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Original article

Four- and sixteen-month clinical status of a cohort of patients following hospitalization for COVID-19

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ABSTRACT

Background and objectives: Although many symptoms of post-COVID syndrome have been described, a comprehensive evaluation of their prevalence is lacking. We aimed to describe symptoms at 16 months from hospitalization for COVID-19.

Methods: A telephone assessment was performed one year later in a cohort of COVID-19 survivors hospitalized between March and May 2020 and already evaluated four months after discharge. Patients with relevant symptoms at 16 months, patients who presented symptoms at four months, and all intensive care unit patients were invited for assessment at an outpatient facility. At telephone consultation, respiratory, cognitive, and functional symptoms were assessed. Patients underwent pulmonary function tests, lung CT scans, and psychometric and cognitive tests at the outpatient facility.

Abbreviations: BDI, Beck Depressive Inventory; COVID-19, coronavirus disease 2019; HADS, Hospital Anxiety and Depression Scale; HVPT, hyperventilation provocation test; ICU, intensive care unit; mMRC, modified Medical Research Council; MoCA, Montreal Cognitive Assessment; RT-PCR, reverse transcriptase–polymerase chain reaction; SARS-CoV-2, severe acute respiratory coronavirus 2

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Results: Among 478 patients evaluated four months after discharge, 317 (67 %) were assessed at telephone consultation and 124 at ambulatory assessment. At telephone assessment, ≥ 1 new symptom was reported by 216 patients (68 %), mainly fatigue (53 %), dyspnea (37 %), and memory difficulties (24 %). Seventy-nine patients (25 %) were asymptomatic at four months but declared ≥ 1 symptom one year later. In patients evaluated twice, the prevalence of cognitive impairment was 45 % at four months and 40 % at 16 months. Depression and post-traumatic symptoms prevalence remained stable, and the prevalence of anxiety significantly decreased. Dysfunctional breathing was detected in 32 % of patients. At 16 months after discharge, lung CT-scan exhibited abnormalities in 30/80 patients (38 %), compared to 52/85 patients (61 %) at four months.

Conclusion: At 16 months after hospitalization for COVID-19, 68 % of patients declared symptoms, including patients whose symptoms appeared between 4 and 16 months.

Trial registration: ClinicalTrials.gov, NCT04704388

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Background

The severe acute respiratory coronavirus 2 (SARS-CoV-2) affects many organs in the acute phase, [1] and may induce persistent symptoms in the medium term [2]. In the context of this "long Coronavirus disease 2019 (COVID-19)" or "post-COVID" syndrome, a multitude of symptoms has been described [3–5]. The nature and the incidence of such symptoms must be precisely described to define the care of the patients who suffer from them. The impact of these symptoms on health status and quality of life can be significant, and the fact that the virus has infected so many patients worldwide makes it a significant public health issue [6]. A survey in the United States estimated that 7 % of the total population had ever had long COVID symptoms [7].

The post-COVID-19 syndrome has been the subject of many clinical investigations [8–13]. However, only some have systematically and thoroughly evaluated all possible symptoms several months after the acute episode of COVID-19, including psychiatric questionnaires, cognitive tests, lung CT scans, and respiratory function tests [10,13]. Our group of investigators previously reported on a cohort of 478 patients who had survived hospitalization for COVID-19 between March and May 2020 [14]. Among those, 51 % presented at least one persistent symptom four months after the initial episode. This incidence is close to the result of another large cohort [15]. In the present study, we followed up on those patients 16 months after the initial SARS-CoV-2 infection with a novel systematic assessment.

Patients and methods

Population

The COMEBAC (*C*onsultation *M*ulti-*E*xpertise de *B*icêtre *A*près *C*ovid-19) is a one-center cohort of patients hospitalized for acute COVID-19 at Bicêtre Hospital from March 1 to May 29, 2020, and who survived. Patients provided written informed consent. The Ethics Committee of the French Intensive Care Society (CE20-56) approved the study.

Inclusion and exclusion criteria have been described previously [14]. Briefly, adult patients were included if they had been hospitalized for ≥ 24 h primarily because of COVID-19; had a SARS-CoV-2 infection diagnosed by reverse transcriptase–polymerase chain reaction (RT-PCR) and/or by typical lung CT-scan associated with clinical features; had survived four months following hospital discharge, or Intensive Care Unit (ICU) discharge for patients who had been admitted to an ICU. Patients were excluded if they had died within 16 months after discharge, were still hospitalized, had end-stage cancer or dementia, had nosocomial COVID-19, and had incidental positive SARS-CoV-2 RT-PCR during a hospital stay for a different medical indication. At 4 and 16 months after discharge, the following assessment was performed.

