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Reviews

"A Chain Only as Strong as Its Weakest Link": An Up-to-Date Literature Review on the Bidirectional Interaction of Pulmonary Fibrosis and COVID-19

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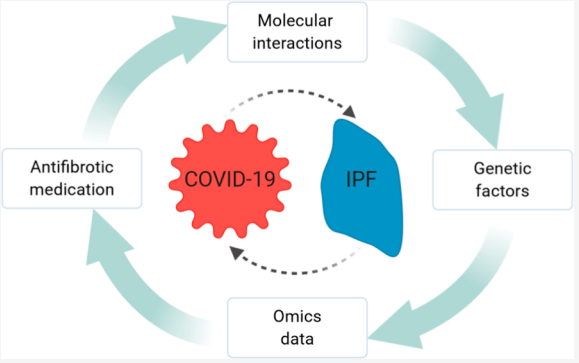
ABSTRACT: The COVID-19 pandemic rapidly became a worldwide healthcare emergency affecting millions of people, with poor outcomes for patients with chronic conditions and enormous pressure on healthcare systems. Pulmonary fibrosis (PF) has been cited as a risk factor for a more severe evolution of COVID-19, primarily because its acute exacerbations are already associated with high mortality. We reviewed the available literature on biochemical, pathophysiological, and pharmacological mechanisms of PF and COVID-19 in an attempt to foresee the particular risk of infection and possible evolution of PF patients if infected with SARS-COV-2. We also analyzed the possible role of medication and risk factors (such as smoking) in the disease's evolution and clinical course. We found out that there is a complexity of interactions between coexisting idiopathic pulmonary fibrosis/interstitial lung disease (ILD) and COVID-19 disease. Also, patients recovering from severe COVID-19 disease are at serious risk of developing PF. Smokers seem to have, in theory, a chance for a better outcome if they develop a severe form of COVID-19 but statistically are at much higher risk of dying if they become critically ill.



KEYWORDS: *pulmonary fibrosis, COVID-19, prognosis, fibrosis pathways, antifibrotic medication*

INTRODUCTION

The 2019 coronavirus disease (COVID-19) outbreak rapidly escalated to a global pandemic affecting millions of people in only a few months,[1] with poor outcomes in individuals with old age/comorbidities such as chronic lung diseases, cardiovascular diseases, or diabetes.[2,3] The pandemic redefined and rearranged health risks for almost all human diseases. The dynamics of the scientific data and the research, conducted fast around the world,[4] united the medical community like never before in covering as many outcome scenarios for their patients as possible, in all medical specialties.

Pulmonary fibrosis (PF) has been cited as a risk factor for a more severe evolution of COVID-19.[5,6] Since its first description, almost 90 years ago by Hamman and Rich,[7] idiopathic pulmonary fibrosis (IPF) has been a challenging disease, passing through many hypotheses for pathogenesis but remaining a devastating condition of unknown cause.[8]

Numerous heterogeneous disorders (with known or unknown etiology) can lead to PF: infectious, immunological, toxic, or idiopathic.[9] In addition to different clinical histories and different pathologies, these diseases have remarkably different prognoses, with a life expectancy varying from a couple of years to decades.[9] Interstitial lung diseases (ILDs) define a complex pathologic category of pulmonary diseases, including over 200 clinical entities that impair the pulmonary function. Many are considered rare diseases,[9] requiring a skilled multidisciplinary medical team to diagnose and initiate treatment. One of the most heterogeneous group of disorders associated with lung fibrosis is represented by the fibrotic ILDs.[9]

The course of most ILDs is characterized by a progressive decline in lung function due to gas exchange impairment and reduced lung compliance, and the decline rate is directly proportional to the dysregulation of fibroblasts.[9] IPF seems to be the most common ILD[10] and often misdiagnosed,[11] categorized as "life-threatening", "under-diagnosed", or "too little studied"—only to emphasize that it is an irreversible and

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progressive respiratory disease, with a rough incidence of 23.4/100 000,[12] and a median survival of 2−3 years after diagnosis.[13,14] The complicated and time-consuming diagnostic,[15] together with the few treatment options, make IPF comparable to many forms of cancer (in terms of survival and death rates).[16]

An acute exacerbation of the IPF (AE-IPF) dramatically shifts the mortality to over 50%.[14] It is associated with certain risk factors such as respiratory infections (both viral and bacterial), a particular pathogen colonization of patients' respiratory tract, abnormally elevated anti-infection immune response, and absence of a smoking history.[14,17]

The SARS-COV-2 pandemic, with its current pattern of affecting (and, unfortunately, killing) especially elderly patients with cardiovascular and respiratory comorbidities,[18] may put the patients with IPF at a higher risk[19] than usual seasonal infections, mostly due to the viral aggressivity and higher occurrence of acute respiratory distress syndrome.[20] A possible explanation for the unfortunate outcome of IPF patients facing SARS-COV-2 infection may be that the early lung injury is often present in the distal airways,[21] where the fibrosis already impairs perfusion. However, factors such as microinjuries consequent to viral aggression,[21] the acute respiratory distress syndrome (ARDS), the extended previous lung fibrosis lesions, and lack of chronic antifibrotic treatment may lead to a catastrophic scenario in which IPF patients will not stand a chance if infected. The use of antifibrotic treatment has been demonstrated to reduce the acute exacerbation of IPF.[22] However, the protective role of antifibrotic medication during the SARS-COV-2 pandemic is a real matter of debate.

