Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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Original article

Long-term outcomes of patients following hospitalization for coronavirus disease 2019: a prospective observational study

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ABSTRACT

Objectives: Few data are available regarding follow up of patients with coronavirus disease 2019 (COVID-19) after their discharge. We aim to describe the long-term outcomes of survivors of hospitalization for COVID-19 followed up first at an outpatient facility and subsequently by telephone.
Methods: Observational prospective study conducted at a tertiary general hospital. Clinical and radiological progression was assessed and data were recorded on a standardized reporting form. Patients were divided into three groups according to Pao_2/Fio_2 at hospitalization: Pao_2/Fio_2 >300, Pao_2/Fio_2 300–200 and Pao_2/Fio_2 <200. A logistic multivariate regression model was performed to identify factors associated with persistence of symptoms.
Results: For facility follow up, 302 individuals were enrolled. Median follow up was 45 days after discharge; 78% (228/294) of patients had COVID-19-related symptoms (53% asthenia, 56% respiratory symptoms) and 40% (122/302) had residual pulmonary radiographic lesions. Pao_2/Fio_2 <200 was an independent predictor of persistent dyspnoea (OR 1.87, 95% CI 1.38–2.52, $p < 0.0001$). Pao_2/Fio_2 >300 was associated with resolution of chest radiographic lesions (OR 0.56, 95% CI 0.42–0.74, $p < 0.0001$). Fifty per cent of patients required specific medical follow up after the first consultation and were transferred to another physician. A total of 294 patients were contacted for telephone follow up after a median follow-up time of 7 months. Fifty per cent of patients (147/294) still presented symptoms and 49% (145/294) had psychological disorders. Asthenia was identified in 27% (78/294) and dyspnoea in 10% (28/294) of patients independently of Pao_2/Fio_2.
Conclusions: Patients with COVID-19 require long-term follow up because of the persistence of symptoms; patients with low Pao_2/Fio_2 during the acute illness require special attention. **Yolanda Meije, Clin Microbiol Infect 2021;27:1151**

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Introduction

Coronavirus disease 2019 (COVID-19) represents a major global medical challenge [1]. A great deal of information has emerged about the epidemiology of acute COVID-19, its clinical features and predictive factors for patients during hospital admission [2,3], but at present very little is known about the subsequent course of COVID-19 survivors after hospital discharge [4]. In fact, the great majority of COVID-19 studies in the literature are either retrospective or report only short-term follow up [5–7]. Data have been published on the long-term clinical outcomes of patients following hospitalization in the Asian setting [8], but to our knowledge no descriptions are as yet available in a European population.

To optimize clinical care, it is imperative to understand the natural history of infection with severe acute respiratory coronavirus 2 (SARS-CoV-2), including the evolution of recovering patients, and to determine predictors that may be useful in longer-term clinical management. Since the beginning of the pandemic, our group has been aware of the need for a specific follow-up facility for patients after discharge from our tertiary care hospital. The identification of possible sequelae is crucial to address the individual requirements of each patient.

The present study aims to describe the mid/long-term outcomes of survivors of COVID-19 discharged from our hospital and who were subsequently followed up both at the outpatient facility visit and by telephone.

The main aim was to systematically characterize the evolution of survivors of COVID-19 admitted to our hospital, in terms of the development and persistence of symptoms, the development of new clinical sequelae, immune status and chest radiography findings. The secondary objective was to identify conditions that were associated with the persistence of clinical symptoms or radiological disease.

Materials and methods

Study design

This observational prospective study was conducted at the Hospital de Barcelona-SCIAS, a 250-bed co-operative non-profit private tertiary care general hospital in Barcelona, Spain.

Patients who were discharged after hospitalization for COVID-19 were selected for follow up, divided into two subcohorts: in the first, all those seen at face-to-face facility visits, and in the second, those who were also followed up by telephone.

