Case Report

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COVID 19, emphysema, and secondary pulmonary fibrosis: About a case report

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Abstract:

Associations have been drawn between pre-existing diseases and adverse outcomes during the course of the ongoing coronavirus 2019 (COVID-19) pandemic, the disease resulting from infection with recently identified severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Patients who have chronic obstructive pulmonary disease with the emphysema-hyperinflated phenotype are one of the population groups with basal risk comorbidities who may have a higher probability of developing secondary pulmonary fibrosis, even in the early stages of COVID-19, potentially leading to permanent adverse functional consequences and even death. The aim of this report was to investigate this pathophysiological association in order to examine potential therapeutic targets for use during the COVID-19 pandemic that could reduce future sequelae using an illustrative clinical case and the available literature.

Keywords:

Chronic obstructive pulmonary disease, COVID-19, emphysema, pulmonary fibrosis, SARS-CoV-2

Introduction

Data related to chronic obstructive pulmonary disease (COPD) among patients with coronavirus 2019 (COVID-19) have revealed a wide range of prevalence (1.1–38%) in the hospital setting.[1] Although the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection rate of patients with COPD does not appear to be significantly different from that of patients with no pre-existing pulmonary disease, adverse outcomes, such as hospitalization, intensive care unit admission, need for mechanical ventilation, and mortality, have been consistently higher in this population group. The prevalence of comorbidities may be directly related to important adverse clinical outcomes.[2–4]

One of the pulmonary complications of COVID-19 associated with severe pulmonary dysfunction and increased mortality is secondary pulmonary fibrosis. There are plausible pathophysiological mechanisms that may link pre-existing conditions, such as smoking and COPD,

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with the development of this complication. This report describes the case of a man who developed pulmonary fibrosis secondary to SARS-CoV-2 infection at an early stage, which led to a fatal outcome. Some of the relevant literature is also reviewed.

Case Report

A 61-year-old man presented with a history of COPD Global Initiative for Chronic Obstructive Lung Disease (GOLD) grade 3 (FEV_1: 40%) group D (>2 exacerbations per year, COPD Assessment Test: 12 points) treated with ipratropium bromide (2 inhalations every 4 to 6 hours, as needed) and supplemental oxygen (2 L/minute) in the context of heavy active smoking (pack/year index: 47). In addition, the patient had type 2 diabetes mellitus, resistant arterial hypertension, and an infrarenal abdominal aortic aneurysm 2.22×2.29 cm in size without mural thrombus treated in outpatient medical management with a diuretic (furosemide), antihypertensive agents (losartan, nifedipine, clonidine, spironolactone, carvedilol), an antidiabetic agent (metformin), and a lipid-lowering agent (atorvastatin).

The patient arrived with a 7-day history of objective fever (38.5°C) associated with a non-productive dry cough and general malaise. An antigenic test for SARS-CoV-2 infection had yielded a positive result 3 days from the onset of symptoms. He was admitted to the emergency department with tachypnea, dyspnea, and desaturation (SpO_2: 82%), and continuous positive airway pressure (positive end-expiratory pressure: 15 cmH_20, FiO_2: 90%) was administered for 6 hours. A portable chest X-ray was also performed [Fig. 1].

The patient was directed to the intermediate respiratory care unit in a poor general condition, with jugular venous distention grade II at 45°, supraclavicular retractions, S2 splitting on inspiration, rales in the middle and basal third of the right lung, and expiratory rhonchi in both lung bases. He was normotensive, with rhythmic heart sounds and afebrile, but required assistance with FiO_2 90%.