In this article, we aimed to review the available literature to investigate and project a possible evolution of IPF patients during the SARS-COV-2 pandemic, the particular risk of infection with SARS-COV-2 in patients with IPF, and the possible role of medication and risk factors (such as smoking) in the evolution and outcome of the disease.

METHODS

The electronic databases of PubMed and preprint servers (medRxiv, arXiv) were searched for relevant articles published from the beginning of the pandemic until May 2020. The search terms used were ["SARS-CoV-2" OR "COVID-19" OR "SARS" OR "SARS-CoV" OR "SARS-CoV-1" OR "MERS-CoV"] AND ["idiopathic pulmonary fibrosis" OR "IPF" OR "interstitial lung diseases" OR "ILD"] AND ["fibrosis pathways" OR "acute exacerbations" OR "acute lung injury" OR "ARDS" OR "antifibrotic medication"]. We included articles that involved data about similarities and differences in fibrogenic pathways, coexisting mechanisms, and reciprocal influences and shared treatment strategies between SARS-CoV-2, SARS-CoV-1, MERS-CoV, and fibrotic lung diseases. Journal articles published with full text or abstracts in English were eligible for inclusion. The study selection process was conducted considering article identification, removing the duplicates, screening titles and abstracts, and assessing eligibility of the selected full texts. Additionally, reference lists of valid articles were checked for studies of relevance.

Additionally, we interrogated the search engine https://covidex.ai made by the University of Waterloo and New York University. Neural Covidex uses natural language processing, state-of-the-art neural network models, and artificial intelligence techniques to answer queries about pathogenic coronaviruses using the COVID-19 Open Research Data set (CORD-19)[23] which is the current largest open data set available with over 134 000 scholarly articles, including over 60 000 with full text about COVID-19, SARS-CoV-2, and other coronaviruses from the following sources: PubMed's PMC open access corpus (maintained by the WHO), bioRxiv, and medRxiv preprints.

RESULTS

Neural Covidex was interrogated with the following queries: "SARS-CoV-2 and pulmonary fibrosis", "COVID-19 and pulmonary fibrosis", "SARS and pulmonary fibrosis," "MERS-CoV and pulmonary fibrosis." The first interrogation returned 21 results, and the second query resulted in 31 articles. The third interrogation returned 43 articles, and the fourth query led to 24 results. After the duplicates were remove and the relevance of the research subject was accessed, 92 articles were included.

DISCUSSION

Pulmonary Fibrosis Patients Facing the COVID-19 Threat: Do They Have a Worse Prognosis?

In general, fibrosis is a normal repair process and is almost invariably preceded by other modifying and reactionary (inflammatory) tissue changes.[24] In the case of repeated or chronic lung injury, fibrosis becomes aberrant wound healing because of dysregulation of fibroblasts and extensive deposition of collagen and elastin that might lead to chronic respiratory failure and even death.[24]

While lung fibrosis is the very definition of IPF, fibrogenic processes are also present in COVID-19 evolution, especially after specific complications such as ARDS. Given the high incidence of ARDS during severe COVID-19 and the fact that up to 85% of ARDS survivors might develop long-term lung function impairment, and CT scans abnormalities,[25] any potential antifibrotic therapy should be taken as soon as possible within the first week of ARDS onset in order to be effective.[25] Special attention is needed for severe COVID-19 patients with pre-existent PF, especially IPF patients, in which mechanical ventilation is associated with a higher mortality rate.[26]

Both COVID-19 and IPF seem to share similar risk factors such as male sex, increasing age, and cardiovascular comorbidities,[25] implying that individuals most likely to be diagnosed with severe IPF (because of risk factors) might also be diagnosed with severe COVID-19.

Although there is no information on IPF/ILD patients infected with SARS-CoV-2, it is worth mentioning other respiratory infections and their impact on preexisting fibrotic pulmonary disease. This comparison is relevant considering that L-SIGN encoded by *CLEC4M* has been documented as an alternate receptor and portal of entry for SARS-CoV-1 as well as for *Mycobacterium tuberculosis* (MTB) and influenza A.[27−29] Although the transmembrane protein angiotensin-converting enzyme-2 (ACE2) is the main entry point for SARS-CoV-1, the L-SIGN receptor can also mediate the infection to a lesser extent. MTB and influenza A virus also use L-SIGN as a portal of entry, which implies possible similarities in disease pathogenesis. Thus, clinical information from MTB and influenza A infections might be useful in the management of coronaviruses infections. MTB infection has been shown to provoke IPF progression,[30] and a five times higher incidence of tuberculosis in IPF than in the general population was

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described.[31] Influenza A immune response was prominently related to the development of AE-IPF.[32] AE-IPF has also been reported after influenza A vaccination.[33] Moreover, enhanced fibrotic response, epithelial apoptosis, and fibrogenesis was described in the fibrotic lung infected with influenza A.[34]