Telephone assessment

Patients were contacted by phone by a medical officer and administered a questionnaire that included general conditions and respiratory and cognitive symptoms (using the Q3PC questionnaire) [16] (see Online supplement). Four months after discharge, this assessment was offered to all eligible patients. At 16 months after discharge, it was provided to all patients who had already been evaluated at telephone consultation four months after discharge.

Ambulatory setting

Four months after hospital or ICU discharge, all symptomatic at telephone assessment (except those with isolated anosmia) and all ICU patients were invited to an ambulatory setting. At 16 months after discharge, all patients who declared symptoms at the telephone assessment performed then, and all patients invited to the ambulatory setting at four months, were invited. This included patients who had not declared symptoms during the telephone assessment at four months but declared some one year later. This also included patients who had been invited at four months but could not attend at this time. During this ambulatory evaluation, the following assessment was performed in an outpatient facility from July to September 2020 and May to September 2021.

General assessment

In addition to clinical examination, quality of life (36-item Short-Form Health Survey, SF-36 questionnaire) [17] and fatigue (Multidimensional Fatigue Inventory, MFI-20 scale) [18] were assessed (Supplementary Table 1).

Pulmonary assessment

Dyspnea was assessed by the modified Medical Research Council (mMRC) scale. A 6-minute walk test [19] and pulmonary function tests were performed (see Online supplement). Dysfunctional breathing was assessed with the Nijmegen questionnaire [20] and a hyperventilation provocation test (HVPT, see Online supplement). Two pulmonologists analyzed patients' medical records reporting new-onset or increased dyspnea to determine its cause, reaching a consensus in case of disagreement.

Lung CT scan

A high-resolution lung CT scan was performed in all patients (see Online supplement). Two readers (AA and OM) reviewed the CT scans, reaching a consensus regarding disagreements.

Cognitive and psychiatric assessment

All patients underwent cognitive tests, a questionnaire for psychiatric symptoms, and an interview with a neuropsychologist and a psychologist. The global cognitive capacity (Montreal Cognitive Assessment (MoCA) [21] adapted to age and education level [22]), attention (d2-R test [23]), and memory (McNair self-questionnaire [23]) were assessed. "Cognitive complaint" was defined by an impaired McNair score or reported cognitive symptoms. "Cognitive impairment" was defined by an impaired MoCA (<21 to <25 depending on educational level) or d2-R score (<76). Anxiety symptoms (anxiety subscale of the Hospital Anxiety and Depression Scale (HADS-A) >7 [24]), depression symptoms (13-item Beck Depressive Inventory (BDI) score [25] > 7) and post-traumatic symptoms (Post Traumatic Stress Disorder scale >30) were also assessed (supplementary table S1).

Statistical analysis

The REDCap electronic data capture tools [26,27] were used to record data. Data are presented as counts, percentages, means (standard deviation, SD), and medians [interquartile range, IQR]. The chi-square, Fisher exact, or McNemar tests for matched patients were used to compare proportions. Continuous variables were compared using the Student's *t*-test or Wilcoxon rank sum test, and the corresponding paired tests for matched patients. No assumptions were made for missing data. Analysis was performed using the R statistical package (version 4.0.0, R Foundation for Statistical Computing, Vienna, Austria).

Results

Patients

Among the 478 patients who had been evaluated four months after discharge, 317 (67%) were re-evaluated during a telephone consultation, including 209 of the 336 non-ICU patients (62%) and 108 of the 142 ICU patients (76%) (Fig. 1). Their characteristics during initial hospitalization are presented in Table 1. The majority were men. Fifty-eight (18%) had required invasive mechanical ventilation, and 51 (16%) high-flow oxygen through a nasal cannula. The characteristics of the patients who were not re-evaluated are presented in Table S2 and Table S3. The telephone and ambulatory assessments were performed 16 [15,16] and 16 [16,17] months after discharge.

