Editorial

The impact of COVID-19 on patients with preexisting interstitial lung disease: High mortality in these high-risk patients

"As the last straw breaks the laden camel's back, this, crushed the sinking spirits of Mr Dombey". Charles Dickens, Dombey and Son.

SARS-CoV-2 continues its relentless march across the globe with a staggering 100 million people infected worldwide. While a lot of attention has focused on the residual lung fibrosis that COVID-19 will leave in its wake,[1] it is also time to consider the devastating impact of this virus in patients with preexisting interstitial lung disease (ILD).

Patients with ILD, by virtue of their poor lung reserve and impaired gas exchange, run a precarious course even under routine circumstances. These patients are often on immunosuppressive medications, are generally older with multiple comorbidities, and are at constant risk of acute exacerbations. When this fine balance is tipped further by infection with SARS-CoV-2, it is often the proverbial straw that breaks the camel's back. The Open SAFELY study,[2] which examined the health records of over 17 million patients in the UK, found that patients with chronic respiratory disease had a hazard ratio (95% confidence interval) for COVID-19-related death of 1.95 (1.86–2.04). This risk of COVID-related death puts patients with chronic lung disease (excluding asthma), at higher risk of death from COVID-19 than those with cancer (1.81), or chronic heart disease (1.57). Within this group of patients with chronic lung disease, those with ILD seem particularly vulnerable to adverse outcomes from the virus. A recent international multicenter study by Drake *et al*.[3] revealed how poorly these patients fare when infected with SARS-CoV-2. They assessed the in-hospital mortality of 161 patients with ILD hospitalized across multiple centers in Europe and found that ILD patients, as a group, fared particularly badly with significantly higher mortality than those without ILD (49% vs. 35%). Within this group, those with idiopathic pulmonary fibrosis (IPF) fared worse than those with other ILDs (hazard ratio, 1.74; $P = 0.007$). Among patients with ILD, other risk factors for death included obesity, male sex, and a pre-illness forced vital capacity of below 80% predicted. A study from the US[4] revealed strikingly similar findings. In this multicenter retrospective case–control study from six Boston medical centers, the authors found that mortality in patients with ILD with COVID-19 was 33% (compared to 13% for matched controls). These patients were found to have a more than four-fold risk of dying and were much more likely to require hospital admission (74% vs. 58%), need intensive care unit (ICU) care (47% vs. 23%), and less likely to be discharged home. Tellingly, those who died were older, had lower diffusion capacity and were more likely to have IPF or a usual interstitial pneumonia pattern on their computed tomography scans. A similar multicenter observational study of 123 ILD patients from France[5] also showed that hospitalization was needed in 84% of patients with 21% needing ICU care. Outcomes were again especially poor in those with fibrotic ILD, lower diffusion capacity and in those needing supplemental oxygen.

Taken together, these findings raise an important red flag for physicians looking after patients with ILD. They must be aware that these patients are particularly vulnerable to the consequences of COVID-19 and must be protected from exposure to the virus as best as possible. If infected, they should be hospitalized, often in the ICU, as from available data they are likely to run a poor course and have a significantly higher mortality.

It cannot be overemphasized that early diagnosis of COVID-19 is important, especially in patients with a preexisting ILD, to optimize care pathways. The cardinal features of COVID-19 illness are fever, cough, and breathlessness.[6] Due to the persistent cough and breathlessness that several patients with ILD are routinely afflicted with, it may be difficult to identify COVID-19 at an early stage in these patients. Furthermore, these patients are often on immunosuppressive drugs that may blunt their febrile response. Conversely, a symptom like diarrhea is often an adverse effect of drugs (such as mycophenolate and nintedanib) used in treating certain ILDs and can be mistaken for a feature of COVID-19. Besides the clinical presentation, the radiologic features also overlap. Ground glass opacities, consolidation, and reticulation, which are the sine qua non of COVID-19 pneumonia, are also characteristic features of common ILD patterns such as organizing pneumonia, nonspecific interstitial pneumonia, and hypersensitivity pneumonia. Moreover, the same imaging abnormalities may indicate the occurrence of an exacerbation in patients with fibrotic ILDs, especially IPF.[7] Finally, a viral illness such as COVID-19 might itself trigger an exacerbation in patients with a fibrotic ILD. Due to all the above reasons, it is of utmost importance that a high of index of suspicion is maintained for COVID-19 in patients with ILD who present with fever, worsening of their respiratory symptoms or a decline in oxygen saturation during the course of this pandemic. A low threshold for

