PULMONARY FUNCTION AND RADIOLOGICAL FEATURES IN SURVIVORS OF CRITICAL COVID-19: A 3-MONTH PROSPECTIVE COHORT

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ABSTRACT

Background

More than 20% of hospitalized patients with coronavirus disease 2019 (COVID-19) develop acute respiratory distress syndrome (ARDS) requiring intensive care unit (ICU) admission. The long-term respiratory sequelae in ICU survivors remain unclear.

Research question: what are the major long-term pulmonary sequelae in critical COVID-19 survivors?

Study Design and Methods

Consecutive patients with COVID-19 requiring ICU admission were recruited and evaluated 3 months after hospitalization discharge. The follow-up comprised symptom and quality of life, anxiety and depression questionnaires, pulmonary function tests, exercise test (6-minute walking test (6MWT)) and chest computed tomography (CT).

Results

125 ICU patients with ARDS secondary to COVID-19 were recruited between March and June 2020. At the 3-month follow-up, 62 patients were available for pulmonary evaluation. The most frequent symptoms were dyspnea (46.7%), and cough (34.4%). Eighty-two percent of patients showed a lung diffusing capacity of less than 80%. The median (IQR) distance in the 6MWT was 400 (362;440) meters. CT scans were abnormal in 70.2% of patients, showing reticular lesions in 49.1% and fibrotic patterns in 21.1%. Patients with more severe alterations on chest CT had worse pulmonary function and presented more degrees of desaturation in the 6MWT. Factors associated with the severity of lung damage on chest CT were age and length of invasive mechanical ventilation during the ICU stay.

Interpretation

Pulmonary structural abnormalities and functional impairment are highly prevalent in surviving ICU patients with ARDS secondary to COVID-19 3 months after hospital discharge. Pulmonary evaluation should be considered for all critical COVID-19 survivors 3 months post discharge.

Keywords:

COVID-19; CT abnormalities; ICU; lung function; SARS; SARS-CoV-2; Sequelae.

ABBREVIATION LIST

CT =computed tomography; COVID-19 = coronavirus disease 2019; ICU = intensive care unit; ARDS= acute respiratory syndrome; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; SF-12= short form health survey.

In December 2019, a novel coronavirus known as severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) [1] was identified as the cause of coronavirus disease 2019 (COVID-19). Through person-to-person transmission [2], it has rapidly spread across China [3] and many other countries [4], causing a global pandemic and a public health emergency of international concern [5]. By 3 October 2020, there were 34,680,199 confirmed cases, including 1,029,525 deaths globally.

There is a wide range of clinical presentations, with the majority of patients having mild disease with a favorable prognosis [6]. However, for a significant proportion of hospitalized patients (20-67%), SARS-CoV-2 may cause severe illness with rapid disease progression resulting in acute respiratory distress syndrome (ARDS) [7,8]. This results in a high rate of intensive care unit (ICU) admission (26-32%) and death (4.3%-15%) [8-9].

Patients with this type of critical illness could show major long-term sequelae, prompting the characterization of "post-ICU syndrome". This syndrome is defined as "new or worsening impairment in physical, cognitive or mental status arising after critical illness and persisting beyond discharge from the acute care setting" [10]. After ARDS, regardless of its origin, patients frequently present with several functional impairments across biopsychosocial domains [11].

In this line, lung damage, impaired lung function and psychological impairment are common and can last for months or even years in patients who have recovered from other types of coronavirus pneumonia, such as severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) [12,13]. In follow-up studis of these patients lasting 0.3-2 years [14,15], impaired lung diffusing capacity for carbon monoxide (DLCO), defective total lung capacity (TLC) and poor 6-minute walking test (6MWT) outcomes were the most common lung function abnormalities. Moreover, approximately one-third of SARS and MERS survivors may have psychological dysfunction, such as depression and anxiety, beyond 6 months [12].