Among the 317 patients evaluated at telephone consultation at 16 months, 124 (39%) were subsequently evaluated at the outpatient clinic. Of these, 86 had been assessed at the outpatient clinics four months post-discharge, and 38 had not (Fig. 1). The main reason patients eligible for the outpatient clinic assessment did not attend, was personal convenience.

Telephone assessment

At least one symptom that did not exist before COVID-19 was reported by 216 patients (68%). This included 137 patients (43%) in whom at least one symptom was present both at four and sixteen months after discharge, 73 patients (23%) who had no symptom, neither at four nor at 16 months, 28 patients (9%) who declared at least one symptom at four months but no more at 16 months, and 79 patients (25%) who were asymptomatic at four months but who declared at least one symptom one year later.

Among the 216 patients who declared symptoms at telephone assessment 16 months from discharge, symptoms triggered an evaluation at the outpatient facility in 165 patients (52%) (Fig. 1). Among the latter, 125 (76%) presented at least one symptom four months after discharge, while in 40 patients (24%), symptoms were absent four months after discharge and appeared between both assessments.

Fatigue was reported by 166 patients (53%) (Table 2, Figures S1 and S2), including 83 patients in whom it had appeared between 4 and 16 months after discharge (Figure S1). Dyspnea was described by 117 patients (37%) (Table 2), among which it was not reported at four months in 80 patients (Figure S1). Paresthesia and headache were reported by 54 (18%) and 53 (17%) patients, respectively (Table 2). Memory difficulties were reported by 75 patients (24%). Among 79 patients (25%) who reported no symptoms at four months but who reported symptoms at 16 months, 38 (48%), 28 (35%), and 11 (14%) reported fatigue, dyspnea, and memory difficulties, respectively.

Ambulatory assessment

General condition

Among the 124 patients who attended the outpatient facility, 72 (58%) presented at least one symptom. The weight variation, evaluated in 85 patients, from baseline to 16 months post-discharge was 0 [-3;4] kg, and 23 (27%) patients had lost more than 5% of their baseline weight (Table S4).

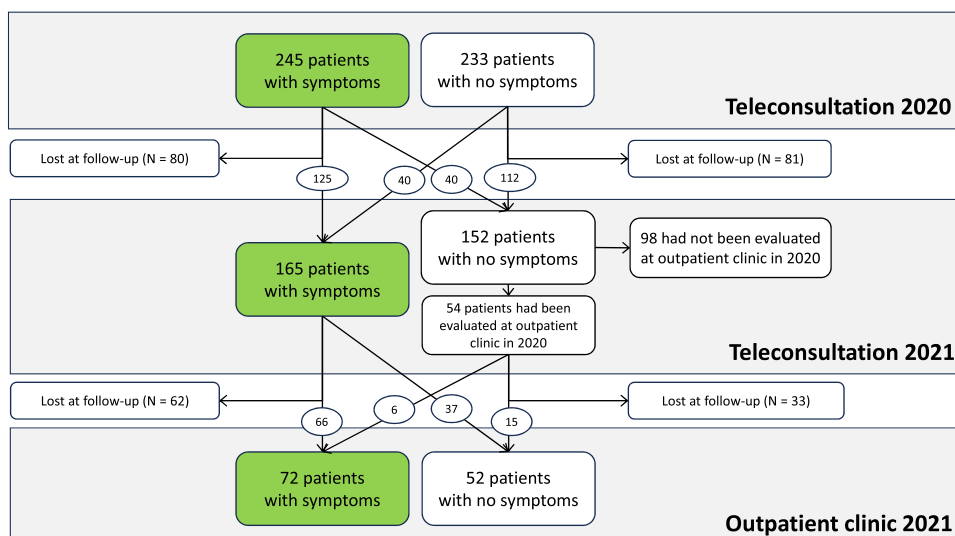


Fig. 1. Flow chart.

Table 1
Baseline and hospitalization characteristics of the patients who had the telephone assessment.

