



Pulmonary Sequelae of COVID-19

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2.1 Introduction

COVID-19 has affected over 280 million people globally, with over 240 million survivors. While the acute effects of COVID-19 are well understood, we are just beginning to understand the long-term effects of COVID-19, particularly as they relate to lung function and recovery. Persistent symptoms have been described as the post-acute sequelae of COVID-19 (PASC) and include short-term and long-term sequelae. Post-COVID-19 conditions can occur in patients who have had varying severity of illness during their acute infection. These include people who have had mild or even asymptomatic infections [1]. Post-COVID-19 conditions are referred to by a wide range of names, including long COVID, post-acute COVID-19, long-term effects of COVID-19, post-acute COVID syndrome, chronic COVID, long-haul COVID, and late sequelae, among others. Although standardized case definitions are still being developed, post-COVID-19 conditions can be considered a lack of return to a usual state of health following acute COVID-19 illness. The time frame for a post-COVID-19 condition is generally considered as 2–4 weeks following acute COVID-19 infection with incomplete resolution of symptoms or the emergence of new symptoms. Post-acute COVID-19 can be a multisystem condition. Around 10–35% of patients who have acute COVID-19 infection go on to develop long COVID symptoms [2]. The most common non-resolving symptoms are dyspnea, fatigue, malaise, cognitive impairment, cough, chest pain, palpitations, arthralgias, diarrhea, sleep difficulties, fever, light-headedness, continued anosmia, and mood changes. For hospitalized patients, the incidence of the post-COVID-19 syndrome may reach as high as 85% [2]. Post-COVID-19 sequelae can be highly

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debilitating and seriously impact occupational and social activities. It also will add significantly to the healthcare burden in addition to its consequences on mental health.

2.2 Pathophysiology

There are several proposed mechanisms for long COVID. One theory proposes that SARS-CoV-2 viral persistence in the body contributes to immune activation and long COVID symptoms. The evidence for this is an increased level of inflammatory biomarkers such as C-reactive protein (CRP), interleukin-6 (IL-6), and D-dimer in patients with long COVID [3]. Another proposed mechanism suggests that cell dysfunction promotes long COVID pathophysiology similar to an autoimmune disorder [4]. There have been autopsy reports of infiltrates in the lungs and other organs that are CD8+ T cell-enriched, which would be evidence of an ongoing autoimmune reaction [5]. There is also evidence that severe COVID-19 causes lymphopenia with both B and T cell deficiency. This causes hyperinflammation as T cells participate in inflammation resolution. Serum samples from COVID-19 patients show an increased incidence of antiphospholipid autoantibodies which is associated with more severe clinical outcomes [6]. However, it is still not completely clear which of these mechanisms is dominant, or whether combinations of mechanisms cause long COVID.

2.3 Respiratory Clinical Features of Post-Acute Sequelae of COVID-19

Patients with acute COVID-19 are expected to have symptoms for up to 4 weeks following an initial illness. Those patients with ongoing symptoms beyond 2 months after their initial COVID-19 illness are considered to have post-acute sequelae of SARS-CoV-2, otherwise known as long COVID [7]. These symptoms vary widely and can include neurocognitive and physical symptoms, many of them respiratory in nature. Based on several published reports, the table below shows the approximate proportion of clinical respiratory symptoms of long COVID. However, this information is evolving as new data emerges (Table 2.1).

Table 2.1 Percentage of patients with respiratory clinical features of long COVID

Long COVID respiratory symptom	Percentage of patients affected
Dyspnea	16 to 66% [8–12]
Chest discomfort	8 to 44% [9–12]
Cough	7 to 34% [10–12]
Fatigue	31 to 72% [8–12]
Throat pain	3% [10]
Sputum production	3% [10]