Laboratory studies were conducted and the following prognostic value scales were calculated:

- National Early Warning Score (NEWS) 2 (7 pts): high risk

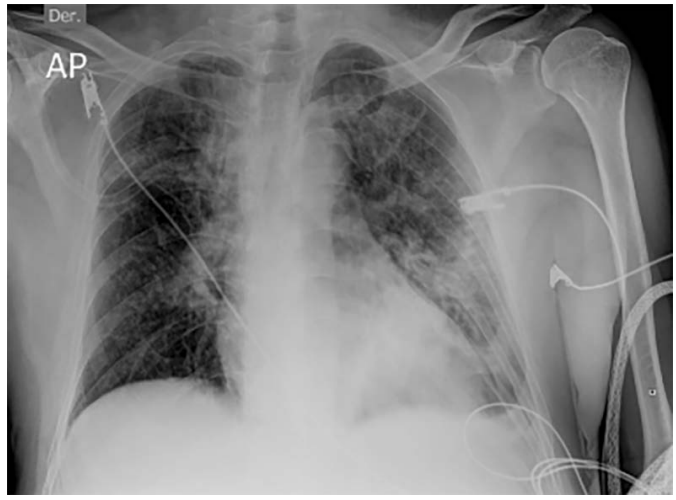

Figure 1: Chest X-ray, anteroposterior (AP) projection. Ground-glass opacities of bilateral parahilar distribution, predominantly toward the left subpleural region, are visible, as well as central peribronchovascular enhancement due to peribronchial inflammatory changes

- CALL Score (C=co-morbidity, A=age, L=lymphocyte count, L=lactate dehydrogenase) class C (12 pts): high risk of COVID-19 progression (>50%).

The admission laboratory results are reported in Table 1.

The patient was transitioned to treatment with methylprednisolone (80 mg/day) after receiving 2 doses of dexamethasone (6 mg/day). Facing a clinical condition that suggested cor pulmonale, a conventional transthoracic echocardiogram was performed and documented a left ventricle with a normal diameter, concentric remodeling, mild global hypokinesia, a mild decrease in ejection fraction estimated at 47%, and altered ventricular relaxation, with signs of a moderate increase in end-diastolic filling pressure. The right ventricle showed mild dilatation without hypertrophy and preserved systolic function; both of the atria had a normal diameter.

The day after admission, the patient became somnolent, showing stable baseline dyspnea (modified Medical Research Council grade 3). Additional paraclinical tests were conducted (Table 2), including complementary high-resolution chest tomography (HRCT) [Fig. 2–4].

The patient was profiled for noninvasive mechanical ventilation (NIV) facilitated with a dexmedetomidine infusion (0.2 ug/kg/hour, titratable dose), completing 2 cycles of 4 hours each with the parameters provided in Table 3.

Table 1. Admission laboratory values

Laboratory parameter	Value reported	Reference values
pH	7.287	7.25–7.35
pCO_2	54.2	35–45
pO_2	90.7	80–100
Tissue oxygen saturation (StO_2)	95%	90–92%
HCO3	25.3	22–26
Base excess (BE)	–1.4	–2/+2
PaO_2/FiO_2 ratio (PaFi)	100	>300
C-reactive protein (CRP)	30.3 mg/L	<10 mg/L
D-dimer	1302 ng/mL	<100 ng/mL
Ferritin	650 ug/L	24–336 ug/L
Lactate dehydrogenase (LDH)	410 UI/L	50–150 UI/L
Hemoglobin (Hb)	15.9	12–16 g/dL
Hematocrit (Ht)	47.1	37–47%
Leukocytes	6560	4500–10000/uL
Neutrophils	4480	1530–7400/uL
Lymphocytes	600	940–4800/uL
Monocytes	1280	90–800/uL
Eosinophils	200	40–400/uL
Platelets	203000	150000–450000/uL
Serum creatinine	1.20	0.8–1.2 mg/dL
Blood urea nitrogen (BUN)	30.3	10–20 mg/dL
Serum glucose (preprandial)	136	80–130 mg/dL

Table 2. Second set of laboratory values

Laboratory parameter	Reported value	Reference values
pH	7.17	7.25–7.35
pCO_2	80	35–45
pO_2	71.2	80–100
Tissue oxygen saturation (StO_2)	95%	90–92%
HCO_3	29.4	22–26
Base excess (BE)	0.8	–2/+2
PaO_2/FiO_2 ratio (PaFi)	101	>300

The respiratory pattern was modulated after this intervention and improvement in consciousness and reduction of respiratory effort was observed. However, 2 days later, the patient developed severe hypoxemia (StO_2: 78–80%, FiO_2: 90%), prolonged expiration, persistent diaphragmatic discharge, and intercostal and subcostal retraction. High-flow nasal cannula support was initiated with the parameters of an FiO_2 rate of 100% and a flow of 60 L/minute and maintained for 6 days. Reduction of these parameters was not possible due to persistent respiratory effort and severe hypoxemia.