Regarding SARS-CoV-2, recent research has demonstrated that nearly half of discharged patients had residual abnormalities on chest CT [16,17]. Moreover, these studies showed that in

early convalescence (one month after discharge), approximately three-quarters of patients with COVID-19 developed pulmonary function impairment represented most frequently again by declines in DLCO [16]. A recent study in noncritical cases [18] demonstrated a considerable proportion of COVID-19 survivors with radiological (70%) and pulmonary function (25%) abnormalities 3 months after discharge. Although short-term radiological and pulmonary function outcomes have been reported [16,19] in noncritical patients, little is known about the outcomes of critical COVID-19 survivors 3 months after discharge. Furthermore, ARDS due to COVID-19 shows a unique phenotype [20,21] that requires a different management strategies for ARDS in the acute phase [22,23] and a more exhaustive and close short-term follow-up [24], including respiratory, mental health and quality of life assessment.

Herein, we report the first descriptive observational recruited ICU survivor cohort of patients with COVID-19. Participants followed up 3 after months hospital discharge and underwent an evaluation of symptoms (involving the short form quality of life questionnaire (SF-12) and Hospital Anxiety and Depression Scale (HADS)) and characterization of pulmonary function, including lung volume (TLC and residual volume) and DLCO assessments and a 6MWT. Moreover, we performed a chest CT scan.

METHODS

Ethical statement

The study was approved by the Medical Ethics Committee of Hospital Universitary Arnau de Vilanova (CEIC/2273). Informed consent was acquired for the majority of patients by using emergency consent mechanisms in accordance with the ethics approval guidelines for the study.

Study design and population

This was a descriptive observational study performed in all patients who had a critical care admission due to COVID-19 in Hospital Universitari Arnau de Vilanova and Hospital Universitari Santa Maria in Lleida (Spain) between March and June 2020. The study is a subset of the ongoing multicenter study CIBERESUCICOVID (NCT04457505). The main objective is to determine the risk of and prognostic factors for critical illness in patients with COVID-19, as well as the impact of COVID-19 on respiratory and cardiovascular function within the first year of follow-up.

All patients were positive for SARS-CoV-2, aged over 18 years old, met the Berlin definition of ARDS [25], and had an ICU admission. Patients were unable to follow-up if they were transferred to another hospital during ICU hospitalization or later; if they were in palliative care; or if they had a severe mental disability that made it impossible to carry out pulmonary function tests after discharge.

Clinical data collection

Baseline and ICU stay

Patient sociodemographic and comorbidity data were obtained. Clinical, vital, ventilatory and laboratory parameters were recorded at ICU admission. The latter include general blood tests with acute markers of inflammation, such as D-dimer, ferritin, C-reactive protein, procalcitonin, lactate dehydrogenase and fibrinogen.

In addition to the baseline records, we collected data, such as length of stay and the need and duration of invasive and noninvasive mechanical ventilation, including high flow nasal canula (HFNC) and prone positioning, during the ICU stay.

3-month follow-up

General and respiratory symptoms, including anosmia, ageusia, fever, dry and wet cough, wheeze, dyspnea measured by the modified Medical Research Council (mMRC), asthenia and muscular fatigue, were assessed in the consultation.

To complete the clinical evaluation, answers to the short form health survey (SF-12) and the Hospital Anxiety and Depression Scale (HADS) questionnaire were self-reported by all patients. The SF-12 is a well-known health-related quality of life questionnaire consisting of 12 questions that measure 8 health domains to assess physical and mental health. These 8 multi-item variables include General Health (GH), Physical Functioning (PF), Role Physical (RP), Body Pain (BP), Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH). This questionnaire has been validated in healthy population and in several chronic diseases and conditions [26,27]. SF-12 was scored according to the normative standards established by *Ware et al*.[28], such that persons with a normal health-related quality of life (HRQOL) would have an average SF-12 score of 50, with a standard deviation (SD) of 10. This scoring system can be used to assess the degree of well-being and functional status of people over 14 years of age, identifying positive and negative physical health (PCS) and mental health (MCS) states, through the analysis of 8 dimensions. Scores <50 indicate a poor HRQOL, while scores >50 indicate a good HRQOL. Its use to evaluate the functional status after hospitalization in ARDS survivors has been previously validated [29]. The HADS is a 14-item self-report screening scale that was originally developed to indicate the possible presence of anxiety and depression states in medical nonpsychiatric outpatient clinic settings [30]. The HADS assesses symptoms over the preceding week and consists of a 7-item anxiety subscale and a 7-item depression subscale. Each item on the questionnaire is scored as 0-3, with a maximum score of 21. A general cutoff of 8 out of 21 is used to identify a possible case of anxiety or depression [31].

