Long-term Outcomes and Recovery of Patients who Survived COVID-19: LUNG INJURY COVID-19 Study

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Background. LUNG INJURY COVID-19 (clinicaltrials.gov NCT 21/399-E) is a registry-based prospective observational cohort study to evaluate long-term outcomes and recovery 12 months after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection according to severity.

Methods. Three hundred five coronavirus disease 2019 (COVID-19) survivors were included (moderate, 162; severe, 143). Twelve months after SARS-CoV-2 infection, there was resolution of respiratory symptoms (37.9% in severe vs 27.3% in moderate pneumonia; P = .089).

Results. Exertional dyspnea was present (20% in severe vs 18.4% in moderate; P = .810). Abnormalities on chest radiology imaging were detected more often in severe COVID-19 infection vs moderate infection (29% vs 8.8%; P < .001). Pulmonary function testing (forced spirometry or diffusion) performed at 12 months of mean follow-up according to protocol detected anomalies in 31.4% of patients with severe COVID-19 courses and in 27.7% of moderate patients. Risk factors associated with diffusion impairment at 12 months were age (odds ratio [OR], 1.05; 95% CI, 1.01–1.10; P = .008), forced expiratory volume in 1 second predicted at follow-up (OR, 0.96; 95% CI, 0.93–0.99; P = .017), and dyspnea score at follow-up (OR, 3.16; 95% CI, 1.43–6.97; P = .004). Computed tomography (CT) scans performed at 12 months of mean follow-up showed evidence of fibrosis in almost half of patients with severe COVID-19 courses, who underwent CT according to protocol.

Conclusions. At 12 months from infection onset, most patients refer to symptoms, particularly muscle weakness and dyspnea, and almost one-third of patients with severe COVID-19 pneumonia had impaired pulmonary diffusion and abnormalities on chest radiology imaging. These results emphasize the importance of systematic follow-up after severe COVID-19, with appropriate management of pulmonary sequelae.

Keywords. long-term effects; SARS-CoV-2 infection; sequelae.

Physicians are observing persisting symptoms and unexpected substantial organ dysfunction after severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection [1], as previously observed in the severe acute respiratory syndrome (SARS) outbreak [2].

In previous coronavirus infections, studies concluded that between 20% and 60% of survivors of the global SARS outbreak caused by SARS-CoV and the Middle East respiratory syndrome coronavirus (MERS-CoV) experienced persistent physiological impairment and abnormal radiology consistent with pulmonary fibrosis [3–6]. The appearance of pulmonary fibrosis correlated with the severity and duration of acute illness [6, 7]. Drawing on these experiences, respiratory complications are predicted to be an important sequela of coronavirus disease 2019 (COVID-19).

In SARS-CoV-2 infection, several studies have reported lingering radiological and pulmonary diffusion abnormalities in a sizeable proportion of patients up to 3–6 months after hospital discharge. More than 70% of patients reported at least 1 symptom that persisted, and >50% of patients presented with residual chest imaging abnormalities 6 months after illness onset [8]. Some reports had data up to 3 months after onset that indicated that one-fifth of the patients displayed a reduced lung diffusing capacity and one-fourth of discharged patients had chest computed tomography (CT) scan abnormalities [9, 10]. This is particularly relevant for patients who required mechanical ventilation during their hospital stay [10].

SARS-CoV-2 infection is a new disease, and uncertainty remains regarding the possible long-term health sequelae, particularly in survivors of severe disease courses, for whom long-term complications and incomplete recovery after discharge would

be expected. The clinical evolution and recovery are heterogeneous. At short-term follow-up, lung parenchymal abnormalities seem to have improved in most cases, while some patients persistently show abnormalities [8–10]. Potential long-term consequences specifically after severe COVID-19 still need to be investigated. Greater knowledge about the evolution of the disease and its possible complications is necessary for proper planning and optimization of resources.

METHODS

Study Design and Population

We initiated LUNG INJURY COVID-19, a registry to assess pulmonary sequelae following moderate or severe COVID-19 infection. This study was designed as a prospective clinical cohort to evaluate long-term outcomes and recovery 12 months after SARS-CoV-2 infection onset according to severity. This study includes adults who survived acute COVID-19 pneumonia and appeared for clinical follow-up after either moderate or severe COVID-19 infection.

This observational cohort study includes consecutive adults aged 18–84 years who survived laboratory-confirmed SARS-CoV-2 pneumonia and were referred to the follow-up clinic in the Pneumology Department at Hospital Clínico San Carlos in Madrid (Spain) from March 23 to August 20, 2020. Patients were referred from primary or specialized care within clinical practice after suffering a moderate or severe SARS-CoV-2 infection for follow-up. There were no exclusion criteria, except for patients' or families' explicit refusal to participate.

In this first analysis of our cohort, we report on chronic pulmonary sequelae in patients who had experienced moderate or severe COVID-19 pneumonia, with the goal of improving the current understanding of the heterogeneous COVID-19 trajectories.

Data Source

Baseline information (demographic data, comorbidities measured by the Charlson index [11], oxygen saturation in emergency room assessment) and clinical assessments during hospitalization (radiology, laboratory findings, clinical signs and symptoms, severity according to the use of ventilatory support and/or admission to the intensive care unit [ICU]) were retrieved from medical records.

