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Four-Month Clinical Status of a Cohort of Patients After Hospitalization for COVID-19

The Writing Committee for the COMEBAC Study Group

IMPORTANCE Little is known about long-term sequelae of COVID-19.

OBJECTIVE To describe the consequences at 4 months in patients hospitalized for COVID-19.

DESIGN, SETTING, AND PARTICIPANTS In a prospective uncontrolled cohort study, survivors of COVID-19 who had been hospitalized in a university hospital in France between March 1 and May 29, 2020, underwent a telephone assessment 4 months after discharge, between July 15 and September 18, 2020. Patients with relevant symptoms and all patients hospitalized in an intensive care unit (ICU) were invited for further assessment at an ambulatory care visit.

EXPOSURES Survival of hospitalization for COVID-19.

MAIN OUTCOMES AND MEASURES Respiratory, cognitive, and functional symptoms were assessed by telephone with the Q3PC cognitive screening questionnaire and a checklist of symptoms. At the ambulatory care visit, patients underwent pulmonary function tests, lung computed tomographic scan, psychometric and cognitive tests (including the 36-Item Short-Form Health Survey and 20-item Multidimensional Fatigue Inventory), and, for patients who had been hospitalized in the ICU or reported ongoing symptoms, echocardiography.

RESULTS Among 834 eligible patients, 478 were evaluated by telephone (mean age, 61 years [SD, 16 years]; 201 men, 277 women). During the telephone interview, 244 patients (51%) declared at least 1 symptom that did not exist before COVID-19: fatigue in 31%, cognitive symptoms in 21%, and new-onset dyspnea in 16%. There was further evaluation in 177 patients (37%), including 97 of 142 former ICU patients. The median 20-item Multidimensional Fatigue Inventory score (n = 130) was 4.5 (interquartile range, 3.0-5.0) for reduced motivation and 3.7 (interquartile range, 3.0-4.5) for mental fatigue (possible range, 1 [best] to 5 [worst]). The median 36-Item Short-Form Health Survey score (n = 145) was 25 (interquartile range, 25.0-75.0) for the subscale "role limited owing to physical problems" (possible range, 0 [best] to 100 [worst]). Computed tomographic lung-scan abnormalities were found in 108 of 171 patients (63%), mainly subtle ground-glass opacities. Fibrotic lesions were observed in 33 of 171 patients (19%), involving less than 25% of parenchyma in all but 1 patient. Fibrotic lesions were observed in 19 of 49 survivors (39%) with acute respiratory distress syndrome. Among 94 former ICU patients, anxiety, depression, and posttraumatic symptoms were observed in 23%, 18%, and 7%, respectively. The left ventricular ejection fraction was less than 50% in 8 of 83 ICU patients (10%). New-onset chronic kidney disease was observed in 2 ICU patients. Serology was positive in 172 of 177 outpatients (97%).

CONCLUSIONS AND RELEVANCE Four months after hospitalization for COVID-19, a cohort of patients frequently reported symptoms not previously present, and lung-scan abnormalities were common among those who were tested. These findings are limited by the absence of a control group and of pre-COVID assessments in this cohort. Further research is needed to understand longer-term outcomes and whether these findings reflect associations with the disease.

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The effects of COVID-19 are highly variable, ranging from individuals who are asymptomatic to patients who develop severe acute respiratory distress syndrome, with potential involvement of almost all organs and systems.[1] These acute symptoms have been well described since the first cohort studies that were published at the beginning of the pandemic.[2]

However, the possible long-term sequelae of COVID-19 have become an increasing concern. The inflammatory storm that characterizes severe forms of the disease suggests that serious tissue sequelae may affect various organ systems. Other coronaviruses have been shown to induce long-term effects, especially in the lungs.[3]

Although the long-term sequelae of individual organ damage have been reported,[3-9] there have been few comprehensive evaluations of long-term consequences of COVID-19.[10-12] In addition, most of the studies have included patients who actively decided to participate in follow-up.[10,12] The aim of the present study was to systematically assess, 4 months after discharge, the clinical status of survivors of COVID-19 disease requiring hospitalization.

Methods

Population

Patients provided written informed consent. The Ethics Committee of the French Intensive Care Society (CE20-56) approved the study. The COMEBAC (Consultation Multi-Expertise de Bicêtre Après COVID-19) uncontrolled cohort study included adult patients admitted to the Bicêtre Hospital (Paris-Saclay University hospitals) in France for COVID-19 from March 1 to May 29, 2020. Inclusion criteria were survival 4 months after hospital discharge or after intensive care unit (ICU) discharge for patients who had been admitted to an ICU (referred to as "ICU patients" hereafter), who were older than 18 years, who had been hospitalized for greater than 24 hours primarily because of COVID-19, and who had received a diagnosis of SARS-CoV-2 infection by reverse transcriptase–polymerase chain reaction (RT-PCR) , by typical computed tomographic (CT) lung scan associated with clinical features, or both.

