

Pulmonary Function and Radiologic Features in Survivors of Critical COVID-19

A 3-Month Prospective Cohort



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BACKGROUND: More than 20% of hospitalized patients with COVID-19 demonstrate ARDS requiring ICU admission. The long-term respiratory sequelae in such patients remain unclear.

RESEARCH QUESTION: What are the major long-term pulmonary sequelae in critical patients who survive COVID-19?

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-min walking test [6MWT]), and chest CT imaging.

RESULTS: One hundred twenty-five patients admitted to the ICU 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 distance in the 6MWT was 400 m (interquartile range, 362-440 m). CT scans showed abnormal results in 70.2% of patients, demonstrating reticular lesions in 49.1% and fibrotic patterns in 21.1%. Patients with more severe alterations on chest CT scan showed worse pulmonary function and presented more degrees of desaturation in the 6MWT. Factors associated with the severity of lung damage on chest CT scan were age and length of invasive mechanical ventilation during the ICU stay.

INTERPRETATION: Three months after hospital discharge, pulmonary structural abnormalities and functional impairment are highly prevalent in patients with ARDS secondary to COVID-19 who required an ICU stay. Pulmonary evaluation should be considered for all critical COVID-19 survivors 3 months after discharge. CHEST 2021; 160(1):187-198

KEY WORDS: COVID-19; CT abnormalities; ICU; lung function; SARS; SARS-CoV-2; sequelae

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ABBREVIATIONS: 6MWT = 6-min walking test; DLCO = diffusing capacity for carbon monoxide; HADS = Hospital Anxiety and Depression Scale; HU = Hounsfield unit; IMV = invasive mechanical ventilation; IQR = interquartile range; LASSO = least absolute shrinkage and selection operator; MERS = Middle East respiratory syndrome; SARS = severe acute respiratory syndrome; SF-12 = Short-Form Health Survey; TLC = total lung capacity; TSS = total severity score

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Take-home Points

Study Question: What are the major long-term pulmonary sequelae in patients who survive critical COVID-19?

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

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

In December 2019, SARS-CoV-2¹ was identified as the cause of COVID-19. Through person-to-person transmission,² it spread rapidly across China³ and many other countries,⁴ causing a global pandemic and a public health emergency of international concern.⁵ By October 3, 2020, there were 34,680,199 confirmed cases, including 1,029,525 deaths globally.

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SARS-CoV-2 infection has 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 ARDS.^{7,8} This results in a high rate of 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 show several functional impairments across biopsychosocial domains.¹¹

Similarly, 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 studies of these patients lasting 0.3 to 2 years,^{14,15} impaired lung diffusing capacity for carbon monoxide (DLCO), defective total lung capacity (TLC), and poor 6-min 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 show residual abnormalities on chest CT scan.^{16,17} Moreover, these studies showed that in early convalescence (1 month after discharge), approximately three-quarters of patients with COVID-19 demonstrated pulmonary function impairment, represented most frequently again by declines in DLCO.¹⁶ A recent study of patients with noncritical disease¹⁸ demonstrated that a considerable proportion of COVID-19 survivors showed radiologic (70%) and pulmonary function (25%) abnormalities 3 months after discharge. Although short-term radiologic and pulmonary function outcomes have been reported^{16,19} in patients with noncritical disease, little is known about the outcomes of patients with critical COVID-19 3 months after discharge. Furthermore, ARDS resulting from COVID-19 shows a unique phenotype^{20,21} that requires 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 cohort of recruited patients with COVID-19 who underwent an ICU stay. Participants were followed up 3 months after hospital discharge and underwent an evaluation of symptoms (involving the Short-Form

Health Survey [SF-12] and Hospital Anxiety and Depression Scale [HADS]) and characterization of pulmonary function, including lung volume (TLC and residual volume), DLCO assessments, and 6MWT assessment. Moreover, we performed chest CT scan.

Methods

Ethical Statement

The study was approved by the Medical Ethics Committee of Hospital Universitari Arnau de Vilanova (Identifier: CEIC/2273). Informed consent was acquired for most 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 to include all patients who experienced a critical care admission resulting from 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 Centro de Investigación Biomédica En Red Enfermedades Respiratorias Unidad de Cuidados Intensivos COVID (ClinicalTrials.gov Identifier: NCT04457505). The main objective was 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 showed positive results for SARS-CoV-2, were older than 18 years, met the Berlin definition of ARDS,²⁵ and had undergone an ICU stay. Patients were unable to follow-up if they were transferred to another hospital during ICU hospitalization or later, if they were receiving 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 included 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 for and duration of invasive and noninvasive mechanical ventilation, including high-flow nasal canula and prone positioning, during the ICU stay.

