Review Article

Algorithmic approach in the management of COVID-19 patients with residual pulmonary symptoms

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Abstract:

Coronavirus-19 emerged about 3 years ago and has proven to be a devastating disease, crippling communities worldwide and accounting for more than 6.31 million deaths. The true disease burden of COVID-19 will come to light in the upcoming years as we care for COVID-19 survivors with post-COVID-19 syndrome (PCS) with residual long-term symptoms affecting every organ system. Pulmonary fibrosis is the most severe long-term pulmonary manifestation of PCS, and due to the high incidence of COVID-19 infection rates, PCS-pulmonary fibrosis has the potential of becoming the next large-scale respiratory health crisis. To confront the potentially devastating effects of emerging post-COVID-19 pulmonary fibrosis, dedicated research efforts are needed to focus on surveillance, understanding pathophysiologic mechanisms, and most importantly, an algorithmic approach to managing these patients. We have performed a thorough literature review on post-COVID-19 pulmonary symptoms/imaging/physiology and present an algorithmic approach to these patients based on the best available data and extensive clinical experience.

Keywords:

Acute respiratory distress syndrome, coronavirus-19, post-COVID-19 syndrome-pulmonary fibrosis, post-COVID-19 syndrome, proposed management of post-COVID pulmonary symptoms

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was first reported on December 12, 2019, and declared a global pandemic by the World Health Organization on March 11, 2020. As of June 2022, more than 536 million people have been infected worldwide with more than 6.31 million deaths (with the United States just recently reporting over 1 million deaths).[1,2] Clinical presentations range from asymptomatic, mild respiratory symptoms, pneumonia, acute respiratory distress syndrome (ARDS), or death [Table 1].[3] According to the World Health Organization, only 14% of patients who tested positive for COVID-19 required hospitalization, and about 20%–30% of those hospitalized required intensive care unit (ICU) admission.[4] While the overall mortality rate is low, mortality rates of those requiring ICU care significantly increase to 30%–50%.[5] Independent risk factors associated with ICU mortality include advanced age, male sex, morbid obesity, coronary artery disease, hypercholesterolemia, type II diabetes, low arterial oxygen pressure (PaO_2)/fraction of inspired oxygen (FiO_2) ratio on ICU admission,[5] and acute liver or kidney dysfunction on ICU admission.[6,7]

The true disease burden of COVID-19 remains unknown, as cases have fluctuated at different rates across the globe, but approximately 10%–30% of COVID-19 survivors may develop post-COVID-19 syndrome (PCS),[8] described as persistent symptoms lasting for 12 weeks or more after the acute infection.[9] Pulmonary fibrosis is the most severe long-term pulmonary manifestation of PCS and can have a

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Table 1: Illness severity classification of COVID-19 infection

Illness Severity	Clinical Description
Mild illness	Individuals who have any of the various signs and symptoms of COVID-19 (e.g., fever, cough, sore throat, malaise, headache, muscle pain, nausea, vomiting, diarrhea, loss of taste, and smell) but who do not have shortness of breath, dyspnea, or abnormal chest imaging
Moderate illness	Individuals who show evidence of lower respiratory disease during clinical assessment or imaging and who have an $SpO_2 \geq 94\%$ on room air at sea level
Severe illness	Individuals who have SpO_2<94% on room air at sea level, a ratio of arterial (PaO_2/FiO_2) <300 mmHg, a respiratory rate >30 breaths/min, or lung infiltrates>50%
Critical illness	Individuals who have respiratory failure, septic shock, and/or multiple organ dysfunction

SpO_2=Oxygen saturation, PaO_2/FiO_2=Partial pressure of oxygen to fraction of inspired oxygen

profound long-term impact on patients' respiratory health. Longitudinal studies of previous strains of the coronavirus family, such as SARS coronavirus and Middle East respiratory syndrome (MERS), have shown that pulmonary fibrosis is one of the consequences of postviral pneumonia.[10,11] In a study of 71 SARS patients over 15 years, fibrotic changes were observed in 9.4% of patients at the beginning of the study, in 4.6% at 1-year follow-up, and in 3.2% at 15-year follow-up.[11] Due to the high incidence of COVID-19, PCS-pulmonary fibrosis has the potential of becoming the next large-scale respiratory health crisis. To confront the potentially devastating effects of emerging post-COVID-19 pulmonary fibrosis, dedicated research efforts are needed to focus on surveillance, understanding pathophysiologic mechanisms, and most importantly, an algorithmic approach to managing these patients.