Given his poor functional reserve and extensive areas of pulmonary fibrosis documented with HRCT, in addition to a fluctuating clinical course, the possibility of requiring orotracheal intubation and invasive mechanical ventilation was discussed with the patient, however, he and his family members declined this course of action. Facing these circumstances, and in view of the severe dyspnea and clinical deterioration, an end-of-life protocol was initiated with a morphine infusion and ensuring an FiO_2 rate of 90%. The patient died after 10 days in the unit.

Discussion

The presentation of pulmonary fibrosis secondary to viral infection can vary. In a retrospective cohort study conducted on post-mortem specimens (159 patients meeting the diagnostic criteria for acute respiratory distress syndrome [ARDS]), pulmonary fibrosis was observed in 3 of 82 patients (4%) with an ARDS duration of <1 week, 13 (24%) of 54 patients with a disease duration of 1–3 weeks, and 14 (61%) of 23 patients with a duration of >3 weeks.[5]

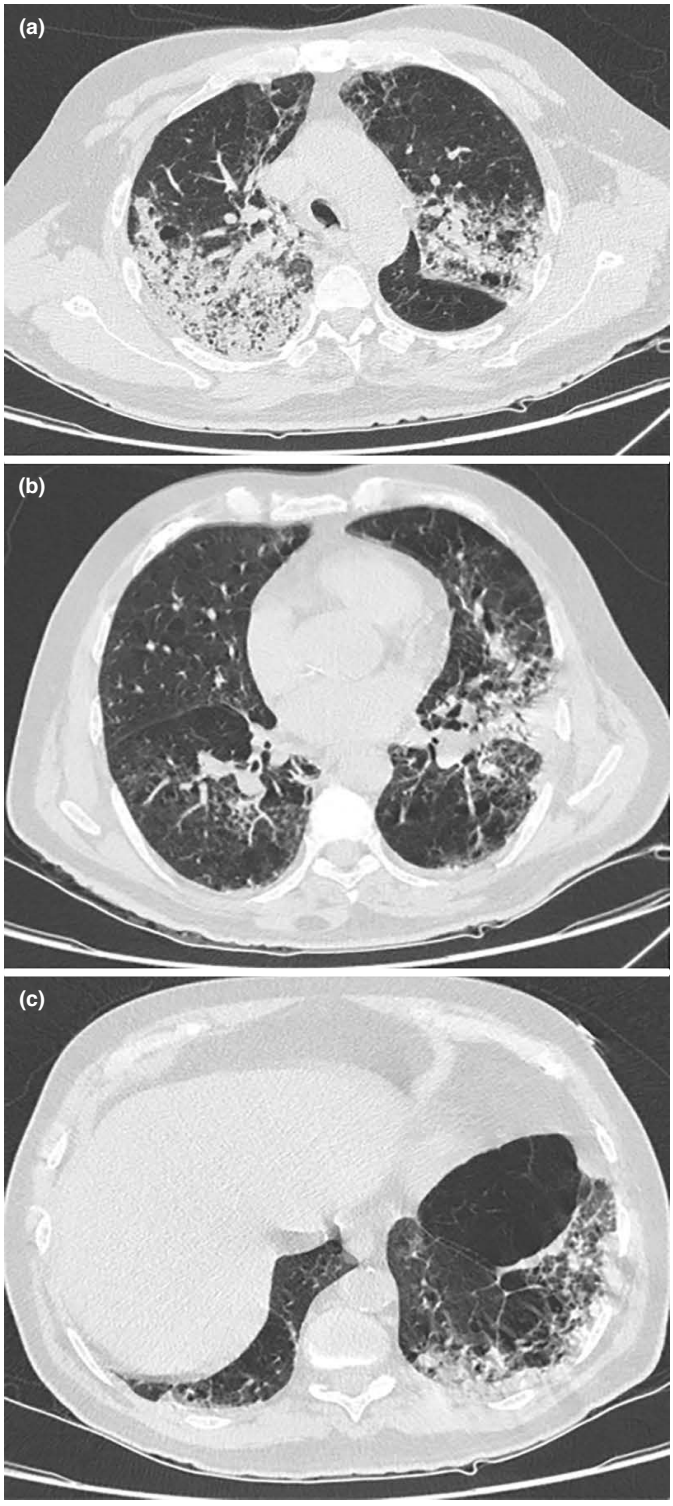

Figure 2a-c: Peripherally distributed alveolar opacities can be seen in the lower segments of both upper lobes with a tendency to consolidation in the posterior segment of the right upper lobe. Thick reticular opacities in the lower lingular segment with a tendency to consolidation associated with adjacent bronchiectasis are also visible. In the left lung base, an area of centrilobular emphysema, associated with diffuse distribution of thick reticular opacities, is suggestive of initial fibrotic process