Exclusion criteria were death within 4 months after discharge, persistent hospitalization, end-stage cancer, dementia, nosocomial COVID-19 infection, and incidental positive SARS-CoV-2 RT-PCR result during a hospital stay for a different medical indication. Medical charts of patients were reviewed to establish that patients met the eligibility criteria.

Description of the Study Hospital

The Bicêtre Hospital is one of the university hospitals in the Paris region (Assistance Publique-Hôpitaux de Paris). It has 907 beds, including 53 in adult ICUs, 30 in adult intermediate severity units, 8 in a pediatric ICU, and 12 in a pediatric intermediate-severity unit. In 2019, 18 678 adult patients were admitted to the hospital. At the peak of the first wave of COVID-19, from March to May 2020, the total number of ICU beds with mechanical ventilation capacity was increased to 101 from 53,

with adult patients undergoing invasive ventilation in the adult and pediatric ICUs and intermediate-severity units, the operating rooms, and the recovery room. High-flow nasal canula and noninvasive and invasive mechanical ventilation were used only in these areas.

Initial Hospitalization

Patient medical history, illness evolution, and treatment during hospitalization were retrospectively collected from medical records. Kidney failure was diagnosed according to the KDIGO criteria.[13]

Telephone Assessment

Three to 4 months after hospital or ICU discharge, patients were contacted by telephone by a medical officer and administered a questionnaire that included general condition and respiratory, cognitive, and neurologic symptoms (with the Q3PC cognitive screening questionnaire).[14] The questionnaire and the list of symptoms in question are shown in the Supplement. Patients were asked whether symptoms existed before they developed COVID-19. All symptoms were listed, without any interpretation. No psychological evaluation was performed.

In addition, patients with no history of chronic kidney disease and with high plasma creatinine levels (>1.47 mg/dL [130 µmol/L]) or estimated glomerular filtration rate less than 60 mL/min/1.73 m^2 at hospital discharge were requested to have their serum creatinine levels reassessed. Patients were asked whether a lung CT scan had been performed after hospitalization, and if so, the lung CT scan was reviewed.

All ICU patients and those who were symptomatic were invited for further evaluation in the ambulatory setting. Symptomatic patients were defined as those reporting symptoms at the telephone interview (except for anosmia), all patients who had persistent creatinine-level elevation, and all those who had persistent abnormalities on a lung CT scan conducted after hospitalization (including any residual ground-glass opacities, bronchial or bronchioloalveolar abnormalities, lung condensations, or interstitial thickening).

Key Points

Question What are the clinical outcomes after hospitalization for COVID-19?

Findings Four months after hospitalization, in an uncontrolled cohort study of 478 survivors of COVID-19, at least 1 new-onset symptom was reported by telephone interview by 244 patients (51%), including fatigue in 134 of 431 (31%), cognitive symptoms in 86 of 416 (21%), and dyspnea in 78 of 478 (16%). Computed tomographic lung scan abnormalities were reported in 63% of 171 patients assessed at an ambulatory visit, mainly subtle ground-glass opacities. Fibrotic lesions were observed in 19% of these 171 patients.

Meaning This study provides clinical status of a cohort of patients 4 months after hospitalization for COVID-19, but further research is needed to understand longer-term outcomes.

Ambulatory Setting

The following assessments were performed in the outpatient facility between July 15 and September 18, 2020.

General Assessment

In addition to receiving a general clinical examination and a having a blood sample taken, patients were evaluated for their quality of life (36-Item Short-Form Health Survey questionnaire)[15] and fatigue (Multidimensional Fatigue Inventory scale)[16] (eTable 1 in the Supplement). The 36-Item Short-Form Health Survey questionnaire evaluates 8 domains: physical functioning, role limitations owing to physical health, role limitations owing to emotional problems, energy/fatigue, emotional well-being, social functioning, pain, and general health. Each sub-scale ranges from 0 to 100, corresponding to the worst and best health state, respectively. The 20-item Multidimensional Fatigue Inventory questionnaire evaluates 4 domains: general fatigue, reduced activity, motivation, and mental fatigue. Each sub-scale ranges from 1 to 5, corresponding to the best and worst feeling owing to fatigue for each domain, respectively.[16]

Respiratory Assessment

In addition to its evaluation at the telephone interview, dyspnea was assessed by the modified Medical Research Council scale. A 6-minute walk test was performed according to current recommendations.[17] Patients completed pulmonary function tests (see the Supplement). Dysfunctional breathing was assessed with the Nijmegen questionnaire[18] (eTable 1 in the Supplement) and a hyperventilation provocation test. Medical records of patients reporting new-onset or increased dyspnea compared with before COVID-19 infection were analyzed by 2 pulmonologists to determine its cause, who reached consensus in case of disagreement.

Lung CT Scan

A high-resolution lung CT scan was performed for all patients (Supplement). Two readers, blinded to clinical evaluation, reviewed the CT scans, reaching consensus regarding any disagreements.

Cardiac Assessment

All ICU patients, those with pulmonary embolism during hospitalization, and those with cardiac symptoms on examination at the outpatient clinic were evaluated with transthoracic echocardiography.