Methods

We performed an exhaustive narrative literature review focusing on residual pulmonary changes post-COVID-19 infection, and are incorporating our extensive clinical experience treating COVID-19 patients to propose a potential algorithmic approach to surveillance and management of these patients. We suspect that over the next 5-10 years more patients may be developing post-COVID-19 chronic pulmonary changes and an algorithmic approach may be very beneficial in the management of these patients.

Prevalence of Pulmonary Fibrosis Post-COVID-19 Infection

Data from previous viral outbreaks (SARS, MERS, and to a lesser extent other entities such as H1N1) have shown the presence of fibrotic lung changes and pathophysiologic sequelae postinfection,[10-12] raising concern for the incidence of post-COVID-19 pulmonary fibrosis. The reported prevalence of post-COVID-19 interstitial lung disease (ILD) ranges from 39% to 67%; however, these reports should be cautiously interpreted for multiple reasons: small sample sizes, lack of long-term follow-up, inconsistent terminology describing "fibrotic" changes, and preexisting underlying interstitial lung abnormalities (ILAs) in patients without prior imaging.

Most reports describing functional and radiological pulmonary abnormalities in COVID-19 survivors lack sample size and follow-up duration. To date, only a few studies have a 12-month follow-up.[13-16] In a longitudinal study, 114 patients with severe COVID pneumonia and the presence of computed tomography (CT) imaging abnormalities during hospitalization were evaluated for radiographic changes at 6 months and 1 year after hospitalization. At 6 months, 43 of 114 (38%) participants had complete resolution of radiologic abnormalities present during hospitalization, 31 of 114 (27%) participants had ground-glass opacities and/or interstitial thickening, and 43 of 114 (38%) participants had fibrotic changes (traction bronchiectasis, parenchymal bands, and/or honeycombing).[13] One-year follow-up CT scans were obtained on 62 participants (35 with fibrotic changes and 27 participants with ground-glass opacity). In the fibrotic group, all participants (35 of 35, 100%) had persistent fibrotic changes on 1-year follow-up CT scans, 27 of 35 (77%) participants had stable lung fibrosis, and 8 of 35 (23%) participants had slightly reduced fibrosis. In the nonfibrotic group, 17 of 27 (63%) participants showed complete resolution on 1-year follow-up CT scans, whereas 6 of 27 (37%) participants showed partial resorption of abnormalities and 4 of 27 (15%) participants did not have any radiologic changes.

Nonspecific radiologic terminologies (fibrotic strips, irregular lines, interlobular septal thickening/bands) have been used in different reports and have been categorized into "fibrotic-like" changes which may overestimate the incidence of post-COVID-19 ILD. Separating fibrotic and nonfibrotic radiologic abnormalities in the post-ARDS setting is challenging, as remodeling of immature fibrosis and regression of radiologic abnormalities can occur several months after recovery.[17] We are observing an analogous behavior of radiologic abnormalities in COVID-19 patients. Recent studies have shown an improvement in radiographic abnormalities in the first 3 months to 1 year.[14-16] In a study of 209 participants, 30% of the participants (62 of 209) had focal subpleural reticular or cystic lesions and bronchial dilation on CT chest at discharge from the hospital, and more than half of the participants had resolution of CT abnormalities within the first 3 months, suggesting remodeling of immature fibrosis.[15] Similarly,

in a longitudinal study with serial CT imaging up to 12 months postinfection (2 months, 3 months, 6 months, and 12 months), an improvement of CT abnormalities was observed at each follow-up; however, 63% (31 of 49) of participants did not show any further improvement after 6 months.[14]

Progressive fibrosis due to COVID-19 has not yet been documented in any of the studies to date. Further large population investigations with long-term follow-up are needed to determine the persistence or regression of residual CT abnormalities after 12 months.