Following the British Thoracic Society Guidance on Respiratory Follow Up of Patients with Diagnosis of COVID-19 Pneumonia [12], the following procedures were performed: assessment of symptoms and breathlessness, British modified Medical Research Council (mMRC) [13] dyspnea score determination, assessment of oxygen saturation, routine blood examinations, and chest x-ray. Pulmonary damage was quantified by adapting the Radiographic Assessment of Lung Edema (RALE) score to COVID-19 [14]. If chest x-ray changes had fully resolved and the patient had made a good recovery, we considered

discharge. If chest x-ray had not cleared satisfactorily and/or the patient had ongoing respiratory symptoms, we considered pulmonary function testing including spirometry and measurement of carbon monoxide diffusing capacity (DLCO; Masterscreen, Jaeger, Germany). All procedures were carried out according to American Thoracic Society (ATS) and European Respiratory Society (ERS) guidelines [15, 16]. Arterial blood gases were obtained when hemoglobin oxygen saturation was below 90% or at the physician's discretion. When there were persistent alterations in the radiography and/or impairment in pulmonary function tests (forced vital capacity [FVC] <80% without forced expiratory volume in 1 second/FVC <70% and/or DLCO <80%), a high-resolution CT scan was performed. HRCT scans (Optima CT660, General Electric, Boston, Massachusetts, USA) were obtained in the supine position during end-inspiration breath-holding. If there was clinical suspicion for pulmonary embolism (PE), additional contrast CTs were performed. The images were classified according to guidance by the Fleischner Society [17] based on the presence of ground-glass opacities, parenchymal bands, bronchiectasis, irregular lines, and reticular patterns. Images were interpreted by 2 senior radiologists experienced in chest radiology. All imaging data were analyzed in the absence of clinical or laboratory results or pulmonary function tests. After independent evaluation, any discrepancies were resolved through discussion and negotiation. A normal radiological pattern was defined as the absence of abnormalities.

Patients were stratified into 2 groups following the World Health Organization Clinical Progression Scale [18] according to severity: (1) moderate disease: patients with clinical signs of pneumonia and oxygen saturation (SpO2) ≥90% requiring supplemental oxygen by mask or nasal prongs; (2) severe disease: hospitalized patients who require respiratory support through noninvasive ventilation (NIV), high-flow nasal cannula oxygen (HFNC), or intubation and mechanical ventilation (IMV).

Statistical Analysis

Descriptive statistics are reported as mean (SD) or median (interquartile range [IQR]). Differences between the moderate and severe COVID-19 groups were analyzed for statistical significance using the chi-square or Fisher exact test for categorical variables and the 2-sample *t* test or Wilcoxon rank-sum test for continuous variables, as applicable. Demographic factors, pulmonary and pulmonary function tests, and radiological sign associations with the COVID-19 severity groups were estimated using linear or logistic regression models where applicable. The conventional level of statistical significance of .05 was used for all analyses.

RESULTS

Between March 23 and August 20, 2020, this registry evaluated 305 patients with pneumonia from SARS-CoV-2 who were treated at Hospital Clínico San Carlos and referred to the follow-up clinic in the Pneumology Department. Sixty-seven were

not considered for follow-up because they were living outside the hospital care area (Figure 1).

Baseline Characteristics and Symptoms

Three hundred five patients were included in the analysis (143 with severe COVID-19 infection and 162 with moderate infection); 75.5% of patients with severe infection required ICU admission, and 63.5% of patients with moderate pneumonia were hospitalized. Patients with severe COVID-19 were older than patients with moderate disease (mean [SD] age, 64.7 [15] vs 60.4 [14.2] years; P = .010), were mostly male (63.6% vs 41.3%;