	All patients (n = 317)	No ambulatory visit (n = 193)	Attended the ambulatory visit (n = 124)	p-value	N
Age, years, mean (SD)	57.7 (14.3)	57.1 (15.5)	58.5 (12.2)	0.376	317
Women/men No. (%)	129 (40.7 %) / 188 (59.3 %)	76 (39.4 %) / 177 (60.6 %)	53 (42.7 %) / 71 (57.3 %)	0.633	317
Body mass index, mean (SD) [No.]	29.4 (5.8)	29.1 (6.1)	29.8 (5.5)	0.345	243
Comorbidities, No. (%)					
Hypertension	138 (43.5 %)	82 (42.5 %)	56 (45.2 %)	0.724	317
Obesity	100 (41.2 %)	53 (39.3 %)	47 (43.5 %)	0.590	243
Diabetes	83 (26.2 %)	54 (28.0 %)	29 (23.4 %)	0.437	317
Chronic heart disease	34 (10.7 %)	23 (11.9 %)	11 (8.87 %)	0.503	317
Respiratory disease (other than COPD)	50 (15.8 %)	28 (14.5 %)	22 (17.7 %)	0.540	317
Chronic kidney disease	28 (8.83 %)	20 (10.4 %)	8 (6.45 %)	0.320	317
Declared psychiatric disorder	16 (5.05 %)	11 (5.70 %)	5 (4.03 %)	0.690	317
Neurodegenerative disorder	3 (0.95 %)	3 (1.55 %)	0 (0.00 %)	0.283	317
Alcohol abuse	12 (3.97 %)	6 (3.26 %)	6 (5.08 %)	0.548	302
Active cancer	8 (2.52 %)	4 (2.07 %)	4 (3.23 %)	0.716	317
Other immunosuppression	13 (4.10 %)	9 (4.66 %)	4 (3.23 %)	0.734	317
COPD	7 (2.21 %)	6 (3.11 %)	1 (0.81 %)	0.253	317
Long-term dialysis	12 (3.79 %)	9 (4.66 %)	3 (2.42 %)	0.378	317
HIV infection	9 (2.84 %)	7 (3.63 %)	2 (1.61 %)	0.491	317
Solid organ transplantation	5 (1.58 %)	3 (1.55 %)	2 (1.61 %)	1.000	317
Liver disease	5 (1.58 %)	2 (1.04 %)	3 (2.42 %)	0.383	317
Pregnancy	4 (1.26 %)	2 (1.04 %)	2 (1.61 %)	0.646	317
Bone marrow transplantation	1 (0.32 %)	1 (0.52 %)	0 (0.00 %)	1.000	317
Smoking, No./total (%)				0.813	302
Active	22 (7.28 %)	12 (6.52 %)	10 (8.47 %)		
Former (≥5 pack-years)	50 (16.6 %)	31 (16.8 %)	19 (16.1 %)		
No (<5 pack-years)	230 (76.2 %)	141 (76.6 %)	89 (75.4 %)		
Specific treatments, No. (%)					
Azithromycin	89 (28.1 %)	56 (29.0 %)	33 (26.6 %)	0.736	317
Tocilizumab (anti-IL-6)	32 (10.1 %)	15 (7.77 %)	17 (13.7 %)	0.128	317
Hydroxychloroquine	24 (7.57 %)	13 (6.74 %)	11 (8.87 %)	0.629	317
Corticosteroids	20 (6.31 %)	13 (6.74 %)	7 (5.65 %)	0.878	317
Lopinavir/ritonavir	13 (4.10 %)	7 (3.63 %)	6 (4.84 %)	0.810	317
Remdesivir	5 (1.58 %)	3 (1.55 %)	2 (1.61 %)	1.000	317
Anakinra (anti-IL-1RA)	10 (3.15 %)	4 (2.07 %)	6 (4.84 %)	0.197	317
Vasopressors, No. (%)	55 (17.4 %)	30 (15.5 %)	25 (20.2 %)	0.364	317
Active anticoagulation (at full therapeutic dose), No. (%)	59 (18.6 %)	38 (19.7 %)	21 (16.9 %)	0.641	317
Acute kidney injury during hospitalization, No (%)	60 (20.8 %)	36 (20.9 %)	24 (20.7 %)	1.000	288
Pulmonary embolism during hospitalization, No. (%)	33 (11.4 %)	18 (10.2 %)	15 (13.4 %)	0.516	289
Hospitalization in ICU, No. (%)	108 (34.1 %)	60 (31.1 %)	48 (38.7 %)	0.202	317
Intubation in the ICU, No. (%)	58 (53.7 %)	29 (48.3 %)	29 (60.4 %)	0.290	108
High-Flow Humidified Oxygen, No. (%)	51 (47.2 %)	20 (42.6 %)	31 (50.8 %)	0.510	108
Duration of ICU stay, days median [Q1;Q3]	9.00 [4.00;20.0]	8.00 [4.00;16.0]	10.0 [4.00;22.2]	0.350	107
Total duration of hospitalization, days, median [Q1;Q3]	9.00 [4.00;16.0]	9.00 [4.00;14.0]	10.0 [5.00;18.5]	0.039	317

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

Table 2
Results of the telephone assessment performed at 4 and 16 months.