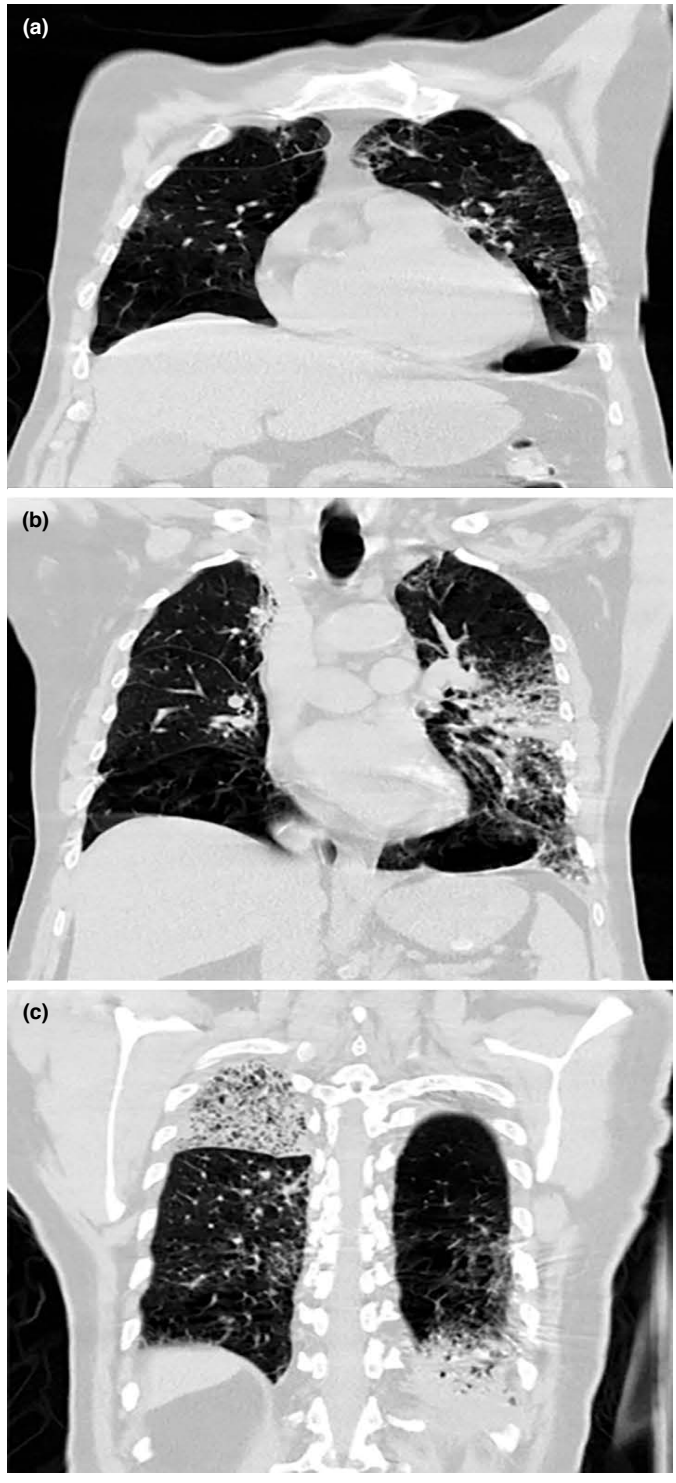

Figure 3a-c: In the upper and middle third of the left hemithorax posterior aspect, fine reticular opacities of diffuse distribution can be observed. In the upper and lower lingular segment and upper segment of the left lower lobe, thick reticular opacities with a tendency to consolidation, associated with bronchiectasis and bronchiolectasis, are visible. In the posterior segment of the left upper lobe, consolidated reticular opacities can be seen without a clear cobblestone pattern. In the left pulmonary base, there are thick reticular opacities with a tendency to consolidation