Pulmonary function tests

Airway function (spirometry, lung volume and diffusing capacity) was measured in all participants using a flow spirometer (MasterScreen; Jaeger, Germany) according to the guidelines of the American Thoracic Society [32]. Pulmonary parameters included TLC, forced vital capacity (FVC), residual volume (RV), forced expiratory volume in the first second (FEV_1), the FEV1/FVC

ratio, and DLCO. The results were expressed as a percentage of the predicted value according to the European Community Lung Health Survey [33]. Additionally, spirometric postbronchodilation measurements were determined 15 minutes after inhalation of 400 μg of salbutamol. The 6MWT was performed according to the current American Thoracic Society guidelines [34].

Chest CT examinations

Patients were scanned using a sixteen- and sixty-four-slice multidetector CT scanner (Brilliance 16 and 64; Philips Healthcare) with the following scan parameters: 16x1.5 mm slice collimation, 0.75 s gantry rotation time, 120 kV tube voltage, and 3 mm section thickness with a 1.5-mm reconstruction interval. Images were acquired with patients in the supine position in the cranio-caudal direction at end-inspiration. The resulting images were visualized with an image archiving and communication system with standard lung (level, -450 Hounsfield unit [HU]; width, 1,600 HU) and mediastinal (level, 40 HU; width, 400 HU) windows. Chest CT was not performed or was not available in five patients.

Image analysis and quantification

All CT images were reviewed by a pulmonologist (JG) with experience in imaging who was blinded to the clinical data. CT images were evaluated as previously described [17] for the presence of the following characteristics: (1) density: ground-glass opacities, mixed ground-glass opacities, or consolidation; (2) internal structures: air bronchogram, interlobular septal thickening, cavitation, pulmonary nodules; (3) number of lobes affected by ground-glass or consolidative opacities; (4) fibrotic or reticular lesions; (5) pleural effusion; (6) thoracic lymphadenopathy; and (7) underlying lung disease (tuberculosis, emphysema, or interstitial lung disease). Fibrotic pattern was defined according to the Fleischner Society glossary of terms for thoracic imaging: reticulation, architectural distortion, traction bronchiectasis, and honey combing [35]. Due to the nature and the atypical presentation of COVID-19, most frequently we saw these components separately, and the clinical image did not fit into a classic interstitial lung disease pattern. The coexistence of ground-

glass opacities with a predominantly upper and sometimes bilateral but usually asymmetrical (often unilateral) presentation without immediate subpleural sparing and the coexistence in some cases of pulmonary nodules does suggest a typical pattern of usual interstitial pneumonia or non-specific interstitial pneumonia. For that reason, we used the term “fibrotic pattern”.

To quantify the severity of lung affectation, the “total severity score (TSS)” was assessed. Each of the five lung lobes was determined for the percentage of lobar involvement. Following this, the severity of each lobe was classified as none (0%), minimal (1-25%), mild (26-50%), moderate (51-75%), or severe (76-100%), with a corresponding score of 0, 1, 2, 3 or 4, respectively. The TSS is calculated by summing the five lobe scores (range from 0 to 20) [36].

Statistical analysis

Descriptive statistics of the mean (standard deviation) or median (interquartile range) were estimated for quantitative variables with a normal or nonnormal distribution, respectively. The normality of the distribution was analyzed using the Shapiro–Wilk test. The absolute and relative frequencies were used for qualitative variables. To assess the pulmonary inflammation severity, the CT score was categorized by tertiles. Lung function parameters were compared according to pulmonary inflammation severity using the appropriate tests (analysis of variance or a nonparametric Kruskal-Wallis for quantitative variables and Fisher’s exact test for qualitative variables). The p value for trend was computed from the Spearman rank correlation coefficient when the variable was continuous and from the $\chi 2$ test for trend if the variable was categorical.