P < .001), and, as expected, they had more comorbidities (mean [SD] Charlson, 2.9 [2.2] vs 2.3 [2.2]; P = .024). Latin race (26.6% vs 7.9%; P < .001) and obesity (55.9% vs 33.3%; P < .001) were more prevalent in the severe group (P < .001). In addition, body mass index (BMI) was significantly higher in patients with severe disease (31.3 [5.3] vs 28.5 [5.3]; P < .001). However, in severe and moderate COVID-19 patients, history of lung disease (27.9% vs. 37.3%; P = .062) and smoking history were not significantly different. A logistic regression analysis showed that male sex, Latin race, and BMI were factors significantly associated with severe COVID-19 infection (Table 1).
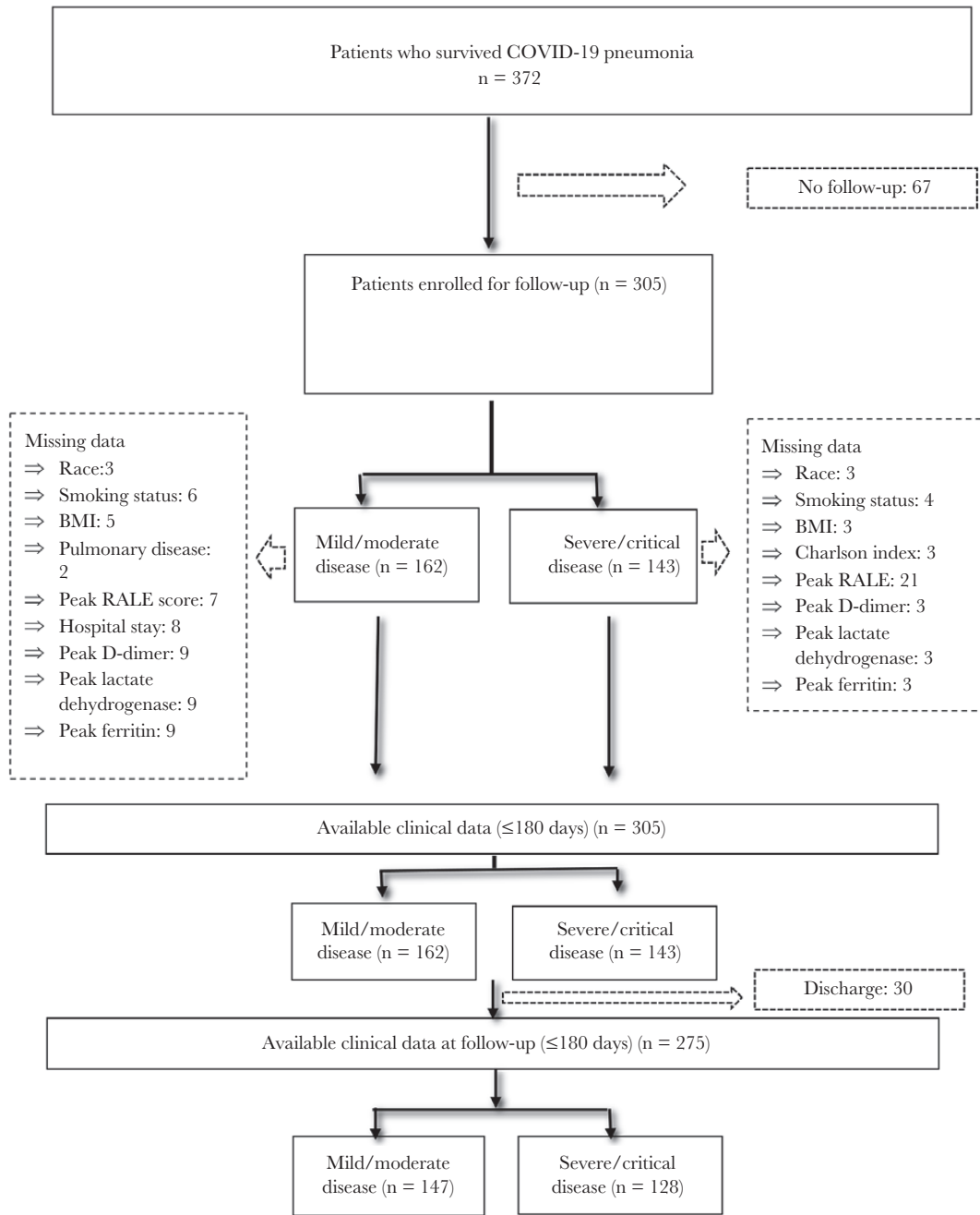
Figure 1. Flowchart of the sampling process. Abbreviations: BMI, body mass index; COVID-19, coronavirus disease 2019; RALE, Radiographic Assessment of Lung Edema.

Table 1. Baseline Characteristics of Enrolled Patients With Severe and Moderate Infection

Enrolled Patients	Severe Disease (n = 143)	Moderate Disease (n = 162)	P Value[a]
Characteristics at baseline			
Gender (male), %	63.64	41.36	<.001
Age, y (%)	64.79 (15.05)	60.46 (14.20)	.010
Race, %			<.001
-Caucasian	73.64	92.06	
-Latin	26.36	7.94	
-Asian-Indian	0.77	0	
Smoking status, %			.728
-Never-smoker	60.16	57.14	
-Current smoker	9.38	7.94	
-Former smoker	30.47	34.92	
Body mass index, mean (SD), kg/m^2	31.36 (5.38)	28.52 (5.38)	<.001
Charlson index, mean (SD)	2.98 (2.20)	2.31 (2.26)	.024
Obesity, %	55.91	33.33	<.001
Pulmonary disease, %	27.94	37.32	.062
COPD, %	9.6	12	.342
Asthma, %	11.81	15.57	.248
SAHS, %	8	11.76	.220
ILD, %	0	2.54	
Neoplasia, %	14.69	13.58	.445
AATD, %	0.81	3.3	.145
PTE, %	1.65	0	.257
Home oxygen therapy, %	2.43	2.36	.976
Characteristics of acute COVID-19			
Hospitalization, %	100	63.58	<.001
Length of hospital stay, median (IQR), d	28 (20–39)	5 (0–11)	<.001
ICU/UCIR, %	75.52	0	<.001
Ventilatory support therapy, %	98.60	0	<.001
Tracheostomy, %	13.77	0	<.001
PTE, %	3.45	0	.158
RALE			
-Peak RALE score, mean (SD)	4.66 (2.29)	2.51 (2.01)	<.001
-RALE score at discharge, mean (SD)	4.53 (2.29)	3.0 (2.25)	<.001
Bilateral involvement, %	91.06	68.09	<.001
Laboratory findings[b]			
-Lactate dehydrogenase, median (IQR), U/L	474 (389.5–561)	460 (378–545)	.850
-Ferritin, median (IQR), ng/mL	446 (237–749)	420 (225–675)	.813
-D-dimer, median (IQR), ng/mL	941 (474–1548)	566.5 (379–1207)	.004
-D-dimer >500 ng/mL, %	71.56	63.64	.177
Clinical associations with a severe COVID-19 disease course	**OR (95% CI)**		**P-value**
Age	.997 (.956-1.040)		.920
Sex (male)	3.102 (1.520-6.331)		.002
Race (Latin)	8.444 (2.527-28.212)		.001
Body mass index	1.106 (1.036-1.180)		.002
Never smoker	.905 (.429-1.906)		.793
Charlson	1.230 (.915-1.655)		.169
Respiratory comorbidity	.498 (.232-1.069)		.074

Data are expressed as No. (%), mean (SD), or median (IQR).