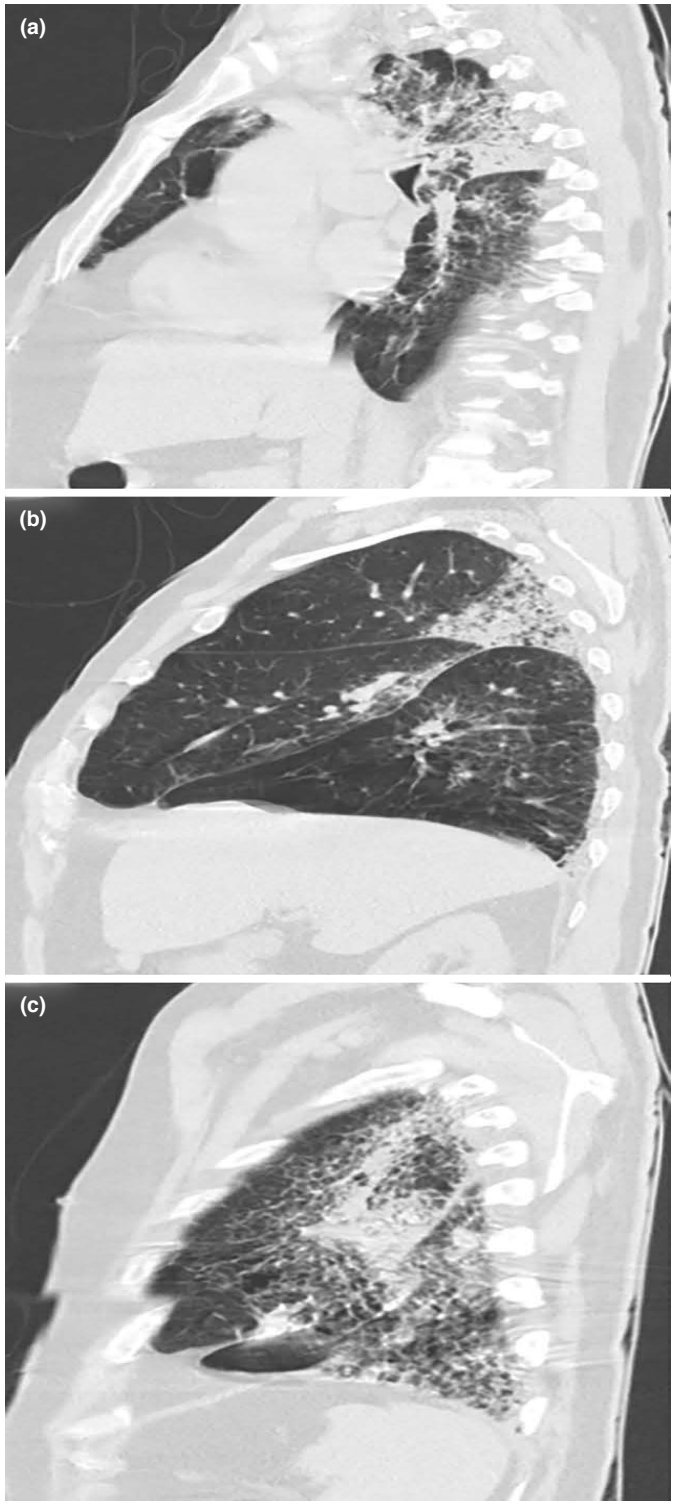

Figure 4a-c: Reticular opacities with a tendency to consolidation globally involving the left hemithorax with traction bronchiectasis and without frank honeycombing or parenchymal destruction, signs of fibrosis in the initial phase. Reticular opacities with a tendency to consolidation can be seen in the posterior segment of the left upper lobe and the middle lobe, and in the lower lobe, there are fine reticular opacities without consolidation foci