Three-Month Follow-up: General and respiratory symptoms, including anosmia, ageusia, fever, dry and wet cough, wheeze, dyspnea measured by the modified Medical Research Council, asthenia, and muscular fatigue, were assessed in the consultation. To complete the clinical evaluation, answers to the SF-12 and the 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 eight health domains to assess physical and mental health. These eight multi-item variables include general health, physical functioning, role physical, body pain, vitality, social functioning, role emotional, and mental health. This questionnaire has been validated in healthy populations and in patients with several chronic diseases and conditions.^{26,27} The SF-12 was scored according to the normative standards established by Ware et al²⁸ such that persons with a normal health-related quality of life would

have an average SF-12 score of 50, with an SD of 10. This scoring system can be used to assess the degree of well-being and functional status of people older than 14 years, identifying positive and negative physical health and mental health states, through the analysis of eight dimensions. Scores of < 50 indicate a poor health-related quality of life, whereas scores of > 50 indicate a good health-related quality of life. Its use to evaluate the functional status after hospitalization in patients who survived ARDS has been validated.²⁹ The HADS is a 14-item self-report screening scale that was developed originally 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 seven-item anxiety subscale and a seven-item depression subscale. Each item on the questionnaire is scored as 0 to 3, with a maximum score of 21. A general cutoff of 8 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) according to the guidelines of the American Thoracic Society.³² Pulmonary parameters included TLC, FVC, residual volume, FEV₁, FEV₁ to 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 min after inhalation of 400 µg of salbutamol. The 6MWT was performed according to the current American Thoracic Society guidelines.³⁴

Chest CT Scan Examinations

Patients were scanned using a 16- and 64-slice multidetector CT scanner (Brilliance 16 and 64; Philips Healthcare) with the following scan parameters: 16 × 1.5-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 craniocaudal direction at end-inspiration. The resulting images were visualized with an image archiving and communication system with standard lung (level, -450 Hounsfield units [HU]; width, 1,600 HU) and mediastinal (level, 40 HU; width, 400 HU) windows. Chest CT imaging was not performed or was not available for five patients.

Image Analysis and Quantification

All CT images were reviewed by a pulmonologist (J. G.) with experience in imaging who was blinded to the clinical data. CT images were evaluated as described previously¹⁷ 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 (TB, 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 Because of 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 nonspecific interstitial pneumonia. For that reason, we used the term “fibrotic pattern.”

To quantify the severity of lung affection, the total severity score (TSS) was assessed. Each of the five lung lobes was determined for the percentage of lobar involvement. After 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, 0-20).³⁶

Statistical Analysis

Descriptive statistics of the mean (SD) or median (interquartile range [IQR]) 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 scan 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 test for quantitative variables and Fisher 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 χ^2 test for trend if the variable was categorical.

Furthermore, we evaluated the associations among demographic data, clinical data, and ICU stay in patients with pulmonary inflammation measured by CT scan 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. 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 lesions. R statistical software version 4.0.1 (R Foundation for Statistical Computing) 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 twenty-five critically ill patients with ARDS resulting from 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 undergo extracorporeal membrane oxygenation). After hospital discharge, three patients were receiving 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 with 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-aged, overweight, and male. Most of them were former smokers. The prevalence of pre-existing hypertension, diabetes mellitus, chronic heart disease, asthma, and COPD was 37.1%, 14.5%, 9.7%, 4.8%, and 4.8%, respectively. The median ICU stay was 14.5 days (IQR, 7.0-25.8 days), and the median overall hospitalization was 26 days (IQR, 15-38.5 days). Thirty-nine survivors (62.9%) required invasive mechanical ventilation (IMV)

for a median duration of 17.4 days (SD, 8.5 days). In seven patients, both IMV and noninvasive mechanical ventilation modes were used. During the ICU stay, prone positioning was needed in 35 of the patients (56.5%). All patients needed a high-flow nasal canula

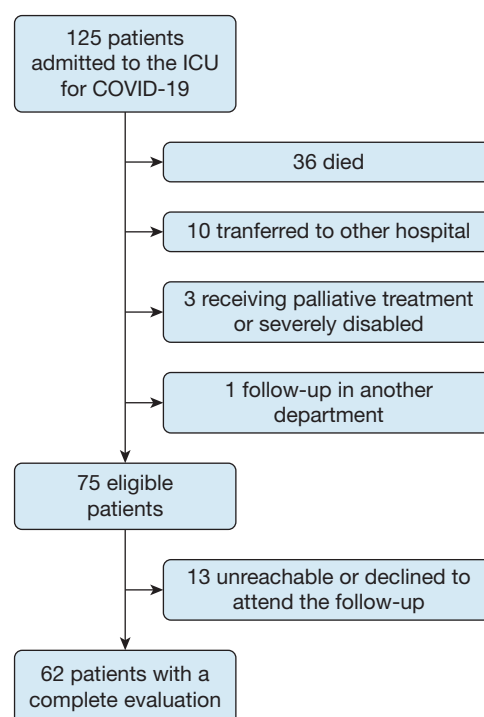


Figure 1 – Flowchart showing patients with critical COVID-19 included in the study.

