

Pneumologia

Severe COVID-19: How are these patients today

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Abstract

English:

Background: The coronavirus disease 2019 (COVID-19) pandemic has had a profound global impact, affecting millions of individuals. Long-term sequelae associated with this infection have been reported, compromising patients' quality of life.

Objective: This study aimed to evaluate patients with severe COVID-19 over a follow-up period of up to 26 months after discharge from the Intensive Care Unit (ICU).

Methods: This retrospective and observational study included patients with severe SARS-CoV-2 infection admitted to ICU 1 of Unidade Local de Saúde de Lisboa Ocidental between January and September 2021. Participants were those who had persistent respiratory symptoms or functional limitations 3 months after discharge. Respiratory symptoms were evaluated, and respiratory function tests and chest computed tomography (CT) scans were performed.

Results: Thirty-four patients were included. Dyspnoea was the most prevalent symptom, reported by all patients during the first assessment at 4 months and by 51.5% ($n = 17$) at 7–10 months, showing gradual improvement. Respiratory function tests revealed reduced diffusing capacity of the lung for carbon monoxide, restrictive ventilatory impairment, and decreased muscle strength. Imaging findings showed ground-glass opacities, organizing pneumonia, and pulmonary fibrosis, with fibrotic changes persisting in 37.5% ($n = 12$) of patients throughout the evaluation period.

Conclusion: While many patients with severe COVID-19 fully recover with minimal sequelae, some develop long COVID, characterised by persistent symptoms, respiratory function impairment, and imaging abnormalities beyond 12 months post-infection. These findings highlight the need for further research to understand the long-term consequences of COVID-19 and identify factors contributing to long COVID syndrome.

Keywords

long COVID • respiratory impairment • pulmonary fibrosis • severe COVID-19 • follow-up assessment

COVID-19 sever: Cum sunt acești pacienți astăzi?

Rezumat

Romanian:

Abstract: Pandemia provocată de coronavirus (COVID-19) a avut un impact global profund, afectând milioane de persoane. S-au raportat sechele pe termen lung asociate cu această infecție, compromițând calitatea vieții pacienților.

Obiectiv: Acest studiu a avut ca scop evaluarea pacienților cu COVID-19 sever pe o perioadă de urmărire de până la 26 de luni după externarea de la Terapie Intensivă (ATI).

Metodă: Acest studiu retrospectiv și observațional a inclus pacienți cu infecție severă cu SARS-CoV-2 internați în secția ATI 1 a Unidade Local de Saúde de Lisboa Ocidental, în perioada ianuarie - septembrie 2021. Participanții au fost selectați dintre cei care au prezentat simptome respiratorii persistente sau limitări funcționale la 3 luni după externare. Au fost evaluate simptomele respiratorii, s-au efectuat funcționale respiratorii și tomografiile computerizate (CT) toracice.

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Rezultate: Treizeci și patru de pacienți au fost incluși. Dispneea a fost cel mai frecvent simptom, raportat de toți pacienții la prima evaluare, la 4 luni, și de 51,5% (n = 17) la 7–10 luni, indicând o îmbunătățire progresivă. Testele funcționale respiratorii au arătat o capacitate redusă de difuziune pulmonară pentru monoxid de carbon, afectare ventilatorie restrictivă și scăderea forței musculare. Imagistica a evidențiat opacități în sticlă mată, pneumonie organizată și fibroză pulmonară, modificările fibrotice persistând la 37,5% (n = 12) dintre pacienți pe toată perioada de evaluare.

Concluzie: Deși mulți pacienți cu COVID-19 sever se recuperează complet cu sechele minime, unii dezvoltă long-COVID, caracterizat prin simptome persistente, afectarea funcției respiratorii și anomalii imagistice care se mențin la peste 12 luni de la infecție. Aceste constatări subliniază nevoia de cercetări suplimentare pentru a înțelege consecințele pe termen lung ale COVID-19 și pentru a identifica factorii care contribuie la sindromul long-COVID.