Abbreviations: AATD, alpha 1 antitrypsin deficiency; COPD, chronic obstructive pulmonary disease; ICU, intensive care unit; ILD, diffuse interstitial lung disease; IQR, interquartile range; PTE, pulmonary thromboembolism; RALE, Radiographic Assessment of Lung Edema; SAHS, sleep apnea hypopnea syndrome; UCRI, intermediate respiratory care unit.

[a] P values from 2-sample *t* tests, Wilcoxon rank-sum test, chi-square test, or Fisher exact.

[b] All laboratory findings are values at discharge.

Outcomes at Medium-term Follow-up

At follow-up, patients in both COVID-19 severity groups indicated relevant symptoms, with persistent exertional dyspnea in both groups. Dyspnea ≥2 mMRC among severe cases was significantly more prevalent than in moderate cases (55.5% vs 44%; P = .042). More than half of the patients with severe

infection (58.1%) had unresolved x-ray abnormalities affected by either pulmonary opacities, parenchymal bands, or reticulations. Only 23.7% of patients in the moderate COVID-19 group had imaging abnormalities. In 161 (52.7%) patients, pulmonary function was tested due to the chest x-ray not having cleared satisfactorily and/or the patient having ongoing respiratory symptoms. Of these, impaired functional data were present in more patients with severe COVID-19 infection vs the group of moderate patients (59.4% vs 40.2%; $P < .001$). The median (SD) DLCO in severe vs moderate patients was 70.8 (21.3) vs 82.6 (25.7; $P < .001$). More than a third of patients in both groups had elevated D-dimer >500 ng/mL, although levels were higher in patients with severe COVID-19 infection vs in the group of moderate patients (median [IQR], 432 [278–742] vs 350.5 [219–597]; $P = .023$). Only 30 (10%) patients were considered

for discharge and did not continue follow-up. Findings in the medium-term follow-up are provided in Table 2.

Outcomes at Long-term Follow-up

The assessment of symptoms after more than 10 months since SARS-CoV-2 infection showed resolution in a third of patients in both groups (37.9% in severe vs 27.3% in moderate; $P = .089$). Long-term abnormalities in chest x-ray imaging after SARS-CoV-2 infection were more common in patients with severe COVID-19 infection vs in the group of moderate patients (29% vs 8.8%; $P < .001$). In 153 (55.6%) patients, pulmonary function was tested due the chest x-ray not having cleared satisfactorily and/or the patient having ongoing respiratory symptoms. Of these, functional normalization dates were more common in patients with moderate COVID-19 infection vs the

Table 2. Features at Medium-term Follow-up (≤180 Days From Initial Symptoms)

Clinical Characteristics	Severe Disease (n = 143)	Moderate Disease (n = 162)	P Value[a]
Symptom resolution, %	13.08	14.06	.817
Symptoms, %			
-Cough	14.41	26.32	.033
-Chest pain	24.11	31.37	.235
-Asthenia	29.46	37.00	.244
-Memory loss	10.48	4.55	.125
-Hair loss	16.51	6.59	.032
Dyspnea mMRC, mean (SD), No.	1.45 (0.07)	1.33 (0.06)	.143
Dyspnea mMRC ≥2, %	55.55	44.09	.042
Crackly, %	16.52	8.33	.090
Average time,[b] median (IQR), d	135 (116–153)	133 (116–158)	.777
Radiological Features	Severe Disease (n = 139)	Moderate Disease (n = 157)	
Normal radiological pattern, %	41.86	76.30	.001
RALE score, mean (SD)	0.62 (0.14)	0.12 (0.06)	.002
RALE score 0, %	85.27	95.56	.033
Pulmonary opacities, %	42.15	13.11	.001
Bands or reticulations, %	33.06	14.75	.001
Hypoattenuation, %	5.79	5.00	.506
Average time,[b] median (IQR), d	119 (91–144)	93 (61–128)	.001
Pulmonary Functional Data	Severe Disease (n = 79)	Moderate Disease (n = 82)	
Functional data normalization, %	40.51	59.76	<.001
FEV1, mean (SD), % predicted	92.58 (20.51)	99.83 (20.88)	.048
FVC, mean (SD), % predicted	94.90 (25.71)	102.89 (20.93)	.036
FEV/FVC, mean (SD)	76.83 (12.67)	75.98 (1.40)	.681
SpO2, mean (SD), %	96.02 (1.86)	96.81 (11.65)	.002
DLCO, mean (SD), % predicted	70.84 (21.35)	82.60 (25.73)	<.001
Average time,[b] median (IQR), d	138 (117–156)	131 (109–147)	.271
Serum Biomarkers	Severe Disease (n = 86)	Moderate Disease (n = 97)	
Lactate dehydrogenase, median (IQR), U/L	387 (347–442)	387 (327–415)	.180
Ferritin, median (IQR), ng/mL	88 (39–173)	65 (34.5–110)	.287
D-dimer, median (IQR), ng/mL	432 (278–742)	350.5 (219–597)	.023
D-dimer >500 ng/mL, %	37.35	33.33	.347
Average time,[b] median (IQR), d	120 (109–130)	115 (107–122)	.445

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council; RALE, Radiographic Assessment of Lung Edema; SpO2, oxygen saturation.

[a] P values from 2-sample t test, Wilcoxon rank-sum test, chi-square test, or Fisher exact test. Average time from initial symptoms to evaluation.

