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Journal of Clinical Oncology Reports
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ISSN: 2836-5062 RESEARCH ARTICLE

Pulmonary features of Long Covid-19: Where are we now?

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Received: 04 January 2023; **Accepted:** 12 January 2023; **Published:** 25 January 2023.

Citation: Som Biswas, (2023). Pulmonary features of Long Covid-19: Where are we now? Journal of Clinical Oncology Reports. 2(1). DOI: 10.58489/2836-5062/007.

Abstract

Severe acute respiratory syndrome coronavirus 2 has led to the Covid-19 pandemic that has resulted in millions of deaths and severe morbidity worldwide. Clinicians are now faced with an increasing number of long-term complications of Covid-19, defined as “post-acute COVID-19 syndrome”. Most studies have focused on severe COVID-19, however post-acute COVID-19 syndrome mostly exists in outpatients and had limited published literature. Given the diversity of its symptoms and the persistence of its symptoms, the management of these patients requires a multidisciplinary approach, that will result in the utilization of large amounts of health resources in the coming months and even years. In this review, we discuss the clinical and radiological presentation, pathophysiology, and management of post-acute COVID-19 syndrome. The persistence of respiratory symptoms, like dyspnea and cough, beyond 4 weeks from the onset of symptoms is considered Long Covid-19 syndrome. Dyspnea is the most frequent respiratory symptom reported after COVID-19. Symptom of cough is found to be less common than dyspnea after Covid-19 infection. Post-COVID-19 dyspnea can affect patients with even initially mild COVID-19 and no evidence of organ damage. In this review, we have discussed the clinical and radiological presentation, pathophysiology, and management of pulmonary features associated with post-acute COVID-19 syndrome. For radiologists, this is an upcoming topic of extreme significance and few published literatures exist on this specific evolving disease.

Keywords: *Pulmonary features, Long Covid-19*

Background

The Covid-19 pandemic has affected millions of people worldwide and continues to do so. The acute symptoms of the disease were reported in early 2020. It caused predominantly pulmonary infections.

The coronavirus infection causes a cytokine “storm”, which affects multiple organs, including the lungs, heart, and brain, and leads to chronic disease [1]. Survivors were observed to present with persistent respiratory, neurological, or cardiovascular symptoms, leading to what has been called “post-acute COVID-19 syndrome” or “long COVID-19” that lasts for weeks or months. These symptoms are frequent and affect even those patients who have not experienced the severe forms of COVID-19.

This topic is very important as these symptoms exert a major effect on patients’ quality of life. The current incidence suggests that a considerable number of patients will be affected in the future.

What are the symptoms and signs of Long Covid-19 syndrome? What are its pathogenesis and risk factors? Does it disappear over time? How do we evaluate these patients? This review of ours tries to seek answers to these questions.

Respiratory disorders

Respiratory symptoms

The persistence of respiratory symptoms, like dyspnea and cough, beyond 4 weeks from the onset of symptoms is considered Long Covid-19 syndrome. Dyspnea is the most frequent respiratory symptom reported after COVID-19 in both hospitalized (up to 50%) [2-8] and non-hospitalized patients with mild COVID-19 (up to 14%) [9]. The persistence of dyspnea is not closely related to the initial severity of COVID-19. Dyspnea has been reported almost equally in patients who initially required initial intensive care unit (ICU) admission compared to those hospitalized in wards. Dyspnea causes a major

effect on the quality of life and socioeconomic status, as many patients do not return to work for 6 months after COVID-19 due to dyspnea. The etiopathology of dyspnea after COVID-19 is multifactorial, including dysfunctional breathing, cardiovascular dysfunction, parenchymal sequelae, and muscular deconditioning.

Symptom of cough is found to be less common than dyspnea after Covid-19 infection, however, it can also persist for weeks or months after infection and has been reported in 2–42% of these patients [3–7,]. Persistent cough also alters the quality of life. In a large study conducted on patients, months after discharge, no clinical or hospitalization factors were associated with long-term cough post-COVID-19 [9]. Recently, Song et al. [10] hypothesized that cough after COVID-19 was due to activation of the vagal sensory nerves, which leads to a cough hypersensitivity state and neuroinflammatory events in the brain.

HUANG et al. [11] showed a slight deterioration of dyspnea scores between 6 and 12 months after COVID-19. By contrast, WU et al. [4] showed in the first 1-year follow-up studies after Covid-19 that among 83 patients with severe COVID-19 who did not require mechanical ventilation, dyspnea scores and exercise capacity improved over time. However, some patients had persistent symptoms and radiographic changes even after a year. Therefore, the precise evolution of respiratory symptoms, of functional and radiological lung damage, remains to be determined in additional long-term prospective follow-up studies.