Furthermore, we evaluated the association among demographic data, clinical data and ICU stay in patients with pulmonary inflammation measured by CT score at the 3-month follow-up. Selection of variables was carried out using a relaxed least absolute shrinkage and selection operator (LASSO) model [37,38]. Five-fold cross-validation was carried out to determine the lambda parameter of the LASSO model [39] . Lambda was selected as the value that minimized the mean square error (MSE). A Spearman correlation test between the independent risk factors from

the LASSO analysis and the rest of the variables was performed. To perform the LASSO analysis, missing values were replaced by the means of the nonmissing values. The same analysis was performed for the presence of lung lesions (Reticular or fibrotic/No lesions) and type of lesion (Reticular/Fibrotic) among patients with lesion. R statistical software, version 4.0.1, was used for all the analyses.

RESULTS

Characteristics of the study population and ICU stay

Figure 1 shows the flowchart of the study. One hundred and twenty-five critically ill patients with ARDS due to COVID-19 were admitted during the study period. Thirty-six died during the ICU stay (28.8%), and 10 were transferred to other hospitals (only two patients were transferred to perform extracorporeal membrane oxygenation). After hospital discharge, three patients were under palliative treatment or were severely disabled, and one was undergoing follow-up in another center. Of the 75 eligible patients who completed the 3-month follow-up, 13 were unreachable or decided not to participate in follow-up. The latter did not differ in sociodemographic or clinical characteristics compared to the final cohort. A total of 62 patients completed the evaluation.

The characteristics of the study population are displayed in **Table 1**. Briefly, they were predominantly middle age, overweight and male. The majority of them were former smokers. The prevalence of pre-existing hypertension, diabetes mellitus, chronic heart disease, asthma and chronic obstructive pulmonary disease was 37.1%, 14.5%, 9.7%, 4.8% and 4.8%, respectively. The median (IQR) of ICU stay was 14.5 (7.0-25.8) days, and the overall hospitalization was 26 (15-38.5) days. Thirty-nine survivors (62.9%) required invasive mechanical ventilation (IMV) for a median (SD) duration of 17.4 (8.5) days. In seven patients both invasive and non-invasive mechanical ventilation modes were used. During the ICU stay, prone positioning was needed in 35 of the patients (56.5%). All patients needed an HFNC during their ICU stay. Patients were mostly treated with hydroxychloroquine (98.4%), corticosteroids (58.3%), tocilizumab (25.8%) and interferon beta (17.7%). Ninety per cent of patients received methylprednisolone and 10% hydrocortisone with a median (IQR) maximum dose of 500 (300) mg. Lopinavir/ritonavir only was used in two cases (3.23%). All patients received antibiotic treatment, and only one patient received antifungal treatment.

Only two patients were readmitted after the hospital discharge, one because respiratory problems and the other for other causes.

Symptoms and SF-12 and HADS questionnaires at the 3 month follow up

At the 3-month follow-up, the most common symptoms were dyspnea (46.7%), followed by muscular fatigue (29.5%) and wet and dry cough (18.0% and 16.4%, respectively) (**Table 2**). Only one patient had fever or anosmia after discharge, and none suffered wheeze, anosmia or abdominal pain. Five patients were receiving supplemental oxygen after hospital discharge. There was only one patient with incidental pulmonary thromboembolism on chest CT after discharge.

The SF-12 showed median (IQR) scores of 45.9 (36.1;54.4) and 55.8 (40.6;58) in the physical and mental domains, respectively. Degree of dyspnea showed a strong correlation only with the physical component of SF-12 (**e-Figure1**). A total of 15.2% and 22.1% of patients presented altered depression and anxiety scores, respectively, on the HADS questionnaire (**Table 2**).