2.4 Radiological Abnormalities

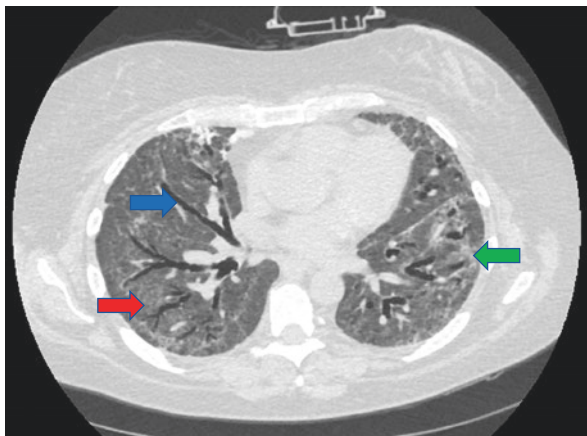
Many reports have found radiological evidence of lung fibrosis that can last up to 6 months after initial hospital discharge from COVID-19 pneumonia [13, 14]. In a 3-month follow-up study of COVID-19 survivors, pulmonary radiological abnormalities were detected in 71% of patients, and functional impairments were detected in 25% of participants. Only 10% of patients in this study had severe pneumonia when diagnosed initially with COVID-19 [15]. Another study observed reduced lung diffusion capacity that correlated with radiological abnormalities in 42% of COVID-19 survivors at 3 months posthospital discharge, regardless of initial disease severity [16]. Even 6 months after symptom onset, lung radiological abnormalities associated with persistent symptoms were still present in about half of COVID-19 survivors [17]. There is evidence of chronic scar formation in the lungs that may be responsible for persistent dyspnea and cough. This scarring may not always be visible on a CT scan but indirectly suggested by a reduction in diffusion capacity [18]. In addition, another study of COVID-19 survivors with persistent symptoms after 4 weeks showed persistent inflammation via increased FDG uptake in the bone marrow and blood vessels [19].

2.5 Pulmonary Function Testing

While the COVID-19 pandemic is still ongoing and long-term data is limited, there is some prior experience in similar diseases for clinicians to better understand what to expect with post-COVID-19 patients, especially those who develop acute respiratory distress syndrome (ARDS). Patients who develop ARDS are known to have long-term pulmonary sequelae. In a study of 78 patients with ARDS, 80% had persistent reduction in DL_{CO} on pulmonary function tests (PFTs) 1 year post-hospitalization [20]. Twenty percent had a restrictive lung disease pattern, and 20% had obstructive lung disease patterns, although most of these patients were smokers at the time of their infection [14]. This held true regardless of the ventilation strategy the patient underwent during their ARDS, either low or high tidal volume ventilation. This is particularly relevant to COVID-19 patients given the heterogeneity in lung compliance and ventilation strategies [21]. In addition to PFT abnormalities, patients are known to have abnormalities on imaging that persist even 1 year post-ARDS, particularly related to signs of pulmonary fibrosis [14] (Fig. 2.1).

The influenza A (H1N1 subtype) pandemic in 2009 gives us some guidance on what we may come to expect with patients recovering from COVID-19. During the H1N1 pandemic, the US Centers for Disease Control and Prevention (CDC) estimated that there were over 60 million cases in the United States, of which over 270,000 were hospitalized and over 12,000 died. Patients with H1N1 typically developed pneumonia-like symptoms of hypoxemia, with many developing ARDS. In a study of nine patients with H1N1-related ARDS, six had at least a mild reduction in FEV₁, and five of the nine had at least a mild reduction of FVC 1 month

Fig. 2.1 CT chest features of post-covid pulmonary abnormalities. This CT shows traction bronchiectasis (blue arrow) and reticular markings (red arrow) in a background of ground glass opacities (green arrow)



after discharge from their hospitalization [22]. At 6 months post-discharge, all patients had normalized FEV1, and most had normalized FVC. Total lung capacity (TLC) was reduced in six patients at 1 month, with only two patients regaining normal TLC by 6 months. DLCO was low in seven of nine patients at 1 month and remained persistently low in four of the nine patients at 6 months. Almost all patients had reduced six-minute walk distances (6MWD) based on their predicted values at 1 month post-discharge, with improvement to normal at 3 months. Of note, all these patients were enrolled in pulmonary rehabilitation programs. This study, therefore, showed that all patients with H1N1-related ARDS developed some pulmonary function abnormalities. While most of them had largely recovered, some continued to have persistent abnormalities, especially reduced diffusion even at 6 months post-discharge.

