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Post COVID-19 interstitial lung disease- A systematic review

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A B S T R A C T

Background: The novel Coronavirus SARS-CoV-2 that broke out in December 2019 became the main source of morbidity and mortality around the world. As efficient vaccines and medicines started to emerge , it became necessary to recognize and proactively deal with the long term respiratory difficulties that arise due to extreme illness. Patients with extreme Coronavirus pneumonia have the tendency of advancing to Interstitial Lung Diseases (ILD) and persistent pulmonary vascular disease. In this paper, we shortly review the pathophysiology of interstitial lung disease (ILD), lung injury resulting from serious Coronavirus disease. We also outline the potential viral and secure intervention processes for stopping the advancement of Post-Coronavirus pulmonary Fibrosis (PCPF). Post-Coronavirus pulmonary fibrosis is presently treated in only symptomatic patients, which is, to a great extent, a neglected perspective. Before this lethal illness can be treated, it has to be fully researched clinically in order to know its danger in Coronavirus survivors. Strong clinical and research biomarkers ought to be considered in order to know the subgroup of patients that will deteriorate or advance to post Coronavirus interstitial lung disease. Customized medication is a decent method that can be used to treat patients with Post Coronavirus interstitial lung diseases.

Keywords: COVID-19; Interstitial Lung Disease; Fibrotic Pulmonary Disease; Infection

Introduction

In late 2019, a novel Covid, serious intense respiratory condition coronavirus 2 (SARS-CoV-2), arose in Wuhan, China, from where it spread all around the world, contaminating more than 31 million individuals. The clinical course of its contamination seems, by all accounts, to be an incredible factor: it starts from asymptomatic to serious pneumonia with multiorgan failure that needs to be given attention. At the time this study was done, around 1,122,036 individuals were known to have died due to the disease, yet there are few studies on the disease survivors. Lung injury is a prevalent component of intense SARS-CoV-2 disease, and it is important to understand its long term implications given the number of infected patients.

Serious acute respiratory disorder Coronavirus-2 (SARS-CoV-2), the infection behind one of the most shocking pandemics of the century, leaves a path of decimating pulmonary fibrosis among the infection survivors. There is a great deal of research on its pathophysiology, clinical course and management. Specific attention is given to its treatment modalities. At present, only patients wiht post-Coronavirus pulmonary fibrosis that are symptomatic are treated, and it is generally not given much attention.

Coronavirus has diverse bad effects, ranging from mild upper respiratory tract manifestations to extreme intense respiratory distress conditions.[1] The people at high risk of contracting serious Coronavirus are the aged, males and patients with diabetes and hypertension.[2] After the outbreak of Coronavirus, a large number of patients that survived and tested negative for it still experienced its manifestations. This increased the significance of dealing with this Coronavirus sequelae. Coronavirus sequelae could start with a mild type of fatigue followed by serious conditions, that require long haul oxygen treatment or even lung transplantation attributable to pulmonary fibrosis.[3]

Preceding Covid-19 pandemic was associated with impressive post-viral fibrosis and physical disabilities. It is obligatory to regularly follow-up patients after they recover from Coronavirus.[4] Coronavirus prompts different types of respiratory diseases with a high event of intense respiratory distress conditions.[5]

It was predicted that the heap of fibrotic pulmonary changes following SARS-CoV-2 infection was probably going to be high, and the worldwide burden of fibrotic pneumonic infection would increase altogether.[6] Fibrosis does not always occur after other viral pneumonia and has never been said to occur after H1N1 pneumonia. Fibrotic changes have been observed in about 8% of patients with SARS and 20% of patients with H7N9 flu.[7]

Around 92 million individuals were infected by Coronavirus due to the pandemic, while many people were mildly infected . It was predicted that around 15% would have extreme Coronavirus pneumonia, and 5% would advance to ARDS. This implies that practically 4.8 million people would have severe pulmonary issue. However, most of them would be cured without having lung damage. It is most likely that a significant number of patients would suffer residual sequelae.[8] Despite that, there was no certifiably demonstrated treatment for post-Coronavirus aspiratory pulmonary fibrosis during the time this study was done. Using harsh treatment for the lungs with fibrosis in the early intense period of serious infection with ARDS might it.[9]

Diao et al.[10] showed that significant intense extra pulmonary appearances can happen in essentially any organ (Figure 1).