TABLE 1] Demographic and Biological Characteristics of Patients Who Survived Critical COVID-19 Included in the Follow-up

Characteristic	Data (N = 62)
Age, y	60 (48-65)
Sex	
Male	46 (74.2)
Female	16 (25.8)
BMI, kg/m ²	28.2 (25.4-32.6)
Smoking history	
Current	3 (5.0)
Former	31 (51.7)
Nonsmoker	26 (43.3)
Comorbidities	
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	
Length, d	14.5 (7.0-25.8)
Mechanical ventilation	
Invasive	39 (62.9)
Length, d	17.4 ± 8.5
Noninvasive	30 (49.2)
Length, d	2 (1-4)
Prone positioning	35 (56.5)
Length, h	43.9 ± 30.7
Hydroxychloroquine	61 (98.4)
Interferon-β	11 (17.7)
Tocilizumab	16 (25.8)
Methylprednisolone	35 (56.4)
Maximum daily dose, mg	500 (120-500)
Antibiotics	62 (100)
APACHE	13.5 ± 4.3
Worst Pao ₂ to Fio ₂ ratio	126.0 (90.1-173.0)
Worst Spo ₂ to Fio ₂ ratio	172 (124-215)
Laboratory data on ICU admission	
CRP, mg/dL	182 (102-243)
Hemoglobin, g/L	13.2 ± 1.84
Platelet count, × 10 ⁹ /L	224 (172-305)
White blood count, × 10 ⁹ /L	9.18. (5.99-10.40)
Lymphocyte count, × 10 ⁹ /L	0.80 (0.57-1.14)
Urea nitrogen, mM/L	29 (24-48)
Creatinine, mg/dL	0.8 (0.65-0.95)
LDH, U/L	836 ± 341
Ferritin, mg/dL	602 (464-2112)
D-dimer, mg/L	430 (285-756)

Data are presented as No. (%), mean ± SD, or median (interquartile range). No. of missing: smoking history, n = 2; BMI, n = 2; Pao₂ to Fio₂ ratio, n = 11; CRP, n = 2; LDH, n = 44; ferritin, n = 45; D-dimer, n = 14; and worst Pao₂ to Fio₂ ratio, n = 11. APACHE = Acute Physiology And Chronic Health Evaluation; CRP = C-reactive protein; LDH = lactate dehydrogenase.

during the ICU stay. Patients mostly were treated with hydroxychloroquine (98.4%), corticosteroids (58.3%), tocilizumab (25.8%), and interferon- β (17.7%). Ninety percent of patients received methylprednisolone and 10% hydrocortisone with a median maximum dose of 500 mg (IQR, 300 mg). Lopinavir plus ritonavir was used in only two patients (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 experienced fever or anosmia after discharge, and none experienced wheeze, anosmia, or abdominal pain. Five patients were receiving supplemental oxygen after hospital discharge. Only one patient showed incidental pulmonary thromboembolism on chest CT scan after discharge.

The SF-12 showed median scores of 45.9 (IQR, 36.1-54.4) and 55.8 (IQR, 40.6-58) in the physical and mental domains, respectively. Degree of dyspnea showed a strong correlation only with the physical component of the SF-12 (e-Fig 1). A total of 15.2% and 22.1% of patients showed altered depression and anxiety scores, respectively, on the HADS questionnaire (Table 2).

Lung Function, 6MWT Results, and Chest CT Scan Findings 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, 23 survivors (37.1%) showed altered TLC. The median distance in the exercise test was 400 m (IQR, 362-440 m), with a mean oxygen saturation of 96%. Severe decrease of oxygen saturation (< 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 equations⁴⁰ adjusted by sex, age, weight, and height. The results show a significant reduction in the distance in the study patients compared with the healthy population (median difference, -128.43 [IQR, -185.03 to -62.66]; $P < .001$) (e-Table 1).