While more severe outcomes in patients with IPF/ILD, associated with infection and inflammation, are expected, the role of inflammation (especially the role of inflammatory cells) in lung fibrosis resolution has been previously documented.[35] Although once considered irreversible, there is now growing evidence suggesting that lung fibrosis can be reversible in murine models[36] and human fibrotic disorders, under some circumstances.[24] Besides their contribution to fibrogenesis, inflammatory cells, especially macrophages, can be programmed to play an essential part in reversing fibrosis by the degradation of the extracellular matrix, of phagocytosis of collagen, of cellular debris and apoptotic cells, and by recruitment of other inflammatory cells associated with fibrosis suppression.[35]

As proof, a study shows that pulmonary delivery of the proinflammatory cytokine TNF-α to mice with established bleomycin-induced PF reduced pulmonary fibrotic burden, improved lung function, and architecture and reduced the number of profibrotic programmed macrophages, speculating an unexpected role of TNF-α in the resolution of established PF.[37]

At the same time, both SARS-CoV-1 and SARS-CoV-2 infections are associated with higher TNF-α.[38,39] Another study on the roles of TNF-α gene polymorphisms in the progress of SARS-CoV-1 infection showed that TNF-α alleles were not related to interstitial lung fibrosis in cured SARS patients and that the CT genotype at the −204 locus was found associated with a protective effect on SARS.[40] Even if one could speculate a beneficial effect of elevated TNF-α from pathogenic coronavirus infection on IPF/ILD patients, the crucial role of TNF-α in the "cytokine storm" pathogenesis and its devastating consequences on COVID-19 and SARS must also be considered. Moreover, despite macrophages' ability to be programmed for fibrosis suppression, a proteomic and metabolomic profiling of sera from COVID-19 patients uncovered the downregulation of apolipoprotein A1, a vital fibrosis suppressor, and modulator of macrophages function.[41]

One of the most sustained theories about IPF is that senescent cells contribute (with a growing pallet of evidence) to the pathophysiology[42−44] through ATII-cells, fibroblasts, and bronchial epithelial cells that also show senescent phenotypes.[45] One of the latest findings by De Biasi and Gibellini showed that COVID19 patients present, besides altered differentiation of T cell subtype and highly modified plasma cytokines, increased markers of T-cells activation, exhaustion, and senescence.[46]

The role of cellular apoptosis in the pathogenesis of IPF has been described over 20 years ago and seems to involve the overwhelming of the clearing mechanism of cellular homeostasis, thus maintaining inflammation and overgrowth of the mesenchymal cells.[47] It seems though that cellular apoptosis is inhibited by the ACE/ACE2 balance.[48] The SARS-COV-2 infection is known to downregulate the ACE2 expression and, in this way, is unbalancing the ACE/ACE2 ratio accelerating inflammation (primarily through macrophagic activation) and, without a doubt, fibrogenesis as well.[49]

Of course, the multifactorial inflammation of IPF involves, beside genetic factors, the innate immune cells and the proinflammatory cytokines, especially IL-1, TNF-α, and IL-6 secreted by the activated M1 macrophages.[50] The presence of elevated IL-6 levels in the bronchoalveolar lavage of IPF patients[51] strengthens the idea that besides regulating inflammatory processes in the lung, there is an association between the development of pulmonary fibrosis and elevated levels of IL-6.[52] Nevertheless, a comprehensive study from 2001 reveals elevated levels (as high as 100 times usual) of IL-6 in the bronchoalveolar lavage of ARDS patients that persists up to 21 days of illness[53] indicating the important binomial role IL-6 plays as both pro- and anti-inflammatory agent.[54]

COVID-19 patients degrading to severe ARDS seem to follow a cytokine profile with increased IL-1β, IL-2, IL-6, IL-17, IL-8, TNF, and monocyte chemoattractant protein (CCL2)[55] that is consistent with the macrophage associated syndrome (MAS, or the proverbial "cytokine storm") and also includes hyperferritinemia, coagulopathies, and liver function failure.[56] During the acute response to SARS-COV-2 infection, it seems that, within a matter of minutes, IL-1β and TNF-α accumulate rapidly, followed by a sustained expression of IL-6,[57] which seems to be a class particularity of the coronaviruses of inducing exaggerated response concerning IL-6 in the infected host.[58] As hyper-inflammation seems to be the critical feature of MAS associated with COVID-19, the involvement of elevated IL-6 is also sustained by biochemical modifications such as hyperferritinemia[59] and the driving interest anti-IL-6 agents such as tocilizumab for the treatment of severe COVID19 complicated with ARDS.[60]

Even before the SARS-COV-2 pandemic, there were controversies of either a protective or aggravating role of IL-6 during viral infections: on the one hand, the IL-6 role in inflammation after viral infection comes from the differentiation of CD4-cells to TH17[61] and the cytolytic capacity of CD8 cells[62] promoting inflammatory resolution, tissue remodeling repair, optimal regulation of T-cells response and inhibition of the viral-induced apoptosis in infected lung cells,[63] but on the other hand, it sustains the induced viral persistence by impairing the polarization and functionality of Th1 cells and CD8 T-cells.[64] Because of the synergistic interactions between IL-6 and IL-17, an inhibition of the cellular apoptosis favors the virus survival.[65] So, with elevated levels of IL-6, patients with IPF might be more susceptible to COVID-19 severe complications such as MAS, but there are data of several other cytokines and pathways (for example, JAK1) that influence macrophage function and IL-6 production during the "cytokine storm".[66]