Cuvinte-cheie

long-COVID • afectare respiratorie • fibroză pulmonară • COVID-19 sever • evaluare de urmărire

Introduction

The coronavirus disease 2019 (COVID-19) pandemic infected over 700 million people, causing >6 million deaths worldwide (1).

COVID-19, caused by the SARS-CoV-2 virus, is a multiorgan disease, mostly affects the respiratory system. Viral pneumonia and respiratory failure are the leading causes of hospitalisation (2), with a high admission rate to both hospital wards (20%) and Intensive Care Units (ICUs) (6%) (3).

The natural history of COVID-19, as well as its long-term sequelae that are estimated to occur in about 10% of infected individuals (4), are not fully understood (5). The National Institute for Health and Care Excellence, the Scottish Intercollegiate Guidelines Network, and the Royal College of General Practitioners proposed a definition for long COVID syndrome as ‘signs and symptoms that develop during or after an infection consistent with COVID-19 and persist for >12 weeks and are not explained by an alternative diagnosis’ (6). Common symptoms are dyspnoea (7), fatigue, anxiety, depression, and sleep problems, which can significantly impair health-related quality of life (8). To identify these patients, the British Thoracic Society has suggested algorithms for assessing survivors of COVID-19 in the first 3 months after hospital discharge based on the severity of acute COVID-19 (9). The European Respiratory Society (ERS) Task Force has also concurred with the recommendation (2). Pulmonary fibrosis (PF), persistent ground-glass opacities (GGOs), reduced carbon monoxide diffusion capacity, restrictive ventilatory impairment, and fatigue 1–8 months after infection are predictors of the long-term consequences of COVID-19 (2). Patients with SARS-CoV-2 may experience a range of clinical presentations, from asymptomatic infection to critical illness (10).

The aim of this study is to evaluate patients who had severe COVID-19 requiring admission to ICU in three different periods after infection: up to 6 months, between 7 months and 12 months, and after 12 months.

According to COVID-19 Treatment Guidelines, severe illness corresponds to ‘individuals who have peripheral oxygen saturation (SpO_2) <94% on room air at sea level, a ratio of arterial partial pressure of oxygen to fraction of inspired oxygen ($\text{PaO}_2/\text{FiO}_2$) <300 mmHg, a respiratory rate >30 breaths/min, or lung infiltrates >50%’; critical illness relates to ‘individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction’ (10).

Materials and methods

This is a retrospective, observational, and descriptive study including patients with severe SARS-CoV-2 infection admitted to ICU 1 at Unidade Local de Saúde de Lisboa Ocidental from January to September 2021. Patients with respiratory symptoms or functional limitations (≥ 1 point on the modified Medical Research Council Dyspnoea Scale (11) or ≥ 2 points on the Post-COVID Functional Status Scale (12)) 3 months post-discharge were included.

Symptoms were assessed at two points: 4 months post-discharge and three to 6 months after the first evaluation. Functional and imaging assessments were performed up to 6 months, between 7–12 months and beyond 12 months post-discharge.

Respiratory function was assessed through spirometry, plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO) by single breath, and assessment of muscle strength through maximal respiratory pressures. Patients were classified according to ERS/ American Thoracic Society (ATS) 2005 and ACCP 2000–2002 criteria, as having restrictive ventilatory impairment (forced vital capacity [FVC] <80% of predicted and total lung capacity [TLC] <80% of predicted) or obstructive impairment (forced expiratory volume in 1 s [FEV_1/FVC] <lower limit of normal), reduced DLCO (<80% of predicted), and decreased maximal respiratory

pressures (maximal inspiratory pressure [MIP] and maximal expiratory pressure [MEP] <60% of predicted). Acceptability criteria followed ERS/ATS 2005 guidelines.

