–34.9%)	53 (38.4)	48 (38.7)	37 (38.5)	11 (39.3)	
Very high risk (61.5–66.2%)	2 (1.5)	2 (1.6)	2 (2.1)	0 (0.0)	
ICU admission and respiratory supportive treatment					
Oxygen therapy	106 (76.8)	97 (78.2)	71 (74.7)	26 (92.9)	0.039
ICU admission	39 (28.3)	35 (28.2)	25 (26.0)	10 (35.7)	0.317
Tracheal intubation	14 (10.1)	13 (10.5)	7 (7.3)	6 (21.4)	0.032
ICU length of stay days	5.5 (4–15)				
In-hospital length of stay days	7 (4–12)	7 (4–12.5)	7 (4–12)	9 (3–17.5)	0.574
Symptoms at last follow-up visit					
Fever		0 (0.0)	0 (0.0)	0 (0.0)	0.999
Asthenia		39 (31.5)	23 (24.0)	16 (57.1)	0.001
Dyspnoea		37 (29.8)	24 (25.0)	13 (46.4)	0.029
Cough		11 (8.9)	9 (9.4)	2 (7.1)	0.715
Myalgia or arthralgia		8 (6.5)	5 (5.2)	3 (10.7)	0.297
Ageusia/anosmia		2 (1.6)	2 (2.1)	0 (0.0)	0.441
Headache		4 (3.2)	2 (2.1)	2 (7.1)	0.182
Neuropsychological symptoms[+]		22 (17.7)	19 (19.8)	3 (10.7)	0.269
Any symptom[§]		69 (55.7)	50 (52.1)	19 (67.9)	0.139
Number of symptoms		1 (0–2)	1 (0–2)	1 (0–2)	0.177
Radiographic findings on the last chest CT scan					
Time to last CT scan days		99 (91–280)	98 (88–116)	306.5 (102–614)	<0.001
No or minimal damage		101 (81.5)	80 (83.3)	21 (75.0)	0.318
Reduced radiographic damage		115 (93.5)	90 (94.7)	25 (89.3)	0.304
COVID-19					
Vaccination[##]		111 (91.0)	84 (89.4)[¶¶]	27 (96.4)	0.252
Re-infection[++]		9 (8.4)[§§]	4 (5.1)	5 (17.9)	0.036
Length of follow-up days		844 (830–866.5)	845 (834–865)	820.5 (787–876.5)	0.040

Data shown are n (%), mean±SD or median (interquartile range), unless otherwise stated. Missing values were <5% of the study population except for the re-infection variable as 21 (16.9%) values were missing. p-value: comparison between patients with or without PFTs at 28 months. CT: computed tomography; ICU: intensive care unit. [#]: all patients who attended in-person at 28 months underwent PFTs. [¶]: fever refers to increased temperature (>37.9°C) before or at presentation to the hospital. [+]: neuropsychological symptoms: sleep disturbances (6/124), imbalance (6/24), mood disturbances (2/124), memory impairment (6/124), missing words (1/124), concentration problems (6/24) and dysesthesias. [§]: at least one complaint among the following: fever, asthenia, cough, dyspnoea, myalgia/arthralgia, ageusia/anosmia, headache and neuropsychological symptoms. [f]: D-dimer threshold depended on patients' age: in patients <50 years, D-dimer values above 500 $\mu g \cdot L^{-1}$ was considered abnormally high, and in older patients, the D-dimer threshold was determined using the following formula – age ×10 [46]. [##]: vaccination: patients who received at least the first two doses of mRNA COVID-19 vaccines (Comirnaty or Spikevax). [¶¶]: two patients were unaware of their vaccination status. [++]: re-infection: symptomatic or asymptomatic COVID-19 infection. [§§]: There were 21 missing values, of which 17 pertain to the 124 patients who were followed up to 28 months. All missing values were from the 96 patients who did not have face-to-face visits. [ff]: ground glass opacities or alveolar consolidation (homogeneous opacification with obscuration of the underlying vasculature).

