The prolonged Clinical, Radiological Consequences in covid 19 servivors :A review article

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Abstract

The pandemic coronavirus disease 2019 (COVID-19) can cause multi-systemic symptoms that can persist beyond the acute symptomatic phase. The post-acute sequelae of COVID-19 (PASC), also referred to as long COVID, describe the persistence of symptoms and/or long-term complications beyond 4 weeks from the onset of the acute symptoms and are estimated to affect at least 20% of the individuals infected with SARS-CoV-2 regardless of their acute disease severity. This narrative review aims to provide information on the prolonged COVID-19 Clinical and Radiological Consequences in recovered patients. A systematic search was conducted in PubMed, Embase, Cochrane Library and Web of Science databases, WHO and CDC websites, and grey literature was searched through Google Scholar included all scientific literature published from May 2020 until April 2023.We also address several undetermined concerns and key future research directions.

Keywords: covid 19, long covid , SARS-CoV-2, pulmonary fibrosis.

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Introduction

A growing body of clinical data, reports, and testimony from recovered COVID-19 (coronavirus disease 2019) patient advocacy groups has helped increase recognition of the postinfectious sequelae of SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) infection since the initial waves of the pandemic **(1)**

Early in the pandemic, many people believed that COVID-19 was a short-term illness. World Health Organization (WHO) in February 2020, using preliminary data available at the time, reported the time from onset to clinical recovery for mild cases was approximately 2 weeks and that recovery took 3 to 6 weeks for patients with the severe or critical disease. More recently, however, it has become clear that in some patients debilitating symptoms persist for weeks or even months. In some of these patients, symptoms have never gone away **(2)**

Although the lungs are the first target organ of COVID-19 infection, accumulating evidence indicates that the virus may exhibit infections in different organs, including the heart, blood vessels, kidneys, gut, oral cavity, eyes, and brain **(3).**

According to the World Health Organization (WHO), the mortality rate of COVID-19 patients is 3% to 5%. Reports have suggested that patients who survive COVID-19 may experience impairment or prolonged symptoms in their overall health status after their acute phase recovery (4). According to the WHO, patients who recover from COVID-19 can have persistent symptoms such as fatigue, dyspnea, dry coughing, congestion or shortness of breath, loss of taste or smell, loss of hearing, body aches, diarrhea, nausea, chest or abdominal pain **(5).** Other complications include acute kidney injury with little evidence of renal failure and hepatic impairment in severely ill patients **(6).** Moreover, there have been records of changes in the clotting system, such as disseminated endovascular coagulopathy (DIC), decreased platelet count, and prolonged prothrombin time (PT). Additionally, hypercoagulability and potential thromboembolic disorders are a few of these patients' common manifestations **(7,8)**

Long term effect of covid -19

Persistent symptoms

It appears that fatigue is one of the most frequently reported symptoms that patients experience after recovery from acute SARS-CoV-2 infection. Carfi et al. report persistent symptoms in 143 patients evaluated after hospitalization due to COVID- 19 **(9).** An online-questionnaire-based study on 2113 post-COVID-19 patients reported only 0.7% of symptom-free subjects at 79 days after acute COVID-19 pneumonia**(10).** It also reported fatigue (87%) and dyspnea (71%) as the most prevalent symptoms at 79 days after onset of acute illness**(10).** A survey-based study consisting of post-discharged hospitalized subjects (n=143) found fatigue (53%), dyspnea (43%), loss of memory (34%), sleep disorders (30.8%), impairment of concentration (28%), and joint pain (27%) as the frequently reported persistent symptoms at 110 days after discharge from the

hospital(11). The other cardiopulmonary, musculoskeletal, gastrointestinal, and neuropsychiatric symptoms are reported in the multiple studies during the post-recovery phase between 60 to 180 days(12-15). Davis et al also revealed the probability of having prolonged symptoms of moderate, severe, and very severe category noted in 36.6%, 14.5%, and 5.2% of the Long-COVID-19 patients six months after the onset of acute illness. Further, it also stated that fatigue, dyspnea, and cognitive abnormalities (brain fog) as the major debilitating manifestations leading to the decreased quality of life(15).