Patients with mild influenza developed longer-term PFT abnormalities as well. In another study of 48 patients with mild H1N1, 33% had a persistent reduction in DLCO 1 year post-discharge, along with 33% with evidence of small airway disease, as evidenced by decreased forced expiratory flow at 50% and 75% of forced vital capacity [23]. Many patients had evidence of restrictive lung disease that persisted for 1 year post-discharge, though whether this was merely due to unmasking of underlying lung disease pre-H1N1 is unclear as most of these patients did not have a prior spirometry.

Another correlate for the current pandemic is based on the literature from the severe acute respiratory syndrome (SARS) pandemic in 2003, which was also caused by a coronavirus. One study found that one-third of SARS survivors had impairments in pulmonary function 1 year post-discharge, with the most common abnormalities seen in the FEV1 and DLCO [24]. There was no significant difference between patients with varying disease severity 1 year post-discharge, although the patients with decreased DLCO were more likely to have fibrosis on imaging.

In summary, previous literature has shown that patients who become hospitalized with ARDS are known to have abnormal pulmonary function tests up to 1 year post-discharge, marked by restrictive lung disease patterns and reduced DLCO. Some patients who had H1N1 or SARS had abnormal PFTs at least 1 year post-discharge, though the improvement was noted in those who underwent pulmonary rehabilitation. This is critical to understand as it informs our ongoing management of patients with post-acute sequelae of COVID-19.

2.6 Current Understanding of Lung Function Tests in Patients with COVID-19

While PFTs are integral to objectively determine the actual effect of COVID-19 on the lungs, given the concern of how the virus is transmitted, pulmonary function laboratories have been cautious about restarting testing. Many of the patients from early in the COVID-19 pandemic are just starting to have meaningful pulmonary function follow-up almost 2 years after their initial diagnoses. As a result, we are just starting to understand the longer-term implications of COVID-19 infection on pulmonary function.

Of patients admitted early in the pandemic, many now display restrictive patterns of lung disease like other viral pneumonia and ARDS patients in the past. In an Italian study of patients with COVID-19 early in the pandemic, FEV1 and FVC were all lower than their lower limit of normal values and only started to improve after 6 weeks post-discharge [25]. However, these were patients that were sick enough to require hospital admission, and results were available based on a short-term follow-up only. The restrictive pattern seen on these PFTs mirrors the pattern seen after long-term follow-up of past respiratory diseases like influenza and SARS.

It is less clear if the severity of the initial COVID-19 illness has a bearing on pulmonary function over a long period of time. Most studies to date have broken down COVID-19 disease by those with mild symptoms (no clinical pneumonia), moderate disease (clinical pneumonia but no significant hypoxemia), and severe disease ($RR > 30$, $SpO_2 < 94\%$ on room air). In a study of 57 patients, of which 70% had non-severe COVID-19 and completed PFTs at least 2 weeks post-discharge, the group means for FEV1, FVC, and FEV1/FVC ratio were within normal limits, with no statistically significant difference between disease severity in these parameters [26]. However, many patients had abnormal values in each of these domains. Patients with severe disease did have a more significant decline in total lung capacity compared to non-severe disease. About 52.6% had abnormal diffusion capacity, with a higher impairment rate in patients with severe disease. Similarly, patients with severe disease had a significantly shorter 6MWD than those with non-severe disease, both in absolute distance and % predicted, with severe cases achieving 88% predicted 6MWD. While none of the patients in the study had a chronic respiratory disease, over a third had a prior medical illness, including hypertension, and nine patients had a smoking history, all of which may play a role in their persistent PFT abnormalities [20].

