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The Enigma: Chronic Coronavirus Lung Disease.

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ABSTRACT

A systematic review was conducted to address the growing concerns surrounding chronic symptoms and lung complications following COVID-19 infection. Nearly six years since the index case, COVID-19 has led to over 700 million cases globally [6,8], with a noticeable rise in post-COVID symptoms such as cough, breathlessness, fatigue, and brain fog. SARS-CoV-2 induces significant pulmonary inflammation, often progressing to acute respiratory distress syndrome (ARDS), particularly in those with pre-existing conditions like hypertension and type 2 diabetes mellitus. While short courses of corticosteroids have shown benefits in reducing mortality among patients with hypoxia, evidence suggests that chronic inflammation and lung fibrosis may persist despite treatment [4,17]. Elderly males with underlying health conditions are more prone to severe complications [1,3]. This review aims to consolidate existing data on the long-term pulmonary outcomes and the effectiveness of various interventions in mitigating post-COVID lung fibrosis and inflammation.
Keywords: Coronavirus, COVID-19, Chronic Lung Disease, Lung Fibrosis

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INTRODUCTION

The COVID-19 pandemic has profoundly reshaped our understanding of chronic lung diseases (CLD), revealing new challenges and opportunities in their diagnosis, management, and prevention. Chronic lung conditions such as chronic obstructive pulmonary disease (COPD), asthma, interstitial lung disease (ILD), and post-acute sequelae of SARS-CoV-2 infection (PASC) have been disproportionately affected by COVID-19, given the respiratory tropism of the virus and its potential to exacerbate underlying conditions. Moreover, emerging evidence highlights the bidirectional relationship between CLD and COVID-19, with preexisting lung diseases worsening COVID-19 outcomes, while COVID-19 itself may predispose individuals to long-term pulmonary sequelae [9,12]. The interplay between viral-induced inflammation, immune dysregulation, and structural lung damage [2,11] underscores the need for a deeper understanding of CLD in the context of COVID-19. This review aims to synthesize current insights into the impact of COVID-19 on CLD, offering a foundation for improved clinical strategies and future research directions.

METHODOLOGY

Literature Review Strategy

Literature was reviewed systematically using the widely accepted PRISMA guidelines [20]. After considerable deliberation 19 articles were selected from PubMed, Scopus and Google Scholar. The total number of articles found from Pubmed were 3381, Scopus were 2506 and GoogleScholar were 7260. The search plan comprised of using appropriate keywords along with the Boolean operators like “AND” as well as “OR” depending on the nature of the search. The primary keywords used were “COVID” or “COVID-19” or “LONG COVID” AND “CHRONIC” or “FIBROSIS”.

Inclusion Criterion

Articles included in the systematic review met all the following criteria:

- Articles matched with the above keywords, from the listed databases.
- Articles with human participants
- Articles with final outcomes
- Articles in English language

Exclusion Criterion

Studies that didn’t match the inclusion criteria or had any of the following:

- Articles with individuals having pre-existing lung disease malignant or non-malignant.
- Articles with individuals have systemic conditions that may affect respiration. (Cancers, Cardiovascular Disease, Thyroid Disease, Sleep Apnea etc.)
- Pay to access articles or articles outside the above-mentioned databases
- Articles written in foreign languages.

Methods

PRISMA guidelines were utilized to conduct a thorough review of literature. (Figure 1)

DISCUSSION

Given the extensive number of SARS-CoV-2-infected patients, it is imperative to determine the prevalence of Long COVID Interstitial Lung Disease (LC-ILD). Comprehending the natural course of the disease is essential for determining its chronicity and diagnosing it accurately. The disease typically starts with transient inflammation and progresses towards a state of progressive and long-term fibrosis. Understanding

this progression is vital for effective diagnosis and management. Early suspicion and detection play a crucial role in preventing the progression of the disease to an irreversible stage. Exploring the anticipated trajectory of LC-ILD, identifying related risk factors, and researching biomarkers associated with outcomes like disease progression will facilitate the formulation of targeted treatment approaches, such as immunomodulation or antifibrotic therapy.