Imaging changes were also assessed using chest computed tomography (CT). Patients were categorised as having inflammatory changes (GGOs) and fibrotic changes (PF manifested through traction bronchiectasis or honeycomb pattern and residual lung fibrosis with fibrotic cicatricial changes), organising pneumonia (OP), or coexisting inflammatory and fibrotic changes.

Data were collected from clinical records, chest CT reports, and respiratory functional studies. Descriptive analysis of all variables was performed. Categorical variables are presented as frequencies (absolute count and percentage); continuous variables are presented as mean and standard deviation (SD) or median and interquartile range, depending on the empirical distribution of the variables. The Kolmogorov-Smirnov test was used to analyse the normality of the distribution of each continuous variable.

This study was approved by the Unidade Local de Saúde de Lisboa Ocidental Ethics Committee.

Results

This study included 34 patients, with 50.0% ($n = 17$) being female and 50.0% ($n = 17$) male, with a mean age of 66.6 ± 9.9 years (range 40–84 years). Regarding smoking habits, 58.8% ($n = 20$) of patients had no prior smoking habits, and 41.2% ($n = 14$) of patients were former smokers with an average smoking history of 32.0 ± 19.8 pack-years. Thirty patients had at least one comorbidity, with the most frequent being: arterial hypertension ($n = 22$; 64.7%), obesity ($n = 14$; 41.2%), dyslipidaemia ($n = 13$; 38.2%), type 2 diabetes mellitus ($n = 11$; 32.4%), and depression ($n = 5$; 14.7%). Regarding respiratory pathology, 14.7% ($n = 5$) of patients had obstructive sleep apnoea, 8.8% ($n = 3$) had asthma, and 2.9% ($n = 1$) had chronic obstructive pulmonary disease.

During ICU stay, most patients ($n = 26$; 76.5%) required invasive mechanical ventilation with a median duration of 8 days (6–11), range 2–93 days; eight patients (23.5%) required only non-invasive ventilation with a mean duration of 4.8 ± 1.6 days (range 2–6 days). The median length of stay in the ICU was 9 days (6–12), range 4–93 days.

All ICU patients with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) infection received systemic corticosteroids treatment according to ICU's protocol. Patients with SARS-CoV-2 infection and acute respiratory distress syndrome (ARDS) received 1 mg/kg/day of methylprednisolone, and the other patients received dexamethasone 6 mg once daily up to 10 days plus standard of care.

Post-discharge, only four patients (11.8%) still had respiratory insufficiency requiring oxygen therapy, which was discontinued

3 months later, at a post-discharge assessment conducted by the Intensive Care Team. None of the patients required long-term oxygen therapy.

These patients were assessed in their first pulmonology appointment with a median time of 4 months (4, 5), range 2–11 months) after discharge.

Symptoms

In the initial assessment, the main symptoms reported by patients were dyspnoea ($n = 34$; 100.0%), non-productive cough ($n = 12$; 35.3%), and asthenia/fatigue ($n = 7$; 20.6%). Regarding dyspnoea, most patients had Modified Medical Research Council Dyspnea Scale (mMRC) 1 ($n = 17$; 50.0%), followed by mMRC 2 ($n = 9$; 26.5%) and mMRC 3 ($n = 8$; 23.5%).

In the subsequent consultation 3–6 months after the first visit, the main symptoms identified were dyspnoea ($n = 17$; 51.5%), non-productive cough ($n = 6$; 18.2%), and asthenia/fatigue ($n = 3$; 9.1%). Notably, 36.4% ($n = 12$) of patients were asymptomatic. One patient discontinued follow-up. Regarding dyspnoea, most patients had mMRC 0 ($n = 16$; 48.5%), followed by mMRC 1 ($n = 12$; 36.4%) and mMRC 2 ($n = 5$; 15.2%), with no patients having mMRC 3.

Respiratory functional assessment

Up to 6 months

A total of 24 patients underwent pulmonary function tests (PFTs) during this period, with a median time of 5 months (4, 5), range 1–6 months (Table 1). The respiratory tests of two patients were not acceptable, so they were excluded.