Secondary pulmonary fibrosis as a complication of COVID-19 is a matter under study, but in previous epidemics, such as severe acute respiratory syndrome (SARS) and the Middle East respiratory syndrome (MERS), the association was evident, demonstrated by compatible imaging findings of pulmonary fibrosis in the short, medium, and long-term follow-up.[6–7]

There are multiple host and infectious agent-related pathophysiological mechanisms that can interconnect to promote progression to pulmonary fibrosis in a subset of individuals who develop ARDS. Important mediators include the excessive release of extracellular matrix metalloproteinases during the inflammatory phase of ARDS, which causes injury to both epithelial and endothelial cells, inducing a state of uncontrolled fibroproliferation.[8–9] In the COVID-19 setting, this seems to have the greatest effect on active smokers or patients with a history of heavy smoking. Chronic exposure to cigarette smoke alters the molecular expression of the angiotensin-converting enzyme 2 (ACE2) receptor, which is primarily responsible for the binding and entry of SARS-CoV-2 to the cell and the cofactor transmembrane serine protease 2.[10] Moreover, it compromises host immunity through several mechanisms, involving both innate and adaptive immune responses. Strikingly, cigarette smoke exposure increases the number of alveolar macrophages in COPD; however, their phagocytic capacity, expression of antiviral mediators, and clearance of apoptotic cells is reduced.

Some of the macrophage-derived proteinases (e.g., disintegrin A and metalloproteinase A 17) can shed both SARS-CoV-2 protein S, inducing virus entry into host cells, and ACE2, by releasing it from the epithelial surface into the airways. Additionally, a reduction and functional attenuation of important antiviral molecules, such as interferon β, has been seen in the lung epithelium and alveolar macrophages of COPD patients.[11–12] The pro-inflammatory state evidenced by overexpression and cellular release of cytokines and growth factors, such as monocyte chemotactic protein-1, vascular endothelial growth factor, transforming growth factor beta-1, tumor necrosis factor alpha, fibroblast growth factor, platelet-derived growth factor, interleukin (IL) 1 beta, and IL-6, is common in the presence of lung damage in pulmonary fibrosis and in COVID-19 severe pneumonia, suggesting a common pathophysiological state.[13]

Table 3. Noninvasive mechanical ventilation (NIV) parameters

NIV	Pressure support (PSV)	Positive end-expiratory pressure (PEEP)	Respiratory rate (RF)	Tissue oxygen saturation (StO_2)	Tidal volume (VT)	Fraction of inspired oxygen (FiO_2)	Interface
Programming	14 cm H_2O	10 cm H_20	20 rpm	90%	7 cc/kg/min	100%	Oronasal mask

The association between previous pulmonary emphysema and secondary pulmonary fibrosis in the course of SARS-CoV-2 infection has been cited mostly in the post-acute COVID-19 setting, defined as more than 3 weeks from symptom onset.[14] Mazzolini et al.[15] reported the case of a 74-year-old woman with a personal history of ischemic heart disease and mixed dyslipidemia and COPD with previous findings of bilateral centrilobular emphysema with a diagnosis of severe SARS-CoV-2 infection determined with a reverse transcription polymerase chain reaction test and managed with NIV. Despite initial improvement, there was subsequent clinical and radiological deterioration, with tomographic findings of volume loss, distortion of the architecture, and traction bronchiectasis predominantly in the lower lobes secondary to extensive pulmonary fibrosis that led to a fatal outcome in the short term.