Psychological and Cognitive Assessment

All patients underwent psychometric tests, an interview with a neuropsychologist, and an interview with a psychologist. Global cognitive assessment was performed with the Montreal Cognitive Assessment[19] adapted to age and education level[20] (eTable 1 in the Supplement). Attention was assessed through the d2-R test.[21] Memory complaint was assessed through the McNair self-questionnaire.[21] "Cognitive complaint" was defined by an impaired McNair score, reported cognitive symptoms, or both. "Cognitive impairment" was defined by an impaired Montreal Cognitive Assessment or d2-R score.

Anxiety symptoms were evaluated with the anxiety subscale of the Hospital Anxiety and Depression Scale,[22] depression symptoms with the 13-item Beck Depression Inventory score,[23] insomnia with the Insomnia Severity Index, and posttraumatic symptoms with the Posttraumatic Stress Disorder Checklist (PCL-5 scale)[24] (eTable 1 in the Supplement).

Serologic Tests

In all outpatients, anti–SARS-CoV-2 total immunoglobulin level (Elecsys; Roche Diagnostic) and IgM and IgG levels (NG-Biotech) were assessed.[25]

Statistical Analysis

Study data were collected and managed with Research Electronic Data Capture tools hosted at Assistance Publique-Hôpitaux de Paris.[26,27] Data are presented as counts and percentages, means (SD), and medians (interquartile range [IQR]). All participants for whom the variables of interest were available were included in the final analysis and no assumptions were made for missing data. Because of the importance of understanding the effect of intubation on patient outcomes, the outcomes have been categorized as nonintubated vs intubated. Analysis was performed with the R statistical package version 4.0.0 (R Foundation for Statistical Computing).
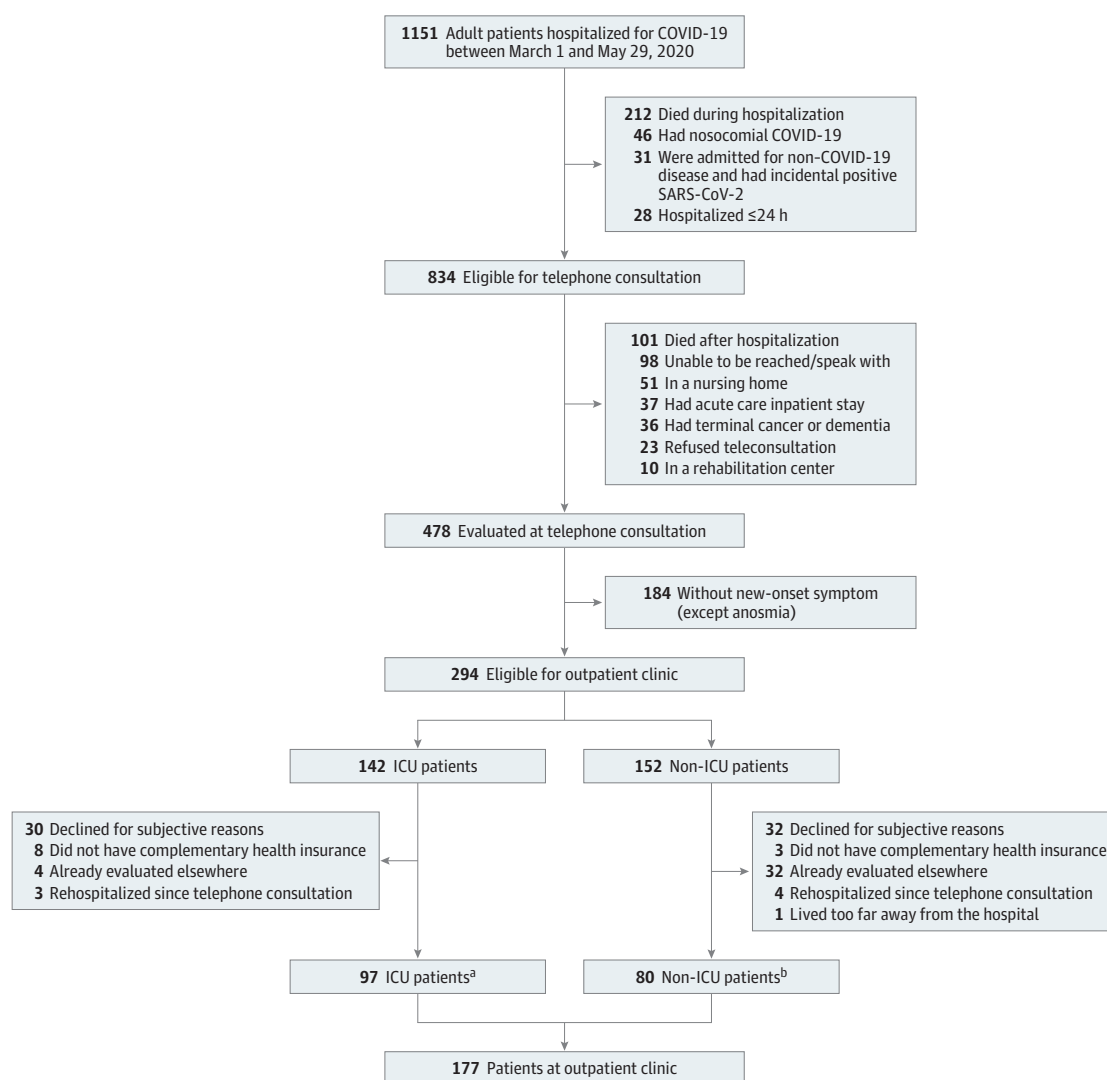
Results