Of the remaining 22 patients, the following mean values were obtained: FVC ($103.6 \pm 13.7\%$), FEV₁ ($105.8 \pm 13.4\%$), FEV₁/FVC ratio ($81.1 \pm 4.7\%$), and TLC ($87.8 \pm 10.5\%$). From the analysis of these data, it was found that one patient (4.6%) had restrictive ventilatory impairment (TLC 69.0%). Obstructive ventilatory impairment was not identified.

Regarding diffusing capacity of the included patients, the DLCO mean value was $70.6 \pm 14.1\%$, and diffusing capacity of the lung for carbon monoxide divided by alveolar volume – the DLCO/VA mean value was $84.6 \pm 12.3\%$. Of these patients, nine (40.9%) showed a decrease in DLCO but a normal DLCO/VA (mean $67.6 \pm 4.6\%$ and $86.0 \pm 5.2\%$, respectively). Six patients (27.3%) had a decrease in both DLCO and DLCO/VA (mean $56.3 \pm 12.2\%$ and $70.2 \pm 6.7\%$, respectively).

Considering maximal respiratory pressures, only 20 patients underwent this test, with a MIP mean value of $102.4 \pm 33.6\%$ and a MEP mean value of $86.8 \pm 33.7\%$. Of these patients, two patients (10.0%) showed a decrease in both MIP and MEP (mean 51.5% and 49.0%, respectively), and two patients (10.0%) showed only a decrease in MEP (48.0%).

Patient			Up to 6 months post-discharge										7-12 months post-discharge										>12 months post-discharge									
			Age (years)	Sex	Months	FVC (%)	FEV ₁ (%)	FEV ₁ /FVC (%)	TLC (%)	DLCO (%)	DLCO/VA (%)	PIM (%)	PEM (%)	Months	FVC (%)	FEV ₁ (%)	FEV ₁ /FVC (%)	TLC (%)	DLCO (%)	DLCO/VA (%)	PIM (%)	PEM (%)	Months	FVC (%)	FEV ₁ (%)	FEV ₁ /FVC (%)	TLC (%)	DLCO (%)	DLCO/VA (%)	PIM (%)	PEM (%)	
1	56	M	4	93	100	85.9	80	91	116	144	110	x	x	x	x	86.99	x	94	106	71	62	x	x	x	x	x	x	x	x	x	x	
2	68	M	4	95	103	83.65	81	72	86	58	50	12	103	116	86.99	x	94	106	71	62	x	x	x	x	x	x	x	x	x	x	x	
3	70	F	4	89	94	88.37	80	60	81	60	94	12	104	111	88.84	x	64	89	122	184	x	x	x	x	x	x	x	x	x	x	x	
4	67	F	F	5	No accept-ability criteria	12	93	90	79.84	x	x	60	54	54	54	54	54	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
5	55	M	2	103	118	90.27	90	82	92	107	74	11	121	125	81.57	x	76	79	x	x	x	x	x	x	x	x	x	x	x	x	x	
6	75	F	x	x	x	x	x	x	x	x	x	7	101	110	83.34	77	79	106	62	58	x	x	x	x	x	x	x	x	x	x	x	
7	72	M	x	x	x	x	x	x	x	x	x	12	83	87	79.26	x	98	139	60	58	x	x	x	x	x	x	x	x	x	x	x	
8	72	F	5	105	108	84.41	89	68	83	126	70	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
9	66	F	5	107	104	80.67	85	68	88	105	78	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
10	63	M	4	115	116	78.95	89	75	83	79	67	x	x	x	x	x	x	x	x	x	x	22	99	103	80.35	x	68	87	x	x	x	
11	72	F	5	138	138	79.54	112	92	87	122	110	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
12	81	F	5	107	119	79.97	82	67	88	120	98	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
13	62	M	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	16	110	107	75.56	x	95	103	103	70	x	x
14	69	F	5	104	103	80.87	81	49	66	164	141	x	x	x	x	x	x	x	x	x	x	13	103	104	82.12	x	64	82	x	x	x	
15	77	F	2	100	100	80	90	70	85	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
16	63	F	3	91	98	89.92	85	60	75	113	90	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
17	72	F	5	121	116	79.77	107	91	90	106	155	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
18	77	M	4	96	101	79.2	95	55	69	71	66	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
19	68	M	5	101	108	82.18	85	48	60	92	68	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
20	67	M	5	78	73	72.75	69	47	72	90	78	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
21	67	M	6	107	105	76.23	89	86	102	60	41	x	x	x	x	x	x	x	x	x	x	18	115	118	79.9	x	x	x	x	x	x	
22	66	M	x	x	x	x	x	x	x	x	x	11	90	100	86.3	x	83	119	106	85	x	x	x	x	x	x	x	x	x	x	x	
23	70	M	x	x	x	x	x	x	x	x	x	9	113	115	78.18	x	86	88	x	x	x	x	x	x	x	x	x	x	x	x	x	
24	62	F	5	111	108	81.8	x	86	94	162	157	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
25	52	F	3	120	115	81.97	106	78	84	45	48	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
26	75	M	5	106	112	79.71	80	62	82	103	55	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
27	67	M	1	113	109	74.96	x	79	79	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
28	71	M	x	x	x	x	x	x	x	x	x	8	98	114	88.42	67	51	80	120	101	x	x	x	x	x	x	x	x	x	x	x	
29	70	F	6	80	80	73.91	81	66	98	120	86	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
30	77	F	4	No accept-ability criteria	No accept-ability criteria	x	x	x	x	x	x	x	x	x	x	x	18	80	94	93.29	x	x	x	x	x	x	x	x	x	x	x	x