The patients were divided into three groups according to their worst ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (Pa_{O_2}/Fi_{O_2}) during hospitalization: Pa_{O_2}/Fi_{O_2} >300, Pa_{O_2}/Fi_{O_2} 300–200 and Pa_{O_2}/Fi_{O_2} <200. Pa_{O_2}/Fi_{O_2} has been used by other investigators to study patient outcomes based on a standardized measure of lung injury [9]. Pa_{O_2}/Fi_{O_2} was calculated according to arterial gasometry values. For those patients in whom arterial gasometry was not performed, Pa_{O_2} was replaced by oxygen saturation in accordance with the Severinghaus–Ellis equation [10].

Population

Patients aged >15 years who had been discharged following hospitalization for COVID-19 between 1 March and 31 May 2020 were included. Patients were identified in the electronic hospital database through a specific coding for COVID-19. Data collected during admission included demographic characteristics, co-morbidities, symptoms, radiological manifestations and clinical management (see Supplementary material, Table S1). Eight internal medical physicians from the COVID-19 hospital team performed the data collection.

Once discharged, patients were contacted 45 days (range 43–47 days) later, in chronological order, and were scheduled for an outpatient clinic appointment in the following week. All patients who attended the facility were included (Fig. 1).

Procedures in the outpatient facility assessment (face-to-face assessment applied to all patients) were as follows. (a) A standard follow-up protocol checklist of symptoms and adverse events, including psychological manifestations, was administered to prospectively record the variables at the facility (see Supplementary material, Table S1). (b) Medical histories were reviewed and a physical examination was performed. (c) Laboratory testing, chest X-ray and SARS-CoV-2 serological testing were performed. (d) Ten internal medicine and family medicine physicians with experience in the management of hospitalized COVID-19 patients were enrolled in the follow up.

For the telephone follow-up, all patients seen at the outpatient facility were contacted 7 months (range 6–7.4 months) after discharge by telephone. A second follow up was conducted. All patients who agreed to the telephone interview were included.

Procedures in the telephone follow up were as follows. (a) The same follow-up protocol checklist of clinical manifestations and adverse events performed to report the variables at the facility was used to record the persistence of symptoms in the telephone interview (see Supplementary material, Table S1). (b) Data related to demographic characteristics or patient co-morbidities that were missing in the previous data collection were obtained from the patient. (c) The same initial eight internal medicine physicians from the COVID-19 hospital team conducted the telephone interview.

All patients gave informed consent before participation in the study. The research protocol was approved by the hospital's institutional review board (identification code: HdB-COVIDFOLLOW-2020/04).

Variables and definitions

Individuals diagnosed with COVID-19 included both confirmed and probable cases. Confirmed cases met clinical criteria (acute respiratory syndrome), radiological criteria and had a positive PCR result for SARS-CoV-2. Probable cases were those with clinical criteria (acute respiratory syndrome), radiological criteria, but with a negative or inconclusive PCR result for SARS-CoV-2, in accordance with the protocol in force in Spain [11], and were diagnosed with COVID-19 by two independent clinicians in the absence of an alternative cause of pneumonia.

The Rockwood score was used as a global clinical measure of frailty in elderly people [12]. The MuLBSTA score was used for the risk stratification of hospitalized patients; values > 12 were perceived as high risk [13]. All variables and definitions are given in the Supplementary material (Table S1). The hospital protocol is described in the Supplementary material (Figure S1).

Laboratory data

The presence of SARS-CoV-2 in nasal and pharyngeal respiratory swabs was identified by RNA extraction followed by RT-PCR through the identification of SARS-CoV-2 RNA (three specific regions: *E* gene, *RdRP* gene and *N* gene), (AllPlex 2019-nCoV Assay; Seegene, Seoul, Korea).