A larger systematic review including 380 patients post-COVID-19 showed that 15% of patients had a restrictive pattern on spirometry, 7% had an obstructive pattern, and 39% had impaired DLCO [27]. The prevalence of impaired DLCO was greatest in those with severe COVID-19. However, some patients had pulmonary function testing done 1 month after the onset of symptoms or 1 to 3 months post-discharge, which may skew the results, as some of the abnormalities may just be due to the acute phase of the disease. This mirrors another systematic review of 57 studies, including over 250,000 survivors of COVID-19 who were assessed for PASC at least 1 month after COVID-19 infection [28]. In this review, 65% of patients had increased oxygen requirements, 30.3% had diffusion abnormalities, and 10% had restrictive lung disease on spirometry.

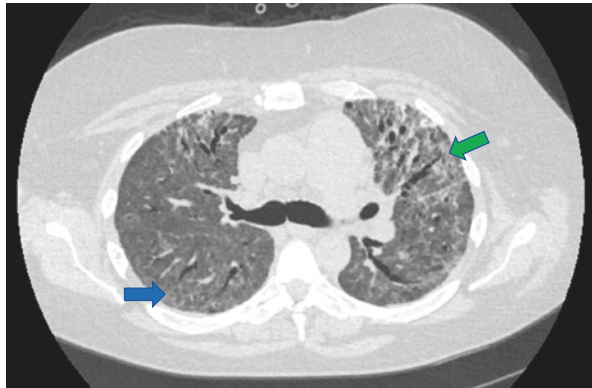
Patients with pulmonary function test abnormalities after COVID-19 are also more likely to have radiographic abnormalities that persist months after their initial diagnosis. As many as 55% of patients in one study had some radiographic abnormality after a mean follow-up of approximately 12 weeks after their COVID-19 diagnosis [29]. Of this group, 85% had ground-glass opacities, and 65% had reticulation on imaging, suggesting developing fibrosis from the profound inflammatory response from ARDS due to COVID-19.

Together, these studies suggest that patients with COVID-19 are likely to develop at least short-term pulmonary function test abnormalities showing restrictive lung disease and impaired diffusion, with a smaller subset developing obstructive lung disease. Most patients with mild and moderate COVID-19 disease will recover some degree of their FEV1, FVC, and TLC, though as disease severity worsens, patients are more likely to have persistent impairments in DLCO. Further long-term data is needed to assess the long-term effect of COVID-19 on pulmonary function truly. In addition, the impact of pulmonary rehabilitation on improving lung function akin to its effect on other viral syndrome-associated ARDS also needs to be studied.

2.7 Illustrative Case

A 55-year-old smoker male had required hospitalization and supplemental oxygen due to severe COVID-19 pneumonia. His CT thorax done 2 months following discharge demonstrates bilateral peripheral linear opacities and ground-glass opacities (Fig. 2.2). His pulmonary function testing was done 3 months post-COVID-19 infection and was suggestive of restrictive lung disease with a decreased FEV1 compared to the lower limit of normal (LLN) and decreased diffusion capacity (DLCO) (Figs. 2.3 and 2.4).

Fig. 2.2 CT chest of illustrative case. This CT shows peripheral linear opacities (blue arrow) and ground glass opacities (green arrow)



Spirometry		Ref	LLN-ULN	Pre	% Ref
FVC	Liters	4.48	(3.6 - 5.3)	3.24	72
FEV1	Liters	3.44	(2.7 - 4.2)	2.54	74
FEV1/FVC	%	77	(67.0 - 86.4)	78	
FEV1/SVC	%			78	
FEF25-75%	L/sec	2.98	(1.5 - 4.5)	2.23	75
PEF	L/sec	8.97	(6.8 - 11.1)	10.27	115
FET100%	Sec			8.45	
FEF/FIF50				0.50	
Vol Extrap	Liters			0.02	