Patients

Among the 1151 adult patients hospitalized in the Bicêtre Hospital because of COVID-19 from March 1 to May 29, 2020, 834 were eligible for telephone assessment and 478 (57%) consented, including 142 of 172 ICU patients and 336 of 662 non-ICU patients (**Figure 1**). The characteristics of the 673 patients who did not participate in the study are shown in eTable 2 in the Supplement. The patients who did not consent were similar to those who did.

COVID-19 had been diagnosed with RT-PCR in 415 patients (86.8%) and by an association of typical clinical signs and CT-scan lung images in 63 patients (13.2%). Of 294 patients who were eligible for an ambulatory assessment (n = 135 ICU patients and 159 non-ICU patients), 177 consented (n = 97 ICU patients and 80 non-ICU patients). The median time to telephone assessment was 113 days after hospital discharge (IQR, 94-128 days) and the median time of the ambulatory assessment was 125 days after discharge (IQR, 107-144 days). The mean age of the 478 patients was 60.9 years (SD, 16 years) and 57.9% were men. The patients who attended the ambulatory visit were younger (mean age, 56.9 years) and generally had more comorbid conditions. The 2 most common treatments for all patients were azithromycin and tocilizumab (**Table 1**). Of the 142 patients in the ICU, 73 had been intubated (Table 1). Comparisons of the characteristics of patients who attended vs did not attend the ambulatory facility, of those who visited the outpatient facility for neurocognitive vs respiratory symptoms, and by younger and older than 75 years are shown in eTables 3, 4, and 5 in the Supplement, respectively.

Figure 1. Flow of Patient Screening and Enrollment

1151 Adult patients hospitalized for COVID-19 between March 1 and May 29, 2020

- **212** Died during hospitalization
- **46** Had nosocomial COVID-19
- **31** Were admitted for non-COVID-19 disease and had incidental positive SARS-CoV-2
- **28** Hospitalized ≤24 h

834 Eligible for telephone consultation

- **101** Died after hospitalization
- **98** Unable to be reached/speak with
- **51** In a nursing home
- **37** Had acute care inpatient stay
- **36** Had terminal cancer or dementia
- **23** Refused teleconsultation
- **10** In a rehabilitation center

478 Evaluated at telephone consultation

- **184** Without new-onset symptom (except anosmia)

294 Eligible for outpatient clinic

142 ICU patients | **152** Non-ICU patients

- **30** Declined for subjective reasons
- **8** Did not have complementary health insurance
- **4** Already evaluated elsewhere
- **3** Rehospitalized since telephone consultation

- **32** Declined for subjective reasons
- **3** Did not have complementary health insurance
- **32** Already evaluated elsewhere
- **4** Rehospitalized since telephone consultation
- **1** Lived too far away from the hospital

97 ICU patients[a] | **80** Non-ICU patients[b]

177 Patients at outpatient clinic

[a] Including 51 of 97 patients (53%) with invasive mechanical ventilation, 51 (53%) receiving vasopressors, and 8 (8%) with extracorporeal membrane oxygenation.

[b] Including 44 of 80 patients (55%) with persistent neurologic symptoms, 27 (34%) with persistent respiratory symptoms, 5 (6%) with abnormal computed tomographic scan results, and 2 (3%) with persistent kidney failure.

Telephone Assessment

Of the 478 patients, 244 (51%) reported at least 1 symptom that did not exist before COVID-19 infection (eFigure 1 in the Supplement; **Table 2**), including fatigue, 31.1% (134 of 431); memory difficulties, 17.5% (73 of 416); dyspnea, 16.3% (78 of 478); and persistent paresthesia, 12.1% (51 of 421).

Eighty-six of 416 patients (20.7%) reported at least 1 cognitive symptom. Memory difficulties, mental slowness, and concentration problems more than once a week were reported by 73 of 416 patients (17.5%), 42 of 415 (10.1%), and 41 of 412 (10%), respectively (Table 2; eFigure 1 in the Supplement).

The results of the telephone assessment according to age and to the reported symptoms are shown in eTables 5 and 6 in the Supplement, respectively.