DLCO, diffusing capacity of the lung for carbon monoxide; DLCOVA, carbon monoxide diffusion capacity adjusted to alveolar volume in 1 s; FEV₁, forced vital capacity; M, male; PEM, maximum expiratory pressure; PIM, maximum inspiratory pressure; TLC, total lung capacity; x, evaluation not performed. The values presented are in%.

Table 2. Imaging evaluation.

Patient	Age (years)	Sex	Up to 6 months post-discharge		7–12 months post-discharge		13–18 months post-discharge		>18 months post-discharge	
			Months	Findings	Months	Findings	Months	Findings	Months	Findings
1	56	M	4	OP	x	x	x	x	21	PFr
2	68	M	4	OP	10	GGO + PFr	x	x	22	GGO + PFr
3	70	F	3	GGO	12	GGO subtle	x	x	24	GGO subtle
4	67	F	5	PFr	12	PFr	x	x	x	x
5	55	M	2	GGO	8	GGO	x	x	24	GGO
6	75	F	4	GGO + PF	x	x	x	x	x	x
7	72	M	5	GGO + OP	12	N	x	x	24	N
8	72	F	5	GGO	12	PFr	x	x	23	PFr
9	66	F	5	N	x	x	x	x	x	x
10	63	M	3	PF	11	PF	x	x	24	PFr
11	72	F	6	GGO	x	x	x	x	x	x
12	81	F	6	GGO + PFr	12	PFr	x	x	x	x
13	62	M	x	x	7	PF	18	GGO + PF	x	x
14	69	F	3	GGO	10	GGO	x	x	x	x
15	77	F	2	GGO	7	GGO	x	x	20	GGO subtle
16	63	F	3	GGO	x	x	x	x	x	x
17	72	F	5	N	11	N	x	x	24	N
18	77	M	5	GGO	x	x	x	x	x	x
19	68	M	5	PF; 16 mm nodule in the RUL – primary lung adenocarcinoma	x	x	13	PF	26	PF
20	67	M	3	GGO	x	x	x	x	20	GGO
21	66	M	6	N	x	x	x	x	x	x
22	70	M	x	x	7	GGO	18	N	x	x
23	62	F	4	N	x	x	15	N	x	x
24	52	F	3	GGO	7	GGO	x	x	x	x
25	75	M	6	GGO + PF	9	PFr	x	x	x	x
26	67	M	x	x	7	GGO + PFr	x	x	x	x
27	71	M	x	x	9	PFr	17	OP	22	PFr
28	70	F	x	x	7	GGO	x	x	x	x
29	46	M	x	x	7	N	15	N	x	x
30	46	F	x	x	12	N	x	x	x	x
31	40	M	4	N	x	x	x	x	x	x
32	77	F	5	GGO	x	x	13	GGO	x	x