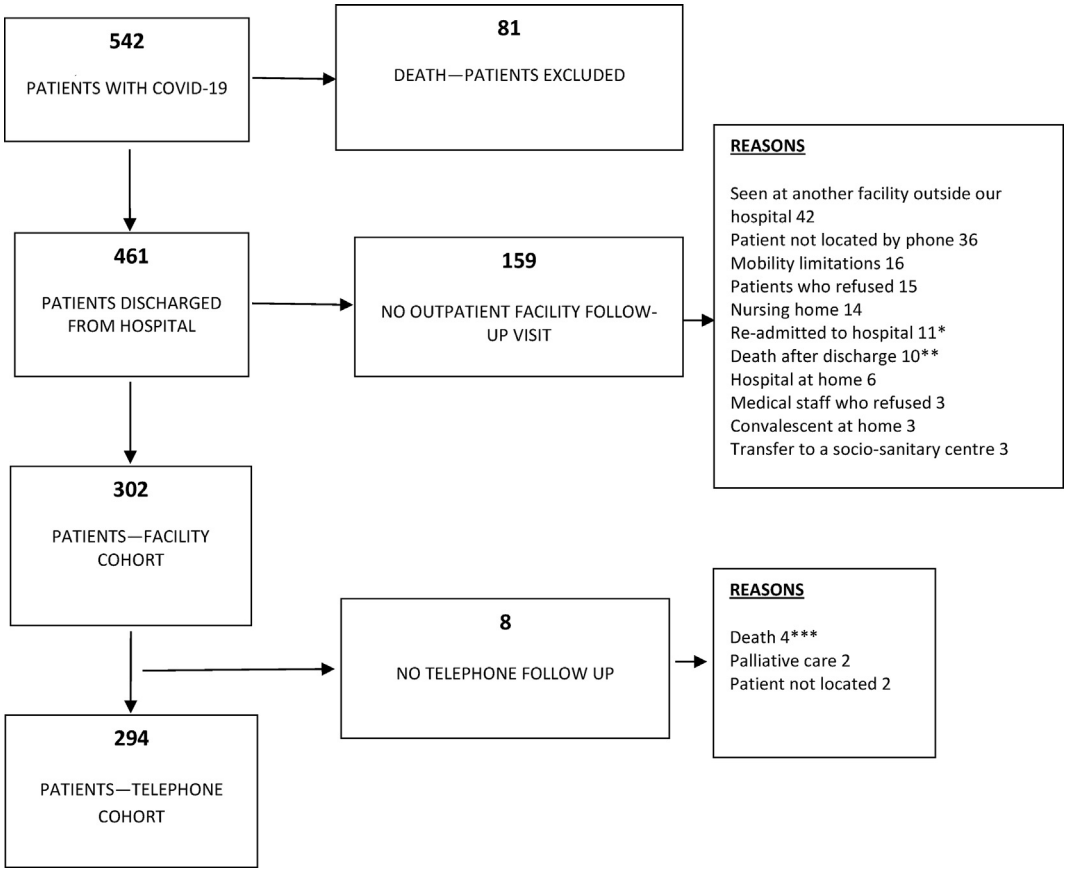

Fig. 1. Patient selection flow chart. *Re-admitted to hospital: five for respiratory insufficiency related to COVID-19, two for bacterial pneumonia, one for diarrhoea, one for pulmonary embolism, one for ovarian neoplasia, one for acute pyelonephritis. **Death after discharge: seven at home, three at hospital (two due to respiratory insufficiency related to COVID-19, one due to cerebral stroke). ***Death: two at home, two at hospital (one due to septic shock, one due to pancreatic neoplasia).

Statistical analysis

For descriptive analysis, quantitative results of variables were expressed as means and standard deviations (SD) or medians and interquartile ranges (IQR), and categorical variables were reported as absolute numbers and percentages. To detect significant differences between groups, the χ^2 test or Fisher's exact test for categorical variables was used, as appropriate.

Characterization of disease evolution and long-term severe outcomes were analysed. The purpose of the model was to identify risk factors related to outcomes using logistic multivariate analysis. First, a logistic bivariate regression analysis was conducted to identify variables associated with the most severe persistent symptoms or residual lesions (any of the following: dyspnoea, asthenia and pathological X-ray findings; dependent variables). We included variables associated with the dependent variable in the bivariate analysis ($p < 0.1$) and pre-defined variables that were clinically relevant. Once the significant variables (independent variables) were identified, a logistic multivariate regression model was performed. The variables included in the final model were selected by an automatic backward stepwise procedure. Interactions between variables were considered based on those that could be related clinically ($r > 0.4$ were eliminated). A two-sided α of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS Statistics for Windows v.25 (IBM, Armonk, NY, USA) and Analyse-it Software, Ltd. for Windows v.3.