As the number of patients with long Covid having pulmonary difficulties increases this will lead to a severe strain on the health resources.

Dysfunctional breathing

Dysfunctional breathing is defined as irregular breathing patterns in the absence of active pulmonary disease. Post-COVID-19 dyspnea can affect patients with even initially mild COVID-19 and no evidence of organ damage [12], and a high prevalence of post-COVID-19 dysfunctional breathing has been found [13]. However, there is scarce literature. The Nijmegen Questionnaire is a measure of functional respiratory complaints [14, 15] and has been used COMEBAC (Consultation Multi-Expertise de Bicêtre Après COVID-19) cohort study to detect patients with dysfunctional breathing. A positive Nijmegen Questionnaire (score >22 out of 64) was found in 20.9% of the patients. Motiejunaitie et al. [16] reported ventilatory inefficiency during cardiopulmonary exercise testing in patients with post-COVID-19 unexplained dyspnea. These results were similar to the study by Taverne et al. [17] who had performed a similar study.

The exact mechanism of post-COVID-19 dysfunctional breathing is not completely understood. Anxiety, depression, and psychological trauma are common among patients with dysfunctional breathing. It can be hypothesized that the negative socioeconomic effects of the Covid-19 pandemic on mental health might promote the onset of functional respiratory complaints. Also, since the viral receptor angiotensin-converting enzyme 2 is expressed in the brainstem nuclei involved in the regulation of ventilation, central interference with the respiratory drive should be included. There is a lack of literature regarding its management. Few studies indicate that treatment of dysfunctional breathing usually includes breathing exercises with a physiotherapist.

In conclusion, respiratory symptoms following COVID-19 impose a significant healthcare burden and dysfunctional breathing represents a significant proportion of these complaints. More studies are needed to evaluate the underlying characteristics and pathophysiology of those symptoms.

Pathophysiology

Invasion of alveolar epithelial and endothelial cells by the Covid-19 virus and viral-independent mechanisms such as immunological damage contribute to the breakdown of the endothelial–epithelial barrier. This causes the invasion of inflammatory cells and extravasation of protein-rich exudate into the alveolar space. Diffuse organizing and focal fibroproliferative alveolar damage have been reported in the COVID-19 autopsy reports, similar to other etiologies of ARDS. Rarely areas of myofibroblast proliferation, microcystic honeycombing, and mural fibrosis have also been reported. This fibrotic state can be provoked by cytokines such as interleukin-6 (IL-6) and transforming growth factor-β. Analysis of lung tissue from two autopsy specimens and three specimens from explanted lungs of recipients of lung transplantation showed histopathologic and single-cell RNA expression patterns similar to end-stage pulmonary fibrosis. This suggests that some individuals develop accelerated lung fibrosis after the resolution of the active infection [22].

Pulmonary vascular micro thrombosis and macrothrombosis have been observed in 20–30% of COVID-19 patients. This is higher than in other critically ill patient populations (1–10%). Also, the

severity of the endothelial injury and microangiopathy seen on lung autopsy is greater than that seen in ARDS from influenza [22].

Radiological sequelae

High-resolution computed tomography of the chest is the examination used for the diagnosis and classification of Covid-19 sequelae. HRCT allows a complete analysis of the parenchyma and the detection of pulmonary fibrosis, among other lesions. Three main types of post-COVID-19 sequelae can be distinguished: irreversible lesions, reversible lesions, and lesions of undetermined evolution (figure 2).

Pulmonary fibrosis is the main irreversible lesion post-Covid-19. Post-COVID-19 pulmonary fibrosis occurs along with reticulation, traction bronchiectasis, and even honeycomb lesions. 13–27% of patients have these lesions, post Covid-19 infection [3, 7, 15]. LI et al. [18] identified body mass index, age, and inflammatory markers like procalcitonin as the main risk factors for post-COVID-19 pulmonary fibrosis.

Ground-glass opacities (GGOs) are generally considered the HRCT sign of reversible parenchymal inflammation. However, sometimes GGOs do not disappear completely at follow-up and have been observed up to 12 months from the initial COVID-19 diagnosis [2]. The incidence varies according to the series and is evaluated to range from 7% to 92% [2, 7, 12].

Finally, lesions with indeterminate status are considered residual condensations and ventilatory disorders predominantly located in the subpleural portion of the lung, like the curvilinear opacity. Their evolutionary profile is poorly documented due to the lack of follow-up studies, however, based on the sparse data available, they appear to regress eventually over time [2].