TABLE 2] Symptoms and Quality-of-Life, Anxiety, and Depression Questionnaire Results at the 3-Month Follow-up

Variable	Data
Symptoms	
Asymptomatic	16 (27)
Dry cough	10 (16.4)
Wet cough	11 (18.0)
Dyspnea	
0	32 (53.3)
1	19 (31.7)
2	8 (13.3)
4	1 (1.67)
Muscular fatigue	18 (29.5)
Questionnaires	
SF-12	
Physical score	45.9 (36.1-54.4)
Mental score	55.8 (40.6-58.0)
HADS	
Depression score	1.0 (0.5-4.5)
Normal (0-7)	50 (84.7)
Borderline abnormal (8-10)	6 (10.2)
Abnormal (11-21)	3 (5.0)
Anxiety score	3 (1-6)
Normal (0-7)	46 (78.0)
Borderline abnormal (8-10)	7 (11.9)
Abnormal (11-21)	6 (10.2)

Data are presented as No. (%) or median (interquartile range). No. of missing: SF-12, n = 7; HADS, n = 3; asymptomatic, n = 3; dry cough, n = 1; wet cough, n = 1; and dyspnea, n = 2. HADS = Hospital Anxiety and Depression Scale; SF-12 = Short-Form Health Survey.

Overall, those who underwent an ICU stay continued to demonstrate a wide array of abnormalities on CT scans 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 imaging (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, 40 patients showed the presence of reticular (n = 28 [49.1%]) or fibrotic (n = 12 [21.1%]) lesions (Fig 2). Furthermore, the mean number of lobes affected by ground-glass or consolidative opacities per patient was 2.7 (SD, 2.0), and 34 patients showed at least one affected lobe. The mean TSS, which quantifies the

TABLE 3] Pulmonary Function, 6MWT Results, and Chest CT Scan Findings in All Patients at the 3-Month Follow-up

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

Data are presented as No. (%), mean ± SD, or median (interquartile range). 6MWT = 6-min walking test; Dlco = diffusing capacity for carbon monoxide; RV = residual volume; TLC = total lung capacity; TSS = total severity score.

severity of pulmonary inflammation, was 4.8 (SD, 3.9). Representative CT scans from those discharged from the

ICU 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 Scan Alterations

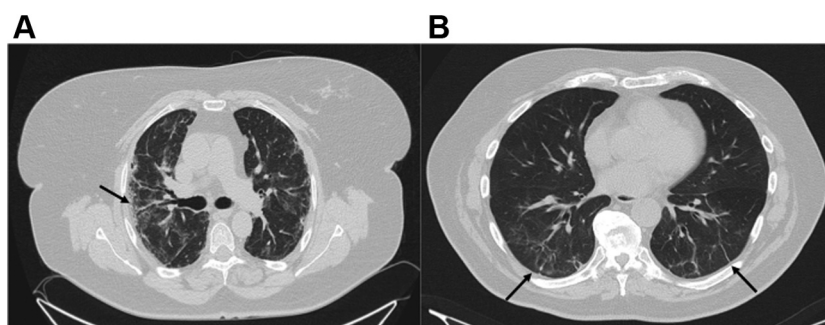
As expected, chest CT scan results severity measured by TSS score were associated intimately with respiratory abnormalities in those who underwent an ICU stay at 3 months after hospital discharge ([e-Table 2](#)). Survivors with CT scan scores in the higher tertiles showed an impaired DLCO, with a mean DLCO of 65.6 (95% CI, 60.1-71.0) in the second tertile and 57.8 (95% CI, 51.7-63.8) in the third tertile ($P \leq .001$ for trend). Consequently, the CT scan score was correlated intimately with diffusing capacity ($\rho = -0.56$) ([Fig 4](#)). For the exercise test, although the mean 6MWT results were similar across CT scan score tertiles ($P = .124$), patients with severe abnormalities on CT scan showed a decreased average oxygen saturation, as well as decreased final and minimal oxygen saturation levels ($P = .028$ and $P = .011$, respectively). A robust and inverse correlation between the CT scan score and the percentage of change in oxygen during the walking test also was observed ($\rho = -0.42$) ([Fig 4](#)).

A predictor selection procedure (LASSO model) was performed using variables from the medical history and ICU stay to explore further the association of clinical profiles of those discharged from the ICU and the outcomes reported for CT scan anomalies: presence of lesions and type of lesions. The results from this analysis suggested an association between CT scan abnormalities and two predictors: age and the length of IMV during the ICU stay. The CT scan score was higher in those patients with longer duration of IMV, and age at admission was robust and correlated positively with the CT scan score ($\rho = 0.40$) ([e-Fig 2](#)). However, the requirement of IMV was the only variable selected for predicting the risk of lung lesions ([e-Fig 3](#)). Additionally, we explored which variables were important for the determination of the type of injury among patients who harbored any pulmonary lesion. The LASSO model showed that the duration of IMV was the only factor that allowed us to discriminate between the types of lesions ([e-Fig 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