[b] time from initial symptoms to the follow-up data.

group of severe patients (64.1% vs 50.6%; $P < .001$). There were no differences between severity groups in spirometry parameters. The mean (SD) DLCO in severe vs moderate patients was 75.7 (24.6) vs 83.7 (21.1; $P = .032$). Seventy-nine patients underwent a CT scan according to protocol, with a greater median time between infection onset and CT in patients with severe COVID-19 infection vs those in the moderate group (median [IQR], 332 [250–381] days vs 306 [239–354] days; $P = .451$). Radiological features were significantly more prevalent after severe infection than after moderate COVID-19, as shown in Figure 2. Serum laboratory testing was carried out in 116 patients (42.1%) because they maintained abnormal results from previous visits. More than a third of patients in both groups had elevated D-dimer >500 ng/mL; no significant differences were found between severity groups. Findings in the long-term follow-up are provided in Table 3.

Prediction of Abnormalities in Long-term Chest Radiology Imaging

Ten months after discharge, abnormalities in chest radiology imaging were detected in 47 patients (17.8%). These patients with abnormalities on chest x-ray vs normal chest radiology were older (mean [SD] age, 68.8 [14.0] vs 60.4 [14.1] years; $P < .001$) and had a significantly longer hospital stay (median [IQR], 26 [22–38] vs 11 [3–22]; $P < .001$) and greater infection severity than patients with normal chest radiology (72.3% vs 38.2%; $P < .001$). Long-term FVC% predicted outcomes and DLCO% predicted outcomes at follow-up were significantly lower in patients with abnormalities on radiology imaging. Results of the multivariable analysis found that the number of days hospitalized and FVC% predicted at follow-up were associated with long-term abnormalities on chest radiology imaging (Table 4).

Prediction of Long-term Lung Function Deficits

Ten months after discharge, impaired pulmonary diffusion was detected in 65 patients (42.4%). These patients with abnormal diffusion vs normal were older (mean [SD] age, 67.7 [14.7] vs 58.8 [11.9] years; $P < .001$), had different smoking histories (never-smoker: 43.6% vs 65.3%; $P = .011$), and history of lung disease was more prevalent (42.3% vs 27.1%; $P = .045$). Hospital stay was significantly longer in patients with abnormal diffusion vs normal (21.5 [10.5–32.5] vs 12.5 [2–26] days; $P = .033$). Results of the multivariable analysis found that age, FEV1% predicted, and dyspnea score at follow-up were independent risk factors associated with the presence of impaired DLCO% (Table 5). There was a significant negative correlation between DLCO% predicted and dyspnea score ($R = -0.225$; $P = .006$) and length of hospital stay ($R = -0.1594$; $P = .0546$), whereas RALE score and D-dimer levels showed no correlation with DLCO% predicted.
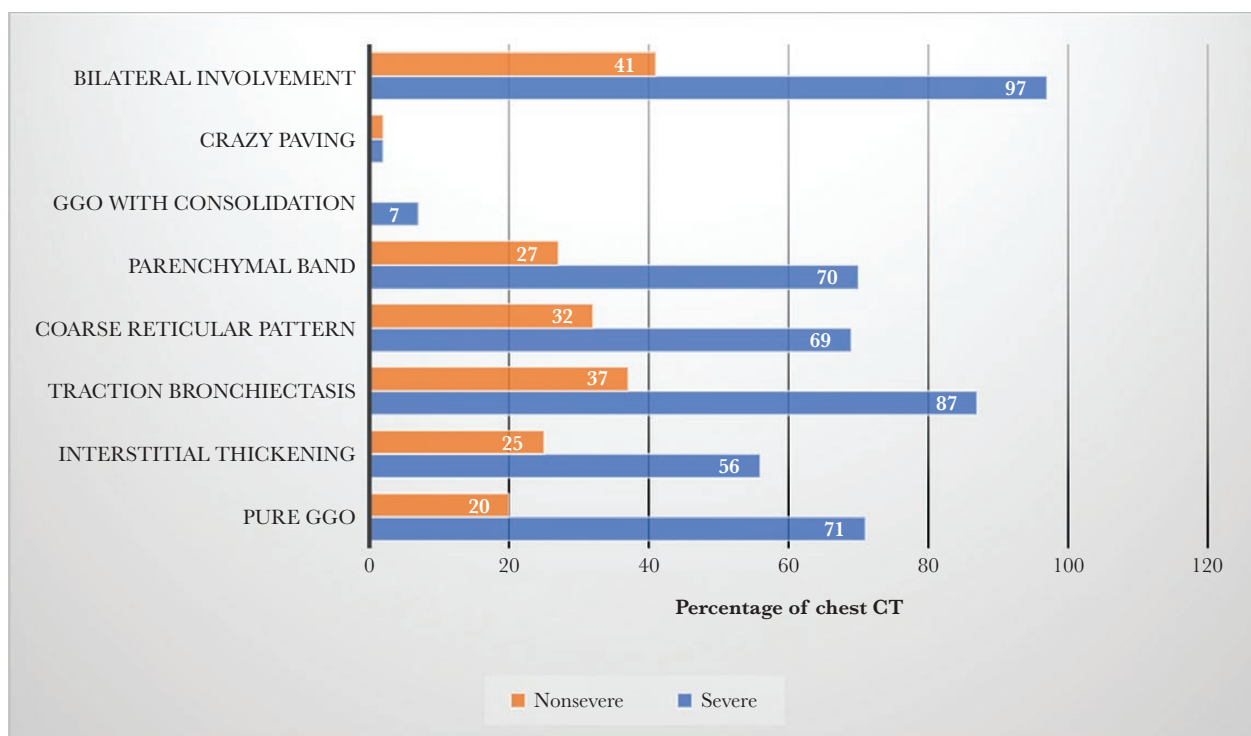
Figure 2. Proportion of chest CT with imaging abnormalities after 1 year in severe vs nonsevere COVID infection. Abbreviations: COVID-19, coronavirus disease 2019; CT, computed tomography; GGO, ground-glass opacity.

