



A REVIEW OF POST COVID19 PULMONARY FIBROSIS

Respiratory Medicine

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ABSTRACT

Background Infection by COVID- 19 can affect a range of clinical sequels, from asymptomatic to severe life-threatening course or death. The development of pulmonary fibrosis is accounted one of the key concerns regarding COVID- 19 pulmonary sequelae as it's associated with architectural deformation of the lung parenchyma and overall impairment of lung function resulting in reduced quality of life. **Aim** The purpose of this review is to present the existing evidence-based literature on the association between Covid 19 and lung fibrosis. **Methods** An extensive search of all materials related to the topic was carried out in the PubMed. Keywords used in the search include calcium and hypertension. A total of 2,563 articles were found, out of which a total of eleven studies similar to the current study objectives and publicly available for free were included in the study and analyzed. **Conclusion** Most of the studies showed a positive correlation between Covid19 and lung fibrosis. The studies are sparse, and the included studies had smaller sample sizes. Hence, more large-scale clinical studies are needed to determine the clinical significance of Covid19 and lung fibrosis.

KEYWORDS

COVID 19, Lung Fibrosis

INTRODUCTION

Since November 2019, the raging coronavirus disease (COVID-19), which was caused by the SARS-CoV-2 infection, has raised public health concerns on a global scale. The global impact of COVID-19 has been quite negative (1).

Infection by COVID- 19 can affect a range of clinical sequels, from asymptomatic to severe life-threatening course or death. Characterization of epidemiological, clinical, and co-morbid features with recovery and mortality of COVID- 19 is vital for the development and perpetuation of effective control strategies and operation protocol. Current estimates are that the incubation period is generally 3 to 7 days, and over to 14 days(1).

Symptoms of COVID- 19 infection in the prodromal phase include fever, dry cough, and malaise, which are nonspecific(2). Some cases may not have any egregious symptoms. Thus, CT and HRCT represent precious tools in relating cases with COVID- 19 infections in an early stage when clinical symptoms may be non-specific. For every speculated case, chest CT is necessary for definitive diagnosis and retrospective. The clinical and imaging manifestations in the early stage of COVID- 19 are particularly significant. They can be employed to validate the diagnosis, tailor the treatment design, and decide the prognosis(3).

Coronaviruses are a big family of different viruses. Some of them bring about the common cold wave in people. Others infect animals, including bats, camels, and cattle. There have been multiple investigations to determine the origins of SARS- CoV- 2 but none have been clear(4). The previous coronaviruses, the Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS) unfolded from bats(5).

The virus first showed up on a small scale in November 2019 with the first large cluster appearing in Wuhan, China in December 2019. It was first documented that humans were infected at Wuhan, China's open-air wet markets. As SARS- CoV- 2 spread both inside and outside China, it spread to people who never had primary contact with animals(6). That denoted the virus is transmitted from one human to another.

The first identified human coronavirus was in 1965(7). It's the common cold. SARS- CoV- 2 is an RNA virus. While the virus gets adjusted to its new hosts, they are prone to genetic evolution and the development of mutations over time. Thus resulting in a new mutant variant that might have distant characteristics when compared to its older strains.

The purpose of our study is to characterize the clinical features, biomarkers and HRCT features in cases with COVID- 19 infection descriptively and for early identification and early isolation. We also aimed to explore the change in HRCT findings based on duration of complaint and whether there was a correlation between clinical features, biomarkers, and imaging features in the course of the illness. Since the commencement of the COVID- 19 outburst, more than 293 million people have been infected worldwide, of whom 256 million have recovered. As the number of recovered patients is increasing, it's obligatory to acquire information about pulmonary sequelae that can persist or develop after the initial recovery at least 4 weeks post-COVID-19 onset(8).

The development of pulmonary fibrosis is accounted one of the key concerns regarding COVID- 19 pulmonary sequelae as it's associated with architectural deformation of the lung parenchyma and overall impairment of lung function resulting in reduced quality of life. Many studies have been carried out on PCPF; however, their results have been assorted in some aspects(9).

The pathogenic sequence of fibrosis post-COVID-19 is considered to be multifactorial.