Ambulatory Assessment

General Condition

The results of the ambulatory assessment according to the symptoms that triggered the visit to this facility are provided in eTable 7 in the Supplement. The median 36-Item Short-Form Health Survey score, evaluated in 130 patients, was 25 (IQR, 25.0-75.0) for the subscale "role limited owing to physical problems," 46.9 (IQR, 31.2-68.8) for "vitality," and 57.5 (IQR, 40.0-75.0) for "general health" (potential best score, 100; worst score, 0). The median score for the 20-item Multidimensional Fatigue Inventory questionnaire, evaluated in 145 patients, was 4.5 (IQR, 3.0-5.0) for reduced motivation and 3.7 (IQR, 3.0-4.5) for mental fatigue (potential best score, 1; worst score, 5) (eFigure 2 in the Supplement).

Table 1. Baseline and Hospitalization Characteristics of the Patients With Telephone Assessment

	No./total (%)		
	All patients (n = 478)	No ambulatory visit (n = 301)	Attended the ambulatory visit (n = 177)
Age, mean (SD), y	60.9 (16.1)	63.4 (17.2)	56.9 (13.2)
Women	201 (42.1)	133 (44.2)	68 (38.4)
Men	277 (57.9)	168 (55.8)	109 (61.6)
Body mass index, mean (SD) [No.]	28.8 (5.6) [351]	28.5 (5.9) [186]	29.1 (5.4) [165]
Comorbidities			
Hypertension	225 (47.1)	150 (49.8)	75 (42.4)
Obesity	130/351 (37.0)	63/186 (33.9)	67/165 (40.6)
Diabetes	128 (26.8)	76 (25.2)	52 (29.4)
Chronic heart disease	77 (16.1)	63 (20.9)	14 (7.9)
Respiratory disease (other than COPD)	75 (15.7)	45 (15.0)	30 (16.9)
Chronic kidney disease	51 (10.7)	34 (11.3)	17 (9.6)
Declared psychiatric disorder	42 (8.8)	30 (10.0)	12 (6.8)
Neurodegenerative disorder	34 (7.1)	32 (10.6)	2 (1.1)
Alcohol misuse	21/450 (4.7)	12/282 (4.3)	9/168 (5.4)
Active cancer	18 (3.8)	15 (5.0)	3 (1.7)
Other immunosuppression	18 (3.8)	11 (3.7)	7 (4.0)
COPD	17 (3.6)	12 (4.0)	5 (2.8)
Long-term dialysis	17 (3.6)	11 (3.7)	6 (3.4)
HIV infection	12 (2.5)	9 (3.0)	3 (1.7)
Solid organ transplantation	9 (1.9)	5 (1.7)	4 (2.3)
Liver disease	7 (1.5)	2 (0.7)	5 (2.8)
Pregnancy	5 (1.0)	3 (1.0)	2 (1.1)
Bone marrow transplantation	2 (0.4)	2 (0.7)	0
Smoking			
No (<5 pack-years)	343/452 (75.9)	214/283 (75.6)	129/169 (76.3)
Former (≥5 pack-years)	83/452 (18.4)	58/283 (20.5)	25/169 (14.8)
Active	26/452 (5.8)	11/283 (3.9)	15/169 (8.9)
Specific treatments			
Azithromycin	120 (25.1)	67 (22.3)	53 (29.9)
Tocilizumab (anti-IL-6)	37 (7.7)	10 (3.3)	27 (15.3)
Hydroxychloroquine	32 (6.7)	14 (4.7)	18 (10.2)
Corticosteroids	24 (5.0)	17 (5.6)	7 (4.0)
Lopinavir/ritonavir	16 (3.3)	8 (2.7)	8 (4.5)
Anakinra (anti-IL-1RA)	11 (2.3)	3 (1.0)	8 (4.5)
Remdesivir	5 (1.0)	2 (0.7)	3 (1.7)
Vasopressors	74 (15.5)	23 (7.6)	51 (28.8)
Active anticoagulation (at full therapeutic dose)	75 (15.7)	26 (8.6)	49 (27.7)
Pulmonary embolism during hospitalization	41 (8.6)	12 (4.0)	29 (16.4)
Acute kidney injury during hospitalization	95 (19.9)	53 (17.6)	42 (23.7)
Hospitalization in ICU	142 (29.7)	45 (15.0)	97 (54.8)
Duration of ICU stay, median (IQR), d	9 (4-19)	6.5 (4-15)	9 (4-22)
Total duration of hospitalization, median (IQR), d	9 (4-15)	8 (4-12)	13 (6-23)

Abbreviations: COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; IQR, interquartile range.

Psychological and Neurologic Assessment

Cognitive impairment was confirmed in 38.4% of patients (61/159) (Table 3, Figure 2), more commonly in patients aged 75 years or older (eTable 5 in the Supplement). In ICU patients, anxiety, depression, and significant posttraumatic symptoms were observed in 22 of 94 (23.4%), 17 of 94 (18.1%), and 7 of 94 (7.4%), respectively.

Muscular weakness compatible with ICU-related neuromyopathy was identified in 14 of 51 patients (27.5%) who had been intubated.