Fig. 2.3 Spirometry of Illustrative case

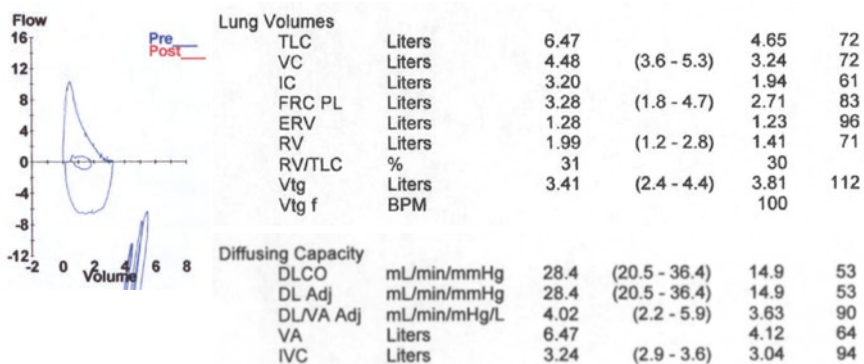


Fig. 2.4 Diffusion capacity and lung volume measurements of illustrative case

2.8 Management of Post-COVID-19 Respiratory Sequelae

Patients who recover from the acute phase of COVID-19 may continue to have signs and symptoms of disease that persist at least 2 months after their initial illness, at which point they would be diagnosed with post-acute sequelae of COVID-19, or long COVID [30]. These symptoms are usually persistent cough, sore throat, fatigue, “brain fog,” and dyspnea. Patients with chronic cough often seek antitussive therapies, but it is unknown whether these are effective in post-COVID-19 cough. In the clinical management of post-COVID-19 chronic cough, it is important to exclude any pathological or structural causes such as fibrotic damage to the lung parenchyma or damage to the airway caused by the acute illness and its treatment (e.g., endotracheal intubation-related complications). The classic evaluation for chronic cough should also be performed to exclude conditions such as gastroesophageal reflux disease, ACE inhibitor-induced cough, lung fibrosis, or airway inflammation [31]. A persistent cough in post-COVID-19 syndrome may be driven by neuroinflammation leading to a state of laryngeal and cough hypersensitivity. Gabapentin and pregabalin, which are neuromodulators, have been shown to be effective in controlling chronic refractory cough [32]. Inhaled steroids have been studied for a chronic cough from COVID-19, and have not been shown to be effective [33]. Management of cognitive impairment and fatigue is currently under evaluation and not yet established. The dyspnea needs a full work-up to evaluate for fibrosis, pulmonary embolism, and other classic causes of dyspnea. With research still ongoing, it is anticipated to have more clarity on effective symptom-based therapies in the future.

There is no universal consensus on how these patients with long COVID should be evaluated, but some societies have proposed guidelines. The British Thoracic Society recommends that patients with mild COVID-19 who are still symptomatic be followed up at 3 months for a clinical assessment and with a chest X-ray, with further work-up, such as PFTs, 6-minute walk tests, and echocardiograms based on clinical judgment [30]. Others suggest getting a chest X-ray, PFTs, and 6-minute walk tests at their initial visit to establish a baseline and then repeating them at three monthly intervals [34]. There is no consensus on the optimum timing for obtaining chest computed tomography (chest CT), though some suggest that it be done in patients with long COVID symptoms at their initial visit and then 6 and 12 months afterward.

Some patients develop ground-glass opacities (GGO) with subpleural and peribronchial consolidations suggestive of organizing pneumonia after having had COVID-19. Corticosteroids are the mainstay of treatment for organizing pneumonia. In a study of patients with persistent interstitial lung changes treated with steroids, many suggestive of organizing pneumonia, the vast majority had improvement in their dyspnea scores, FVC, DLCO, and 6MWT, as well as improvement in their radiographic abnormalities [35]. All patients had presumably cleared their virus based on the timeline of infection. This suggests that in patients with abnormal PFTs with persistent radiographic changes of ground-glass opacities or consolidations post-COVID-19 but no fibrosis or active infection, corticosteroids may be