during the 6MWT (72.0% and 20.0%). Among 28 patients with PFTs at 28 months, 10 have been admitted to the ICU. Their PFT findings show higher desaturation (−4.1 (1.7%) and −1.1 (0.5%), respectively) and lower TLC (74.4 (3.6%) and 88.7 (3.6%), respectively) as compared to the patients not admitted to the ICU. No difference was observed between these two groups regarding the diffusion capacity or Borg scale post-MWT (supplementary table S5) Of the 28 patients tested at 28 months, 27 were also tested at 1 month and 3 months (table 2). Two patients who presented a new episode of venous thromboembolism underwent PFTs at 28 months. Their PFTs findings are compared to those safe of a new episode of thromboembolism in supplementary table S6.

Among the patients tested at 1, 3 and 28 months, TLC increased between 1 and 28 months (mean difference 6% (95% CI: 1.9–10.1); p=0.002) and from 1 to 3 months (mean difference 5.7% (95% CI: 1.4–10.0); p=0.006), but not between 3 and 28 months (mean difference 0.3% (95% CI: −4.0–4.6);

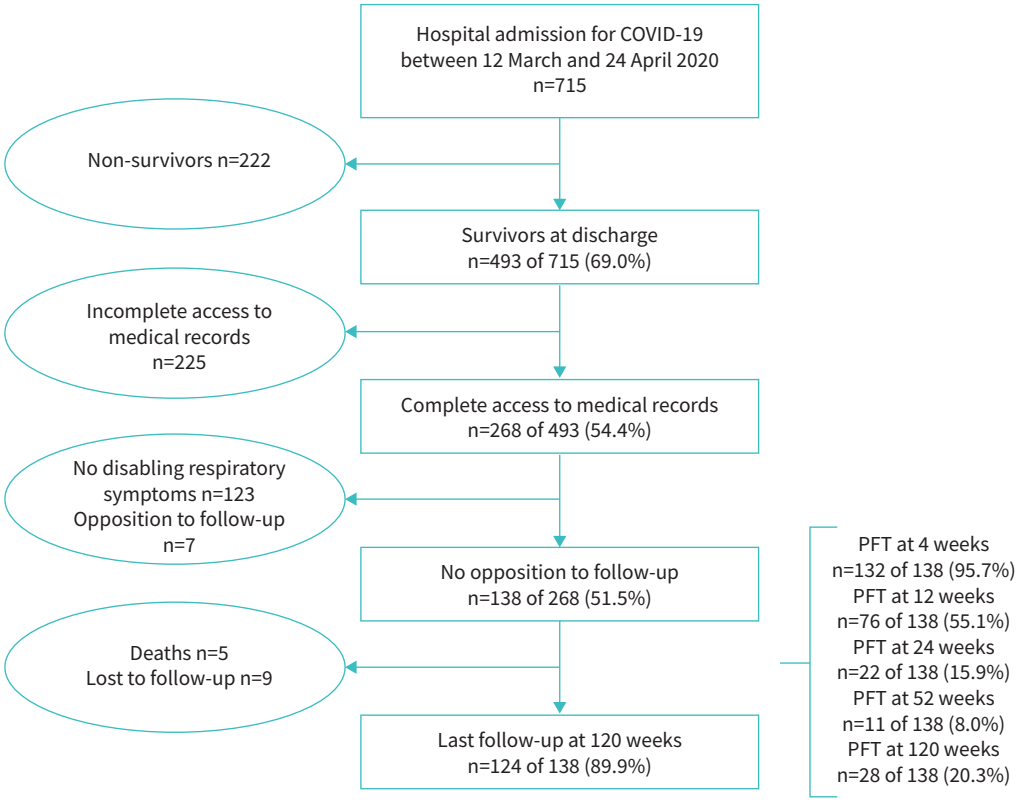

FIGURE 1 Flow chart of the study population. PFT: pulmonary function test.