IL-1β and TNF, along with other cytokines from the inflammatory response, activate glucuronidases that degrade the glycocalyx of the endothelial cells, enhance their contractility, and affects the interendothelial junction, all leading to increased vascular permeability.[67]

Increasing evidence supports dysregulated endothelial permeability and the presence of vascular remodeling both in acute lung injury and repair.[68] Although it is self-limited to conditions such as ARDS or bacterial pneumonia,[68] it seems to persist in progressing fibrosing diseases such as IPF.[68,69]

Endothelium cells play a vital role in the activation of adaptive immunity,[70] expressing class I and class II MHC molecules and mediating memory CD4 or CD8 lymphocytes or Ag-specific stimulation of Ag effector.[70] Moreover, during viral infections, endothelial dysregulation is known to induce a pro-coagulant state, leading to microvascular leak and organ ischemia.[71]

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In COVID-19 patients, a recent histopathological study demonstrated viral elements within endothelial cells and an accumulation of inflammatory cells across vascular beds of different organs with widespread endothelitis.[72] The hypercoagulable state during COVID19 is related to the endothelial cell activation related to IL-1β and TNF-α.[73]

Endothelial involvement seems to be linked to preexisting cardiovascular diseases and diabetes mellitus and is more related to vasoconstriction after the attenuation of agonist-mediated endothelial vasodilation.[74] Endothelial dysfunction is a prevalent affection among patients with IPF, representing a possible link between IPF and cardiovascular diseases.[75] This seems to be related to a significantly reduced tissular and circulatory expression of the vascular endothelium growth factor (VEGF) in patients with IPF.[76] Also, in smokers and patients with pulmonary fibrosis, there is a decreased VEGF level in the broncho-alveolary lavage (BAL), meaning that it (at least) accompanies the lung lesions among these patients.[77] This also accounts for the susceptibility to the SARS-COV-2 infection of patients with endothelium dysfunctions, especially IPF patients who present evidence of microvascular injury and endothelial cell necrosis because of their immune-induced microvascular injuries.[78]

Mechanisms of interaction between coexisting IPF/ILD and COVID-19 diseases are undoubtedly complex, and the in-between relationship of the diseases exerts both negative and positive influences on each other.

Wilk et al. attempted to profile the peripheral immune response to severe COVID-19 by performing Seq-Well-based single-cell RNA sequencing on seven hospitalized COVID-19 patients and six healthy controls.[79] Monocytes, T cells, and natural killer (NK) cells had substantial phenotyping differences between COVID-19 patients and controls, which were severe cases associated with a more robust humoral immune response.[79] Conventional and plasmacytoid dendritic cells, CD16+ monocytes, and NK cells were significantly depleted in samples from ARDS patients, while "developing neutrophils" were significantly increased.[79] A substation expression of proinflammatory cytokine genes by peripheral monocytes, T, or NK cells was not detected, suggesting a minor role in the cytokine storm.

Genetic Factors: Friends or Foes for IPF Patients during the COVID-19 Pandemic?

In 2017, one of the most extensive Genome-Wide Association studies concluded that there is a significant genetic association between IPF and the elevated expression of the A kinase-anchoring protein-13 gene (AKAP13) that is also a Rho guanine nucleotide exchange factor. AKAP13 regulates the activation of the RhoA, a molecule that plays an essential role in profibrotic signaling pathways. This association suggests the implications of epithelial factors in IPF pathogenesis.[80] Antifibrotic drugs, such as nintedanib or pirfenidone, decrease RhoA activity by increasing the Rnd3 expression while decreasing Rnd3 levels, which seems to induce the fibrotic phenotype in regular pulmonary fibroblasts.[81]

A recent review by Abedi et al. showed that the endothelial dysfunction and edema, cell apoptosis, and adhesion in pulmonary endothelial cells, along with increased inflammation and immune cell migration that characterize the ARDS, are promoted through the upregulation of the RhoA/ROCK signaling pathway. The authors suggest that Rho-kinase inhibitors might represent a possible treatment for acute lung injury in ARDS.[82] In animal models, RhoA/ROCK promotes a dysbalance in the renin-angiotensin system (RAS) by down-regulating the ACE2 expression,[83] and it is known that SARS-COV-2 suppresses ACE2 protein by binding with affinity and efficiency its S spike protein.[84] In light of this matter, IPF patients may be at a higher risk due to the possible negative correlation between the RhoA expression and the ACE2 expression.

One could speculate that, rather than discovering a "miracle drug", a more practical approach might consist of properly synchronizing existing medication with the disease phases, which could have a positive effect, and discontinuing it otherwise. Further research should be conducted to characterize the disease course better and identify biomarkers able to support these clinical decisions.