Table 2. Results of the Telephone Assessment in Nonintubated and Intubated Patients

	No./total (%)		
	All patients (n = 478)	Nonintubated (n = 405)	Intubated (n = 73)
Time from hospital discharge to telephone assessment, median (IQR), d [No.]	113 (94-128) [442]	121 (104-131) [375]	93 (77-110) [67]
Declared symptoms[a]			
Dyspnea	78 (16.3)	53 (13.1)	25 (34.2)
Cough	21/420 (5)	16/358 (4.5)	5/62 (8.1)
Chest discomfort/pain	34/418 (8.1)	25/356 (7)	9/62 (14.5)
Fatigue	134/431 (31.1)	110/368 (29.9)	24/63 (38.1)
Anorexia	34/436 (7.8)	25/370 (6.7)	9/66 (13.6)
Weight loss >5% baseline weight	31/342 (9.1)	30/281 (10.7)	1/61 (1.6)
Anosmia	25/419 (6.0)	19/357 (5.3)	6/62 (9.7)
Headaches	23/420 (5.5)	22/358 (6.2)	1/62 (1.6)
Paresthesia	51/421 (12.1)	40/359 (11.1)	11/62 (17.7)
Cognitive testing (Q3PC questionnaire)[a,b]			
Memory difficulties	73/416 (17.5)	63/354 (17.8)	10/62 (16.1)
Mental slowness	42/415 (10.1)	38/353 (10.8)	4/62 (6.5)
Concentration problems	41/412 (10.0)	35/351 (10.0)	6/61 (9.8)

Abbreviation: IQR, interquartile range.

[a] Signs were declared as new onset during or after hospitalization for COVID-19 and persistent at the telephone assessment.

[b] The range, direction, and characteristics of the Q3PC cognitive screening questionnaire are shown in eTable 1 in the Supplement.

Table 3. Results of the In-Person Outpatient Clinic Visit in Nonintubated and Intubated Patients

	No./total (%)		
	All patients (n = 177)	Nonintubated (n = 126)	Intubated (n = 51)
Time from hospital discharge to outpatient clinic, median (IQR), d [No.]	125 (107-144) [157]	134 (116-150) [107]	105 (90.2-119) [50]
Respiratory assessment			
mMRC scale score for dyspnea, median (IQR) [No.][a]	1 (1-2) [115]	1 (1-2) [80]	1 (0.5-2) [35]
Persistent cough	23/172 (13.4)	19/123 (15.4)	4/49 (8.2)
6-Minute walk test, median (IQR), m [No.]	462 (380-507) [161]	464 (382-502) [112]	462 (380-523) [49]
Abnormal lung CT scan result	108/171 (63.2)	71/122 (58.2)	37/49 (75.5)
Persistent ground-glass opacities	72/170 (42.4)	45/121 (37.2)	27/49 (55.1)
Lung fibrotic lesions	33/170 (19.4)	15/121 (12.4)	18/49 (36.7)
FEV$_1$ (expressed as % of theory), median (IQR) [No.]	92 (80-102) [157]	92 (79-103) [108]	90 (80-102) [49]
FEV$_1$/FVC, median (IQR) [No.]	83 (79-87) [157]	81 (78-86) [108]	84 (82-87) [49]
TLC (expressed as % of theory) [No.]	83 (15) [149]	86 (15) [104]	76 (14) [45]
DLCO <70%	33/152 (21.7)	16/105 (15.2)	17/47 (36.2)
Echocardiography assessment			
RV dilatation on echocardiography	20/79 (25.3)	11/35 (31.4)	9/44 (20.5)
LVEF 40%-50% on echocardiography[b]	10/83 (12.0)	2/38 (5.3)	8/45 (17.8)
Neurologic and psychological assessment[a,c]			
Cognitive complaint (impaired McNair score, reported cognitive symptoms, or both)	79/159 (49.7)	55/109 (50.5)	24/50 (48.0)
Cognitive impairment (impairment of either MoCA or d2-R score)	61/159 (38.4)	40/109 (36.7)	21/50 (42.0)
Symptoms of anxiety (HADS-Anxiety)	53/169 (31.4)	40/119 (33.6)	13/50 (26.0)
Symptoms of depression (BDI test)	35/170 (20.6)	26/120 (21.7)	9/50 (18.0)
Insomnia (ISI score)	90/168 (53.6)	68/118 (57.6)	22/50 (44.0)
Symptoms of PTSD (PCL-5 score)	24/169 (14.2)	19/119 (16.0)	5/50 (10.0)

Abbreviations: BDI, Beck Depression Inventory; CT, computed tomography; DLCO, diffusing capacity of the lungs for carbon monoxide; FEV$_1$, forced expiratory volume in the first second of expiration; FVC, forced vital capacity; HADS-Anxiety, anxiety subscale of the Hospital Anxiety and Depression Scale; IQR, interquartile range; ISI, Insomnia Severity Index; LVEF, left ventricular ejection fraction; mMRC, modified Medical Research Council; MoCA, Montreal Cognitive Assessment; PTSD, posttraumatic stress disorder; RV, right ventricular; TLC, total lung capacity.