p=0.999) (table 3 and figure2a). Diffusion capacity increased between 1 and 28 months (mean difference 11.8% (95% CI: 6.7–16.9); p<0.001) and from 1 to 3 months (mean difference 5.6% (95% CI: 0.2–10.9); p=0.040), and from 3 to 28 months (mean difference 6.2% (95% CI: 0.9–11.6); p=0.018) (table 3 and figure 22b). Oxygen desaturation difference had decreased at 28 months compared to 1 month (mean difference 4.8% (95% CI: 1.6–8.1); p=0.002), meaning that O_2 desaturation during the 6MWT was lower at 28 months than at 1 month. This improvement was observed from 3 to 28 months (mean difference 4.0% (95% CI: 0.6–7.4); p=0.015), but not from 1 to 3 months (mean difference 0.8% (95% CI: −2.6–4.2); p=0.999) (table 3 and figure 2d). The odds of moving to a higher Borg scale value decreased globally from 1 month to 28 months (OR 0.09 (95% CI: 0.02–0.33); p<0.001) and from 1 to 3 months (OR 0.12 (95% CI: 0.03–0.44); p=0.001), but not between 3 and 28 months (OR 0.45 (95% CI: 0.15–1.37); p=0.159) (table 3 and figure 2c).

At baseline, 126 (91.3%) patients underwent chest CT scan. Images suggestive of COVID-19 pneumonia and alveolar consolidations were observed in 117 (92.1%) and 89 (64.5%) patients, respectively. 118 (85.5%) patients underwent additional chest CT scans during follow-up (median 98.5 days (IQR: 89–258) and 22 beyond 1 year (median 640.5 days (IQR: 472–780)). A few chest CT scans (5 of 118; 4.2%) showed pathological patterns, but only one patient was diagnosed with lung fibrosis, reduced TLC (82%) and a low D_{LCO} (42%). Specifically, the chest CT scan showed subpleural and intralobular reticulations, along with traction bronchiectasis, bilateral centro- and panlobular emphysema, predominantly affecting the upper lobes, and there was evidence of diffuse bronchial syndrome characterised by bronchial wall thickening and irregular bronchial calibre. This patient had been initially admitted to the ICU, intubated for 22 days and presented an episode of venous thromboembolism during the follow-up. As of now, he is asymptomatic and has no limitation of physical activities; therefore, despite persistent chest CT scan findings, no specific antifibrotic treatment is indicated, but he undergoes regular clinical assessments.

Discussion

This study describes the clinical and functional findings in a prospective cohort of 138 patients who were hospitalised and survived acute COVID-19. A total of 124 patients were followed up to 28 months,

TABLE 2 Symptoms and pulmonary function test (PFT) findings at presentation and 1, 3 and 28 months among the 28 patients tested

Characteristics	Patients[+]			
	Presentation[#]	1 month	3 months	28 months
Symptoms				
Fever[¶]	24 (88.9)	0 (0.0)	0 (0.0)	0 (0.0)
Cough	21 (77.8)	9 (33.3)	3 (11.1)	2 (7.4)
Dyspnoea	22 (81.5)	16 (59.3)	11 (46.2)	12 (44.4)
Asthenia	18 (66.7)	14 (51.9)	8 (29.6)	15 (55.6)
Myalgia/arthralgia	6 (22.2)	7 (25.9)	5 (18.5)	2 (7.4)
Ageusia/anosmia	4 (14.8)	2 (7.4)	1 (3.7)	0 (0.0)
Headache	7 (25.9)	4 (14.8)	2 (7.4)	2 (8.3)
Any symptom[§]	26 (96.3)	24 (89.9)	19 (70.4)	18 (66.7)
Number of symptoms	4 (3–4)	2 (1–3)	1 (0–1.5)	1 (0–2)
Pulmonary function tests[f]				
TLC %		77.4±15.3	80.2±12.0	83.5±15.7
D_{LCO} %		64.8±16.5	70.8±15.4[##]	77.8±14.4[++]
Oximetry drop during 6MWT %		−7.5±6.4	−6.7±5.4[¶¶]	−2.3±3.5[§§]
Borg scale post-6MWT[f]				[§§]
Class 1 (0–2)		4 (14.8)	8 (36.4)[¶¶]	16 (64.0)
Class 2 (3–4)		7 (25.9)	8 (36.4)[¶¶]	3 (12.0)
Class 3 (5–6)		9 (33.3)	6 (22.7)[¶¶]	4 (16.0)
Class 4 (7–8)		6 (22.2)	1 (4.6)[¶¶]	4 (8.0)
Class 5 (9–10)		1 (3.7)	0 (0.0)[¶¶]	0 (0.0)