Lung function, 6MWT and chest CT at the 3-month follow-up

The pulmonary function and exercise test results are detailed in **Table 3**. Only one patient showed lung airway obstruction. Fifty survivors (82%) showed an abnormal DLCO (<80% predicted). Moreover, there were 23 survivors (37.1%) with altered TLC. The median (IQR) distance in the exercise test was 400 (362;440) meters with a mean oxygen saturation of 96. Severe decrease of oxygen saturation (below 88%) was shown in only one patient. We calculated the difference in the distance walked on the 6MWT between our population and reference values from a healthy population using validated reference equations [40] adjusted by sex, age, weight and height. The results show a significant reduction in the distance in the study patients compared to the healthy population (median [IRQ] of difference -128.43 [-185.03;-62.66]; p value <0.001) (e-Table **1**).

Overall, ICU survivors continued to present a wide array of abnormalities in their CT results at the 3-month follow-up (**Table 3**). Ground-glass opacities and consolidations were found in 59.6% and 15.8% of patients, respectively. Interlobular septal thickening and bronchiectasis were the most

frequent abnormalities seen in chest CT (80.7% and 71.9%, respectively). Only 10 patients had emphysema confirmed as a pre-existing comorbidity. The most frequent was the centrilobular subtype, located in the upper lobes with mild severity.

Importantly, forty patients showed the presence of reticular (n=28, 49.1%) or fibrotic (n=12, 21.1%) lesions (**Figure 2**). Furthermore, the mean (SD) number of lobes affected by ground-glass or consolidative opacities per patient was 2.7 (2.0), and thirty-four patients showed at least one affected lobe. The mean (SD) TSS, which quantifies the severity of pulmonary inflammation, was 4.8 (3.9). Representative CT scans from ICU survivors with low and high TSS scores 3 months after hospital discharge are shown in **Figure 3** .

Correlation of pulmonary function and exercise testing characteristics according to CT alterations

As expected, chest CT severity measured by TSS score was intimately associated with respiratory abnormalities in ICU survivors 3 months after hospital discharge (**e-Table 2**). Survivors with CT scores in the higher tertiles showed an impaired DLCO, with a mean (95%CI) DLCO of 65.6 (60.1-71.0) in the second tertile and 57.8 (51.7-63.8) in the third tertile (p for trend≤0.001). Consequently, the CT score was intimately correlated with diffusing capacity (rho=-0.56) (**Figure 4.**). For the exercise test, although the mean 6MWT was similar across CT score tertiles (p value=0.124), patients with severe abnormalities on CT showed a decreased average oxygen saturation, as well as decreased final and minimal oxygen saturation levels (p value=0.028 and 0.011, respectively). A robust and inverse correlation between the CT score and the percentage of change in O_2 during the walking test was also observed (rho=-0.42) (**Figure 4.**).

A predictor selection procedure (LASSO model) was performed using variables from the medical history and ICU stay to further explore the association of ICU survivor clinical profiles and the outcomes reported CT anomalies, presence of lesions and type of lesions. The results from this analysis suggested an association between CT abnormalities and two predictors: age and the length

of IMV during the ICU stay. The CT score was higher in those patients with longer duration of IMV, and age at admission was robust and positively correlated with the CT score (rho=0.40) (**e-Figure 2.**). On the other hand, the requirement of IMV was the only variable selected for predicting the risk of lung lesions **(e- Figure 3)**. Additionally, we explored which variables were important for the determination of the type of injury among patients who had any pulmonary lesion. The LASSO model showed that the duration of invasive mechanical ventilation was the only factor that allowed us to discriminate between the types of lesions (**e- Figure 3**). No other significant differences or correlations (ICU or hospital stay) were found.

DISCUSSION

Since the beginning of the SARS-CoV-2 outbreak, various studies have been performed to describe pulmonary sequalae in COVID-19 patients after hospital discharge. To our knowledge, this is the first well-characterized descriptive observational study of ICU COVID-19 survivors. The most striking finding is the high proportion of patients with DLCO impairment (81.9%) and lung injury (70.2%) 3 months after discharge. The magnitude of lung damage found in our cohort has no precedent [41] even in previous coronavirus outbreaks (SARS and MERS) [13,14]. The quality of life of coronavirus survivors shows mean scores substantially that are lower than those of healthy people [26] (**e- Figure 4.**), those with other chronic diseases [12] and healthy Spanish people [42]. This finding is usually observed in interstitial lung diseases and is important because it correlates with pulmonary function and physical activity [43]. Additionally, the levels of anxiety and depression scores were higher than the reference values.