Finally, an important caveat to keep in mind is the baseline variable that comes with preexisting ILAs in those without CT imaging prior to COVID-19 infection. ILA is present in 2%–9% of the population, with increasing incidence in the older population and tobacco users,[18] a demographic at higher risk of COVID-19 mortality. ILA has been shown to correlate with histologic findings of pulmonary fibrosis,[19] and up to 75% of subjects with ILA showed ILA progression in a 6-year interval study.[20] Without prior imaging, it is challenging to differentiate between ILA progression, either natural progression over time or progression triggered by acute COVID-19 infection, versus genuine post-COVID-19 ILD.

Risk Factors of Developing Fibrosis Post-COVID-19 Infection

There are several proposed factors linked to the development of post-COVID-19 fibrosis, including advanced age, male gender, disease severity, prolonged ICU stay, length of time on mechanical ventilation, smoking, and chronic alcoholism.

Smokers were 1.4 times more likely to have severe symptoms of COVID-19 and 2.4 times more likely to be admitted to an ICU, need mechanical ventilation, or die compared to nonsmokers.[21,22] Chronic alcoholism[23] is linked to recurrent aspiration pneumonitis and/or pneumonia, leading to chronic oxidative stress, inflammation, and induction of transforming growth factor-β (TGF-β).[24] It is associated with a 3–4-fold increased risk of ARDS,[25,26] and increased expression of TGF-β could potentially lead to pulmonary fibrosis.

Pulmonary Function Abnormalities

Multiple case studies and meta-analyses on COVID-19 have found a reduction in diffusing capacity of the lung for carbon monoxide (DLCO) as the most prevalent lung function impairment after infection.[27] This is consistent with studies from SARS and MERS outbreaks. At 12 months, 23.7% of patients had DLCO impairment after SARS infection.[28]

In a prospective study of 83 patients with severe COVID-19 infection, pulmonary function, 6-min walk test (6MWT), and CT imaging were followed at 3, 6, 9, and 12 months after discharge. The most commonly described impairment was reduced DLCO and restrictive lung disease. There was an improvement in pulmonary function and 6MWT at each assessment. At 12 months after discharge, residual abnormalities of pulmonary function were observed in about a third of patients, with the most common impairment being a reduced DLCO.[29] A meta-analysis of 18 studies regarding long-term lung function post-COVID-19 infection showed similar results. At 6 months, the most prevalent abnormalities are noted in DLCO, forced vital capacity, and total lung capacity. Most abnormalities improved after 6 months; however, DLCO impairment persisted after 12 months in 24.3% of participants.[30] Furthermore, the degree of DLCO impairment may be related to infection severity. In a study of 120 participants, diffusion impairment was noted in 24 of 99 (24.2%) patients with nonsevere disease and 6 of 16 (37.5%) patients with severe disease at 12-month follow-up.[31]

Management

Pulmonary fibrosis is one of the most feared complications of the COVID-19 pandemic. Although available literature suggests that patients with COVID-19 infection can develop pulmonary fibrosis, the natural history of the disease is still unclear. In our experience over the last 2 years, acute-phase infection is characterized by bilateral, peripheral ground-glass opacities, followed by the development of dense consolidations as the disease progresses. These changes tend to regress within weeks to months upon recovery, and in many cases, complete resolution is achieved. Reticulations with architectural distortion, traction bronchiectasis, parenchymal bands, and honeycombing (rare) are seen in patients with severe/critical disease with prolonged ventilator dependence, prolonged ICU stay, and the presence of ARDS. These fibrotic changes tend to be more stable in the postrecovery time. Some radiologic improvements are noted up to 6–12 months following initial infection, but without complete resolution [Figures 1 and 2]. Time will tell if these changes will persist or slowly regress; however, data from previous coronavirus outbreaks have shown that there is little regression of fibrosis over the years.[10]

If pulmonary fibrosis is indeed a sequela of COVID-19 infection, we will likely face a second wave of health crisis related to morbidity and mortality of pulmonary fibrosis. Therefore, it is of paramount importance that we develop an algorithmic approach to surveillance and management of pulmonary symptoms in COVID-19 survivors. In this article, based on our expertise and