Data shown are n (%), mean±SD or median (interquartile range). TLC: total lung capacity; D_{LCO}: diffusing capacity of the lung for carbon monoxide; 6MWT: 6-min walk test. [#]: presentation refers to the symptoms collected at presentation to the hospital. [¶]: fever refers to increased temperature (>37.9°C) before or at presentation to the hospital. [+]: among the 28 patients who attended the 28-month follow-up visit, 27 underwent PFTs at 1 month. The missing patient was a 39-year-old woman transferred to the intensive care unit on the 3rd day of presentation and subsequently intubated for 11 days. She had a Charlson Comorbidity Index class of 0 and a 4C mortality score of 2. She was discharged on day 47. At 28 months, her PFTs were within the normal range. [§]: any symptom among the following: at least one complaint among fever, asthenia, cough, dyspnoea, myalgia/arthralgia, ageusia/anosmia and headache. [f]: three patients did not undergo PFTs at 3 months. A female patient with bronchiectasis attended her usual pulmonologist in the outpatient setting and a male patient who did not participate because his previous PFTs at 1 month were normal and another male patient who could not participate for personal reasons. [##]: four missing values for D_{LCO} at the 3-month visit. In addition to the three patients described in the previous note (see note [f]), the fourth patient was a female with several severe comorbidities (muscular, renal and respiratory diseases). [¶¶]: five missing values for the Borg scale and O_2 desaturation at 3 months. The patients concerned were those flagged in the previous note (see note [##]), plus a male patient whose lung volumes, flows and diffusion capacity were within the normal range; therefore, a 6MWT was considered unnecessary. [++]: one missing value for D_{LCO} at the 28-month visit. This female patient had several comorbidities (muscular, renal and respiratory diseases). D_{LCO} was not measured because at months 3 and 28, her vital capacity was <1.5 L and she could not perform the 6MWT due to musculoskeletal issues. [§§]: two missing values for the Borg scale and O_2 desaturation during the 6MWT at the 28-month visit. The two female patients depicted in notes [##] and [++] could not perform the 6MWT because of physical disabilities related to comorbid conditions that preceded the COVID-19 infection.

including 28 with persistent symptoms, mostly asthenia, dyspnoea and neuropsychological symptoms. To our knowledge, this is one of the first studies to report respiratory functional defects in some patients up to 28 months after an initial episode of acute COVID-19.

27 patients underwent PFTs at 1, 3 and 28 months and demonstrated progressive improvement over time. The dynamics of improvement differed during the early period, from 1–3 months, compared to the late period, from 3–28 months. TLC and the Borg scale improved predominantly in the early period, whereas there were distinctive patterns for O_2 desaturation during exercise and D_{LCO}. While O_2 desaturation improved predominantly in the late period, D_{LCO} improved throughout the 28-month follow-up. These different patterns may reflect distinctive healing processes.