METHODS

An extensive search of all materials related to the topic was carried out in the PubMed. Relevant research articles focusing on the association between serum calcium levels and hypertension published in the period 2021 - 2022 were included in the review. A total of 386 articles were found, out of which a total of seven studies similar to the current study objectives were included in the study and analyzed. Keywords used in the search include calcium and hypertension.

Post-COVID-19 Pulmonary Fibrosis

Since the commencement of the COVID- 19 outburst, more than 293 million people have been infected worldwide, of whom 256 million have recovered. As the number of recovered patients is increasing, it's obligatory to acquire information about pulmonary sequelae that can persist or develop after the initial recovery at least 4 weeks post-COVID- 19 onset(8).

The development of pulmonary fibrosis is accounted one of the key concerns regarding COVID- 19 pulmonary sequelae as it's associated with architectural deformation of the lung parenchyma and overall impairment of lung function resulting in reduced quality of life. Many studies have been carried out on PCPF; however, their results have been assorted in some aspects(9).

The pathogenic sequence of fibrosis post-COVID-19 is considered to be multifactorial. Whatever the cause, fibrosis is considered to be due to the aberrant healing of the injured lung parenchyma(10).

In COVID- 19 patients, possible origins of injury include cytokine storm due to inappropriate inflammatory response, bacterial co-infections, and thromboembolic events causing microvascular damage and endothelial dysfunction. The renin-angiotensin system is also accepted to be involved due to the high affinity of SARS- CoV- 2 viral spike protein to the angiotensin-converting enzyme- 2(ACE2) receptor(11).

To date, PCPF does have any proven treatment, which makes the condition even more dangerous and concerning. However, anti-fibrotic drugs may be used to reduce pulmonary injury in cases with severe COVID- 19(12). Previous studies have been quite indiscriminate regarding the prevalence of PCPF.

Aul et al. reported a low prevalence of 9.3% in their study population(13). Meanwhile, the rest of the available studies have reported a much higher prevalence, ranging from 25.5% to 84.15%(14), with the highest being reported by Zou et al(15). The overall prevalence of PCPF in all the studies was around 44.9%, which is lower than the SARS epidemic but higher than MERS.

The fibrotic patients had a mean age of around 59 years but patients with no fibrotic changes had a mean age of only 48.5 years(16). COVID-19 is seen as more common in older age. A meta-analysis on post-covid-19 fibrosis by BJH Amin noted that fibrosis was more common in the older age group and the mean age of lung fibrosis was 59 years(17).

A review by Shirley V.Sylvester et al which came out early in 2022 published post-covid-19 lung fibrosis was more common in a female who was more than 60 years old (18).

Parul Mrigpuri et al and Shital Vishnu Patil et al, found that with a history of diabetes prevalence of lung fibrosis was common when compared with nondiabetic patients(19).

A study by RMM Ali et al found systemic hypertension to be a risk factor for lung fibrosis post-Covid-19(17).

Smoking is associated with a lot of chronic lung diseases like chronic bronchitis, emphysema, and pulmonary fibrosis. Smoking is associated with an increased level of inflammatory cytokine and it also produces oxidative stress which would lead to pulmonary fibrosis. Most of the studies including a meta-analysis done by Vardavas et al and Nikitara **et al showed that patients with a history of smoking have 1.4 times more risk of developing lung fibrosis(20).**

According to two studies by Han et al. and Aul et al., recovered COVID- 19 patients who have developed pulmonary fibrosis, suffer from persistent symptoms, which include dyspnea, cough, chest pain, fatigue, and myalgia more frequently when compared to non-fibrotic patients(14,21).

According to the literature, pulmonary fibrosis can even develop right after discharge or several weeks later. However, a lot of these cases have been reported as having improved in a few months after COVID-19 recovery(22).

In their study, Zou et al showed that 30-, 60-, and 90- day follow-ups of PCPF patients have confirmed that pulmonary fibrosis in some patients will improve over time; however, most fibrosis in the majority of the patients won't resolve. In another study by Nabahati et al, a 6th-month follow-up of PCPF patients showed that in 33.9% of the patients, pulmonary fibrosis had nearly decreased in comparison to 3- month follow-up CT scans; however, in 66.1% of the patients, no sizable changes were witnessed(23).