The effect on pulmonary function tests is modest for most patients on long-term follow-up post-COVID-19. In the COMEBAC cohort study, fibrotic lesions were seen in 19.3% of the patients reassessed at the ambulatory care visit [7]. Pulmonary function tests were mildly impaired in patients with fibrotic lesions. WU et al. found a mild impairment in DLCO and forced vital capacity (FVC) at 3 months with a progressive improvement at 6 months (DLCO 76% (68–90%) predicted and FVC 94% (85–104%) predicted) and 12 months (DLCO 88% (78–101%) predicted and FVC 98% (89–109%) predicted) [2].

Remy-Jardin et al. [19] reported widespread microangiopathy leading to perfusion abnormalities in 65.5% of patients. Four patients had normal CT scans and perfusion defects were detected using double-energy CT. The risk factors and the evolution of these perfusion disorders are unknown.

Thus, we conclude that the prevalence of radiological abnormalities is much greater than that of respiratory function tests, with an unclear link between those two abnormalities [7]. Also, as the majority of the studies lack a control group, the abnormalities observed on HRCT cannot be conclusively identified as being specifically due to Covid-19 infection or a consequence of the diffuse alveolar damage occurring during pulmonary parenchyma infection and/or ARDS.

Potential sequelae of pulmonary embolism

The exact incidence of pulmonary embolism in Covid-19 is poorly known as CT pulmonary angiography (CTPA) was not routinely performed during Covid-19 infection. Riyahi et al. [20] have reported a 25% incidence of pulmonary embolism in 413 hospitalized Covid-19 patients. Jevnikar et al. [21] reported pulmonary embolism in 15 patients, with an incidence of 14.2% in a prospective study on 106 patients with Covid-19 who underwent systematic CTPA. In a large meta-analysis of 27 studies, this high incidence of pulmonary embolism was confirmed, as the authors reported pooled incidence rates of 16.5% for pulmonary embolism and 14.8% for deep vein thrombosis. The exact pathophysiology of pulmonary embolism in patients with Covid-19 infection is not clear, however, it can be at least partially due to the pulmonary endothelial dysfunction associated with Covid-19 infection. To date, no cases of post-COVID-19 chronic thromboembolic pulmonary hypertension (CTEPH) have been reported. However, physicians should be aware of this potential complication, which can be easily screened by echocardiography and ventilation/ perfusion lung scans.

Management considerations

Post-hospital discharge care of COVID-19 survivors is an area of ongoing research. Home pulse oximetry has been suggested as a useful tool for monitoring patients with persistent symptoms; however, supporting evidence is currently lacking. Some experts have also proposed evaluation with high-resolution computed tomography of the chest, and serial PFTs for those with persistent dyspnea, at 6 and 12 months.

In a guidance document by the British Thoracic Society, algorithms for evaluating COVID-19 survivors after hospital discharge are based on the severity of acute COVID-19 and whether or not the patient received ICU-level care. It recommended clinical assessment and chest radiograph in all

patients at 12 weeks, along with PFTs, sputum sampling, and echocardiogram based on clinical judgment for both severe and mild-to-moderate COVID-19 groups [22]. Based on this assessment at 12-week, patients are further recommended to be evaluated with high-resolution computed tomography of the chest, computed tomography pulmonary angiogram, or echocardiogram. In addition to this 12-week assessment, clinical assessment for respiratory, psychiatric, and thromboembolic sequelae, as well as rehabilitation needs, is also recommended at 4–6 weeks after discharge for those who had severe pneumonia, required ICU care, are elderly, or have multiple comorbidities.

As suggested by a preliminary observation in a small UK cohort of COVID-19 survivors with organizing pneumonia at 6 weeks after hospital discharge, treatment with corticosteroids may be beneficial in a subset of patients with post-COVID inflammatory lung disease. Lung transplantations with varying levels of success have been performed for fibroproliferative lung disease after ARDS due to COVID-19. Clinical trials of antifibrotic therapies to prevent pulmonary fibrosis after COVID-19 are underway [22].

Conclusion

In this review, we have discussed the clinical and radiological presentation, pathophysiology, and management of pulmonary features associated with post-acute COVID-19 syndrome. This is an upcoming topic of extreme significance and few published literatures exist on this specific evolving disease.

List of Abbreviations

ARDS: acute respiratory distress syndrome.

CTEPH: Chronic thromboembolic pulmonary hypertension

CTPA: CT pulmonary angiography

DLCO: diffusing capacity for carbon monoxide

FVC: forced vital capacity

GGO: Ground-glass opacities

ICU: Intensive Care Unit

PFTs: Pulmonary Function Tests

RNA: Ribonucleic Acid

UK: United Kingdom

Conflict of interest

The author declares no conflict of interest.

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