	At 4 months	n	At 16 months	n	p-value	New symptom at 16 months	n
Time from hospital discharge to telephone assessment, median (IQR), d [No.]	110 [93.0;127]	289	474 [454;498]	317			
Declared symptoms' No (%)							
Dyspnea	65 (20.5 %)	317	117 (37.3 %)	314	<0.001	80 (25.5 %)	314
Cough	17 (5.99 %)	284	35 (11.2 %)	312	0.0673	28 (10.0 %)	279
Chest Pain	31 (11.0 %)	282	36 (11.5 %)	313	1.00	18 (6.47 %)	278
Anorexia	21 (7.17 %)	293	13 (4.15 %)	313	0.170	9 (3.11 %)	289
Fatigue	95 (32.5 %)	292	166 (53.0 %)	313	<0.001	83 (28.8 %)	288
Anosmia	22 (7.75 %)	284	18 (5.75 %)	313	0.286	8 (2.86 %)	280
Headache	19 (6.71 %)	283	53 (17.0 %)	311	<0.001	38 (13.7 %)	277
Paresthesia	38 (13.4 %)	284	54 (17.6 %)	307	0.203	30 (10.9 %)	275
Cognitive testing (Q3PC questionnaire ^{a,b} , No (%))							
Memory difficulties	49 (17.3 %)	284	75 (24.0 %)	312	0.002	42 (15.1 %)	279
Mental slowness	28 (9.89 %)	283	31 (9.94 %)	312	1.00	20 (7.19 %)	278
Concentration problems	29 (10.3 %)	281	32 (10.3 %)	312	0.863	18 (6.52 %)	276
Any cognitive symptom	165 (52.1 %)	317	216 (68.1 %)	317	<0.001		

^a Signs were declared as newly-onset during, since or after hospitalization for COVID-19 and persistent at the time of telephone assessment.^b The range, direction and characteristics of the Q3PC questionnaire can be found in Supp Table 1.

Table 3
Results of the ambulatory visit performed at 16 months.

		N
Time from hospital discharge to ambulatory visit, days median [Q1;Q3]	492 [473;517]	124
SF-36 subscales		
Physical functioning	70.0 [55.0;85.0]	115
Role limitations due to physical health	25.0 [0.00;100]	115
Role limitations due to emotional problems	66.7 [0.00;100]	117
Energy/fatigue	50.0 [37.5;62.5]	118
Emotional well-being	75.0 [55.0;85.0]	120
Social functioning	75.0 [62.5;100]	115
Pain	70.5 [41.5;100]	124
General health	55.0 [40.0;70.0]	103
Respiratory assessment		
Dyspnea, No (%)	45 (36.3 %)	124
mMRC scale score for dyspnea, median [Q1;Q3]	1.00 [0.00;2.00]	45
Persistent cough, No (%)	13 (10.6 %)	123
6-minute walk test, min median [Q1;Q3]	508 [426;562]	124
Abnormal lung CT scan result, No (%)	50 (43.1 %)	116
Persistent ground-glass opacities, No (%)	34 (29.1 %)	117
Lung fibrotic lesions, No (%)	21 (17.6 %)	119
FEV1 (expressed as% of theory), median [Q1;Q3]	95.0 [85.6;106]	118
FEV1/FVC, median [Q1;Q3]	81.7 [77.7;85.5]	118
TLC (expressed as% of theory), median [Q1;Q3]	83.6 [78.4;94.8]	39
DLCO <70 %, No (%)	7 (17.5 %)	40
Hyperventilation syndrome, No (%)	33 (32.4 %)	102
Neurologic and psychological assessment ^a		
Symptoms of anxiety (HADS-Anxiety), No (%)	24 (19.4 %)	124
Symptoms of depression (BDI test), No (%)	24 (22.0 %)	109
Symptoms of PTSD (PCL-5 score), No (%)	14 (14.3 %)	98
Cognitive complaint (impaired McNair score, reported cognitive symptoms, or both), No (%)	73 (60.3 %)	121
Cognitive impairment (impairment of either MoCA or d2-R score), No (%)	54 (45.0 %)	120
Any neurologic or cognitive symptom, No (%)	72 (58.1 %)	124

CT: computed tomography, DLCO: diffusing capacity of the lungs for carbon monoxide, FEV1: forced expiratory volume in one second, FVC: forced vital capacity, PTSD: post-traumatic stress disorder, TLC: total lung capacity.