Smoking, ACE2, and Pulmonary Fibrosis

Prolonged exposure to nicotine is the highest well-recognized risk factor for atherosclerosis[85] and chronic respiratory disorders, in particular, PF, because it upregulates proinflammatory and profibrotic pathways (through accelerating fibroblasts proliferation and cytokines secretion - tumor necrosis α (TNF-α) and interleukin 1β (IL-1β).[86,87] Smoking is associated with telomere shortening[88] and the production of reactive oxidative species,[86] increased epithelial permeability, and aberrant tissue regeneration.[88] However, new data suggest that it also upregulates the ACE2 receptor,[6] thus increasing the susceptibility to SARS-CoV-2 infection.[89]

SARS-COV-2 uses the ACE2 receptor as an entry point using its spike "S" protein,[90] and therefore reduces the ACE2 activity, which increases vascular permeability.[73]

One of the roles of ACE2 is to convert angiotensin II (Ang II) to Ang-(1−7). Ang II has fibrogenic effects by upregulating the expression of the profibrotic cytokine TGF-β1, which is involved in converting fibroblasts to myofibroblasts and accumulating collagen, and it is inhibited by adrenomedullin, a vasoactive peptide.[91] Contrarily, Ang-(1−7) inhibits fibrosis pathways, reduces inflammation by lowering cytokine secretion, and protects the lung from injury.[92] Electrostatic forces and van der Waals forces seem to play a significant part in SARS-CoV-2 envelope spike protein high affinity for ACE2 receptor[93] downregulating ACE2, increasing the Ang II level, decreasing Ang-(1−7) amount and promoting inflammation and lung injury.[92] A study showed that ACE2 is protective but downregulated in experimental lung fibrosis[94] and, presumably, in fibrotic ILD patients.[94] Thus, the infection with SARS-CoV-2 will decrease the ACE2 levels even further, exposing the lungs to even more aggressivity.

Severe lung failure via Ang II has also been described in the ARDS pathogenesis by driving lung failure via the Ang II type 1 (AT1) receptor. The downregulation of ACE2 by the SARS-CoV-2 infection enhances AT1 receptors' activation contributing to ARDS development.[89] Thus, active smoking may exert a protective role by upregulating ACE2, which seems to be a critical factor in preventing acute lung injury or respiratory failure.[89] Subsequently, smoking might contribute to the prevention of post-COVID-19 PF in a non-ILD patient.[6]

The Fibrotic Stage of the Clinical Course of SARS-CoV-2 Infection

Many similar features specific for SARS and MERS are found in COVID-19 infection.[95] The real risk of developing PF in SARS-CoV-2 is unknown, but possible data can be extrapolated from previous epidemics with SARS and MERS.

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Prevalence of secondary PF in SARS was reported in 45% of patients one month after infection,[96] reaching 30% at six months.[97] A 15-year follow-up study of 71 survivals of the SARS-CoV-1 epidemic determined persistent imagistic fibrotic changes in 38% of patients.[98] In a series of 36 patients recovered from MERS, lung fibrosis was described in 33% of cases at a median follow-up of 43 days.[99] In the context of the SARS-CoV-2 pandemic, the future incidence of PF is entirely speculative. Probably, due to the increased number of COVID-19 patients, even a small incidence of PF will have a significant impact.

Regeneration of damaged lung structures after infectious aggression or mechanical injury follows a series of consecutive events triggered by signals released by injured cells; these induce migration of inflammatory cells and release proinflammatory factors that activate basement membrane repair resulting in the healing of damaged tissue.[100] Usually, the process is self-limited after resolution. However, when the system is overwhelmed, and the injury is persistent, the healing response becomes dysfunctional and results in excessive scarring and fibrosis.[101]

There is no precise mechanism that triggers IPF. Some epidemiological reports emphasized the importance of environmental exposures.[102] Smoking is one of the factors that continue damaging alveolar epithelium even after cessation.[103] Correlations with a genetic predisposition were identified, MUC5B gene expression having the most considerable risk for IPF.[104] Even infectious agents such as viruses, fungi, and bacteria seem to play a role in the etiology of IPF.[105] The macroscopic appearance of the lungs in IPF shows the specific distribution of fibrosis along the lobes' inferior poles with a bosselated pleural surface aspect. This pattern of fibrosis has been termed "gross honeycombing".[106] The progressive evolution of the disease is still unclear. Some theories explain this process through the disruption of the pulmonary epithelium.[107] Despite this hypothesis, microscopic findings in IPF biopsies revealed healthy alveolar epithelium in proximity to compromised lung tissue.[106]

In contrast to the smoldering evolution of IPF, SARS-CoV and MERS-CoV infection trigger an aggressive cascade of proinflammatory cytokines IFN-g, IL-6, TNF-a, IL-18, CXCL10, MCP1, and TGF-b[108] leading to acute lung injury or in severe cases to ARDS. Histological findings describe inflammatory cell infiltrates, hemorrhage, alveolar edema, and hyaline membrane formation.[109] During the reparative stage of ARDS in SARS-CoV infection, Venkataraman et al. reported that the upregulation of epidermal growth factor receptor (EGFR) in mice model leads to enhanced lung disease and abnormal wound healing dynamics.[110]

Post-ARDS fibrosis and IPF that occur in ILD have distinct differences. The first one is typically not progressive but can be severe and limiting. The second one is chronic and progressive. The recovery period for post-ARDS fibrosis is approximately one year, and the residual deficits persist, but generally do not progress.