[a] Signs were declared as new onset during or after hospitalization for COVID-19 and persistent at the assessment at the outpatient facility.

[b] No patient had an LVEF less than 40%.

[c] The range, direction, and characteristics of the McNair, MoCA, and d2-R scores; of the anxiety subscale score of the HADS; of the BDI test results; and of the ISI and PCL-5 scores are shown in eTable 1 in the Supplement.

Lung CT Scan

Lung CT scan was performed for 171 patients and showed abnormalities in 37 of 49 intubated individuals (75.5%) and 71 of 122 nonintubated ones (58.2%). Abnormalities were most commonly ground-glass opacities (Table 3). Fibrotic lesions were observed in 19.3% of patients (33/171), with subpleural predominance in 30 of 33 individuals (90.9%). Fibrotic lesions affected 4 lobes (IQR, 3-5) and involved less than 25% of lung parenchyma in all but 1 case. In the 49 patients who had received a diagnosis of acute respiratory distress syndrome, fibrotic lesions and reticulations were observed in 38.8% (19/49) and 69.4% (34/49), respectively.

Respiratory Assessment

The Nijmegen score was greater than 22 in 37 of 177 cases (20.9%), indicating dysfunctional breathing. This was confirmed by a positive hyperventilation provocation test result in 21 of 177 patients (11.9%) (Table 3), of whom 4 had a history of asthma, with normal pulmonary function test results and satisfactory control of asthma at the assessment. No fibrotic lesions were reported in these patients with confirmed dysfunctional breathing.

Among the 78 patients attending the ambulatory facility who reported new-onset dyspnea, a cause was identified in 61 cases (78.2%). Dyspnea was attributed to abnormalities on lung CT scan in 44 of 78 patients (56.4%), including fibrotic lesions in 18 of 78 cases (23.1%), and to hyperventilation provocation test-confirmed dysfunctional breathing in 14 of 78 patients (17.9%). Dyspnea was potentially explained by underlying chronic lung diseases in 7 patients (4 with uncontrolled asthma; 2, chronic obstructive pulmonary disease; and 1, obstructive sleep apnea), by left ventricular dysfunction in 3 patients, and by physical deconditioning in 2 patients.

The mean diffusing capacity of the lungs for carbon monoxide was 87% of the predicted value (SD, 23%) in 152 patients. It was 77% (SD, 17%) in the 49 patients with previous acute respiratory distress syndrome. Twenty-three of 33 patients (69.7%) with diffusing capacity of the lungs for carbon monoxide less than 70% had persistent lung CT-scan abnormalities, including 12 of 33 patients (36.4%) with fibrotic lesions.

Cardiovascular Assessment

Echocardiography identified a left ventricular ejection fraction less than 50% in 8 of 83 patients (9.6%), with no value less than 40% (Table 3). All patients with left ventricular ejection fraction less than 50% had been ICU patients. Left ventricular dilatation was identified in only 1 patient, in whom it preexisted.

Kidney Assessment

Among the 95 of 478 patients (19.9%) who had experienced acute kidney injury during hospitalization, 2 displayed a persistent alteration of kidney function at 4 months. Both had required ICU care.

Anti–SARS-CoV-2 Serology

A positive serology result was obtained for 172 of 177 patients (97.2%). Three of these 172 patients never had a positive RT-PCR

Figure 2. Visualization of Symptoms and Findings That Did Not Exist Before COVID-19 Infection in 177 Patients at the Outpatient Clinic, 4 Months After COVID-19 Hospitalization

Cognitive impairment (n = 61)
Dysfunctional breathing (n = 21)
Fibrotic lesions (n = 33)
Psychiatric symptoms (n = 63)
No symptoms reported (n = 60)
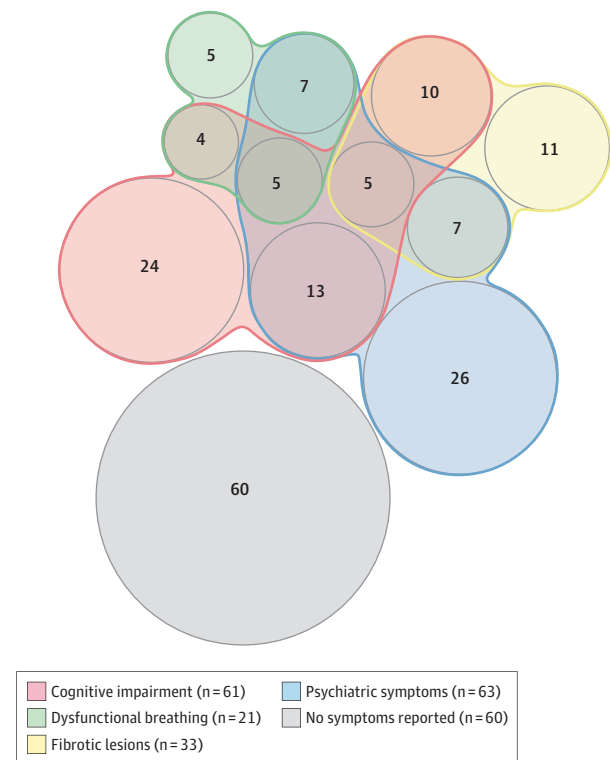
Numbers represent patients with the symptoms/findings or association of symptoms; 60 patients did not report these symptoms or have these findings. Patients could have more than 1; hence, the sum of the groups exceeds 177.