Our patients were predominantly male, and differences in disease severity between the sexes may reflect different immune responses linked to the protective immunomodulatory and anti-inflammatory actions of 17β-oestradiol and progesterone in women [20]. Studies have shown that males with infectious diseases are

TABLE 3 Association between total lung capacity, diffusion capacity, post-6-min walk test (6MWT) 5-class Borg scale, difference in peripheral oxygen saturation and the follow-up times at 1, 3 and 28 months

	Mean difference % (95% CI)[#]	p-value
Total lung capacity (% of reference value)		
3 months *versus* 1 month	5.7 (1.4–10.0)	0.006
28 months *versus* 3 months	0.3 (−4.0–4.6)	0.999
28 months *versus* 1 month	6.0 (1.9–10.1)	0.002
Diffusion capacity (% of reference value)		
3 months *versus* 1 month	5.6 (0.2–10.9)	0.040
28 months *versus* 3 months	6.2 (0.9–11.6)	0.018
28 months *versus* 1 month	11.8 (6.7–16.9)	<0.001
Difference in S_{pO_2} (post-6MWT minus pre-6MWT S_{pO_2})		
3 months *versus* 1 month	0.8 (−2.6–4.2)	0.999
28 months *versus* 3 months	4.0 (0.6–7.4)	0.015
28 months *versus* 1 month	4.8 (1.6–8.1)	0.002
	Odds ratio (95% CI)[¶]	**p-value**
Post-6MWT Borg scale		
3 months *versus* 1 month	0.12 (0.03–0.44)	0.001
28 months *versus* 3 months	0.45 (0.15–1.37)	0.159
28 months *versus* 1 month	0.09 (0.02–0.33)	<0.001

6MWT: 6-min walk test; S_{pO_2}: peripheral oxygen saturation. [#]: Bonferroni-adjusted confidence intervals; [¶]: odds ratios denote the risk of moving from any post-6MWT 5-class Borg scale class to a higher one at the next follow-up time.

at greater risk of adverse outcomes, including higher rates of hospitalisation and mortality [21–23]. Obesity is also a risk factor and applied to 20.3% of our patients, which is similar to the obesity rates in other prospective cohorts in Europe [24, 25].

Consistent with previous reports on patients hospitalised for COVID-19, the most prevalent symptoms (fever, cough, dyspnoea and fatigue), physical examination (high temperature, respiratory rate and low S_{pO_2}) and chest radiographic findings (GGO and alveolar consolidations) underlined the tropism of SARS-CoV-2 for the respiratory system [24]. Other symptoms such as musculoskeletal pain, taste and smell deficits, and headache may indicate enduring consequences of the acute effect of the virus on multiple organ systems [26] as well as nonspecific sequelae or functional disorders triggered by the infection or the hospitalisation [27]. High C-reactive protein and D-dimer without neutrophilia mirror the viral-driven systemic inflammatory state caused by SARS-CoV-2 [28].

Almost three-quarters of the patients had no or light comorbidity according to the CCI. Amongst those with underlying conditions, hypertension, diabetes mellitus, cardiovascular diseases, and solid and haematological neoplasms were the most frequent. According to their 4C mortality score, 39.9% of our patients were at high or very high risk of in-hospital mortality, reflecting the impact of COVID-19 infection on multiple organ systems [29]. In line with this, there was a relatively high admission rate to the ICU (28%), where 36% of the patients were intubated.

At the last follow-up visit, the patients' health status had improved significantly, and almost half had no residual symptoms, with a median number of 1 symptom (IQR 0–1)) compared to 4 (IQR 3–5)), initially. Dyspnoea and asthenia were the most prevalent but declined from 70.3% (97 of 138) to 29.8% (37 of 124) and from 65.2% (90 of 138) to 31.5% (39 of 124), respectively. Nearly 18% (22 of 124) complained of neuropsychological symptoms at this time. These results are comparable to previous reports that followed patients for 1 year or more [30]. However, the prevalence of persisting symptoms after COVID-19 varies across study reports, depending on the population profile, study design and investigators' perspective [31, 32]. Most authors have confirmed dyspnoea and fatigue as the most prevalent symptoms along with neurosensory and psychological symptoms [3, 30, 33].