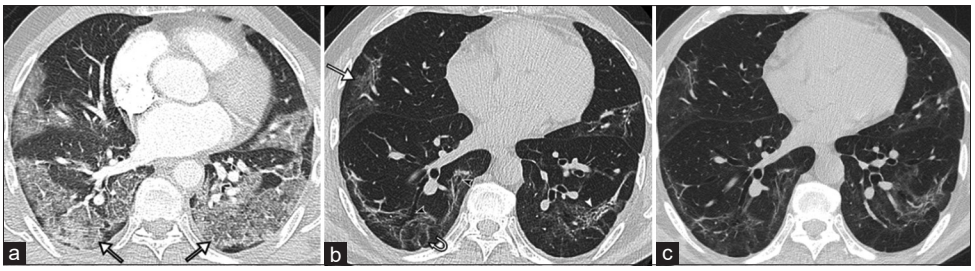

Figure 1: A 66-year-old male with COVID-19 pneumonia. (a) Axial contrast-enhanced chest CT image demonstrates acute lower-lobe predominant bilateral ground-glass opacities (arrows). (b) Axial noncontrast chest CT image performed 1 month later demonstrates substantially improved ground-glass opacities (white arrow), new superimposed curvilinear opacities (curved arrow), and reticulation (white arrowhead), associated with mild architectural distortion and traction bronchiectasis (black arrowhead), consistent with mild pulmonary fibrosis. (c) Axial noncontrast chest CT image performed 6 months after initial CT shows unchanged mild fibrosis. CT: Computed tomography

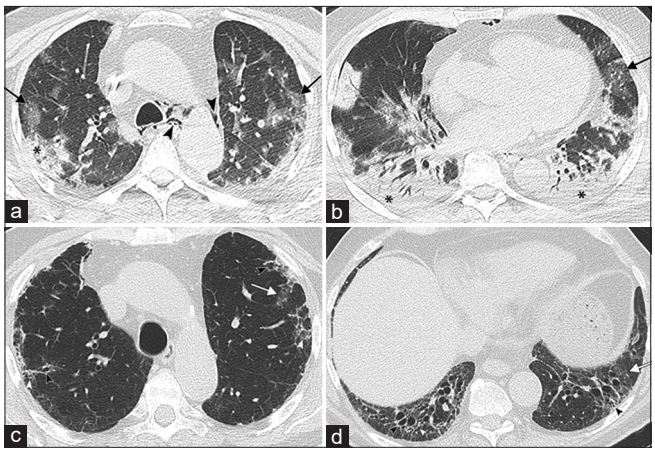

Figure 2: A 63-year-old male with COVID-19 pneumonia. (a and b) Axial contrast-enhanced chest CT images demonstrate bilateral upper lobe-predominant ground-glass opacities (black arrows) and lower lobe-predominant consolidation (*), consistent with COVID-19 and acute lung injury. Pneumomediastinum is also visible (black arrowheads). (c) Axial noncontrast chest CT image through the upper lobes, performed 7 months after initial CT, demonstrates peripheral predominant ground-glass opacities (white arrows) and reticulation (white arrowheads), associated with architectural distortion and traction bronchiectasis/bronchiolectasis (black arrowheads), consistent with pulmonary fibrosis. (d) Axial noncontrast chest CT image through the lower lobes, performed 7 months after initial CT, shows more pronounced fibrosis, characterized by GGO (white arrow) and reticulation (white arrowhead) with architectural distortion and traction bronchiectasis/bronchiolectasis (black arrowheads). GGO: ground-glass opacity, CT: Computed tomography

careful review of the available literature, we propose a surveillance and management algorithm for COVID-19 survivors [Figure 3] using illness severity classification and radiological change classifications as described in Tables 1 and 2.

Role of Antifibrotics in Management of Post-COVID-19 Pulmonary Fibrosis

To date, there are only two Food Drug and Administration-approved antifibrotics, pirfenidone and nintedanib, and their role is well established in fibrotic ILD. The ASCEND trial showed the benefit of pirfenidone in reducing disease progression in patients with idiopathic pulmonary fibrosis (IPF).[32] INPULSIS 1 and 2 showed similar results with nintedanib in IPF.[33] The INBUILD trial showed the effectiveness of nintedanib not only in IPF but also in other fibrotic ILDs.[34]

The role of antifibrotic drugs in post-COVID pulmonary fibrosis is not clear at present, but it has become a topic of great interest for research in recent months. Pirfenidone has several suggested mechanisms of action that could be useful in post-COVID-19 fibrosis, including a downregulating effect on cytokines such as TGF-β1, connective tissue growth factor, platelet-derived growth factor, and tumor necrosis factor-α.[35-39] In addition, pirfenidone is a reactive oxygen species scavenger,[40,41] inhibiting apoptosis,[42] and downregulates the expression of ACE receptors.[43] There are several ongoing trials investigating the use of antifibrotics in the prevention and treatment of post-COVID-19 fibrosis. While we eagerly await the results of these studies, equal efforts should be focused on early recognition and surveillance of patients at high risk for developing chronic lung changes and impairment after combating COVID-19 infection.