A recent meta-analysis [12] of clinical outcomes after hospitalization or ICU admission in patients with SARS and MERS showed a pooled prevalence of impaired DLCO at 6 months of 24.35% (95% confidence interval (CI): 11.05-45.46). There are two studies [44,45] that included some SARS ICU patients, showing a prevalence of impaired DLCO ranging from 13.5% to 24% at the 3- and 12-month follow-ups. Regarding SARS-CoV-2, a recent study [19] performed at the time of hospital discharge and excluding critical cases found DLCO and TLC anomalies in 47.2% and 25%, respectively, being more frequent in patients with severe pneumonia (84%, p=0.001). Recent research in early convalescence (one month after discharge) demonstrates that approximately three-quarters of patients with COVID-19 develop pulmonary function impairment, which is represented by a decline in DLCO decline in more than half of patients [16].

A similar phenomenon is noticeable with exercise capacity. Previous SARS studies including ICU patients show a mean 6MWT distance at the 3-month follow-up ranging from 454 [46] to 464 meters [44], with a pooled distance estimate of 461.18 (95% CI: 449.66-472.71) [12]. Those distances are significantly longer than the mean distance observed in our patients (400

meters). In SARS-CoV-2, the 6MWT distance was significantly shorter in severe patients (517 meters) than in nonsevere patients (573.52 meters), indicating poor exercise tolerance [16].

The same phenomenon can be noticed in chest CT abnormalities found during follow-ups of survivor patients. In a recent SARS-CoV-2 series, the rate of radiological abnormalities remained high 3 months after discharge (74.55%), although it was lower than that at the time of admission (84%) [47,48]. A study also performed at the 3-month follow-up showed that fibrosis was present in 23.6% and the mean TSS was 8 in the abnormal CT group [18]. This finding is in line with our findings, although the rate of reticular and fibrotic lesions was higher in our cohort (49.1 and 47.1%, respectively). This rate was even higher than that of residual radiographic survivors with other viral pneumonias, including SARS, H1N1 and H7N9 [49,50]. As expected and as previously described [16,18], severity, as measured by TSS in chest CT, correlated with pulmonary function. However, we also demonstrated this correlation with the decrease in oxygen saturation during the 6MWT.

Our data suggest different clinical and pulmonary effects for COVID-19 in comparison with other forms of viral respiratory illnesses, regardless of important ICU variables (need and length of tracheal intubation). Recent studies [51] have shown that COVID-19 patients are hospitalized more often and have longer hospitalizations with a higher probability of developing ARDS than patients with other acute respiratory illnesses. This hypothesis could be explained by the particuar pathological findings that occur in severe COVID-19 patients compared with those with other viral pneumonias [52]. In addition to the typical diffuse alveolar damage, compared with lungs from H1N1 patients, lungs from critical COVID-19 patients showed severe endothelial injury associated with the presence of intracellular virus, disrupted cell membranes and a higher prevalence of thrombosis and microangiopathy [52]. Moreover, COVID-19 severe patients show a unique inflammatory and proteomic profile as well as a different immune response compared to non-COVID-19 critical patients [21], leading to an organ-specific cellular death and damage.

Our findings have several clinical implications. As more severe differential lung involvement is seen in critically ill patients with COVID-19, close monitoring after discharge is deserved. Therapies such as pulmonary rehabilitation and physical conditioning should be the cornerstone of follow-up. Empirical treatment with systemic glucocorticosteroids should be considered in selected cases. The long-term pulmonary sequalae are unknown, but these data encourage close follow-up of these patients.

There are some limitations to our study. First, we have a small cohort from a single city, and a larger sample size from different hospitals would be ideal for this type of study. However, generalization of our results is facilitated by our cohort being well-characterized and prospective. Moreover, due to the methodological characteristics of the study we did not calculate a previous sample size. Second, even if the 13 patients lost to follow-up were considered, there would have been a minimal influence on the results as there are no sociodemographic and clinical differences compared to theinal cohort. Third, it is uncertain whether lung lesions were present before the study. Fourth, the reversibility of the parenchymal involvement is uncertain due to short-term follow-up, further long-term analysis should clarify this issue.