Figure 2 – A, B, CT scans comparing a patient with a fibrotic pattern (A) and a patients with a reticular pattern (B). A, CT scan showing subpleural predominant affection, visible parenchymal bands, architectural distortion with irregular interface, and traction bronchiectasis (black arrow). B, CT scan showing only subpleural reticular bands (black arrow) accompanied by interlobular septal thickening.



pulmonary sequelae in patients with COVID-19 after hospital discharge. To our knowledge, this is the first well-characterized descriptive, observational study of COVID-19 survivors who underwent an ICU stay. 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 this cohort has no precedent,⁴¹ even in previous coronavirus outbreaks (SARS and MERS).^{13,14} The quality of life of COVID-19 survivors showed mean scores that are substantially lower than those of healthy people (e-Fig 4),²⁶ those with other chronic diseases,¹² and healthy Spanish people.⁴² This finding usually is 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-analysis¹² 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% CI, 11.05%-45.46%). Two studies^{44,45} included some patients with SARS who required ICU treatment, 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 study¹⁹ performed at the time of hospital discharge and excluding patients with critical disease found DLCO and TLC anomalies in 47.2% and 25%, respectively, being more frequent in patients with severe pneumonia (84%; $P = .001$). Recent research in early convalescence (1 month after discharge) demonstrated that approximately three-quarters of patients with COVID-19 experience pulmonary function impairment, which is represented by a decline in DLCO in more than half of patients.¹⁶

A similar phenomenon is notable with exercise capacity. Previous SARS studies including patients requiring ICU treatment showed a mean 6MWT distance at the 3-month follow-up ranging from 454

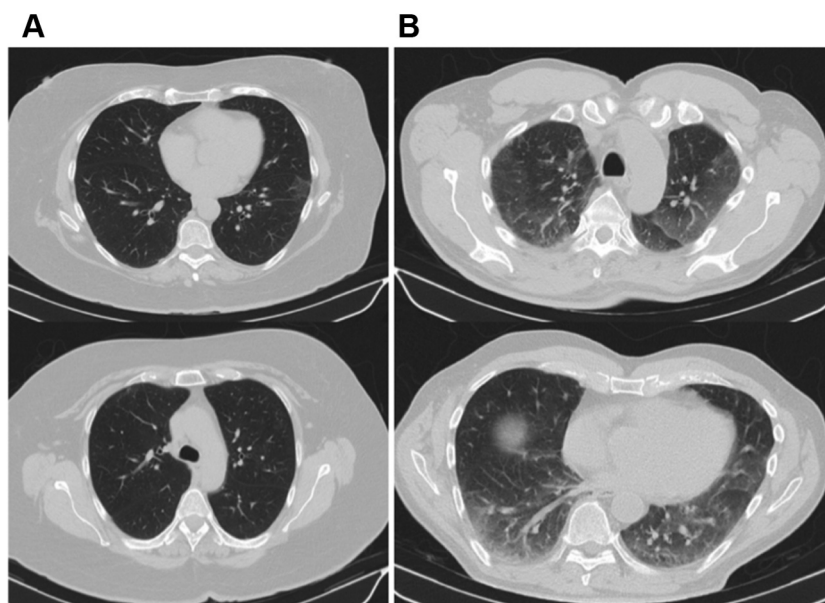


Figure 3 – A, B, CT scans comparing a patient with a total severity score (TSS) score of 2 (A) and a more severe patient with a TSS score of 14 (B).