GGO, ground-glass opacity; N, normal; OP, organising pneumonia; PF, pulmonary fibrosis; PFr, pulmonary fibrosis residual; RUL, right upper lobe; x, evaluation not performed.

7–12 months

In this period, nine patients underwent pulmonary function assessment, with a mean time of 10.4 ± 1.9 months (Table 1). Of these patients, the following mean values were obtained: FVC ($100.7 \pm 11.6\%$), FEV_1 ($107.6 \pm 12.6\%$), and FEV_1/FVC ratio ($83.6 \pm 4.1\%$). Among them, only two patients underwent plethysmography, and both of them showed restrictive ventilatory impairment (mean TLC 72.0%). No patient had obstructive ventilatory impairment.

Regarding diffusing capacity, only eight patients were tested, with a DLCO mean value of $78.9 \pm 15.4\%$ and DLCO/VA of $100.8 \pm 20.9\%$. Of these, two patients (25.0%) had a decrease in DLCO with normal DLCO/VA (mean 57.5% and 84.5%, respectively), and one patient (12.5%) had a decrease in both DLCO and DLCO/VA (76.0% and 79.0%, respectively).

Only seven patients underwent measurement of MIP ($85.9 \pm 28.9\%$) and MEP ($86.0 \pm 46.5\%$). Two patients (28.6%) had a decrease in MEP (mean 56.0%).

After 12 months

Five patients underwent pulmonary function assessment, with an average time of 17.4 ± 3.3 months (Table 1).

Within these patients, the following mean values were acquired: FVC ($101.4 \pm 13.5\%$), FEV_1 ($105.2 \pm 8.6\%$), and FEV_1/FVC ratio ($82.2 \pm 6.6\%$). None of them underwent plethysmography, so it is impossible to assess the presence of restrictive ventilatory impairment. No obstructive ventilatory impairment was found.

Three patients underwent diffusion tests (mean DLCO 75.7% and DLCO/VA 90.7%), and two patients (66.7%) had a decrease in DLCO with normal DLCO/VA (mean 66.0% and 84.5%, respectively).

Only one patient underwent MIP and MEP measurement, and no alterations were observed.

Of the 22 initial patients, only six patients underwent two respiratory functional assessments due to reasons such as normal initial evaluation, subtle changes, or missed appointments, among others. Of these, five patients had function impairments in the first assessment: two with decreased DLCO; one with decreased DLCO and DLCO/VA; one with decreased DLCO, MIP, and MEP; and one with decreased MEP. Upon reassessment, 40.0% of patients ($n = 2$) improved: one with improvement in DLCO/VA and one in DLCO, MIP, and MEP. Patient with reduced MEP did not have MEP measured in the second assessment.

Imaging evaluation

Up to 6 months

During this period, 25 patients underwent chest CT scans, with an average time of 4.2 ± 1.2 months. The following changes were identified: GGOs ($n = 12$; 48.0%), OP

($n = 3$; 12.0%), PF ($n = 3$; 12.0% – evident fibrosis $n = 2$, 8.0% and residual fibrosis $n = 1$, 4.0%), and GGOs with fibrosis ($n = 3$; 12.0%). Five patients (20.0%) showed no abnormalities. Incidentally, a 16 mm nodule was identified in one of the exams, which was confirmed to be a primary lung adenocarcinoma. The patient was referred to an oncology pulmonology consultation.