Table 3. Features at Long-term Follow-up (>180 Days From Initial Symptoms)

Clinical Characteristics	Severe Disease (n = 128)	Moderate Disease (n = 147)	P Value[a]
Symptom resolution, %	37.96	27.35	.089
Symptoms, %			
-Cough	3.30	11.90	.030
-Chest pain	4.35	13.95	.025
-Asthenia	7.69	20.00	.017
-Memory loss	4.55	3.95	.850
-Hair loss	0.00	1.27	.287
Dyspnea mMRC, mean (SD), No.	0.82 (0.07)	0.89 (0.06)	.392
Dyspnea mMRC ≥2, %	20	18.42	.249
Crackly, %	8.43	6.49	.642
Average time,[b] median (IQR), d	300 (245–352)	306 (254–363)	.352
Radiological Features	Severe Disease (n = 117)	Moderate Disease (n = 147)	
Normal radiological pattern, %	70.94	91.15	.001
RALE score, mean (SD)	0.09 (0.05)	0.00 (0.00)	.085
RALE score 0, %	97.06	99.35	.176
Pulmonary opacities, %	10.34	2.19	.006
Parenchymal bands or reticulations, %	21.05	7.25	.001
Hypoattenuation, %	6.20	2.88	.154
Average time,[b] median (IQR), d	260 (228–320)	274 (225–353)	.262
Pulmonary Functional Data	Severe Disease (n = 75)	Moderate Disease (n = 78)	
Functional data normalization, %	50.66	64.10	<.001
FEV1, mean (SD), % predicted	101.84 (21.38)	103.70 (19.62)	.620
FVC, mean (SD), % predicted	103.44 (22.59)	110.55 (20.55)	.074
FEV/FVC, mean (SD), %	78.46 (8.66)	75.51 (7.53)	.033
SpO2, mean (SD), %	95.83 (4.05)	97.18 (1.15)	.008
DLCO, mean (SD), % predicted	75.73 (24.68)	83.79 (21.18)	.032
Average time,[b] median (IQR), d	277 (224–350)	268 (218–344)	.609
Serum Biomarkers	Severe Disease (n = 58)	Moderate Disease (n = 58)	
Lactate dehydrogenase, median (IQR), U/L	366 (326–427)	363 (316–410)	.445
Ferritin, median (IQR), ng/mL	114 (55.5–304.5)	72.75 (45–143)	.047
D-dimer, median (IQR), ng/mL	415 (265–831)	390 (242–502)	.374
D-dimer >500 ng/mL, %	36.36	25	.131
Average time,[b] median (IQR), d	289 (273–306)	275 (255–294)	.256

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council; RALE, Radiographic Assessment of Lung Edema; SpO2, oxygen saturation.

[a]P values from 2-sample t tests, Wilcoxon rank-sum test, chi-square test, or Fisher exact test. Average time from initial symptoms to evaluation.

[b]Time from initial symptoms to the follow-up data.

D-dimer Relationship at Long-term Follow-up

Ten months after discharge, abnormal D-dimer >500 ng/mL was detected in 31% of patients. These patients with abnormal D-dimer were older (mean [SD] age, 72.3 [14.1] vs 57.2 [12.5] years; $P < .001$) and had a higher peak D-dimer during hospitalization (median [IQR], 5062 [1800–22 840] vs 1748 [800–4568]; $P < .020$). At follow-up, impaired FEV1% predicted, SpO2, and DLCO% predicted functional data were more common in patients with abnormal D-dimer (Table 6).

DISCUSSION

To our knowledge, this is the first study reporting on long-term outcomes in respiratory follow-up after SARS-CoV-2 infection. Few reports have described sequelae in COVID-19 survivors, and this analysis is the first to investigate the long-term effects on changes in symptoms, pulmonary function, and chest radiology in patients with severe infection and moderate infection 1 year after infection.

This analysis demonstrates that nearly two-thirds of the cohort suffered symptoms almost a year after SARS-CoV-2 infection onset, particularly fatigue or muscle weakness and dyspnea. This is consistent with data from previous long-term SARS follow-up studies [19]. A follow-up study of SARS survivors showed that 40% of patients still had a chronic fatigue problem for a mean period of 41.3 months after SARS infection [20]. The underlying mechanism of fatigue or muscle weakness post-COVID-19 is likely multifactorial and might include the direct effects of viral infection, the immunological response,

Table 4. Relationship Between Radiological Features and Clinical Characteristics, COVID-19 Disease Severity and Features at Long-term Follow-up