Unfortunately, viral aggression on lung tissue is not the only cause of PF sequalae post coronavirus infection. The dual effect of mechanical ventilation, which is one of the cornerstones of the contemporary ARDS treatment, is widely discussed. Worsening of previous lung injury and initiating aggression in a healthy lung by mechanical ventilation is well-known. The injury is defined by pathological inflammatory cells infiltrates, hyaline membranes, and increased vascular permeability.[111] The association of these changes determined by mechanical ventilation is named ventilator-induced lung injury.[111] Mechanical ventilation induces activation of stretch-sensitive channels in alveolar epithelium and endothelium and disruption of cell plasma membranes leading to associated lung fibrosis.[112] In IPF exacerbation, mechanical ventilation is associated with a 7-fold mortality increase,[113] due to altered elastances and resistances of the lungs.[114]

Patients follow-up after recovery from SARS and MERS revealed persistence of pulmonary symptomatology (fatigue, shortness of breath), but with an excellent progressive resolution. Thereby, a publication reported data of 3 months follow-up on 69 SARS patients and identified pulmonary interstitial fibrosis and pleural adhesions in 24 cases.[115]

Antifibrotic Medication—A Cornerstone in the Evolution of the Two Coexisting Diseases

Antifibrotic medication is expected to have potential in protecting patients from severe forms of COVID-19, and some of the theoretical suppositions describing their possible effects are summarized in Table 1.

Table 1. Possible Beneficial Impact of Antifibrotic Drugs on Coronavirus Infection and ARDS Development

targets	antifibrotic drugs
modulated inflammation	Nintedanib, Pirfenidone, Rapamycin, TD139, PRM-151, C21, MSCs
EGFR Inhibition	Nintedanib
lowered ACE2 expression	Nintedanib
protection against viral infections	BG00011
protection against bleomycin and TGF-β-induced lung injury	TD139
reduced viral replication	Rapamycin, PDE5-i
prevention of viral internalization and inhibition of viral infection	PRM-151
decreased risk of severe COVID-19	C21
protection against ALI/ARDS	BG00011, Ang(1−7), MSCs
reduced ARDS mortality	MSCs

a. Standard Agents. Several studies showed that currently available antifibrotic drugs, nintedanib and pirfenidone, significantly reduced the decline rate of lung function and forced vital capacity (FVC), downtrend acute exacerbations, and reduced mortality in IPF patients.[116−118] Recent NICE (https://www.nice.org.uk/guidance/ng177) and British Thoracic Society guidance (https://brit-thoracic.org.uk/media/455101/bts-management-advice-for-ild-patients-v10-23-march-2020.pdf) advise patients under antifibrotic treatment not to discontinue their medication because there is no evidence of increased risk of SARS-CoV-2 infection or more severe disease course. Even so, data concerning the safety and impact of current medication in PF patients infected with SARS-CoV-2 is still sparse, and no randomized clinical trials are yet completed.

The current hypothesis is that antifibrotic medication may exert a protective effect and achieve better outcomes in patients on antifibrotic therapy infected with the novel coronavirus.[119−121] Indeed, nintedanib, a tyrosine kinase inhibitor, is currently investigated as a repurposed drug undergoing a clinical trial for COVID-19 (NCT number 04338802). Another study selected nintedanib as a possible repurposing candidate.[122] Possible beneficial effects in COVID-19 are likely due to nintedanib anti-inflammatory

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and antifibrotic activity, among others. Specifically, a leading cause of fibrosis in SARS-CoV infection seems to be the hyperactive response to lung injury mediated by epidermal growth factor receptor (EGFR).[123] Nintedanib is an EGFR inhibitor that may help prevent excessive fibrotic response in SARS and, by extension, in COVID-19.[119] Additionally, a proteome-wide mendelian randomization analysis identified proteins inhibited by nintedanib that are causally linked to elevated ACE2.[120] This result might also imply a possible contribution of nintedanib on lowering ACE2 expression, thus mediating a decreased susceptibility to SARS-CoV-2 infection.

A randomized clinical trial is currently in process for assessing the efficacy and safety of pirfenidone in severe or critical SARS-CoV-2 infected patients (NCT number 04282902). Pirfenidone was shown to significantly reduce serum and lung interleukin-6 (IL-6) concentrations,[121] which plays a crucial role in the "cytokine storm" pathogenesis from SARS-CoV-1 and SARS-CoV-2 infections.[124]

Certain limitations are to be considered when using the two standard antifibrotic agents in the COVID-19 setting. First, the side effects of these medications and symptoms of COVID-19 (diarrhea, fatigue, loss of appetite) may overlap, possibly delaying diagnosis.[1] Although antifibrotic therapy may protect patients with fibrotic lung disease against the infection with the novel coronavirus, infected patients must be diagnosed and treated promptly. Second, both drugs can have hepatotoxic consequences, and liver injury is often reported in patients infected with SARS-CoV-2, especially in severe cases.[125] Third, anticoagulant therapy in patients with severe COVID-19 and coagulopathy may limit the use of nintedanib that is declared to increase the risk of bleeding in anticoagulated patients.[125]

b. New Agents. The advent of high-throughput multiomics data generation alongside the improvement of modern computational techniques led to numerous proteomic studies in COVID-19. Targeted proteomics assays identified molecular changes in COVID-19 patients that can be used as therapeutic targets to prevent viral replication. Thereby, proteome-wide studies revealed that SARS-CoV-2 induces dysregulation of macrophages, massive metabolic suppression, and reshapes the complement system pathways, the platelet degranulation,[41] and the central cellular pathways such as translation, splicing, carbon metabolism, protein homeostasis (proteostasis), and nucleic acid metabolism.[126] Multiomics analysis might also facilitate the process of identifying therapeutic targets directed toward both COVID-19 and IPF.