7–12 months

Twenty patients underwent chest CT evaluation, with an average time of 9.5 ± 2.2 months. The following changes were recognised: GGOs ($n = 7$; 35.0%), PF ($n = 7$; 35.0% – evident fibrosis $n = 2$, 10.0% and residual fibrosis $n = 5$, 25.0%), and GGOs with PF ($n = 2$; 10.0%). Four patients (20.0%) showed no abnormalities.

13–18 months

Seven patients underwent imaging evaluation, with an average time of 15.6 ± 2.2 months. The following changes were identified: GGOs ($n = 1$; 14.3%), OP ($n = 1$; 14.3%), PF ($n = 1$; 14.3% – evident fibrosis), and GGOs with fibrosis ($n = 1$; 14.3%). Three patients (42.9%) showed no abnormalities.

After 18 months

Twelve patients underwent chest CT scans, with an average time of 22.8 ± 1.9 months. The following changes were recognised: PF ($n = 5$; 41.7% – evident fibrosis $n = 1$, 8.3% and residual fibrosis $n = 4$, 33.3%), GGOs ($n = 4$; 33.3%), and GGOs with fibrosis ($n = 1$; 8.3%). Two patients (16.7%) showed no abnormalities.

In this study, 22 patients underwent two or more pulmonary imaging evaluations. Table 2 presents the main imaging findings of each patient at the different assessment times. From data analysis, 54.6% ($n = 12$) of the patients remained stable and 45.5% ($n = 10$) had a progressive imaging improvement over the evaluations. Of these 10 patients, 6 (60.0%) patients had residual fibrosis, 2 (20.0%) improvement in inflammatory changes, and 2 (20.0%) complete resolution of initial findings. 32 patients were submitted at least to one chest CT scan (2–26 months). Analysing latest CT scans, 11 patients (34.4%) presented inflammatory changes, 8 (25.0%) fibrotic changes, and 4 (12.5%) had both. CT scan was normal in 9 patients (28.1%).

Discussion

The main purpose of this study was to evaluate patients with severe SARS-CoV-2 infection, who had been admitted to ICU, for a follow-up period up to 18 months post-discharge. Our study shows that persistent symptoms and physiologic and radiologic abnormalities are common at 3-month follow-

up. Dyspnoea was the primary symptom reported by patients after SARS-CoV-2 infection, followed by dry cough and asthenia/fatigue. There was a progressive improvement in this symptomatology in the second assessment. In line with our results, dyspnoea was the most frequent respiratory symptom 1–4 months after infection in some reports (13, 14); however, these studies assessed patients with different severity levels of COVID. In a study involving patients with ICU admission, dyspnoea was also the most frequently reported symptom (15). Previously, significant improvements in dyspnoea were also observed in assessments conducted between 6 months and 1 year after SARS-CoV-2 infection in ICU-admitted patients (16, 17).

Regarding the main respiratory functional changes between 3 months and 12 months post-COVID infection, some studies showed a persistently decrease in DLCO, as well as a restrictive ventilatory impairment and obstructive ventilatory impairment (16, 18). In a 6-month evaluation study, in addition to the reduction in DLCO, a decrease in MIP was one of the most frequent alterations (19).

In our evaluation up to the first 6 months post-discharge, the main lung function abnormalities observed were a decrease in DLCO, followed by a decrease in MIP and MEP, and restrictive ventilatory impairment. A decrease in MIP was present in 10.0% of our patients. Longitudinal analysis between 7 months and 12 months after SARS-Cov-2 infection also showed us that the main alterations were a decrease in DLCO, restrictive ventilatory impairment, and a decrease in MEP. After 12 months post-discharge, the only lung function impairment that persisted was a decrease in DLCO. Our results are in line with other study of Wu and colleagues that showed that approximately one-third of COVID-19 patients had persistently impaired DLCO at 12 months after COVID-19 (20). Among patients who underwent two respiratory functional assessments, five (83.3%) had some impairment in their function, with improvement observed in 50.0% ($n = 3$) of the patients. The literature also demonstrated a gradual improvement in respiratory function in critically ill COVID patients throughout the period from discharge to 6 months (21) and 12 months (22).