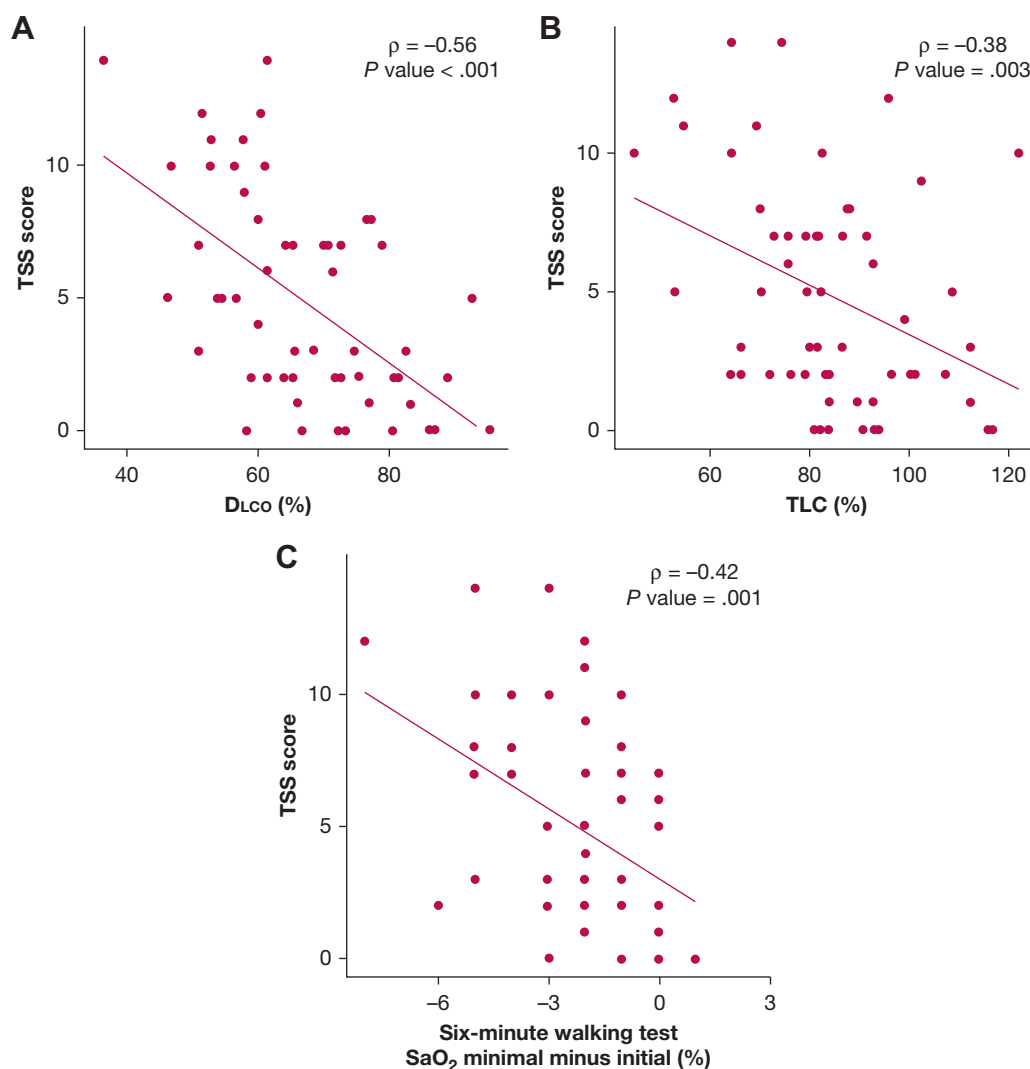


Figure 4 – A-C, Scatterplots showing correlation between lung function and the rate of decrease in SaO₂ and TSS score. P values were computed from the Spearman rank correlation coefficient. A, Scatterplot showing correlation between diffusing capacity for carbon monoxide and TSS score. B, Scatterplot showing correlation between total lung capacity and TSS score. C, Scatterplot showing correlation between rate of decrease in SaO₂ in six-minute walking test and TSS score. DLCO = diffusing capacity for carbon monoxide; SaO₂ = oxygen saturation; TLC = total lung capacity; TSS = total severity score.

m⁴⁶ to 464 m,⁴⁴ with a pooled distance estimate of 461.18 m (95% CI, 449.66-472.71 m).¹² Those distances are significantly longer than the mean distance observed in the present patients (400 m). In SARS-CoV-2, the 6MWT distance was significantly shorter in patients with severe disease (517 m) than in patients with nonsevere disease (573.52 m), indicating poor exercise tolerance.¹⁶

The same phenomenon can be noted in chest CT scan abnormalities found during follow-up examinations of patients who survive COVID-19. In a recent SARS-CoV-2 series, the rate of radiologic 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% of patients and the mean TSS was 8 in the group with abnormal CT scan findings.¹⁸ This finding is in line with our results, although the rate of reticular and fibrotic lesions was higher in the present 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 described previously,^{16,18} severity, as measured by TSS on chest CT imaging, 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 studies⁵¹ showed that patients with COVID-19 are hospitalized more often and have longer hospitalizations with a higher probability of ARDS developing than patients with other acute respiratory illnesses. This hypothesis could be explained by the particular pathologic findings that occur in patients with severe COVID-19 compared with those with other viral pneumonias.⁵² In addition to the typical diffuse alveolar damage, compared with lungs from patients with H1N1, lungs from patients with critical COVID-19 disease showed severe endothelial injury associated with the presence of intracellular virus, disrupted cell membranes, and a higher prevalence of thrombosis and microangiopathy.⁵² Moreover, patients with severe COVID-19 show a unique inflammatory and proteomic profile as well as a different immune response compared with patients with noncritical COVID-19,²¹ leading to organ-specific cellular death and damage.

Our findings have several clinical implications. Because 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 patients. The long-term pulmonary sequelae are unknown, but these data encourage close follow-up of these patients.