INTERPRETATION

In conclusion, survivors of critical COVID-19 show a higher proportion of DLCO impairment and chest CT abnormalities at the 3-month follow-up. A complete evaluation including chest CT and pulmonary function and exercise tests 3 months post discharge should be considered for these survivors of critical COVID-19.

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intellectual content. Statistical analysis was performed by IdB, Patients' recruitment and evaluation was done by PC, SS, AM, AM-M, CG-P, LP, AC, and MZ. The rest of CIBERESUCICOVID group (RF, AC, LF, AM, JR, RM, DdG-C, OP, JB-M, GL, and JC) contributed to correct and improve the manuscript. David de Gonzalo Calvo acknowledges receiving financial support from Instituto de Salud Carlos III (ISCIII); Miguel Servet 2020: CP20/00041), co-funded by the European Social Fund (ESF), "Investing in your future"

Take-Home Point pullout:

Study Question
What are the major long-term pulmonary sequelae in critical COVID-19 survivors?

Results
At the 3-month follow-up, 82% of critical COVID-19 survivors showed a lung diffusing capacity of less than 80% and an abnormal chest CT scan in 70.2%, with reticular lesions in 49.1% and fibrotic pattern in 21.1% of them.

Interpretation
Pulmonary structural abnormalities and functional impairment are highly prevalent in surviving critical COVID-19 patients 3 months after hospital discharge. A complete evaluation including chest CT and pulmonary function and exercise tests at this time should be considered for these patients.

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TABLES

Table 1. Demographic and biological characteristics of critical COVID-19 patients included in the follow-up.

Characteristics	ALL (N=62)
Age (years), median (IQR)	60 (48;65)
Sex, N (%):	
Male	46 (74.2)
Female	16 (25.8)
BMI (kg/m2), median (IQR)	28.2 (25.4;32.6)
Smoking history, N° (%):	
Current	3 (5.0)
Former	31 (51.7)
Nonsmoker	26 (43.3)
Comorbidities, N° (%)	
Hypertension	23 (37.1)
Diabetes Mellitus	9 (14.5)
Chronic heart disease	6 (9.7)
Asthma	3 (4.8)
COPD	3 (4.8)
ICU stay	
Days, median (IQR)	14.5 (7.0; 25.8)
Mechanical ventilation	
Invasive, N° (%)	39 (62.9)
Days, mean (SD)	17.4 (8.5)
Noninvasive, N° (%)	30 (49.2)
Days, median (IQR)	2 (1;4)
Prone positioning, N° (%)	35 (56.5)
Hours, mean (SD)	43.9 (30.7)
Hydroxychloroquine, N° (%)	61 (98.4)
Interferon beta, N° (%)	11 (17.7)
Tocilizumab, N (%)	16 (25.8)
Methylprednisolone, N (%)	35 (56.4)
Maximum daily dose (mg), median (IQR)	500 (380)
Antibiotics, N (%)	62 (100)
APACHE, mean (SD)	13.5 (4.3)
Worst PaO_2/FiO_2, median (IQR)	126.0 (90.1;173.0)
Worst SpO_2/FiO_2, median (IQR)	172 (124;215)
Laboratory data in ICU admission	
CRP, mg/dL, median (IQR)	182 (102;243)
Hemoglobin, g/L, mean, (SD)	13.2 (1.84)
Platelet count, $x10^9$/L, median (IQR)	224 (172;305)
White blood count, $x10^9$/L, median (IQR)	9.18. (5.99;10.40)
Lymphocyte count, $x10^9$/L, median (IQR)	0.80 (0.57;1.14)
Urea nitrogen, mmol/L, median (IQR)	29 (24;48)
Creatinine mg/dL, median (IQR)	0.8 (0.65;0.95)
LDH, U/L, mean (SD)	836 (341)
Ferritin, mg/dL, median (IQR)	602 (464;2112)
D-dimer, mg/L, median (IQR)	430 (285;756)

SD=standard deviation; IQR= interquartile range (p25;p75); BMI=body mass index; COPD=chronic obstructive pulmonary disease; ICU= intensive critical unit; CRP=C-reactive protein; LDH=lactate dehydrogenase.