In terms of average values of respiratory function tests, severe abnormalities were not observed, being a decrease in DLCO the most pronounced impairment. These are in line with findings in the literature, as demonstrated in a study of 18 patients who survived COVID-19 and required mechanical ventilation, where lung function tests at 6 months post-discharge did not show significant limitations (FVC: $92 \pm 16\%$; FEV₁: $92 \pm 20\%$; and DLCO/VA: $81 \pm 16\%$) (23).

We evaluated MIP and MEP as indicators of inspiratory and expiratory muscle strength, respectively (24), useful for assessing muscle function in lower respiratory tract infections

(25), including severe SARS-CoV-2 infection, which can cause lung damage leading to limitations in respiratory muscle strength (26). MIP and MEP can be influenced by ICU-related myopathy and corticosteroid-induced myopathy (27). Over half of the patients in this study required invasive mechanical ventilation, likely contributing to observed abnormalities and complicating interpretation. The prevalence of respiratory muscle weakness post-SARS-CoV-2 remains unclear, as these assessments are rarely reported. Small studies suggest that inspiratory muscle training offers physiological benefits during recovery (28).

Regarding pulmonary radiological abnormalities, up to the first 6 months after SARS-CoV-2 infection, the main radiological findings were GGOs, OP, fibrosis, and ground-glass opacities with fibrosis (GGO-F). Between 7 months and 12 months, the more frequent CT pattern findings were GGO, fibrosis, or both simultaneously. After 12 months, the CT findings observed were the same: GGO, PF, or both. Over time, there was a decrease in GGOs (consistent with inflammatory changes) and persistence of fibrotic changes. Two patients initially described as having marked PF transitioned to residual fibrosis in the re-evaluation. This chest CT longitudinal evaluation reveals persistent abnormality in the lung interstitium and may suggest an explanation for the observed reduction of the diffusion capacity of the lung physiologically. Several studies assessing patients after hospitalisation for COVID-19 show that fibrotic sequelae were present four to 12 months post-discharge in 20 to 33.3% of patients (29, 30). In this study, fibrotic changes were present in 37.5% of patients 4–26 months after infection. Therefore, it is evident that fibrosis occurs in a significant proportion of individuals who had COVID-19 pneumonia. Some authors also found that abnormalities present in chest CT eventually decrease over time (17, 30). Our results support this, since in 45.5% of the patients, there was an improvement of CT abnormalities after 12 months of follow-up. Thus, in some patients, these sequelae may represent a regressive interstitial syndrome (2) and not a diffuse progressive interstitial lung disease. However, more long-term studies are needed to evaluate these patients.

A main limitation of our study was the small sample size, preventing us from correlating PFT changes with radiological abnormalities. However, according to the literature, respiratory functional impairment after COVID-19 pneumonia is associated with persistent pulmonary radiological abnormalities (13, 18, 20).

Another limitation is the study's retrospective nature, which hindered the collection of certain variables within specific time frames, complicating analysis. Additionally, the evaluation of CT scans by different radiologists and machines introduced subjectivity and potential bias.

Conclusions

Our study shows that patients with severe COVID-19 requiring ICU admission can fully recover. However, some patients may experience persistent symptoms, commonly referred to as long COVID, which can last beyond 12 months after hospitalisation. This persistent symptomatology with respiratory functional changes (particularly a reduction in DLCO) and imaging findings (most frequently residual PF) tends to improve over time.

Nevertheless, further studies are required to assess the long-term consequences of this disease in patients requiring ICU admission.

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