A recent paper described several developing antifibrotic medications that target various molecules in the TGF-ß fibrogenic pathway that has an essential contribution in fibrotic changes both in IPF and COVID-19. Drugs against avß6 integrin (BG00011) and galectins (TD139) were described considering the domain binding similarities with the SARS-CoV-2 spike protein and the experimental data that supports their use in viral-induced lung injury.[125] Also, the paper recounts the mTOR inhibitor (rapamycin), the JNK inhibitor (PRM-151), and the agonist of angiotensin type 2 receptor (C21) that are all showing promise in IPF trials. All three drugs were described to have effects on viral replication or internalization (e.g., influenza) or modulating inflammatory pathways.

Another paper discusses phosphodiesterase type 5 inhibitors (PDE5-i) used in PF management and has proven an inhibiting effect on coronavirus replication.[127]

Standard and novel antifibrotic therapies might prove helpful in the context of the COVID-19 epidemic by going beyond their antifibrotic properties and proving anti-inflammatory and antiviral effects that need to be further studied for efficacy and safety.

c. Antifibrotic Medication Role in Preventing Acute Lung Injury (ALI) and ARDS. Both fibrotic lung diseases and COVID-19 pneumonia face the threat of disease exacerbations with ALI's development and, at the severe end of the disease spectrum, ARDS. It is essential to underline possible countermeasures since the proper management of ALI/ARDS episodes is the key to preventing post-COVID-19 secondary fibrosis and averting further aggravation in fibrotic lung disease. Appropriate care in COVID-19 patients is all the more critical as the pulmonary fibrotic changes appear to be more prevalent following SARS-CoV-1 infection than other various respiratory viral infections.[123]

The issue regarding frequent exacerbations in critically ill COVID-19 patients could receive an answer after the ongoing controlled trial assessing the efficacy, safety, and clinical impact of administering Ang(1−7) in COVID-19 patients requiring mechanical ventilation (NCT number: 04332666). The hope is high in recent evidence showing that experimentally ARDS and lung fibrosis were prevented by the Ang(1−7) treatment.[128]

The increasing trend in the use of stem cell treatment in IPF suggests their potential therapeutic benefit in recent years. Bone marrow mesenchymal stem cell (MSC) therapy has proven to be safe in humans with IPF. Clinical and animal studies suggest it is as effective as pharmaceutical therapies in treating PF.[129] Although they have uncertain mechanisms of action, MSCs have been proven to exert a modulating effect in lung inflammation and fibrosis.[130] Experimental models on human tissue and animal studies have also reported that MSCs achieve excellent outcomes in ALI/ARDS by attenuating the severity of lung injury and by reducing mortality.[131,132]

Moreover, small-scale studies on the efficacy of MSCs treatment in COVID-19 demonstrated improved outcomes, especially for the patients in critically severe conditions, believably due to the regulation of inflammatory response and the promotion of tissue repair and regeneration.[133] Notably, MSCs do not express ACE2 and TMPRSS2 (cellular protease used by SARS-CoV-2 for entering target cells), making them safe and effective to use in COVID-19 infection.[134] While current antifibrotic medication can only slow the progression of fibrotic lung disease without reversing the fibrogenic process, MSCs might be exploited for their potential regenerative capacity and recovery of healthy lung tissue structure epidemiological context, considering its beneficial effects in ARDS and COVID-19 disease.

N-Acetylcysteine (NAC) is a mucolytic drug used in IPF with some proven beneficial role,[135,136] due to its antioxidant effect. However, its use on IPF patients has been discontinued by the lack of clinical outcome (conditional recommendation against use in monotherapy). It has been banned in combination with azathioprine and prednisone (strong recommendation against use) since the issue of the ATS/ERS/JRS/ALAT Clinical Practice Guideline in 2015, especially in combination with azathioprine and prednisone.[137] There is currently an ongoing clinical trial on the efficacity of NAC in patients with COVID-19 (NCT number 04374461). It is thought that NAC may prevent COVID-19-associated cytokine storm and ARDS due to accumulating evidence of