Total (n = 264)	Abnormal Radiological Pattern (n = 47)	Normal Radiological Pattern (n = 217)	P Value
Age, mean (SD), y	68.89 (14.02)	60.40 (14.16)	<.001
Never-smoker, %	50	58.79	.187
Pulmonary disease, %	24.44	32.16	.203
Body mass index, mean (SD), kg/m^2	30.43 (4.46)	30.17 (5.80)	.475
Length of hospital stay, median (IQR), d	26 (22–38)	11 (3–22)	<.001
Peak RALE score, mean (SD)	4.73 (2.29)	3.69 (2.47)	.014
Severe disease, %	72.34	38.25	<.001
Features at long-term follow-up (>180 d)			
mMRC dyspnea, mean (SD)	0.91 (0.78)	0.82 (0.70)	.492
FEV/FVC, mean (SD), %	78.91 (7.80)	76.60 (8.48)	.355
FEV1, mean (SD), % predicted	97.34 (18.15)	104.28 (21.09)	.105
FVC, mean (SD), % predicted	96.89 (18.72)	110.11 (21.84)	.007
SpO2, %	96.38	96.81	.122
DLCO, mean (SD), % predicted	69.06 (21.04)	83.56 (22.65)	<.001
D-dimer, median (IQR), ng/mL	302.5 (215–867.5)	400 (242–551)	.812
D-dimer >500 ng/mL, %	35	27.06	.326
Predictors of long-term abnormalities on chest radiology imaging			
		OR (95% CI)	P Value
Age		0.964 (0.928–1.003)	.072
Length of hospital stay		0.966 (0.939–0.994)	.019
FVC at long-term follow-up		1.026 (1.002–1.051)	.032

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council; RALE, Radiographic Assessment of Lung Edema; SpO2, oxygen saturation.

corticosteroid therapy, ICU stay, or isolation. In our analysis, fatigue or muscle weakness, chest pain and cough were more common in patients with moderate COVID-19 courses.

Our results showed significant improvement in symptoms between 5 and 10 months after infection onset. In patients with a severe course of COVID infection, dyspnea ≥2 mMRC was present in 55% of patients at midterm follow-up visits but only in 20% in the long term. This recovery has also been described in SARS. Many patients who recovered from SARS have complained of limitation in general physical function and/or shortness of breath in the early rehabilitation phase [20].

The results of radiological features showed that only 17.8% of patients had chest x-ray abnormalities in the long term, which was more frequent in patients with severe COVID-19 courses (29%) and associated with the number of days hospitalized. The rate of radiological anomalies was 40.2% in our series at an average follow-up of 5 months and was higher (58.2%) in patients with severe COVID-19 infection. These results indicate that radiological abnormalities caused by SARS-CoV-2 might get better over time. In relation to the abnormalities on chest x-ray after COVID infection, the first reports from discharged patients with SARS-CoV-2 pneumonia showed that 83% had chest x-ray alterations a few days after discharge [21, 22]. Data at 3 months showed that 74.5% had radiological abnormalities [23]. In our study, CT scans showed evidence of fibrosis as a combination of findings including parenchymal bands, coarse reticular patterns, irregular interfaces, and traction

bronchiectasis in almost half of patients with severe COVID-19 courses and in a quarter of patients with moderate COVID infection, who underwent CT according to protocol. Data from a cohort of patients examined 153 days after hospital discharge showed abnormal CT findings in 44% [8].

In our cohort, the results of lung function assessment showed that 42.4% of patients had decreased pulmonary diffusion 10 months after infection onset. However, it is important to note that not all patients underwent pulmonary function testing, as per protocol. Pulmonary function was tested at the long-term follow-up in only 153 (55.6%) patients due to the chest x-ray not having cleared satisfactorily and/or the patient having ongoing respiratory symptoms. Of these, functional normalization dates were more present in patients with moderate COVID-19 infection vs the group of severe patients (64.1% vs 50.6%; P < .001) at 10 months from infection onset. If we consider the total number of patients in our cohort, assuming functional normality for those patients whose lung function was not tested due to resolution of symptoms and radiological findings, we could state that we detected functional alterations in 31.4% of patients with severe COVID-19 courses and in 27.7% of moderate patients at 10 months of mean follow-up. Previous reports from SARS outbreak survivors showed that 20% had long-term altered diffusion [3, 6].

In relation to lung function involvement after COVID-19 infection, the first reports from discharged patients with SARS-CoV-2 pneumonia showed that 47% had diffusion impairment

Table 5.   Relationship Between Lung Diffusion and Clinical Characteristics, COVID-19 Disease Severity and Features at long-term Follow-Up

Total (n = 153)	DLCO <80% (n = 65, 42.48%)	DLCO ≥80% (n = 88, 57.52%)	*P* Value
Age, mean (SD), y	67.75 (14.74)	58.80 (11.94)	<.001
Never-smoker, %	43.64	65.33	.011
Pulmonary disease, %	42.37	27.16	.045
Body mass index, mean (SD), kg/m^2	29.94 (4.81)	30.43 (5.62)	.603
Severe disease, No. (%)	37 (56.92)	38 (43.18)	.064
Length of hospital stay, median (IQR), d	21.5 (10.5–32.5)	12.5 (2–26)	.033
Peak RALE score, mean (SD)	4.31 (2.28)	3.73 (2.43)	.214
Peak D-dimer, median (IQR), ng/mL	1858 (971.5–6974)	2358 (1157–6675)	.387
Features at long-term follow-up (>180 d)			
mMRC dyspnea, mean (SD)	1.08 (0.66)	0.70 (0.65)	<.001
FEV/FVC, mean (SD), %	75.43 (10.68)	78.35 (5.53)	.078
FEV1, mean (SD), % predicted	93.29 (20.15)	109.69 (17.90)	<.001
FVC, mean (SD), % predicted	98.98 (21.20)	112.64 (20.60)	<.001
DLCO, mean (SD), % predicted	58.95 (17.69)	95.27 (12.11)	<.001
SpO2, mean (SD), %	96.22 (1.19)	97.05 (1.35)	<.001
RALE score, mean (SD)	0.12 (0.70)	0.05 (0.44)	.497
D-dimer, median (IQR), ng/mL	701.55 (467.86– 935.24)	531.85 (299.56–764.14)	.299
Predictors of long-term DLCO impairment			
	OR (95% CI)		*P* Value
Age	1.059 (1.014–1.105)		.008
Pulmonary disease	1.711 (0.542–5.393)		.359
Never-smoker	0.359 (0.125–1.029)		.057
Length of hospital stay	0.989 (0.954–1.026)		.571
FEV1 at long-term follow-up	0.962 (0.932–0.993)		.017
Dyspnea at long-term follow-up	3.169 (1.439–6.977)		.004
Severe disease	1.953 (0.440–8.653)		.378

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council; RALE, Radiographic Assessment of Lung Edema; SpO2, oxygen saturation.