testing (and retesting, if required) for SARS-CoV-2 in these patients is desirable. In the absence of evidence, we believe that standard tests for SARS-CoV-2, such as reverse transcriptase-polymerase chain reaction (RT-PCR) from nasopharyngeal and oropharyngeal swabs, may have similar performance characteristics in patients with preexisting ILD, as in those without ILD. These samples have an imperfect sensitivity for detection as opposed to a more invasive test like bronchoalveolar lavage. Therefore, it has been suggested that COVID-19 should not be excluded as a clinical possibility for patients with ILD with a worsening of unknown etiology, even with an initial negative result on RT-PCR.[8]

The major uncertainties in the management of ILD in COVID remain in the use of common ILD pharmacotherapies, limited ability to monitor disease severity and the presence of medication adverse effects, and significantly curtailed research activities. The pathogenesis of COVID-19 has implications for immunomodulatory as well as antifibrotic medications for the underlying disease[8] Although data suggest an increased risk of viral infections like influenza, rhino- and adenovirus infection in patients with ILD receiving immunomodulatory therapy,[9] there is an absence of robust data linking these therapies with severe disease in corona virus infections such as SARS, Middle East respiratory syndrome, or COVID-19. Evidence from previous coronavirus infections has suggested that corticosteroid treatment may lead to increased viremia, delayed clearance of viral RNA from respiratory tract secretions[9,10] and an increased length of hospital stay.[10,11] Given the absence of data, the initiation, maintenance or dosing of immunomodulatory therapy for fibrotic ILD in COVID pandemic remains unknown.[8] Thus, in patients with progressive disease, it remains reasonable to limit the use of corticosteroids and prioritizing steroid-sparing therapies where possible. Treatment initiation should be considered on a case-by-case basis, and it may be appropriate to delay initiation of non-urgent therapy if there is limited likelihood of short-term progression. For patients already receiving immunomodulatory therapy, there are again limited data on continuing or altering the dosing or even discontinuation of therapy.[8] Since rapid taper of therapy may result in a flare of the underlying disease, particularly in patients with CTD, which can subsequently precipitate the need for more aggressive immunosuppression or hospitalization to regain disease control, it seems most appropriate to maintain patients on low doses of immunomodulatory therapy and prioritizing steroid-sparing medications over prednisone.[8]

There are no data to suggest that antifibrotic therapies like nintedanib or pirfenidone are associated with increased risk of COVID-19 or more severe disease. Although both these drugs have pleiotropic effects, neither is immunosuppressive *per se*, and so there is no rationale for their discontinuation in the face of viral or bacterial infection.[12] It is, however, unknown if antifibrotics may attenuate COVID-19 infection or prevent post-infectious fibrotic lung disease.[11] In the absence of such data, the decision to initiate or continue antifibrotic medication should follow standard clinical practice. Pertinently, available antifibrotic therapies have broad antifibrotic activity regardless of etiology, and these drugs might have a role in attenuating profibrotic pathways in SARS-CoV-2 infection.[12] Pulmonary function tests should be considered nonurgent and should be postponed or waived during routine follow-up. This recommendation is supported by the sustained effects of antifibrotic medications beyond 1 year, in patients with severe ILD, and in patients with progression while on therapy, suggesting the safety and likely efficacy of continued therapy in these situations. Finally, it is also important to note that patients with SARS-CoV-2 infection often require anticoagulant therapy which might mandate stopping antifibrotic therapy with nintedanib because of its potential interactions with anticoagulants and consequent increased risk of bleeding.[12]

In conclusion, COVID-19 pneumonia has a higher mortality in patients with preexisting ILD. COVID-19 should be considered in the diagnosis of patients with ILD who present with fever or worsening of their respiratory symptoms, and an early confirmation should be attempted. Avoidable visits to health-care facilities should be curtailed for stable patients with ILD, to reduce the risk of exposure to SARS-CoV-2. The use of immunosuppressive agents should be limited to the lowest effective dosing, according to best practice, while antifibrotics may be used without any change in approach.