In the 28 patients reassessed at 28 months, a greater need for oxygen therapy at baseline and a higher rate of transfer to the ICU indicate a more severe disease. Altogether, asthenia and dyspnoea were more prevalent than in the rest of our population, unlike neuropsychological symptoms, a fact consistent with the

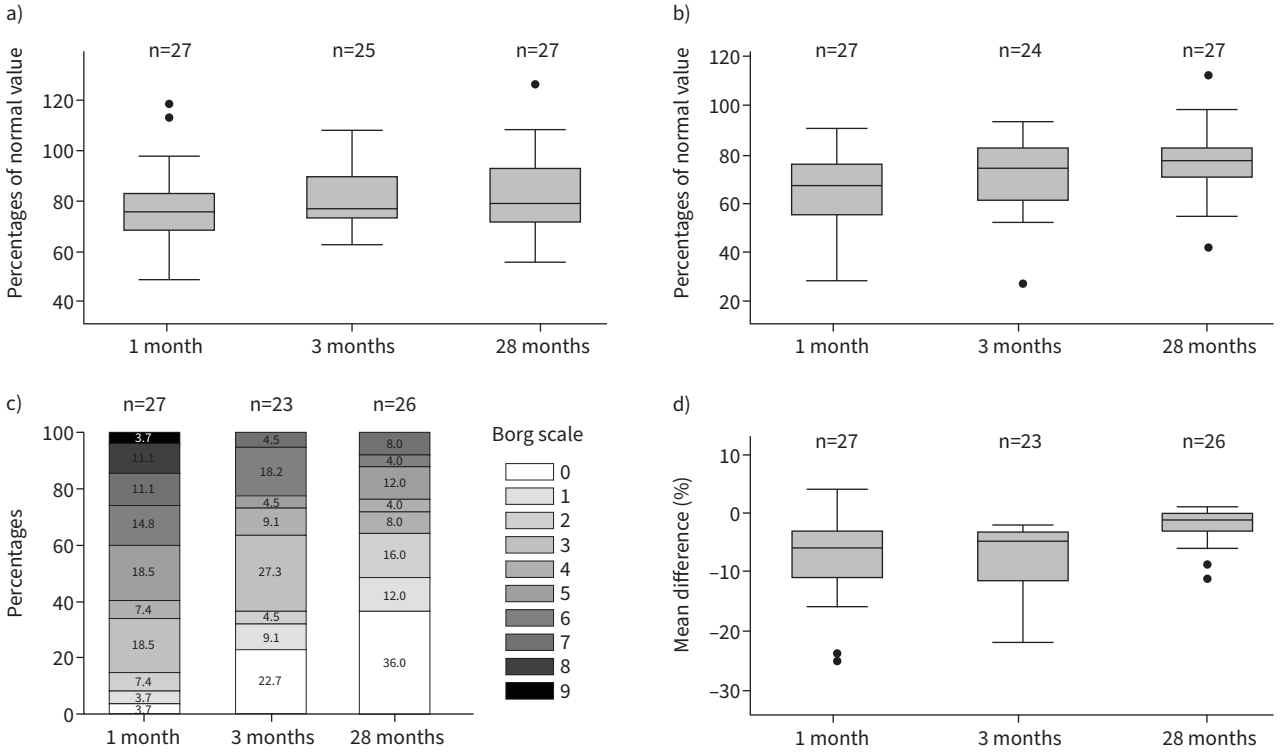

FIGURE 2 Changes in a) total lung capacity (TLC), b) diffusion capacity of the lung for carbon monoxide, c) post-6-min walk test (6MWT) 5-class Borg scale and d) differences in pulse oxygen saturation during the 6MWT (post-6MWT minus pre-6MWT pulse oximetry) in the 27 patients followed up at 1, 3 and 28 months. The causes of missing values are given in the footnote to table 1.

perceived need for in-person visits with chest specialists and performing PFT (table 1). Alveolar and capillary damage, fibrous proliferation of the alveolar septa and pulmonary consolidation adversely impact PFT findings [34]. Many reports show changes in D_{LCO} as the most frequent physiological consequence of severe COVID-19 along with underperformance in the 6MWT [33, 35]. Most of our patients had normal PFTs at 28 months, except for one patient with previous bronchopulmonary disease and one patient with abnormal chest radiographic findings suggesting a low-grade fibrotic process. Previous studies with shorter follow-up periods showed similar trends [8, 36, 37].

