Chest Heart Journal
Vol. 44, No. 2, July 2020

EDITORIAL

Management of post-COVID-19 lung fibrosis: It's the high time for the Pulmonologists to show their wisdom

[Chest Heart J. 2020; 44(2) : 57-60]
DOI: http://dx.doi.org/10.33316/chab.j.v44i2.2019619

It's nearly one and a half year have passed since the world first encountered one of the deadliest tsunami of this century – the coronavirus disease (COVID-19). At the time of writing this editorial, globally there are 177,435,887 cases, which cost 3,842,319 lives. Bangladesh is also not out of this inferno. Currently we are facing the second wave with a burden of 8,41,087 cases and 13,345 deaths.[1]

Viral infection has a potential to cause airway epithelial injury, apoptosis, and long standing lung damage.[2] The mechanism of post-viral lung fibrosis has been extensively studied in other influenza epidemics. Looking back at severe H1N1, a study in China among hospitalized patients with pneumonia caused by the 2009 H1N1 influenza showed high levels of transforming growth factor beta 1 (TGF β1).[3] In the SARS CoV 1 outbreak in 2002, high levels of TGF β1 were also observed in serum and bronchoalveolar lavage.[4]This cytokine is known to induce fibrosis by various mechanisms which include increased deposition of extracellular matrix proteins, stimulation of fibroblast chemotactic migration, and fibroblast to myofibroblast transition. In the current SARS CoV 2 pandemic, the molecular basis of progression to pulmonary fibrosis is still unclear but is believed to be multifactorial. Direct viral effects, the upregulating effect of the virus on cytokines like TGF β1, IL-6, IL-1 and, increased oxidative stress have all been postulated.[5] There is a pivotal role of the renin–angiotensin system, as the high affinity binding between the SARS CoV 2 viral spike protein and the angiotensin converting enzyme 2 (ACE 2) receptor has been shown to downregulate the level of the ACE2 receptor.[6] The decreased ACE 2 expression, in turn, leads to high angiotensin-2 levels, leading to fibrotic process, signaling cellular and molecular events, and ultimately development of pulmonary fibrosis. The iatrogenic factors potentially contributing to the fibrosis encountered in survivors of severe COVID 19 pneumonia are oxygen toxicity and ventilator induced lung injury (VILI). Patients who develop post COVID fibrosis are invariably those who had extensive, bilateral involvement at the outset, had required high concentrations of oxygen, often for prolonged duration. Extended exposure to high concentrations of oxygen produces oxygen derived free radicals which can damage the pulmonary epithelium.[7]

As we have already known, though most of the SARS-CoV-2 infections are mild to moderate, nearly 5–10% patients may progress to severe or critical disease, including pneumonia and acute respiratory failure.[8,9] Fibrotic abnormalities of the lung have been detected as early as 3 weeks after the onset of symptoms regardless of whether the acute illness was mild, moderate, or severe.[10,11] Abnormal lung function (i.e., restrictive abnormalities, reduced diffusion capacity, and small airways obstruction) has also been identified at the time of discharge from hospital and 2 weeks thereafter.[12] These lung function abnormalities appear to be more common among patients whose acute COVID-19 was severe with high levels of inflammatory markers, and are often accompanied by evidence of pulmonary fibrosis including interstitial thickening, coarse reticular patterns, and parenchymal bands.[13]

Submission on: 5 May, 2020 **Accepted for Publication:** 30 May, 2020
Available at http.//www.chabjournal.org

