[Indian J Chest Dis Allied Sci 2021;63:61-64]

Editorial

Post-COVID Pulmonary Sequelae: The Management Strategy

COVID–19 pandemic has placed a huge burden on health authorities worldwide. The epidemiology, clinical characteristics, management and complication of acute phase of COVID–19 has been well described.[1,2] However, the data for its long-term complications and management remain still unclear. Post-COVID patients may continue to report variety of signs and symptoms which may range from milder ones to serious organ specific manifestations.[3,4] Recently, some management strategies for Long COVID–19 has been formulated by Goel and co-authors, published in this issue of the journal.[5]

The terms like 'Post-COVID syndrome', Long Haul COVID' and 'Post-COVID Sequelae' have been used in the literature for such persistent signs and symptoms.[6] NICE (National Institute for Health and Care Excellence) describe Acute COVID, Ongoing COVID and Post-COVID having symptoms ≤4 weeks, 4-12 weeks, >12 weeks, respectively. It has coined the term 'Long-COVID' for symptoms persistent beyond four weeks from acute COVID-19 infection.[7,8]

In most of the studies[8-12], the most common observed post-COVID symptom are fatigue and weakness (63%), dyspnoea (26%), sleeping difficulty (26%), anxiety and depression (23%), hoarseness (22%), smell disorder (11%), palpitation (9%), joint pain (9%), etc. Post-COVID symptoms mostly depends on the severity of the infection during acute phase, patients who were more severely ill during their hospital stay had more sever impaired pulmonary diffusion capacity and abnormal chest imaging manifestations.[10,11] In another study[13], at 8-12 weeks post admission, 74% persisted with symptoms (notably breathlessness and excessive fatigue) with reduced health related quality-of-life (HRQoL). Further 59%, 75%, 89% at least one symptom persisted in mild COVID (without oxygen), moderate COVID (with oxygen), and severe COVID (NIV [non-invasive ventilation]) at 8-12 weeks, respectively. The study demonstrate the persistence of symptom at 12 weeks in majority of patients even those with mild disease initially.

In studies[14-16], which followed COVID-19 patients every three monthly for one year post discharge, found that almost 24% had persistent radiological abnormalities and DLCO abnormality in 33% after one year of acute illness. Patient receiving high flow nasal cannula (HFNC), NIV or both and having more length of stay in hospital, were more likely to have abnormal high-resolution computed tomography (HRCT) at 12 months compared to patients who did not have HFNC or NIV. It highlights the importance of respiratory follow-up of patients with COVID-19 and to see the long-term consequences of COVID-19 pneumonia.

The risk factors for the development of lung fibrosis[15] are: (a) advanced age, (b) sever illness, (c) long stay in the intensive care unit (ICU), (d) mechanical ventilation and (e) smoking and chronic alcoholism. Moreover, elderly patients who required ICU admission and were on mechanical ventilation were at a greater risk to develop fibrosis.

There are some guidance[17,18] available on the management part, however clear guidelines regarding the pharmacological management of these long-COVID patients are still lacking. The following can be the management modalities: (a) domiciliary oxygen therapy, (b) steroids, (c) anti-fibrotic drugs, (d) pulmonary rehabilitation.

Domiciliary Oxygen. Long-term oxygen therapy is recommended for the patients with pulmonary fibrosis with a resting partial pressure of oxygen (PaO_2) <55mmHg. Further, short-term oxygen therapy may be considered for patients with oxygen saturation (SpO_2) of 93% at rest or when the patient is ambulatory for one minute provided the patient is able to maintain the stable SpO_2 with the low flow nasal cannula.[17,19]

Steroids. The available guidelines on 'Long-COVID' till now have not given a clear road-map of pharmacological management, *e.g.* use of systemic corticosteroids in these patients.[6] Although some workers have suggested the use of systemic corticosteroids in this scenario.[18] In a study[20], at 4 weeks after discharge, 39% patients reported ongoing symptoms and were assessed. Interstitial lung disease (ILD), predominantly organising pneumonia, with significant functional deficit was observed in 35/837 (4.8%) survivors. Thirty of these patients received steroids (0.5 mg per kg, max 26.6 mg and a rapid weaning over 3 weeks) resulting in a mean relative increase in transfer factor following treatment of 31.6% (standard deviation [SD] ± 27.6, $P<0.001$), and forced vital capacity of 9.6% (SD ± 13.0, $P=0.014$), with a significant symptomatic and radiological improvement. It was concluded that following SARS-CoV-2 pneumonitis, a cohort of patients are left with both radiological inflammatory lung diseases and persistent physiological and functional deficit. Early treatment with corticosteroids was well tolerated and associated

with rapid and significant improvement. These preliminary data should inform further study into the natural history and potential treatment for the patients with persistent inflammatory ILD following SARS-CoV-2 infection. No worsening from inflammation to fibrosis was observed in 2-3 patients who did not receive steroids, but developed traction bronchiectasis.