result for SARS-CoV-2 and had received a diagnosis of COVID-19 according to clinical and lung CT-scan findings. The serologic index (ie, serologic titer of total Ig) was similar between ICU and non-ICU patients and lower in immunocompromised ones (eFigure 3 in the Supplement).

Discussion

In a cohort study of 478 patients who were evaluated 4 months after hospitalization for COVID-19, 51% reported at least 1 symptom that did not exist before the disease. The most common symptoms were fatigue, cognitive problems, and new-onset dyspnea. Among patients who returned for further evaluation, CT scan frequently revealed lung persistent abnormalities, as well as lung fibrotic lesions in a minority of patients. Persistent cardiac dysfunction and kidney failure were uncommon. Almost all patients had positive anti–SARS-CoV-2 serology.

There have been substantial concerns about the respiratory sequelae of COVID-19.[1] However, severe pulmonary sequelae were infrequent in the patients in the present study,

although all had experienced a severe or very severe form of COVID-19. Results for lung CT scan, performed for all symptomatic and ICU patients, were abnormal in most patients, but the most frequent lesions were subtle ground-glass opacities, confirming previous findings.[11] Fibrotic lesions, suspected because of the severe initial inflammation,[1] were present in only 19% of patients with CT scans, which is consistent with 2 smaller studies reporting CT scan at 3 months after COVID-19.[6,12] In the present cohort, the fibrotic changes affected less than 25% of the lung parenchyma in all but 1 patient and occurred almost exclusively in ICU patients. Although it is possible that patients with mild fibrotic lesions did not report dyspnea at telephone consultation and subsequently did not undergo a CT scan, it appears that this represents a small proportion of the 478 evaluated patients.

Although severe lung sequelae were uncommon, new-onset dyspnea was reported in 16% of patients. If confirmed in other studies and found to be persistent, this could be clinically important, given the large number of seriously ill patients with COVID-19 worldwide. Furthermore, although parenchymal sequelae were the most common finding, dysfunctional breathing was confirmed by hyperventilation provocation test in 12% of patients, a finding that to our knowledge has not previously been described. Dysfunctional breathing is most likely not specific to COVID-19. Nevertheless, it might be the sequela of the dissociation between dyspnea and the severity of hypoxemia described in COVID-19 patients at the acute phase.[28,29]

In the present cohort, cognitive problems, reported by telephone assessment and confirmed at the outpatient clinic, were frequent: 21% of the patients reported at least 1 cognitive symptom, and cognitive impairment was confirmed in 38% of patients who were subsequently evaluated. The underlying mechanisms are unknown, but these symptoms might be the sequala of central nerve system injury by SARS-CoV-2, as occurs during other viral infections such as glandular fever.[30]

Psychological testing was conducted only on patients who returned for an ambulatory assessment, making it difficult to determine the true prevalence of these findings. Symptoms of anxiety were found in 31% of patients and symptoms of depression in 21%. Conversely, the prevalence of psychological symptoms in ICU patients, systematically evaluated at the outpatient clinic, was meaningful. These symptoms appear to have been less common in ICU patients than in the overall assessed population. The psychological consequences of an ICU stay have been well described.[31]

Although echocardiographic evaluation of cardiac function was performed only in ICU and symptomatic patients, systolic left ventricular dysfunction was rare and found exclusively in ICU patients. A critical limitation is that the pre–COVID-19 cardiac function was not known, but these findings suggest that possible heart damage from COVID-19 may not have frequent sequelae. However, patients with severe cardiac injury leading to death within 4 months would have been excluded from this study.

Limitations

This study has several limitations. First, this investigation was an uncontrolled cohort study, which precludes comparison of prevalence of findings with patients not experiencing COVID-19. Second, this study was performed during the first months of the epidemic when corticosteroids, anticoagulation at higher doses, and treatment with other immunomodulators were not systematically used. Third, the absence of a non–COVID-19 control group or even pre–COVID-19 assessments on the same patients limits the ability to conclude that findings after 4 months are temporally related to COVID. Fourth, many patients who were invited to participate declined both the telephone assessments and the subsequent ambulatory assessments. It is possible that patients who did not participate had fewer symptoms than those who did.

Conclusions

Four months after hospitalization for COVID-19, a cohort of patients frequently reported symptoms not previously present, and lung-scan abnormalities were common among those who were tested. These findings are limited by the absence of a control group and of pre–COVID-19 assessments in this cohort; further research is needed to understand longer-term outcomes and whether these findings reflect associations with the disease.

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