The results were reported in accordance with the Strobe statement (see Supplementary material, Table S2).

Results

Population recruited

From 1 March 2020 to 31 May 2020, 562 individuals were admitted to the hospital with a suspected diagnosis of COVID-19; of these, the diagnosis was confirmed in 542. Of the 461 individuals eventually discharged, 302 were enrolled in the final outpatient follow-up cohort. The remaining 159 patients were excluded for the reasons explained in Fig. 1. Two hundred and ninety-four patients were included in the final telephone cohort.

Characteristics of the hospitalized population

The demographic and clinical characteristics of the study cohort (302 patients) are described in Table 1. Median hospital stay was 8 days (IQR 5–12 days). Sixty-eight (22.5%) patients were PCR-negative for SARS-CoV2. The comparison of the characteristics and outcomes of patients according to PCR+/− for SARS-CoV-2, and according to the inclusion and exclusion criteria of the cohort, is detailed in the Supplementary material (Tables S3 and S4).

Table 1
Demographic and clinical characteristics of the study cohort ($n = 302$)

Characteristics of the cohort	Value	Characteristics of the cohort	Value
Age (years), mean (SD)	68.8 (SD 12.7)	Oxygen supplementation	
Male sex	171 (56.6%)	Not needed	76 (25.2%)
Smoking status		Low flow	182 (60.3%)
Active smoker	14 (4.6%)	High flow	44 (14.6%)
Ex-smoker	109 (36.1%)	Oxygen delivery system	
Co-morbidities		No oxygen supplies	76 (25.2%)
Hypertension	137 (45.4%)	Nasal cannula	130 (43%)
Dyslipidaemia	117 (38.7%)	Venturi mask	30 (9.9%)
Diabetes mellitus	37 (12.3%)	Non-rebreather mask	31 (10.3%)
Overweight (BMI ≥25 kg/m^2)	149 (49.3%)	High-flow nasal cannula	3 (1%)
Obesity (BMI ≥30 kg/m^2)	41 (13.6%)	NIMV	29 (9.6%)
Metabolic syndrome	64 (21.2%)	IMV	3 (1%)
Chronic pulmonary disease	41 (13.6%)	ICU admission	27 (8.9%)
Cardiovascular disease	32 (10.6%)	Overweight and ICU admission	20 (74%)
Moderate or severe liver disease	2 (0.7%)	At discharge	
Moderate to severe chronic kidney disease	16 (5.3%)	Oxygen therapy at home	12 (3.9%)
Immunosuppression	18 (6%)	Decreasing doses of corticosteroids	66 (21.8%)
Rockwood Frailty Score (median, IQR)	3 (IQR 2-3)	Heparin prophylaxis	72 (23.8%)
MuLBSTA Mortality Risk Score (median, IQR)	9 (IQR 6-12)	Hospital readmission	6 (2%)
MuLBSTA Mortality Risk Score >12	81 (26.8%)	At facility	
Pneumonia pattern		X-ray	
Bilateral interstitial	126 (41.7%)	Residual pulmonary lesions	122 (40.4%)
Condensations	65 (21.5%)	Laboratory results	
Ground-glass opacities	50 (16.6%)	Lymphophenia (<1000 cells/μL)	19 (6.3%)
Crazy paving pattern	47 (15.6%)	Ferritin alteration (>260 ng/mL)	42 (13.9%)
Unilateral interstitial	14 (4.6%)	Lactate dehydrogenase (>220 UI/L)	46 (15.2%)
Treatment		D-dimer elevation	
		(>500)	47 (15.6%)
		(>1000)	17 (5.6%)
A drug regimen including hydroxychloroquine	290 (96%)	Serology status	
A three-drug regimen including a protease inhibitor	115 (38.1%)		
A two-drug regimen with hydroxychloroquine and azithromycin	118 (39.5%)	PCR-SARS-CoV-2-positive: 234 (77.5%)	IgM−/IgG+: 129 (55.1%)
			IgM+/IgG+: 79 (33.8%)
Antibiotic	268 (88.7%)		IgM+/IgG−: 1 (0.4%)
			IgM−/IgG−: 8 (3.4%)
			No serology available: 17 (7.3%)
Heparin	266 (88.1%)	PCR-SARS-CoV-2-negative: 68 (22.5%)	IgM−/IgG+: 32 (47.1%)
Tocilizumab	67 (22.2%)		IgM+/IgG+: 16 (23.5%)
			IgM−/IgG−: 16 (23.5)
			No serology available: 4 (5.9%)
Corticosteroids	125 (41.4%)		