Although the diagnosis of COVID-19 is often based on pneumonia symptoms (e.g., dry cough, fatigue, myalgia, fever, and dyspnea) and recent travel history to China or exposure to known patients, chest imaging plays a crucial role in disease assessment and follow-up.

Chronic COVID-19 pneumonia may result in clinically significant restrictive pattern alterations in pulmonary function tests. Notably, pulmonary function recovery in COVID-19 patients differs from that observed in other cases of atypical pneumonia. Although pulmonary function tests show significant improvement within the first three months of post-infection, no further significant improvement is observed from three to six months. Patients who experienced ARDS or required Intensive Mechanical Ventilation during their COVID-19 illness tend to experience more significant impairment in respiratory function and exercise capacity post-recovery. For these individuals, respiratory rehabilitation and a gradual increase in physical activity have proven effective in swiftly restoring normal functional parameters.

Elevated mortality rates have been noted among patients with ILD, even after accounting for factors such as age, sex, race, smoking status, cardiovascular disease, and chronic immunosuppression. Further analyses have indicated that neither oxygen supplementation, corticosteroid use alone, nor other forms of chronic immunosuppression altered the significance of the relationship between ILD and the likelihood of death.

Studies indicate that between 31% and 69% of individuals who have recovered from COVID-19 may experience persistent symptoms in the long term [6,8]. Typically, these symptoms encompass fatigue (29%), muscle pain, palpitations, cognitive impairment (28%), dyspnea (21%), anxiety (27%), chest pain, and arthralgia (18%). Long COVID primarily affects the respiratory system due to the initial infection of the alveolar epithelium by SARS-CoV-2, which triggers chronic inflammation responses sustaining the production of inflammatory cytokines and reactive oxygen species (ROS). [11,14] Moreover, the disruption of cellular integrity triggers the activation of fibroblasts, which deposit collagen and fibronectin, ultimately resulting in fibrosis of lung tissue. As time progresses, viral-induced complement activation and subsequent disruption of coagulant pathways contribute to prolonged inflammation and a hypercoagulable state, thereby increasing the risk of thrombosis.

Any infection, whether bacterial or viral, has the potential to induce injury and apoptosis in airway epithelial cells, thus influencing the host's response to damage. There is considerable evidence indicating a strong association between respiratory viral infections and the development of pulmonary fibrosis. Previous viral epidemics like influenza and SARS have been extensively researched, shedding light on the mechanisms underlying post-viral lung fibrosis, and offering valuable insights for managing the current uncertain scenario. COVID-19's pathophysiology is diverse but involves a dysregulated and disproportionate immune response, particularly in cytokine production [18]. Uncontrolled release of pro-inflammatory cytokines, including Interleukin (IL)-1β, IL-6, IL-8, IL-17, and Tumor Necrosis Factor (TNF), by immune and non-immune effector cells contributes to disease severity. Recent organoid models have provided novel platforms for studying SARS-CoV-2 pathogenesis [10]. Additionally, the role of complement activation in COVID-19 pathogenesis is increasingly acknowledged. Although information on adaptive immune responses in COVID-19 is limited, it is hypothesized that T cell reduction and functional exhaustion during SARS-CoV-2 infection may occur, indicating the virus's immunosuppressive capabilities. ICU-hospitalized patients show increased incidence of autoimmune disorders post-COVID [13], suggesting systemic immune dysregulation.

Two iatrogenic factors that could potentially contribute to fibrosis in severe cases of COVID-19 pneumonia are oxygen toxicity and ventilator-induced lung injury (VILI). Individuals who develop post-COVID fibrosis usually exhibit severe illness with significant bilateral lung involvement from the outset, frequently necessitating prolonged exposure to high levels of oxygen during the acute phase of their condition.

Prolonged exposure to elevated concentrations of oxygen can result in heightened production of oxygen-derived free radicals, which can cause damage to the pulmonary epithelium.