In many studies[20-23], where follow-up being done at one-and-half month, 8-12 weeks, 30 days, 3 months, 4 months, significant clinical and radiological and in PFT parameters improvement without any treatment was observed. Hence, it is suggested to wait to observe the resolution of symptoms on its own of post-COVID; but for how long is an important question.

Previous studies[16] have found significant improvement in grades of dyspnoea and gain in six-minute walk distance in post-COVID patients at the end of one year follow-up even without any treatment (no mention of any specific treatment). In an earlier study on follow-up of severe COVID-19 patients, radiological improvement was observed in about 22% at 12 weeks[16] and at 6 months in 38%[24], without any specific treatment. The question remains whether these changes self-resolve or subside as observed in other studies[14,15], we understand that above subset of patients warrant therapeutic intervention to provide quicker relief. Also, we cannot over-emphasise the caution against the immunosuppressive effects of systemic corticosteroids.

Role of Anti-fibrotic Agents. One possible complication of pulmonary involvement in COVID-19 is pulmonary functions which will lead to long-term disability. There is no specific mechanism that lead to fibrosis, but it can be hypothesised by some information available from previous sever acute respiratory syndrome (SARS) or middle-east respiratory syndrome (MERS) epidemic. The mechanism[25] of fibrosis may be: (a)*viral activate pathway:* viral may decrease angiotensin converting enzyme-2 (ACE-2) and dysregulation of Lenin angiotensin system. Its entry may also alter growth factor production and receptor expression, thereby promoting profibrotic pathway. Host cell disruption and inhibition of host protein translator can lead to inhibition of heat repair mechanism. Cytoskeleton re-arrangement during virus release can also lead to fibroblast activation and other profibrotic down-steam effect; (b) *cellular injury/response:* the epithelial, endothelial and macrophage cell death, increased vascular permeability, barrier dysfunction and fluid accumulation; (c) *inflammation:* inflammation induced every injury which contribute to acute respiratory distress syndrome (ARDS); and (d) *mechanical injury:* mechanical ventilated, barotrauma, volutrauma may contribute to cause profibrotic pathways.

The role of anti-fibrotic drugs in the prevention and treatment of post-COVID fibrosis is unclear at present. Both COVID and idiopathic pulmonary fibrosis (IPF) share many common demographic factors. Fibrosis with fibroblasts and honey-combing has clearly been demonstrated in autopsies and explanted lungs of patients with SARS-CoV-2.[26,27] Hence, it is reasonable to assume that there may be a role of anti-fibrotic drugs, like perfenidone and nintedanib. It is also important that antifibrotic drugs may be used responsibly and carefully and monitored for the toxic effects. There may be reason for the hypothetical use of antifibrotic drugs but no study has been published, to establish the role of anti-fibrotic in post-COVID pulmonary fibrosis accept for few case reports.[28] Hence, it will be not advisable to use these drugs till a good controlled trial is done, seeing the toxicity of the drug.

Combination therapy. Again may be rationale for using anti-fibrotics in combination with anti-inflammatory drugs, like steroids, so that both inflammatory and fibrotic limbs are addressed together. The management of inflammation and fibrotic start with combination therapy could represent a pharmacology synergy but again there is a need of published data in this regard.

Pulmonary rehabilitation. In mild to moderate disease, pulmonary rehabilitation should be started as early as possible and in severe cases it should be carried out after patient became stable. In a review article on rehabilitation in post-COVID-19 infection, it was concluded that pulmonary rehabilitation restores physiological and respiratory function and further reduces anxiety and depression and improves the quality-of-life.[29]

In conclusion, the post-COVID symptoms vary from mild to severe and may persist till one year or more. The symptoms may resolve in due course of time but there are few pulmonary symptoms and radiological parameters which does not respond. For post-COVID management, the role of steroids and the anti-fibrotic agents still is not clear, as not much studies are done in this regard. Hence, pulmonary rehabilitation must be continued for these cases and further research is needed for the management post-COVID patients.

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