This study has some limitations. First, the study examined 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 the cohort being well characterized and prospective. Moreover, because of the methodologic characteristics of the study, we did not calculate a previous sample size. Second, even if the 13 patients lost to follow-up were considered, a minimal influence on the results would have ensued because no sociodemographic and clinical differences are available to compare with the final cohort. Third, it is uncertain whether lung lesions were present before the study. Fourth, the reversibility of the parenchymal involvement is uncertain because of 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 scan abnormalities at the 3-month follow-up. A complete evaluation including chest CT imaging and pulmonary function and exercise tests 3 months after discharge should be considered for these survivors of critical COVID-19.

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Additional information: The e-Figures and e-Tables can be found in the [Supplemental Materials](#) section of the online article.

References

1. Lu R, Zhao X, Li J, et al. Genomic characterisation and epidemiology of 2019 novel coronavirus: implications for virus origins and receptor binding. *Lancet*. 2020;22:395(10224):565-574.
2. Li Q, Guan X, Wu P, et al. Early transmission dynamics in Wuhan, China, of novel coronavirus-infected pneumonia. *N Engl J Med*. 2020;382(13):1199-1207.
3. Toit A Du. Outbreak of a novel coronavirus. *Nat Rev Microbiol*. 2020;18(3):123.
4. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. *N Engl J Med*. 2020;382(10):929-936.
5. Sohrabi C, Alsafi Z, O'Neill N, et al. World Health Organization declares global emergency: a review of the 2019 novel coronavirus (COVID-19). *Int J Surg*. 2020;76:71-76.
6. Cascella M, Rajnik M, Aleem A, Dulebohn SC, Di Napoli R. Features, evaluation, and treatment of coronavirus (COVID-19). In: *StatPearls [Internet]*. StatPearls Publishing; 2021.
7. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069.
8. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481.
9. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506.
10. Rawal G, Yadav S, Kumar R. Post-intensive care syndrome: an overview. *J Transl Intern Med*. 2017;5(2):90-92.
11. Herridge MS, Moss M, Hough CL, et al. Recovery and outcomes after the acute respiratory distress syndrome (ARDS) in patients and their family caregivers. *Intensive Care Med*. 2016;42(5):725-738.
12. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS) coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. *J Rehabil Med*. 2020;52(5):jrm00063.
13. Chan KS, Zheng JP, Mok YW, et al. SARS: prognosis, outcome and sequelae. *Respirology*. 2003;8(suppl 1):S36-S40.
14. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax*. 2005;60(5):401-409.
15. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology*. 2010;15(3):543-550.
16. Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*. 2020;21(1):163.
17. Li K, Fang Y, Li W, et al. CT image visual quantitative evaluation and clinical classification of coronavirus disease (COVID-19). *Eur Radiol*. 2020;30(8):4407-4416.
18. Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*. 2020;25:100463.
19. Mo X, Jian W, Su Z, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. *Eur Respir J*. 2020;55(6):2001217.
20. Gattinoni L, Coppola S, Cressoni M, et al. COVID-19 does not lead to a "typical" acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2020;201(10):1299-1300.
21. Filbin MR, Mehta A, Schneider AM, et al. Plasma proteomics reveals tissue-specific cell death and mediators of cell-cell interactions in severe COVID-19 patients. *bioRxiv [Preprint]*. 2020 Nov 3:2020.11.02.365536.
22. Marini JJ, Gattinoni L. Management of COVID-19 respiratory distress. *JAMA*. 2020;323(22):2329-2330.
23. Bain W, Yang H, Shah FA, et al. COVID-19 versus non-COVID ARDS: comparison of demographics, physiologic parameters, inflammatory biomarkers and clinical outcomes [published online ahead of print February 5, 2021]. *Ann Am Thorac Soc*. <https://doi.org/10.1513/AnnalsATS.202008-1026OC>.
24. van Gassel RJJ, Bels JLM, Raafs A, et al. High prevalence of pulmonary sequelae at 3 months after hospital discharge in mechanically ventilated survivors of COVID-19. *Am J Respir Crit Care Med*. 2021;203(3):371-374.
25. Ranieri VM, Rubenfeld GD, Thompson BT, et al. Acute respiratory distress syndrome: the Berlin definition. *JAMA*. 2012;307(23):2526-2533.
26. Mols F, Pelle AJ, Kupper N. Normative data of the SF-12 health survey with validation using postmyocardial infarction patients in the Dutch population. *Qual Life Res*. 2009;18(4):403-414.
27. Cheak-Zamora NC, Wyrwich KW, McBride TD. Reliability and validity of the SF-12v2 in the medical expenditure panel survey. *Qual Life Res*. 2009;18(6):727-735.
28. Ware JE, Kosinski M, Keller SD. A 12-Item Short-Form Health Survey: construction of scales and preliminary tests of reliability and validity. *Med Care*. 1996;34(3):220-233.
29. Biehl M, Kashyap R, Ahmed AH, et al. Six-month quality-of-life and functional status of acute respiratory distress