The availability of a set of biomarkers independent of symptoms would be beneficial for diagnosing Long COVID. Recent studies suggest that IgM and IgG3 immunoglobin profiles are associated with an increased risk of developing Long COVID. IgM and IgG3, released by B cells in response to interferon induction and IL-4 signaling, may be impaired in interferon synthesis, contributing to inefficient IgG isotype switching and dysregulated immunity [8,16].

Emergency radiology played a crucial role in early COVID-19 diagnosis and severity stratification [15]. Chest radiography typically reveals patchy or diffuse asymmetric airspace opacities [image (A)], akin to other causes of coronavirus pneumonia. Initial chest CT scans of individuals with COVID-19 often reveal bilateral lung involvement [image (B)]. In ICU patients, a consolidative pattern is commonly observed, whereas non-ICU patients typically display a predominantly ground-glass pattern. The prevalence of CT abnormalities varies depending on initial lung involvement severity and time since infection. Residual lung abnormalities may include fibrosis, thickening, honeycombing, cystic changes, and bronchial dilation [image (C) & (D)]. [5,7]

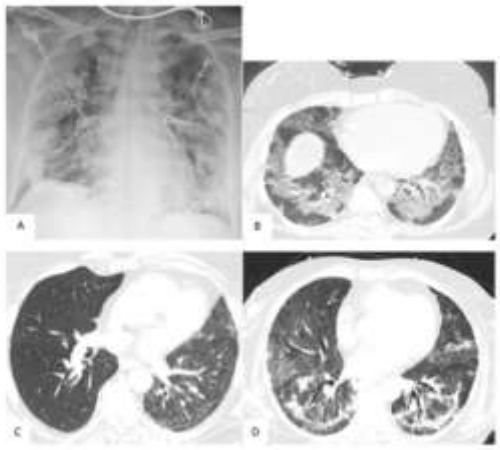

Image (A): Chest X-ray with bilateral airspace opacities. Image (B): Chest CT with bilateral ground glass opacities. Image (C) & (D): Chest CT with bilateral fibrosis.

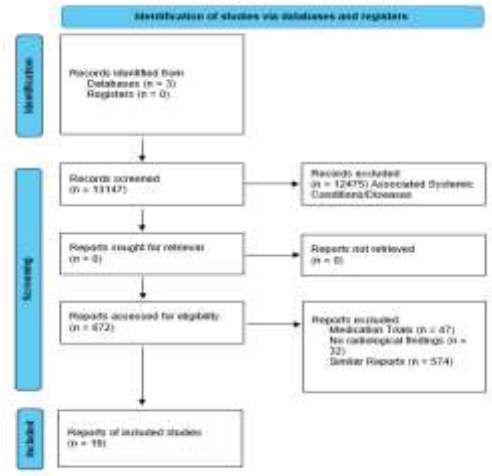

Figure 1: PRISMA Consort Flow Diagram

CONCLUSION

Amidst the ongoing rise in COVID-19 cases again and the widespread infection affecting millions, the long-term implications of the disease are a cause for serious concern. Prospective cohort studies confirm persistent pulmonary abnormalities in 30-40% of survivors at 12 months [19]. This review delves into studies examining the persistent symptoms of long-term COVID, along with potential risk factors contributing to its development and treatment options aimed at alleviating its symptoms. However, the enigma surrounding COVID persists, largely due to uncertainties surrounding the impact of new variants of COVID-19 on its incidence and severity. It is crucial for research efforts to persist in unraveling the post-COVID-19 syndrome. A deeper understanding of its pathogenesis, risk factors, symptoms, and treatment modalities is essential to ease the burden on individuals grappling with the condition and the healthcare systems tasked with their care.

Abbreviations list

- COVID-19 – Coronavirus Disease 2019
- ARDS – Acute Respiratory Disease Syndrome
- SARS-CoV-2 – Severe Acute Respiratory Syndrome Coronavirus 2
- DAD – Diffuse Alveolar Damage
- ILD – Interstitial Lung Disease
- CLD – Chronic Lung Disease
- LC-ILD - Long COVID Interstitial Lung Disease
- ROS – Reactive Oxygen Species
- PRISMA – Preferred reported items in systematic reviews and meta-analysis

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