Brief Summary of Recommendations

- All patients with persistent symptoms (despite the severity of initial infection) and all patients with severe illness without residual symptoms should follow up with a pulmonary specialist 3 months after hospitalization
- Patients with moderate/severe illness with residual symptoms should have pulmonary function test (PFT)/6MWT and chest X-ray (CXR) at 3-month follow-up visit
- Patients with normal lung physiology with abnormal CXR can follow up as needed
- Patients with abnormal lung physiology with abnormal CXR should obtain high-resolution computed tomography (HRCT)
- Patients with critical illness with residual symptoms should have PFT/6MWT and HRCT at 3-month follow-up visit
- Patients with the presence of abnormal lung

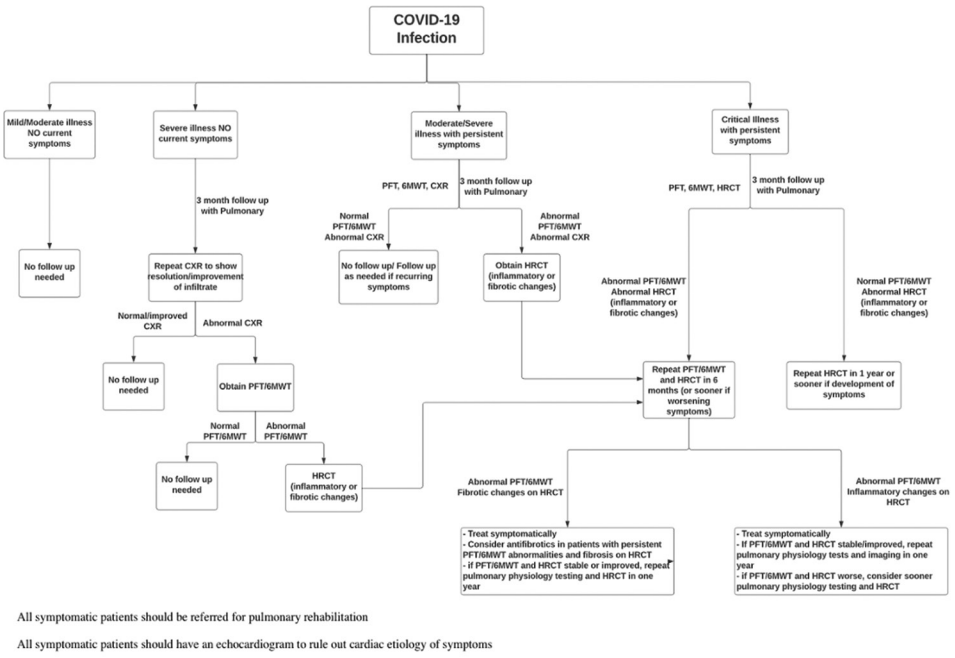

Figure 3: Surveillance and management algorithm for COVID-19 survivors

Table 2: Radiological change classifications

Classification	Description
Inflammatory radiological findings	Ground glass opacification or consolidation without underlying signs of fibrosis
Fibrotic radiological findings	Lung architectural distortion, traction bronchiectasis, and/or honeycombing

physiology and HRCT (inflammatory or fibrotic) should have close surveillance with repeat lung physiology test and HRCT in 6 months

- Patients with the presence of abnormal lung physiology and fibrosis on HRCT at 9-month follow-up consider antifibrotic treatment
- Patients with the presence of abnormal lung physiology and inflammatory changes on HRCT at 9-month follow-up should undergo close surveillance with repeat lung physiology and HRCT in 1 year or sooner if worsening symptoms
- All symptomatic patients should be referred for pulmonary rehabilitation
- All symptomatic patients should have an echocardiogram to rule out the cardiac etiology of symptoms.

Declaration of patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form the patient (s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest

There are no conflicts of interest.

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