^a The range, direction and characteristics of the McNair, MoCA and d2R scores, of the HADS-Anxiety scale, of the BDI test, and of the ISI and PCL-5 scores can be found in Supp Table 1.

Results of the SF-36 score in the 124 patients who attended the outpatient facility at 16 months are presented in Table 3 and Figure S3. In the 77 patients who had already been assessed by this score at the outpatient facility in 2020, between 4 and 16 months after discharge, the SF36 median score had increased from 25.0 [25.0;50.0] to

50.0 [0.0;100.0] ($p = 0.02$) for the subscale "Role limited due to physical problems." The "Vitality" and "General Health" subscales remained unchanged (Table S4, Figure S4).

Cognitive and psychiatric assessment

Cognitive impairment was detected in 135 patients (52 %) at 16 months (Table 2). In patients evaluated at 4 and 16 months after discharge, cognitive impairment was present in 37 (45 %) at four months and 34 patients (40 %) at 16 months ($p = 0.83$), including ten patients with new onset impairment (Table S4, Fig. 2). Among intubated patients evaluated four and 16 months after discharge, the prevalence of cognitive impairment remained stable (55 % versus 48 %, respectively, $p = 0.522$).

At 16 months, anxiety, depression, and post-traumatic symptoms were observed in 24/124 (19 %), 24/109 (22 %), and 14/98 (14 %) patients, respectively (Table 3). In patients evaluated twice, at 16 months after discharge, the prevalence of anxiety symptoms decreased (36 % versus 21 %, $p = 0.0446$). It remained stable for depression (26 % versus 20 %, $p = 0.4533$) and post-traumatic stress symptoms (17 % versus 11 %, $p = 0.182$) (Table S4). In patients intubated at the initial phase, the prevalence of anxiety, depression, and post-traumatic stress symptoms at 16 months were 6/29 (21 %), 5/26 (19 %), and 3/24 (12 %), respectively (Table S5). In the patients who declared a symptom at teleconsultation at 16 months that did not exist at four months and who attended the ambulatory visit, anxiety, depression, and post-traumatic stress symptoms were detected in 5/20 (25 %), 5/15 (33 %), and 4/15 (27 %) patients, respectively.

Lung CT scan

At 16 months after discharge, lung CT scans exhibited abnormalities in 29/80 patients (36 %), while they were present in 52/85 patients (61 %) at four months ($p = 0.08$). No patient exhibited a new abnormal CT scan. Among the 84 patients evaluated twice, fibrotic lesions that had been detected in 20/84 patients (24 %) at four months were still present in 18/83 (22 %) one year later ($p = 0.80$) (Fig. 2, Figure S5). When present, fibrotic lesions involved <25 % of the parenchyma in all cases. These persisting fibrotic lesions were present in 10/26 patients (39 %) previously intubated. The other lesions observed at 16 months were ground glass opacities (Table 3).

Respiratory assessment

Among the 86 patients assessed at both times, dyspnea was present in 45/86 patients (52 %) at four months and 31/86 patients (36 %)