Zarir Farokh Udwadia[1], Parvaiz A Koul[2], Sahajal Dhooria[3]

[1]Department of Pulmonary Medicine, Hinduja Hospital and Research Center, Mumbai, Maharashtra, India, [2]Department of Pulmonary Medicine, SKIMS, Srinagar, Jammu and Kashmir, India, [3]Department of Pulmonary Medicine, Postgraduate Institute of Medical Education and Research, Chandigarh, India.
E-mail: zfu@hindujahospital.com

Submitted: 27-Jan-2021 **Accepted:** 31-Jan-2021
Published: 06-Mar-2021

REFERENCES

1. Udwadia ZF, Koul PA, Richeldi L. Post-COVID lung fibrosis: The tsunami that will follow the earthquake. Lung India 2021;38:S41-7.
2. Williamson EJ, Walker AJ, Bhaskaran K, Bacon S, Bates C, Morton CE, *et al*. Factors associate with COVID-19-related deaths using OpenSAFELY. Nature 2020;584:430-6.
3. Drake TM, Docherty AB, Harrison EM, Quint JK, Adamali H, Agnew S, *et al*. Outcome of hospitalization for COVID-19 in patients with interstitial lung disease. An international multicenter study. Am J Respir Crit Care Med 2020;202:1656-65.
4. Esposito AJ, Menon AA, Ghosh AJ, Putman RK, Fredenburgh LE, El-Chemaly SY, *et al*. Increased odds of death for patients with interstitial lung disease and COVID-19: A case-control study. Am J Respir Crit Care Med 2020;202:1710-3.
5. Gallay L, Uzunhan Y, Borie R, Lazor R, Rigaud P, Marchand-Adam S, *et al*. Risk factors for mortality after COVID-19 in patients with preexisting interstitial lung disease. Am J Respir Crit Care Med 2021;203:245-9. https://doi.org/10.1164/rccm.202007-2638le.

6. Wiersinga WJ, Rhodes A, Cheng AC, Peacock SJ, Prescott HC. Pathophysiology, transmission, diagnosis, and treatment of coronavirus disease 2019 (COVID-19): A review. JAMA 2020;324:782-93.
7. Antoniou KM, Raghu G, Tzilas V, Bouros D. Management of patients with interstitial lung disease in the midst of the COVID-19 pandemic. Respiration 2020;99:625-7.
8. Wong AW, Fidler L, Marcoux V, Johannson KA, Assayag D, Fisher JH, *et al*. Practical considerations for the diagnosis and treatment of fibrotic interstitial lung disease during the coronavirus disease 2019 pandemic. Chest 2020;158:1069-78.
9. Tashkin DP, Elashoff R, Clements PJ, Goldin J, Roth MD, Furst DE, *et al*. Cyclophosphamide versus placebo in scleroderma lung disease. N Engl J Med 2006;354:2655-66.
10. Arabi YM, Mandourah Y, Al-Hameed F, Sindi AA, Almekhlafi GA, Hussein MA, *et al*. Corticosteroid therapy for critically Ill patients with middle east respiratory syndrome. Am J Respir Crit Care Med 2018;197:757-67.
11. Wang P, Li M, Shi Y, Wang S, Liu G. Evaluating the effects of different treatments on severe acute respiratory syndrome. Shanxi Med J 2005;34:270-2.
12. George PM, Wells AU, Jenkins RG. Pulmonary fibrosis and COVID-19: The potential role for antifibrotic therapy. Lancet Respir Med 2020;8:807-15.

Access this article online

Quick Response Code:

Website: www.lungindia.com

DOI: 10.4103/lungindia.lungindia_60_21

How to cite this article: Udwadia ZF, Koul PA, Dhooria S. The impact of COVID-19 on patients with preexisting interstitial lung disease: High mortality in these high-risk patients. Lung India 2021;38:S1-3.