Abbreviations: BMI, body mass index (kg/m^2); ICU, intensive care unit; IMV, invasive mechanical ventilation; IQR, interquartile range; NIMV, non-invasive mechanical ventilation; SD, standard deviation.

Visits at the outpatient facility—ongoing symptomatic COVID-19

The median time of follow up after discharge was 45 days (IQR 43–47 days).

General symptoms

77.6% patients (228/294) had persistent symptoms related to COVID-19 infection, the most frequent being asthenia (53.4%; 157/294) and respiratory symptoms (55.7%; 164/294: dyspnoea, cough or chest pain). The distribution of symptoms is described in Table 2.

Residual respiratory findings

40.4% (122/302) of patients had residual pulmonary lesions and 2.6% (8/302) showed worsening due to acute fibrinous and organizing pneumonia, ground-glass opacity or interstitial fibrosis. As can be seen in Table 3, a logistic multivariate analysis identified a Pa_{O_2}/Fi_{O_2} <200 during hospitalization as an independent predictor of persistent dyspnoea (OR 1.87, 95% CI 1.38–2.52) at the follow-up assessment ($p < 0.0001$). In addition, a Pa_{O_2}/Fi_{O_2} >300 was associated with resolution of X-ray lesions (OR 0.56, 95% CI 0.42–0.74, $p < 0.0001$) (see Supplementary material, Tables S5 and S6 for logistic multivariate and bivariate regression models).

Later follow up

50.3% (152/302) of patients required medical follow up after the first consultation and were referred to another physician, most often a pulmonologist (27.1%, 82/302). Six patients required hospitalization after the outpatient visit: two for dyspnoea and X-ray worsening, two (chronic lung disease patients) for persistent dyspnoea, one for pulmonary embolism, and one for pericardial effusion.

COVID-19 diagnostic biomarkers

At a median of 45 days (IQR 43–47 days) 84.8% (256/302) of the cohort presented IgG and 31.8% (96/302) IgM. Forty-eight of the 68 SARS-CoV2 PCR-negative patients (70.6%) were IgG positive (Table 1).

Outpatients contacted by telephone—long-term outcomes post-COVID-19

The median time from discharge to telephone contact was 7 months (IQR 6–7.4 months).

Table 2
Patients' clinical outcomes related to time of follow up[a]