- syndrome survivors compared to patients at risk: a population-based study. *Crit Care*. 2015;19:356.
30. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiatr Scand*. 1983;67(6):361-370.
 31. Bjelland I, Dahl AA, Haug TT, Neckelmann D. The validity of the Hospital Anxiety and Depression Scale: an updated literature review. *J Psychosom Res*. 2002;52(2):69-77.
 32. Celli BR, MacNee W, Agusti A, et al. Standards for the diagnosis and treatment of patients with COPD: a summary of the ATS/ERS position paper. *Eur Respir J*. 2004;23(6):932-946.
 33. Roca J, Burgos F, Sunyer J, et al. Reference values for forced spirometry. *Eur Respir J*. 1998;11(6):1354-1362.
 34. Crapo RO, Casaburi R, Coates AL, et al. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med*. 2002;166(1):111-117.
 35. Lynch DA, Sverzellati N, Travis WD, et al. Diagnostic criteria for idiopathic pulmonary fibrosis: a Fleischner Society White Paper. *Lancet Respir Med*. 2018;6(2):138-153.
 36. Ooi GC, Khong PL, Müller NL, et al. Severe acute respiratory syndrome: temporal lung changes at thin-section CT in 30 patients. *Radiology*. 2004;230(3):836-844.
 37. Leisman DE, Harhay MO, Lederer DJ, et al. Development and reporting of prediction models. *Crit Care Med*. 2020;48(5):623-633.
 38. Hastie T, Tibshirani R, Tibshirani RJ. Extended comparisons of best subset selection, forward stepwise selection, and the lasso. *Crit Care Med*. 2020;48(5):623-633.
 39. Zhang Y, Yang Y. Cross-validation for selecting a model selection procedure. *J Econom*. 2015;187.1(2015):95-112.
 40. Enrichi PL, Sherrill DL. Reference equations for the six-minute walk in healthy adults. *Am J Respir Crit Care Med*. 1998;158(5 Pt 1):1384-1387.
 41. Ramani C, Davis EM, Kim JS, Provencio JJ, Enfield KB, Kadl A. Post-ICU COVID-19 outcomes: a case series. *Chest*. 2021;159(1):215-218.
 42. Vilagut G, Valderas JM, Ferrer M, et al. Interpretación de los cuestionarios de salud SF-36 y SF-12 en España: componentes físico y mental. *Med Clin (Barc)*. 2008;130(19):726-735.
 43. Bahmer T, Kirsten AM, Waschki B, et al. Clinical correlates of reduced physical activity in idiopathic pulmonary fibrosis. *Respiration*. 2016;91(6):497-502.
 44. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest*. 2005;128(4):2247-2261.
 45. Herridge MS, Cheung AM, Tansey CM, et al. One-year outcomes in survivors of the acute respiratory distress syndrome. *N Engl J Med*. 2003;348(8):683-693.
 46. Li TS, Gomersall CD, Joynt GM, et al. Long-term outcome of acute respiratory distress syndrome caused by severe acute respiratory syndrome (SARS): an observational study. *Crit Care Resusc*. 2006;8(4):302-308.
 47. Xiong Y, Sun D, Liu Y, et al. Clinical and high-resolution CT features of the COVID-19 infection: comparison of the initial and follow-up changes. *Invest Radiol*. 2020;55(6):332-339.
 48. Han X, Cao Y, Jiang N, et al. Novel coronavirus disease 2019 (COVID-19) pneumonia progression course in 17 discharged patients: comparison of clinical and thin-section computed tomography features during recovery. *Clin Infect Dis*. 2020;71(15):723-731.
 49. Ng CK, Chan JWM, Kwan TL, et al. Six month radiological and physiological outcomes in severe acute respiratory syndrome (SARS) survivors. *Thorax*. 2004;59(10):889-891.
 50. Wang Q, Zhang Z, Shi Y, Jiang Y. Emerging H7N9 influenza a (novel reassortant avian-origin) pneumonia: radiologic findings. *Radiology*. 2013;268(3):882-889.
 51. Shah SJ, Barish PN, Prasad PA, et al. Clinical features, diagnostics, and outcomes of patients presenting with acute respiratory illness: a retrospective cohort study of patients with and without COVID-19. *EClinicalMedicine*. 2020;27:100518.
 52. Ackermann M, Verleden SE, Kuehnel M, et al. Pulmonary vascular endothelialitis, thrombosis, and angiogenesis in Covid-19. *N Engl J Med*. 2020;383(2):120-128.