Several observational series describe persistent symptoms in patients following acute COVID-19 with one-third or more experiencing more than one symptom (16). Common persistent physical symptoms include:

•Fatigue (13 to 87 %)- Dyspnea (10 to 71 %)- Chest pain or tightness (12 to 44 %)- Cough (17 to 34 %) . Less common persistent physical symptoms include anosmia, joint pain, headache, sicca syndrome, rhinitis, dysgeusia, poor appetite, dizziness (from orthostasis, postural tachycardia, or vertigo), myalgias, insomnia, hoarseness, alopecia, sweating, reduced libido, and diarrhea.

Three studies, two from China and one from France, reported on chronic or long COVID syndrome (17-19).The largest study on 1733 patients after a 6 month follow-up reported in 63% of patients fatigue or muscle weakness, 26% sleep difficulties, 23% anxiety or de- pression, up to 29% abnormal median 6-min walking distance and importantly, acute kidney injury (AKI) in 13% of patients without AKI at the acute phase (18).Another study that included 538 patients, 39% of them with critical or severe disease, showed that 49.6% of patients presented at least one symptom during follow up, with 28.3% reporting physical decline or fatigue, 39% respiratory difficulties, 21.4% dyspnea, 14.1% chest distress, 12.3% chest pain, 7.1% cough, 13% cardiovascular complications, 23.6% excessive sweating and 18.6% alopecia (17).

CT Change in Long Covid

Chest CT plays a crucial role in the diagnosis and follow-up of patients with COVID-19 pneumonia. Numerous studies have documented radiographic changes in the acute course of COVID-19, which range from mild to severe cases (20). Recent publications (21) have found that approximately 94% of hospitalized patients have persistent lung parenchymal findings on their discharge CT scans. In addition, Liu et al (22) reported that lung opacities in 53.0% of patients with mild COVID-19 resolved with no adverse sequelae within 3 weeks after discharge. A previous meta-analysis investigated lung sequelae of COVID-19 and demonstrated that more than half of the recovered patients still had chest computed tomography (CT) abnormalities 90 days after infection (23). In particular, ground-glass opacities(GGOs), parenchymal bands/fibrous stripes and reticulation were frequently observed. Furthermore, prospective studies have shown that patients with severe diseases tend to have long-term lung abnormalities more

frequently, and GGO and parenchymal bands take longer to resolve than consolidation or crazy-paving patterns **(24).**

Fibrotic changes seem to appear frequently in patients overcoming serious forms of disease, especially those who required intensive care unit (ICU) recovery, longer hospitalizations, and/or with a higher inflammatory load. It is not clear the role of the virus itself and adjuvants factors such as over-infections, far-toxicities, or mechanical ventilation **(25).**

Pulmonary sequelae

In patients with active COVID-19 infection, the major radiological findings include consolidation and ground-glass opacities (GGOs) predominantly in the lung peripheries and lower lobes along with other patterns such as interlobular and intralobular septal thickening, pleural effusion, pericardial effusion, bronchiectasis, bronchial wall thickening, reverse halo, subpleural lines and fibrotic bands **(26).**

Among these, the most common sequelae that have garnered attention is post-COVID-19 pulmonary fibrosis , while most others tend to regress after the acute infection subsides. In a study, it was reported that predischarge CT scans with GGOs were found in 79.2% of patients, which improved in follow-up scans, while fibrosis was seen in 44.8% scans and fibrous stripes in 36.8%. Fibrosis also showed improvement in follow-up scans in 65.3%, while fibrous stripes once developed did not improve in any of the scans **(27).**

In a systematic review published by **Polak et al, 2020 (28)** which studied pulmonary pathology findings of reported cases, fibrosis was seen in 22% of patients. In a study by **Xu et al, 2020 (29)** fibrinous exudates were seen in the alveolar lumen, which is reflected in radiological scans as fibrosis. Development of fibrosis can be rapidly progressive also, with advent as early as 10 days in a case report **(30).**

In postmortem analysis too, there has been evidence of fibrosis with honeycombing like interstitial lung diseases along with diffuse alveolar damage **(31).** Although these findings can be confounding due to ventilator-induced lung injury (VILI) however, with the use of lung-protective ventilation in most centers, fibrosis cannot be attributed only to VILI.