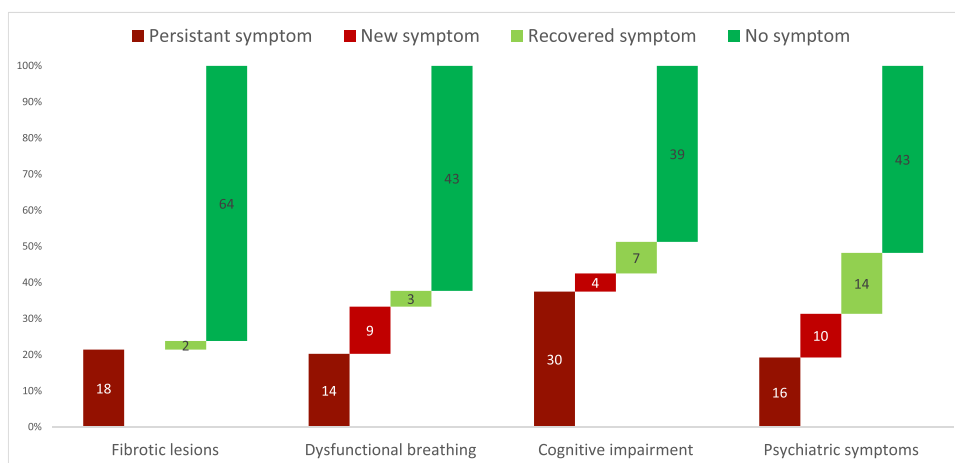


Fig. 2. The evolution of symptoms and findings that did not exist before COVID-19 infection in 86 patients who attended two outpatient clinic visits four months and 16 months after COVID-19 hospitalization.

Persistent symptom: symptom or finding found at 4- and 16-month outpatient clinics. New symptom: symptom or result found at 16 months that did not exist at 4-month evaluation. Recovered symptom: symptom or finding found at four months but absent at 16 months outpatient clinic. No symptom: symptom or finding absent at 4- and 16-month outpatient clinic.

at 16 months ($p = 0.02$) (Table 3), including 21 patients with persistent and 10 patients with new-onset dyspnea. Among the patients with persistent dyspnea, 6/21 (29 %) had been intubated. Persistent dyspnea was attributed to dysfunctional breathing in 18/21 cases (86 %), persistent lung lesions at CT-scan in 1/21 patients (5 %), and no specific cause was found in 2/21 cases (10 %).

Dysfunctional breathing was detected in 33/102 patients (32 %). Among patients evaluated both at 4 and 16 months, it was present in 23/69 patients (33 %) at 16 months and 14/69 patients (25 %) at four months ($p = 0.15$) (Fig. 2). Among patients evaluated twice at functional respiratory tests, a DLCO $<70\%$ was present at 16 months in 2/20 patients (10 %), while it had been measured in 7/20 patients (35 %) at four months ($p = 0.07$).

Discussion

This study, conducted on 317 patients who presented an episode of COVID-19 that required hospitalization from March to May 2020, showed that 68 % of patients had at least one symptom 16 months after the initial hospitalization, mainly fatigue and dyspnea. This prevalence was 51 % of patients at four months from discharge. At 16 months, 25 % of patients presented a symptom that did not exist four months after the initial episode. At the outpatient clinic at 16 months, the prevalence of cognitive impairment tended to decrease but was still 40 %. Within the group of patients who underwent both 4- and 16-month ambulatory evaluations, the prevalence of anxiety symptoms halved and reached 22 %; depression and post-traumatic stress symptoms were still found in 20 % and 11 % of the patients, respectively. Lung CT scan abnormalities were still present in 36 % of patients.

Among the studies that have reported post-COVID-19 symptoms at 12 months or more from discharge, few have documented the evolution of symptoms over time in large numbers [10-12,28-32]. Three of these studies have conducted a comprehensive clinical assessment [10,32]. We repeated the same evaluation one year after an initial assessment of COVID-19 patients Field [12]. In addition to the functional symptoms, as in other studies [8,9,11], we carried out a systematic, objective assessment, including psychometric tests, pulmonary function tests, and lung CT scans.

At 16 months from discharge, 68 % of patients still declared at least one symptom, a prevalence in the middle range of those reported at this term [9-13,28,30,33,34]. The most frequent symptom remained fatigue, reported by 53 % of patients. This symptom is the most common post-COVID-19 syndrome [4,35]. More than a third of patients still described dyspnea. An exciting data from our 4-month evaluation was the demonstration of dysfunctional breathing in almost a third of the dyspneic patients [14]. It was still present in a similar proportion of dyspneic patients a year later, as reported by other studies [36,37]. Functional respiratory complaints are frequently reported after COVID-19. The physiological responses to incremental cardiopulmonary exercise testing may help diagnosing dysfunctional breathing, deconditioning or cardio-vascular disease [38]. This diagnosis is essential as dysfunctional breathing may be accessible to some specific treatment [39].