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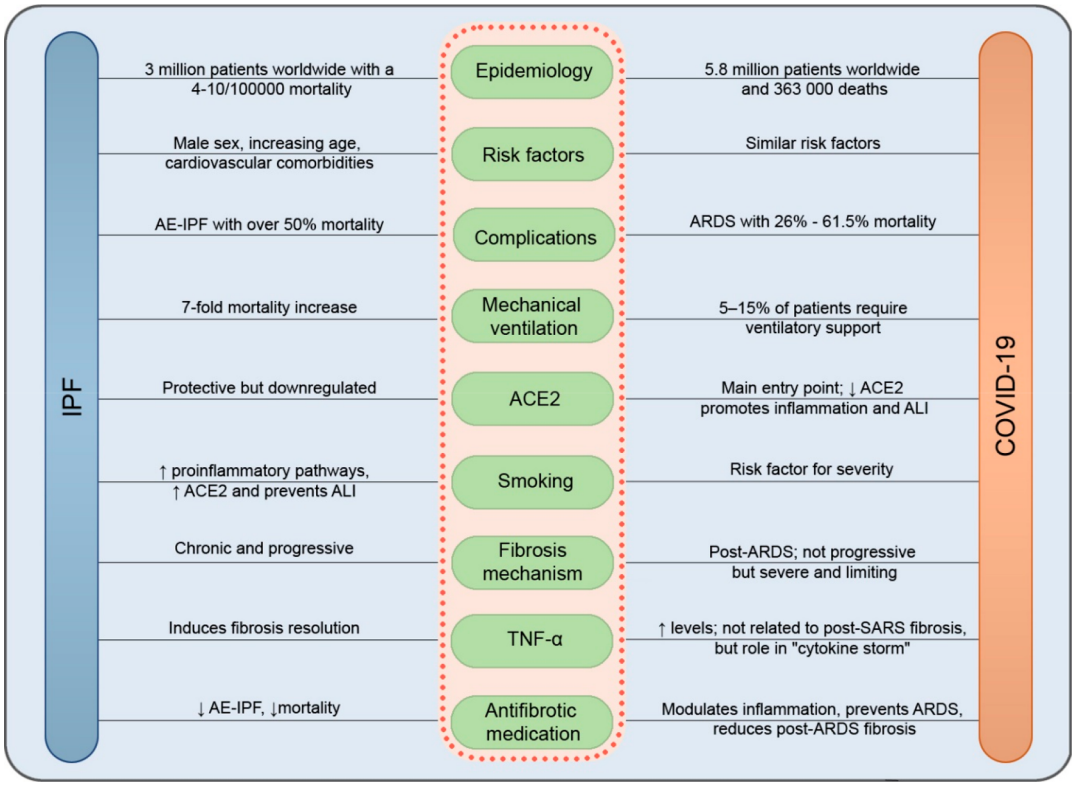

Figure 1. Point by point comparison of the key characteristics of COVID-19 and IPF that might explain or influence diseases' course.

preventing exacerbations, improving oxidative stress and inflammatory response in chronic obstructive pulmonary disease, and community-acquired pneumonia.[138]

Critical points of reciprocal influence for COVID-19 and IPF are synthesized in Figure 1.

The diagnostic of IPF is currently a contextual and an exclusion one, based on a clinical suspicion correlated with thoracic CT scans and ruling out other causes of pulmonary fibrosis.[139] Out of many factors incriminated in the repeated alveolary injury leading to fibrosis, infection, and host's susceptibility to infection, especially viral infection, seems to be one of the most crucial contributors to progression in IPF.[140] While some viruses induce apoptosis of the epithelial cells,[141] others alter the synthesis of surfactant's proteins,[142] and others increase the expression of tumor growth factor TGF-beta, a potent profibrotic growth factor.[143] The first manifestation of the disease may be an acute exacerbation (AE) frequently after a pulmonary infection,[144] and during the SARS-CoV-2 pandemic, the coexistence of COVID-19 and IPF is a possible scenario.

All AE-IPF are emergencies and must be hospitalized as they progress rapidly toward ARDS.[145] The treatment of an AE-IPF usually involves anticoagulant therapy, antibiotics and corticosteroids, and oxygen supplementation,[10] a treatment generally accepted for the management of COVID-19 as well, while pending RT-PCR test results.[146,147]

A clinician's perspective, while in the prolonged pandemic, has to be toward suspecting a SARS-CoV-2 infection, especially in patients of old age with cardiovascular comorbidities. Nevertheless, one can easily misdiagnose an IPF acute exacerbation that even radiologically (not to mention clinically) resembles COVID-19 severe manifestations.[148] Since future cohabitation with SARS-CoV-2 appears to be the "new normality", more standardized approaches and guidelines need to be created for physicians to rapidly differentiate an idiopathic acute exacerbation from an acute infectious exacerbation and, most fearful, SARS-CoV-2 infection on an IPF lung impairment.

■ CONCLUSIONS

This review attempts to shed light on the undoubtful complexity of interactions between coexisting IPF/ILD and COVID-19 diseases concerning both specific molecular pathways and drug effects as well as clinical management of acute exacerbations. Patients recovering from severe COVID-19 disease are at serious risk of developing pulmonary fibrosis[149] and, therefore, irreversible lung lesions (part due to the ALI)—a fact that could aggravate the existing parenchymal modifications on patients with IPF.[150,151] Antifibrotic medication seems to have some potential in protecting patients from severe forms of COVID19,[81,152] but these are only theoretical suppositions lacking clinical experience and needing further confirmation.

As controversial as it may sound, from a biochemical perspective, it seems that some patients with a history of smoking or who are still smoking may, in theory, have a better outcome if they become severely ill with SARS-COV-2. Their outcome may be (theoretically) better but, similar to ILD patients, due to the high viral load and the already impaired lung parenchyma, they may not live to see this possible theoretical scenario. In different disease phases, these interactions seem to be opposing, thus complicating drug discovery and efficient treatments. Thus, an approach as a part of the joint effort to better understand and connect diseases' unfolding mechanisms can lead to identifying critical phase-

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specific molecules and biomarkers helpful in clinical decisions and treatment management.

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