Post-COVID-19 fibrosis may present with shortness of breath and cough or can be asymptomatic owing to minimal scarring of the lung parenchyma. Since CDC advises clinical criteria for discharging patients and does not pay heeds to radiology, these patients might be overlooked and the symptoms might be attributed to deconditioning **(32).** It is imperative to look for post-COVID-19 fibrosis especially in patients with residual dyspnea after ruling out other differential diagnoses that can be seen post-COVID-19 infection including neuromuscular weakness, deconditioning and cardiovascular causes. There are various mechanisms implicated in the development of fibrosis secondary to COVID-19 infection. In the previous SARS pandemic, lung fibrosis as a sequelae to initial infection has been documented **(33).**

The proposed mechanism included the role of transforming growth factor-beta (TGF-β) and connective tissue growth factor, which were elevated in alveolar epithelial cells leading to fibronectin deposition in the extracellular matrix and hence fibrosis **(29).** There occurs a direct stimulation of TGF-β by the nucleocapsid protein of the SARSCoV-1 and since the nucleocapsid core of the SARS-CoV-2 is nearly 90% similar to SARS-CoV-1, this mechanism may hold true. Another postulated mechanism includes downregulation of ACE, which further downregulates angiotensin II leading to TGF-β stimulation. In addition, there seems to be an additional role of oxidative stress and free radical mediated lung injury, a finding similar to that seen in idiopathic pulmonary fibrosis (IPF).There seems to be a homology in the cytokine profiles of IPF and COVID-19 patients suggesting similar pathogenesis of lung fibrosis **(34).**

However, it is still unclear as to why some individuals have complete recovery of lung functions following an initial assault by the virus and why some have unregulated cellular proliferation with an abundant accumulation of fibroblasts leading to excessive deposition of collagen and extracellular matrix proteins **(35).** There have been some predisposing factors associated with the development of post-COVID-19 fibrosis as reported **Yu et al. 2020 (36)** The authors found that patients with lung fibrosis following initial infection were older with a median age of 54 years and had higher levels of inflammatory markers such as C reactive protein, lactate dehydrogenase and IL-6. In addition, these patients also had lower absolute lymphocyte counts, longer hospital stay, initial presentation with shortness of breath and higher respiratory rate, requirement of intensive care unit admission or requirement of longer antiviral therapy and pulsed steroid therapy. This study also found interstitial thickening, irregular interface, coarse reticulation and parenchymal band as early radiological predictors of development of fibrosis **(36).**

Future research perspective

Continuous profiling of the cytokine and chemokine expression levels within the lower airways (e.g., induced sputum) or peripheral blood will help understand the dynamics of residual inflammatory responses .The combination of chest imaging with high-resolution CT or functional magnetic resonance imaging with isotopes and lung function assessment (e.g., lung volume, diffusing capacity, exercise capacity) will provide clinicians an indispensable avenue for tracking the trend of changes in pulmonary functional abnormality**(37-40).**Further extension of the clinical observation is needed to reveal the long-term impact (e.g., 3-5 years) on symptom perception, lung function (particularly the exercise capacity), radiological characteristics, quality-of-life and psychology**(41-44).**

Conclusion

Overall, the available data suggest that a subset of patients who recover from acute SARS-CoV-2 infection will have longer-term sequelae from the disease, due to persistent symptomatology or prolonged organ dysfunction.

The full spectrum of the duration and severity of post-acute COVID-19 is currently unknown. It is quite possible that with the significant number of patients who have already contracted COVID-19 and ongoing disease transmission, post-acute COVID- 19 symptomatology and organ dysfunction could be an important area of resource utilization in the future.

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