In a follow-up study by Han et al., it was observed that even after 1-year post-COVID-19, the majority of the fibrotic patients had persistent pulmonary fibrosis. The exact explanation why some patients heal after the affliction done to them during COVID- 19 and others evolve pulmonary fibrosis is yet to be known.

The reported other risk factors for PCPF are invasive and non-invasive

mechanical ventilation, a CT score of more than 18, ICU admission, and a long hospital period. Furthermore, Zou et al. found that critically ill COVID- 19 patients develop more severe PCPF(8).

Even though it has been suggested that steroid therapy prevents irreversible lung injury, the current meta-analysis showed that PCPF was more common in those cases who had received steroid treatment by three folds. Among the lung anomalies found in fibrotic patients, parenchymal bands, interlobular septal thickening, and uneven reticulations have been described to be the most frequent CT findings(14).

Studies done by Patil et al & BJH Amin et a(24,25) have noted that higher incidence of pulmonary fibrosis in patients requiring NIV early during the admission and prolonged duration.

HRCT chest for diagnosis of Covid -19 has a sensitivity of 80% to 90% and specificity of 83% to 96% which is better than the RT-PCR(26). The DUTCH Radiological Society developed the CO-RADS score (COVID-19 Reporting and Data System) a standardized scoring system to access the pulmonary involvement in patients who are affected by Covid-19. Higher CORADS scores have been linked to the worst prognosis and need for invasive ventilation. Similar findings were noted in the study done by R Yasin et al(27).

LDH (Lactate Dehydrogenase) is an enzyme that is very important in anaerobic metabolism(28). There are multiple conditions where LDH would be elevated like hemolysis, hematological malignancy, rhabdomyolysis, fractures, and sepsis(29). Researchers have found that the COVID-19 virus causes the activation of Inflammasomes which leads to pyroptosis, fibrosis, and elevated LDH level(30). Xiao-Ting et al found that most of the patients with pulmonary fibrosis presented with high LDH (31).

Ferritin is proven to be an acute phase reactant and has been proven to raise in conditions like sepsis and inflammation(32). Inflammatory cytokines and tissue destruction cause a raise in ferritin levels, thus leading to pulmonary fibrosis. Liu et al. and Yasin R. et al found that most of the patients with pulmonary fibrosis presented with high ferritin levels(33).

D-dimer is a by-product when a blood clot begins to break(34). D-dimer is raised in conditions like pulmonary embolism, deep vein thrombosis, and disseminated intravascular coagulation. D.K Rai et al found that most of the patients with pulmonary fibrosis presented with high d-dimer levels. (35).

C-Reactive Protein is a pentameric protein that is synthesized in the liver(36). CRP level increases in response to inflammation(37). CRP levels rise and fall immediately by applying and removing inflammation stimuli CRP. Persistently high CRP levels are seen in the case of chronic inflammation. Colarusso C et al found **that** most of the patients with pulmonary fibrosis presented with high CRP levels.(38)

Interleukin 6 (IL6) is both a pro-inflammatory cytokine and an anti-inflammatory myokine IL6(39). It is an important mediator for fever, acute phase reactant protein, and the production of neutrophils. Early studies have noted that elevated IL6 in COVID-19 patients had poor prognoses. J.N.Zuo et al found **that** most of the patients with pulmonary fibrosis presented with elevated IL6 levels(40).

A patient with severe symptoms and who require NIV or invasive ventilators are only admitted to ICU. Data from China during the early outbreak of covid-19 was 12 to 14%(95). A similar result was not in a study done by S.R Desai found **that** most of the patients with pulmonary fibrosis had a long ICU stay of more the 10 days(41).

CONCLUSION:

As a tsunami comes after an earthquake, pulmonary fibrosis comes after COVID-19 pneumonia. Our review article found lot of positive correlation between Covid-19 and pulmonary fibrosis. The studies are sparse, and the included studies had smaller sample sizes. Hence, more large-scale clinical studies are needed to determine the clinical significance of Covid19 and lung fibrosis.

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