Reviewing literature on other influenza pneumonias, it is observed that H1N1 was only occasionally complicated by fibrosis,[14] whereas as many as 22% of patients with H7N9 pneumonia[15] were left with fibrosis at 6 months. There is limited data from other coronavirus infections such as SARS and Middle East respiratory syndrome (MERS). A study by Chang *et al*.[16] in patients with SARS showed that in follow-up CT scan at 4-6 months, there was significant regression of CT abnormalities. The only long term longitudinal data on MERS by Zhang *et al*., which followed up 81 health care workers with MERS for a period of 15 years.[17] They found that only 5% of patients had residual interstitial fibrosis at 15 years. Variable outcomes have been noted in several studies on COVID-19 patients. A follow up study by Zhao *et al*.[18] of pulmonary function and radiology in 55 COVID 19 survivors 3 months after recovery showed that 71% had residual CT abnormalities, including evidence of interstitial thickening in 27%. A prospective, multicenter, observational study on 86 severe COVID-19 survivors in Austria[19] found that the majority of patients were left with persisting dyspnea (37%), reduction in diffusion capacity (28%), and CT abnormalities (88%) at 6 week post-discharge. At 12th week, there was remarkable improvement of CT abnormalities. Follow up of cohorts of post COVID survivors are already underway at several centers in different countries. The burning question is: whether the chest CT scan abnormalities likely to persist, gradually improve, or even worsen with the passage of time? Long-term follow-up of these patients is the only answer of this question. So, which follow-up model we can apply? Raghu *et al*.[20] have proposed a follow up scheme for these post COVID survivors. They argued for an initial baseline visit once the patient is polymerase chain reaction negative with a baseline non-contrast HRCT, PFTs (spirometry, lung volumes, and diffusion capacity), 6 min walk test, and assessment of quality of life (QOL) with standard questionnaires. Thereafter, to better understand the natural course of the disease, they suggest follow up visits, either remotely or in person at frequent interval up to a total duration of 36 months, based on the degree and extent of lung involvement. Applying this model is not feasible in a resource-limited country like us. We may propose a visit at 3, 6, 9, and 12 month, with lung function test, QOL assessment in each visit and HRCT at 6th and 12th month.

Lot of debate and controversies have been arisen regarding the management of post-COVID lung injury. The role of antifibrotic drugs in the prevention and treatment of post COVID fibrosis is unclear at present. Both COVID and IPF share many common demographic factors, disproportionately affecting males, the elderly, and smokers. These drugs are also believed to be useful in patients with acute exacerbations of ILD (both IPF and other fibrotic ILDs). Finally, fibrosis with fibroblasts and honeycombing has clearly been demonstrated in autopsies of COVID-19 patients. For all these reasons, it is reasonable to assume that antifibrotics may have a potentially valuable role in this setting.[2] Pirfenidone and nintedanib are antifibrotic drugs that, despite having differing modes of action, are similarly effective in attenuating the rate of lung function decline by about 50%.[21,22] Pirfenidone is a pyridone with a poorly understood mechanism of action and nintedanib is a tyrosine kinase inhibitor. These two agents, established to be useful in IPF and other progressive fibrotic ILDs, are known to inhibit experimental lung injury and inhibit IL 6, IL 1, and IL 1B. It is worth noting that both these drugs take at least 1–3 months to demonstrate an effect. This is the time period at which the FVC starts to improve compared to placebo as shown in the INBUILD, INPULSIS, and ASCEND trials.[21-23] CT scan evidence of fibrosis with traction bronchiectasis and/or honeycombing would be useful to identify which patients would potentially benefit from antifibrotics. Though the role of steroid is well proven to treat hypoxaemic COVID patients in RECOVERY trial,[24] steroids alone may not be sufficient to prevent the development of fibrosis.[2]

The benefit of antifibrotic medication in COVID-induced lung injury is still putative. Trials are ongoing in different centers, and we have to wait some more days to come to a conclusion. It is disappointing to observe that some physicians are prescribing these drugs without knowing a clear indication, in a wrong dosage and duration. This malpractice must be eschewed, as these drugs are costly, have side-effects, and will cast a burden over the patients. It is strongly recommended that

antifibrotics should be reserved for those post COVID patients who demonstrate definite evidence of disease progression. Prescribing these drugs to those who are spontaneously improving over time or whose fibrosis is static, is a criminal offence.

The Chest and Heart Association of Bangladesh and Bangladesh Association for Bronchology and Interventional Pulmonology (BABIP) have mounted a task-force to formulate a precise guideline for the appropriate management of post-COVID pulmonary sequelae.

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