Variables ($n = 294$)	Hospitalization ($n = 294$), n (%)	Facility follow up ($n = 294$), n (%)	Phone call follow up ($n = 294$), n (%)
Any symptom[b]	290 (98.6%)	228 (77.6%)	147 (50%)
Dyspnoea	167 (56.8%)	88 (29.9 %)	28 (9.5 %)
Cough	203 (69.0%)	46 (15.6 %)	17 (5.8 %)
Chest pain	35 (11.9%)	30 (10.2%)	8 (2.7%)
Diarrhoea	126 (42.9%)	19 (6.5%)	8 (2.7%)
Migraine	82 (27.9%)	19 (6.5%)	12 (4.1%)
Anosmia	97 (33.0%)	47 (16.0%)	27 (9.2%)
Dysgeusia	106 (36.1%)	47 (16.0%)	26 (8.9%)
Asthenia	259 (88.1 %)	157 (53.4 %)	78 (26.5 %)
Myalgias	143 (48.6%)	63 (21.4%)	39 (13.3%)
Neurological disorder	36 (12.2%)	44 (15%)	52 (17.7%)
Cramps	13 (4.4%)	7 (2.4%)	9 (3.1%)
Tremors	4 (1.4%)	4 (1.4%)	3 (1%)
Tingles	6 (2%)	10 (3.4%)	8 (2.7%)
Visual disturbances	12 (4.1%)	20 (6.8%)	26 (8.8%)
Tinnitus	3 (1%)	9 (3.1%)	13 (4.4%)
Other symptoms			
Alopecia	3 (1%)	20 (6.8%)	30 (10.2%)
Psychological symptoms	Not Apply	138 (46,9%)	145 (49.3%)
Sadness or emotional lability		67 (22.8%)	65 (22.1%)
Fear of relapse		68 (23.1%)	86 (29.3%)
Limitations in their usual life		60 (20.4%)	57 (19.4%)
Insomnia		62 (21.1%)	54 (18.4%)
Stress		47 (16%)	48 (16.3%)
Need for psychological medication		35 (11.9%)	30 (10.2%)

[a] Facility follow up was at 45 days; telephone follow up was at 7 months.
[b] Symptoms refer to: dyspnoea, cough, chest pain, diarrhoea, migraine, anosmia, dysgeusia, asthenia, myalgias, neurological disorder.

Table 3
Logistic multivariate regression models

Variable	OR	95% CI
Dyspnoea prediction at outpatient facility follow up		
Sex (female)	1.38	0.81–2.354
Pa_{O_2}/Fi_{O_2} <200	**1.870**	**1.38–2.52**
Chronic lung disease	1.93	0.94–3.98
Prediction of resolution of X-ray findings at outpatient facility follow up		
Sex (female)	**1.83**	**1.12–3.002**
Pa_{O_2}/Fi_{O_2} >300	**0.56**	**0.42–0.74**
Chronic lung disease	0.83	0.41–1.66

Odds ratio and 95% CI corresponding to the logistic multivariate regression analysis to predict dyspnoea or resolution of chest X-ray findings after 45 days. The multivariate model shows a significant effect for explaining dyspnoea or resolution of X-ray findings ($p < 0.0001$). Pa_{O_2}/Fi_{O_2}: reference category ≥200 for dyspnoea and ≤300 for resolution of X-ray. Significant results are shown in bold type.

General symptoms

50% (147/294) of patients still had COVID-19-related symptoms: the most frequent was asthenia (26.5%; 78/294), followed by neurological disorders (17.7%; 52/294). Almost half of the patients (49.3%; 145/294) presented psychological symptoms. Other persistent symptoms were found in almost 10% of patients, including dyspnoea, anosmia or dysgeusia. In terms of the evolution of symptoms, diarrhoea and migraine rapidly decreased over the course of follow up, whereas others such as anosmia and dysgeusia decreased slowly over time. All symptoms are described Table 2 (and see Supplementary material, Fig. S2).

Patient clinical outcomes and radiology outcomes related to Pa_{O_2}/Fi_{O_2}

A significant relationship was observed between persistent dyspnoea and lower Pa_{O_2}/Fi_{O_2} at medium-term follow up ($p < 0.0001$) (Table 3). However, in the long-term follow up (7 months) the trend was maintained, but was no longer statistically significant. Asthenia occurred in all periods regardless of Pa_{O_2}/Fi_{O_2} (Table 4).

Discussion

At 45 days after hospital discharge, 78% of the participants in this study had COVID-19-related symptoms and more than 40% had residual pulmonary lesions. These rates decreased over time; however, at 7 months after discharge, 50% of patients had persistent symptoms and 49% had psychological disorders. Notably, 50% of patients required specific medical follow up after the first consultation.