A previous study suggests that the use of glucocorticoids or immunomodulatory therapy may contribute to PFT improvement over time [38]. This did not concern the patients in our study since these treatment options were not available during the initial wave of COVID-19.

Interestingly, our study also reveals the dynamics of PFT recovery during the follow-up period. Overall, there was a progressive improvement of all clinical and functional abnormalities over 28 months, but TLC and the Borg scale improved mainly in the early phase, while O_2 desaturation improved between 3 and 28 months. In comparison, D_{LCO} improved progressively over 28 months. These dynamics most likely reflect various phases of pulmonary and cardiovascular healing. In the initial period following the acute episode, macroscopic pulmonary lesions (atelectasis, alveolar condensation, GGO, pleural effusions and musculoskeletal stiffness) resolved rapidly along with the diffusion capacity, which might correlate with the TLC parameter.

In contrast, post-exercise dyspnoea, as measured by the Borg scale, improved slowly. It is possible that O_2 desaturation during exercise might not improve because of underlying cardiovascular deconditioning [39, 40]. During the late phase, there was little improvement in the TLC, probably because histological repair of the alveolar septa and pulmonary microvascular system is still underway. D_{LCO}, a highly sensitive parameter, reflects both aspects, and its progressive improvement over the follow-up period may mirror macroscopic and microscopic healing over time [41]. In contrast, O_2 desaturation during exercise, combining pulmonary and cardiovascular capacities, improved in the early period, but there was no improvement in dyspnoea. Our analysis has limited power (27 patients), but we cannot exclude other

possible causes such as comorbid anxiety and depression, which predict lower dyspnoea recovery rate after COVID-19 [42, 43], functional dyspnoea [44] possibly due to conditioned breathlessness [45], and lethargy due to patients not having completely recovered their pre-COVID-19 state of health [33].

Our study has several limitations. First, our results could not be generalised due to the monocentre study design and the small sample size. In addition, only patients with severe COVID-19 were included so that conclusions may not apply to those experiencing persistent symptoms despite milder episodes. Second, all the patients were not systematically followed up because patient surveillance primarily relied on clinical symptoms, functional abnormalities and/or radiological sequelae. Third, during the first COVID-19 wave, vaccination programmes were not available and specific COVID-19 therapies including antivirals, immunomodulators or antithrombotic therapies were not proposed systematically or were not available. Fourth, we observed only one out of 14 patients initially intubated who presented fibrosis-like radiological patterns without functional limitations at 28-month follow-up. Therefore, we cannot draw significant conclusions from this unique patient. Similarly, as only two patients with newly diagnosed venous thromboembolism underwent PFTs at 28 months, we were unable to draw any conclusions regarding whether venous thromboembolism occurring during the course of COVID-19 has a negative long-term impact on PFTs.

Our study also has several strengths. Patients were evaluated at different time points until 28 months post-discharge, including clinical examination, PFTs based on GLI reference equations and chest CT assessment in patients with persistent symptoms. Additionally, we could explore the dynamics of PFTs recovery by comparing their evolution during the early and late phases of the follow-up.

Conclusion

Post-acute COVID-19 patients showed improvements in lung parameters and clinical assessments 28 months after hospital discharge. However, asthenia, dyspnoea and neuropsychological problems persisted. This highlights the need for multidisciplinary follow-up, through structured respiratory rehabilitation programmes, to address persistent issues such as dyspnoea.

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Ethics statement: This study was conducted in accordance with ethical guidelines. According to French regulations, we obtained non-opposition from all the patients. Patient confidentiality and privacy were strictly maintained throughout the research process.

Conflict of interest: None declared.

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