beneficial for improvement in dyspnea, PFT, and radiographic abnormalities. However, the optimum dose of steroids is not yet standardized. In one observational study of patients with persistent interstitial lung disease (predominantly organizing pneumonia at least 6 weeks after COVID-19 infection), patients received corticosteroids up to a maximum dose of 0.5 mg/kg of prednisolone and were tapered over 3 weeks. This led to an improvement in their functional status, as well as lung function based on PFTs [35]. Another open-label randomized trial of COVID-19 patients with persistent dyspnea, hypoxemia, or radiological abnormalities at least 3 weeks post-COVID-19 illness compared high-dose (prednisolone 40 mg/day tapered over 6 weeks) versus prednisolone 10 mg daily for 6 weeks [36]. Both groups benefited from corticosteroid treatment and demonstrated an improvement in radiological findings, spirometry, and dyspnea at 6 weeks. Most importantly, there was no significant difference in outcomes between the two groups, suggesting that even low-dose corticosteroids may benefit many patients [34].

It is also not clear how to manage patients with obvious fibrotic changes post-COVID-19. After the SARS outbreak in 2003, many patients developed pulmonary fibrosis on CT, with one study showing that 15/24 patients had fibrosis on CT scan at mean follow-up of 37 days post-discharge, with patients requiring ICU being more likely to develop fibrosis [37]. There are many postulated reasons as to why patients with ARDS develop pulmonary fibrosis, starting with the inflammatory phase of ARDS and its progression into the fibrotic phase. These include the dysregulated release of matrix metalloproteinases leading to fibroproliferation and vascular dysfunction leading to fibrosis, possibly due to VEGF, and cytokines such as IL-6 and TNF- α [38].

Since the cascade of events eventually leading to fibrosis starts very early on in ARDS, the role for anti-fibrotic therapies early in COVID-19-related ARDS has been considered and evaluated. Nintedanib can reduce bronchoalveolar lavage concentrations of IL-1, a known player in the pathogenesis of idiopathic pulmonary fibrosis, and pirfenidone reduces serum and lung IL-6 concentrations in mouse models of pulmonary fibrosis [26]. However, this is just a biological rationale for the novel treatment of COVID-19. Based on current evidence, it is still unclear if anti-fibrotic agents have any definite role preventing further fibrosis in patients who have recovered from their acute COVID-19 illness. In the INBUILD trial of nintedanib in patients with progressive pulmonary fibrosis due to various disorders, those who received nintedanib had a reduction in FVC decline and therefore benefited from treatment [35]. Given that some patients with progressive fibrotic lung diseases and even patients with COVID-19 have immune dysregulation as a shared pathogenetic mechanism, it has been hoped that early anti-fibrotic therapy may prevent or retard the development of COVID-19-associated fibrosis. As of now, however, there are no published long-term studies of these anti-fibrotic agents in post-COVID-19 respiratory syndromes, although several trials are ongoing.

Lastly, many patients with persistent dyspnea and impaired lung function post-COVID-19 may benefit from pulmonary rehabilitation. In 1 observational cohort study, 50 patients with mild to severe COVID-19 and reduced 6MWD and impaired FVC at least 3 months after their initial diagnosis were enrolled in pulmonary

rehabilitation. After 3 weeks of pulmonary rehabilitation, all patients demonstrated an improvement in their FVC and 6MWD, with patients with mild COVID-19 gaining a median of 48 meters and those with severe COVID-19 gaining 124 meters [39]. This implies that pulmonary rehabilitation should be an essential part of therapy for patients with respiratory post-acute sequelae of COVID-19.

2.9 Conclusion

Post-COVID-19 sequelae can have a serious impact on the ability to return to normal functional status. There can be significant economic and mental health consequences for the person with the illness, their families, and the communities they live in. Thus, a multidisciplinary and multispecialty approach is required for a holistic management of these patients. Some treatment algorithms include steroid therapy and pulmonary rehabilitation, and interval pulmonary testing. Educational materials to alert patients of symptoms and seek help post-acute infection should also be distributed. Another important aspect is the development of patient registries to support research efforts to understand and treat post-acute COVID-19 sequelae. As a pulmonary community, it seems that we will be dealing with post-COVID-19 syndromes for a long time.

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