The standardized assessment at the outpatient clinic confirmed that the reported prevalence of symptoms did not decrease significantly for many of them. The SF36 quality of life score improved significantly only for the "Role limited due to physical problems" subscale. Still, it remained impaired in its three components 16 months after the initial episode. At cognitive tests, cognitive impairment was observed in 40 % of the patients at 16 months, while they were present in 45 % of the patients one year earlier [14].

Among psychiatric symptoms, only anxiety symptoms decreased significantly between 4 and 16 months after discharge, while the prevalence of depressive symptoms remained unchanged.

Post-traumatic stress syndrome persisted in 11 % of patients, a proportion lower than a comparable study [40].

As observed by Huang et al. [10] and others [32,41], the lesions on the pulmonary CT scan performed at 16 months tended to decrease compared to 12 months earlier. In 39 % of patients previously intubated at the initial phase, CT lesions were found. The prevalence of fibrotic lesions roughly did not change, although parenchymal abnormalities may improve during the first 6 to 12 months following acute illness, including abnormalities associated with the fibrotic process [32]. It should be noted, however, that such lesions only concerned a minority of patients with an acute episode requiring hospitalization and never involved more than 25 % of the lung parenchyma.

Symptoms were most frequent in patients who had been intubated. Respiratory sequelae were also more frequent in these patients, as previously found [42]. The prevalence of fibrotic lesions on lung CT scans and abnormal respiratory function tests were higher. These data confirm that the prevalence of long COVID-19 symptoms is positively related to the severity of the disease, as shown, for example, by Huang et al. [10].

An interesting result might be that, at telephone assessment, 26 % of the patients reported a symptom at 16 months that they did not report at four months. These were fatigue, dyspnea, and memory problems. At the outpatient facility, tests evidenced mainly psychiatric symptoms and dysfunctional breathing. Huang et al. also found an increase in the prevalence of dyspnea and reported anxiety between 6 months and 12 months after the acute infection [10]. This declaration of subjective symptoms appearing between 4 and 16 months after hospitalization may find different explanations.

On the one hand, the resumption of professional and social life may have favored the appearance of symptoms that had been masked until then. On the other hand, the relief experienced by patients who had survived the acute episode, which was severe enough to require hospitalization, could have led to a minimization of symptoms at four months, which were revealed secondarily. Also, the long COVID-19 syndrome was relatively unknown to patients in the summer of 2020, when we conducted the first assessment. Patients could become aware of their symptoms by discovering that they were typically part of this syndrome. Finally, a delayed effect of SARS-CoV-2 infection cannot be ruled out, as autoimmune mechanisms have been suspected following the infection [43,44] as it may happen after other viral infections [45]. However, the absence of objective symptoms revealed by the tests carried out at the outpatient clinic does not support this hypothesis.

Our study has several limitations. First, several patients assessed at four months could not be reevaluated a year later. Second, this cohort only included patients hospitalized in the initial phase. Third, our study only looked at patients hospitalized during the first phase of the outbreak, while the alpha-one SARS-CoV-2 variant was the only one circulating; no vaccination nor specific treatments were available. Fourth, our study is limited by its monocentric nature; hence, the symptoms' prevalence probably depends on the selected population. Fifth, despite being a standardized assessment, most symptoms are reported as present or absent, leading to a missing granularity and lack of precision. Fifth, we did not assess whether patients experienced a new COVID-19 infection between the initial hospitalization and the reevaluation.

In conclusion, our study conducted 16 months after hospitalization for COVID-19 shows that, even if the prevalence of post-COVID-19 symptoms is decreasing, it remains high, particularly in patients who have stayed in critical care. Fatigue and psychiatric symptoms are the most prevalent. Pulmonary sequelae, particularly radiological, are minimal. Functional symptoms with no organic substrate appeared in some patients between the 4-month and 16-month evaluations.

Ethics approval and consent to participate

Patients provided written informed consent. The Ethics Committee of the French Intensive Care Society (CE20–56) approved the study.

Consent for publication

Not applicable.

Availability of data and materials

The datasets used and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' contributions

All the writing committee members collected the data, analyzed the data, and drafted the manuscript. All these members approved the final version of the manuscript.

Authors' information

None.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Xavier Monnet reports financial support was provided by Public Assistance Hospitals Paris. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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The authors would like the names of the individual members of the Group to be searchable through their PubMed records.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.resmer.2024.101099](https://doi.org/10.1016/j.resmer.2024.101099).

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