Table 6.   Relationship Between D-dimer Features and Clinical Characteristics, COVID-19 Disease Severity and Features at Long-term Follow-up

	Abnormal D-dimer >500 ng/mL (n = 36)	Normal D-dimer ≤500 ng/mL (n = 80)	*P* Value
Age, mean (SD), y	72.34 (14.16)	57.2 (12.53)	<.001
Never-smoker, %	62.50	61.54	.554
Pulmonary disease, %	32.35	34.72	.495
Body mass index, mean (SD), kg/m^2	30.46 (4.23)	30.69 (6.12)	.950
Length of hospital stay, median (IQR), d	22 (10–32)	14 (3–25)	.070
Peak RALE score, mean (SD)	4.62 (1.98)	3.94 (2.47)	.186
Peak D-dimer, median (IQR)	5062 (1800–22 840)	1748 (800–4568)	.020
Severe disease, %	57.14	43.75	.131
Features at long-term follow-up (>180 d)			
mMRC dyspnea, mean (SD)	1 (0.87)	0.67 (0.59)	.066
FEV/FVC, mean (SD), %	74.85 (2.81)	78.98 (1.00)	.349
FEV1, mean (SD), % predicted	96 (19.51)	106.97 (18.80)	.028
FVC, mean (SD), % predicted	101.22 (25.86)	110.65 (22.44)	.208
SpO2, %	96.09	97.04	.018
DLCO, mean (SD), % predicted	71.73 (22.92)	86.36 (20.83)	.006
RALE score, mean (SD)	0 (0)	0.01 (0.11)	.505

Abbreviations: DLCO, diffusion capacity for carbon monoxide; FEV1, forced expiratory volume in 1 second; FVC, forced vital capacity; IQR, interquartile range; mMRC, modified Medical Research Council; RALE, Radiographic Assessment of Lung Edema; SpO2, oxygen saturation.

after 1 month [22]. Data at 3 months showed that 24% had reduced DLCO, and opacities on the CT scan were present in 25% of patients, without finding differences between patients admitted to the ICU compared with those who were not severe [10]. A 6-month follow-up study demonstrated reduced pulmonary function in 56% of patients who required high-flow nasal cannula or invasive mechanical ventilation, compared with 29% of those who required only supplemental oxygen [8]. In our study, reduced DLCO was associated with age, FEV1% predicted, and dyspnea score during long-term follow-up. Smoking history, underlying pulmonary diseases, length of hospital stay, and severe disease were not associated with long-term diffusion impairment, despite 75.5% of patients with severe infection requiring ICU admission in our analyzed population. Previous studies demonstrated a negative correlation between the duration of mechanical ventilation during acute disease and pulmonary function at 4 months of follow-up [24].

Our study has several limitations. First, LUNG INJURY COVID-19 is a registry to assess pulmonary sequelae following COVID-19 infection in patients referred to the follow-up clinic in the Pneumology Department, and this may carry some bias. During the first wave of the pandemic, patients with more severe COVID-19 were controlled mainly by pulmonologists. This scenario gives us insight into the cases that will have the highest risk of developing complications. A large proportion of patients in our cohort required support therapies and care in intensive care units, which may result in overestimates of the long-term consequences of COVID-19. However, the sample size was large and stratified by COVID infection severity. Second, not all patients underwent lung function testing and CT as per protocol. This approach, in line with the guidance of the British Thoracic Society [12], was adopted to mitigate overload of the health system. Third, the presence of previous chronic lung abnormalities may be underestimated, as although the clinical history was actively searched, underlying asymptomatic lung disease, though unlikely, cannot be excluded. Fourth, we could not study serum biomarkers in the whole group, mainly for logistical reasons. Fifth, multivariable models did not adjust for coexisting medical comorbidities or differences in therapies that can impact association estimates.

In sum, a comprehensive, longitudinal approach to post-COVID-19 care will require strategies and resources to meet the common and divergent needs of these populations, addressing both pulmonary and extrapulmonary concerns and complications. Multiple centers are creating multidisciplinary ambulatory programs for the post-COVID-19 population to provide a comprehensive evaluation of post-COVID-19 complications, characterize and mitigate pulmonary sequelae of COVID-19, and address persistent symptoms experienced by COVID-19 survivors [12, 25].

CONCLUSIONS

This is the first study to show long-term respiratory outcomes after almost a year. Our cohort confirms that although a substantial proportion of patients have abnormalities in lung function and chest imaging at discharge, progressive improvement occurs in the following months. Only a small percentage of patients who have had a severe infection will continue to have chronic abnormalities. These results emphasize the importance of systematic follow-up after severe COVID-19, with appropriate management of pulmonary sequelae [25]. Comprehensive evaluation of survivors will refine our understanding of the clinical course of COVID-19 and facilitate the development of care plans to mitigate symptoms and complications for survivors.

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