Our understanding of COVID-19 is still incomplete, particularly with regard to its clinical sequelae and long-term outcomes. Although most patients recover from the acute infection, certain long-lasting effects may have significant clinical implications. Concepts such as post-acute COVID-19, chronic COVID-19 and post-COVID-19 are emerging in the light of observations made over the short and medium terms [14,15]; however, little is known about long-term clinical outcomes in COVID-19 patients [16]. In survivors of severe acute respiratory syndrome and Middle East respiratory syndrome, lung function abnormalities, psychological impairment and reduced exercise capacity were reported to be common [17]. A recent study of COVID-19 patients in Italy showed persistence of symptoms after recovery, with only 12.6% of patients completely free of any COVID-19-related symptoms at a 2-month follow up [6]. Other studies have found that 64% of patients had no symptoms 3 months after discharge and that 76% had no symptoms 6 months after discharge [8,18]. Our study, with a considerably longer time span, reported symptoms in 50% of patients at 7 months of follow up.

We assessed the symptoms over 7 months following discharge. The most frequent limiting symptoms were asthenia (over 50% at 1.5 months, and still present in more than 26% at 7 months) and respiratory symptoms, especially dyspnoea (30% at 1.5 months and still above 9% at 7 months). Other authors have reported dyspnoea in 30% of patients and asthenia in 40% at 2 months of follow up [7]. In our study, more than 40% of patients had residual pulmonary lesions 1.5 months after discharge. Similarly, other studies found that around 35% of patients had

Table 4
Patients' clinical outcomes related to Pao_2/Fio_2

Variables	Follow up	Pao_2/Fio_2 >300	Pao_2/Fio_2 300–200	Pao_2/Fio_2 <200	p value
Total patients	294	179 (60.9%)	43 (14.6%)	72 (24.5%)	
Dyspnoea	Hospital	90 (50.3 %)	25 (58.1%)	52 (72.2%)	0.01
	Facility	40 (22.3 %)	13 (39.2%)	35 (48.6%)	0.002
	Phone call	15 (8.4%)	4 (9.31%)	9 (12.5%)	0.60
Cough	Hospital	121 (67.6%)	30 (69.8%)	52 (72.2%)	0.77
	Facility	28 (15.6%)	9 (20.9%)	9 (12.51%)	0.48
	Phone call	9 (5.0%)	3 (7.0%)	5 (6.9%)	0.79
Dysgeusia	Hospital	63 (35.2%)	11 (25.6%)	32 (44.4%)	0.12
	Facility	32 (17.9%)	2 (4.7%)	13 (18.1%)	0.09
	Phone call	18 (10.1%)	2 (4.7%)	6 (8.3%)	0.52
Anosmia	Hospital	62 (34.6%)	10 (23.3%)	25 (34.7%)	0.34
	Facility	33 (18.4%)	5 (11.6%)	9 (12.5%)	0.36
	Phone call	18 (10.1%)	5 (11.6%)	4 (5.6%)	0.45
Asthenia	Hospital	155 (8.6%)	39 (90.7%)	65 (90.3%)	0.61
	Facility	93 (52.0%)	24 (55.8%)	40 (55.6%)	0.83
	Phone call	42 (23.5%)	14 (32.6%)	22 (30.6%)	0.33
Migraine	Hospital	53 (29.6%)	15 (34.9%)	14 (19.4%)	0.14
	Facility	14 (7.8%)	2 (4.7%)	3 (4.2%)	0.49
	Phone call	10 (5.6%)	2 (4.7%)	2 (2.8%)	0.13
Pleuritic pain	Hospital	25 (14.0%)	1 (2.3%)	9 (12.5%)	0.11
	Facility	18 (10.1%)	6 (14.0%)	6 (8.3%)	0.63
	Phone call	5 (2.8%)	1 (2.3%)	2 (2.8%)	0.98
Myalgia	Hospital	80 (44.7%)	22 (51.2%)	41 (56.9%)	0.20
	Facility	35 (19.6%)	7 (16.31%)	21 (29.2%)	0.16
	Phone call	22 (12.3%)	3 (7.0%)	14 (19.4%)	0.13
Diarrhoea	Hospital	77 (43.0%)	19 (44.2%)	30 (41.7%)	0.96
	Facility	13 (7.3%)	2 (4.7%)	4 (5.6%)	0.77
	Phone call	5 (2.2%)	1 (2.3%)	3 (4.2%)	041
Neurological disorders	Hospital	18 (10.1%)	4 (9.3%)	14 (19.4%)	0.45
	Facility	20 (11.2%)	7 (16.3%)	17 (23.6%)	0.04
	Phone call	27 (15.1%)	8 (18.6)	17 (23.6%)	0.12