Hussain et al.[16] published the case of a 58-year-old man with a history of hypertension, diabetes mellitus, and heavy smoking for 20 years, as well as a known history of pulmonary fibrosis combined with emphysema. The patient had been diagnosed with COVID-19 some 45 days prior and received treatment at another facility. He was admitted with signs of impending respiratory failure and progression of fibrotic and emphysematous changes seen on a chest CT. There was a partial response to management with supplemental oxygen, methylprednisolone and pirfenidone, however, ultimately NIV was required.

Unlike these 2 cases, our patient had no known diagnosis of pulmonary emphysema (given poor outpatient follow-up), but he had a similar comorbidity profile and a smoking rate that made the presence of this radiological finding highly probable. It was later confirmed by the chest CT scan performed during his hospital stay. This led us to investigate a possible association between emphysema and pulmonary fibrosis in the setting of COVID-19, based on the extensive interstitial involvement and the torpid clinical course common to all 3 patients. In our case, however, temporal progression of pulmonary fibrosis could not be demonstrated due to the lack of a control chest CT scan as a result of the patient's death.

The spectrum of fibrotic pulmonary disease observed in COVID-19 ranges from incipient fibrosis associated with organizing pneumonia to severe acute lung injury evolving toward a generalized fibrotic change, facilitated in part by prolonged exposure to invasive mechanical ventilation and the phenomena of diffuse alveolar damage and microvascular thrombosis associated with autoimmune dysregulation and viral infection.[17] Taking this into account, it does not seem feasible to consider the use of conventional antifibrotic agents (pirfenidone, nintedanib) in COVID-19 without the associated immunomodulatory agents, despite recognizing the involvement of these drugs in different cell signaling pathways in the pulmonary epithelium and endothelium.

A multinational, phase 2 clinical trial examining the use of pirfenidone and forced vital capacity (FVC) was unable to apply the intended statistical model to assess the change in FVC, but did note that the drug could provide some benefit.[18] Pivotal trials examining the use of nintedanib in both idiopathic pulmonary fibrosis (INPULSIS) and other secondary pulmonary fibrosis (INBUILD) appear to demonstrate a difference in FVC between the intervention and placebo groups at 4–6 weeks; however, there is no evidence to date to support its use in early stage COVID-19 to prevent the development of pulmonary fibrosis.

One proposed therapeutic molecular target for viral-induced pulmonary fibrosis is via the transforming growth factor beta (TGF-β) pathway and a blockade of various integrins and galectins. Considering that the SARS-CoV-2 spike protein contains an Arg-Gly-Asp integrin-binding domain and several coronaviruses contain an N-terminal galectin fold, intervening in this mechanism could not only decrease the risk of contagion and the viral replication rate, but also the endogenous processes that end with the activation of myofibroblasts in the extracellular matrix. Ex-

perimental studies in animal models are still under development, and complementary new evidence is required to make them applicable to the current clinical scenario.[19–20]

Conclusion

- Given that approximately 30% of SARS and MERS survivors have experienced persistent radiological and physiological abnormalities consistent with fibrotic lung disease, the impact of COVID-19 could include a large cohort of individuals with persistent and potentially progressive pulmonary fibrosis. Long-term follow-up studies will be needed to establish the true prevalence of pulmonary fibrosis following COVID-19.

- There are multiple pathophysiological models that endeavor to explain the predisposition to develop pulmonary fibrosis in patients with viral infections (including COVID-19), chronic exposure to tobacco smoke, and previous pulmonary emphysema, involving not only ACE-2 as a regulatory mechanism of TGF-β levels and cytokines involved in fibrogenesis (formation of active myofibroblast foci), but also the participation of other proteinases as a result of alveolar epithelial injury persisting over time due to external factors, such as continuous exposure to tobacco smoke.

- Available antifibrotic treatments have demonstrated broad antifibrotic activity in addition to antiviral and epithelial effects that could recommend a role in the attenuation of profibrotic pathways in the course of SARS-CoV-2 infection; however, follow-up studies are required in the short and medium term to better delineate their effectiveness and the population that could benefit.

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Informed Consent
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