Number of missing: Smoking history= 2; BMI=2; PaO_2/FiO_2=11; CRP=2; LDH=44; Ferritin=45; D-dimer= 14; Worst PaO_2/FiO_2= 11.

Table 2. Symptoms and quality of life and anxiety/depression questionnaire results at the 3-month follow-up.

Symptoms	
Asymptomatic, N° (%)	16 (27)
Dry cough, N° (%)	10 (16.4)
Wet cough, N° (%)	11 (18.0)
Dyspnea, N° (%)	
0	32 (53.3)
1	19 (31.7)
2	8 (13.3)
4	1 (1.67)
Muscular fatigue, N° (%)	18 (29.5)
Questionnaires	
SF-12, median (IQR)	
Physical Score	45.9 (36.1;54.4)
Mental Score	55.8 (40.6;58.0)
HADS, median (IQR)	
Depression score	1.0 (0.5;4.5)
Normal (0-7), Nº (%)	50 (84.7)
Borderline abnormal (8-10), Nº (%)	6 (10.2)
Abnormal (11-21), Nº (%)	3 (5.0)
Anxiety score	3 (1;6)
Normal (0-7), Nº (%)	46 (78.0)
Borderline abnormal (8-10), Nº (%)	7 (11.9)
Abnormal (11-21), Nº (%)	6 (10.2)

IQR= interquartile range (p25;p75); HADS=Hospital Anxiety and Depression Scale

Number of missing: SF-12=7; HADS=3; Asymptomatic= 3; Dry cough=1; Wet cough=1; Dyspnea=2.

Table 3. Pulmonary function, 6MWT and chest CT scan findings in all patients at the 3-month follow-up.

Pulmonary function (n = 62)	
FVC-%, Mean (SD)	81.5 (16.7)
FEV1-%, Mean (SD)	88.9 (19.1)
FEV1/FVC, Mean (SD)	81.4 (4.8)
TLC-%, Mean (SD)	83.8 (16.4)
80%, Nº (%)	39 (62.9)
50-80%, Nº (%)	22 (35.5)
<50%, Nº (%)	1 (1.61)
RV-%, Mean (SD)	89.4 (37.9)
DLCO-mL/min/mmHg, Mean (SD)	67.8 (12.5)
80%, Nº (%)	11 (18.0)
60-80%, Nº (%)	34 (55.7)
<60%, Nº (%)	16 (26.2)
6MWT (n = 60)	
Distance-meters, median (IQR)	400 (362;440)
Oxygen saturation, median (IQR)	
Average	96 (94.5;97)
Initial	97 (96;97)
Final	96 (94.8;96)
Minimal	94 (93;96)
Chest CT (n = 57)	
Density	
Ground-glass, Nº (%)	34 (59.6)
Mixed ground-glass, Nº (%)	9 (15.8)
Consolidation, Nº (%)	9 (15.8)
Internal structures	
Interlobular septal thickening, Nº (%)	46 (80.7)
Bronchiectasis, Nº (%)	41 (71.9)
Atelectasis, Nº (%)	14 (24.6)
Solid nodule, Nº (%)	22 (38.6)
Nonsolid nodule, Nº (%)	2 (3.5)
Number of lobes affected by ground-glass or consolidative opacities, mean (SD)	2.7 (2.0)
Lesions	
Reticular, Nº (%)	28 (49.1)
Fibrotic, Nº (%)	12 (21.1)
None, Nº (%)	17 (29.8)
TSS score	
Score, Mean (SD)	4.8 (3.9)

SD=standard deviation; IQR= interquartile range (p25;p75); FVC=forced vital capacity; FEV1=forced expiratory volume in the first second; TLC=total lung capacity; RV=residual volume; DLCO=diffusing capacity for carbon monoxide; 6MWT=six-minute walking test.

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