Data variables from patients are expressed in numbers and percentages. p value refers to statistical significance (χ^2) for the comparison between Pao_2/Fio_2 percentages.

persistent pulmonary abnormalities after 4 weeks [19], and persistent pulmonary infiltrates in up to 90% using chest CT imaging [5].

The present observational study found that patients with lower Pao_2/Fio_2 values had a higher risk of persistence of dyspnoea (OR 1.9), and that a higher Pao_2/Fio_2 was associated with resolution of X-ray lesions (OR 0.6) at an average of 1.5 months after discharge. Similarly, a recent study showed that patients with more severe illness during their hospital stay presented a higher level of dyspnoea and abnormal chest imaging manifestations after 6 months of follow up [8]. In another study, residual signs suggesting pulmonary fibrosis were found most frequently in a subgroup of critical COVID-19 patients [5]. Comparisons between ward and ICU patients did not reveal statistically significant differences regarding symptoms at 3 months of follow up [20] or between individuals with severe or non-severe disease at 1 month of follow up [21].

The presence of limiting symptoms such as asthenia or neurological sequelae was not negligible in our study. Social monitoring programmes for recovering patients may help improve health, physiological status and physical activity, and the provision of counselling and psychological support to these patients is also important.

This study has several limitations. First, as it is a single-centre study it is not possible to extrapolate the results to other settings. Second, the follow-up period covered the first 7 months after the discharge; a longer follow up might benefit the analysis of longer-term outcomes, and indeed our intention is to continue monitoring these patients and record further data after 12 months. Despite these limitations, the study's prospective design aided data collection; additionally, the fact that all recovered patients come from a centre with a specific, updated COVID-19 treatment protocol meant that there were few deviations in the regular management of patients, which allows the comparison of clinical outcomes in a uniform cohort.

To our knowledge, this is the first study to describe long-term follow up of a large number of COVID-19 survivors after hospitalization. We found that a worse Pao_2/Fio_2 is associated with persistence of dyspnoea for at least 45 days of follow up, and that dyspnoea, asthenia and psychological disorders persist in many patients several months after discharge.

It is important to continue studying the sequelae and prognosis of recovered patients in order to develop guidelines for their multidisciplinary management. Special attention should be paid to patients with Pao_2/Fio_2 <200 during the acute infection. These patients may require close monitoring by a pulmonologist during follow up, and the need for high-resolution CT imaging, and 6-minute walking and pulmonary function tests should also be assessed. Further studies of long-term complications are warranted to enhance the design of future health strategies.

Transparency declaration

The authors have no conflicts of interest to declare, nor any sources of funding to report.

Author contributions

Conceptualization was by YM, AD, XS and BC; methodology was by BC and YM; data were collected by YM, AD, XS, MC, AR, LO, RG, RC, JP, IC, MA, TS, JLL, AA and the Hospital de Barcelona COVID19-team and validated by YM, AD, XS, MC, AR, LO, RG, RC, JP, IC, MA, TS, JLL and AA; formal analysis was performed by BC, YM and NF; investigation was by YM, AD, XS, MC, AR, LO, RG, RC, JP, IC, MA, TS,

JLL, AA, NF, BC and the Hospital de Barcelona COVID19-team; resources were obtained by YM, JLL and BC; data curation was by YM, RG and BC. The original draft was written by YM and reviewed and edited by YM, AR, NF and BE. The study was visualized by YM and AD; supervision and project administration were by YM.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.cmi.2021.04.002.

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