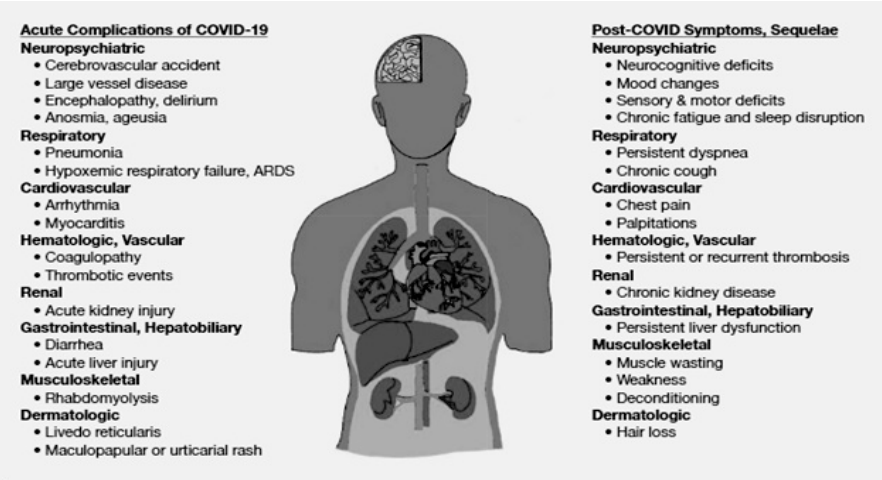

Figure 1. Model of intense pneumonic and extrapulmonary difficulties due to Covid-19 infection with projected post-Coronavirus side effects and end-organ sequelae.[10]

Post-COVID Interstitial Lung Disease (PC-ILD)

Interstitial Lung Disease (ILD) is an umbrella term utilized for many groups of infections that cause scarring (fibrosis) of the lungs. Scarring causes the lungs to be solid which makes it hard to inhale and get oxygen to the circulatory system. Lungs that are harmed by ILDs are frequently irreversible and deteriorate over a long time.[11]

Interstitial Lung Disease (ILD) optional to Coronavirus is believed to be brought about by different pathologies; for example, unnecessary cytokines and abnormal repair processes elaborated by lung cells (epithelium, mesenchyme, and alveolar macrophages) after lung injury rather than the viral attack itself.

This review examines post-Coronavirus interstitial lung infection (PC-ILD), a condition that is prone to be more regularly experienced in the future. Lung injury is an overwhelming component of intense SARS-CoV2 infection, and it is important to understand its longer-term consequences given the number of infected patients. The most well-known radiological example of an intense infection with SARS-CoV2 is of reciprocal ground-glass opacification with or without a union in a sub-pleural conveyance. Also, a radiological and histological example of sorting out pneumonia design is portrayed in many instances .[12,13] Radiological findings show the disease as it progresses. Persistent CT abnormalities beyond day 14 of symptoms and up to day 37 have been reported.[14,15]

Types of Interstitial Lung Diseases

All types of interstitial lung diseases cause the interstitium to thicken. This can occur from aggravation, scarring, or the development of liquid. A few types of ILD last for a brief time (acute); others last long (chronic) and do not disappear. Examples of interstitial lung diseases include the following:

Interstitial pneumonia. Microbes, infections, or organisms can infect the interstitium. A microorganism called mycoplasma pneumoniae is the most well-known cause of the infection.

Idiopathic pulmonary fibrosis. This makes scar tissue to develop in the interstitium. Specialists do not know what causes it.

Non-specific interstitial pneumonitis. This is an interstitial lung infection that regularly affects individuals with immune system conditions like rheumatoid joint pain or scleroderma.

Hypersensitivity pneumonitis. This happens when residue or different things that are inhaled disturb the lungs.

Cryptogenic organizing pneumonia (COP). COP is a pneumonia-like interstitial lung disease without an infection.

Acute interstitial pneumonitis. This is an abrupt, serious interstitial lung infection. Individuals who have it are connected to a ventilator machine that relaxes them.

Desquamative interstitial pneumonitis. This is an interstitial lung infection that is partially caused by smoking.

Sarcoidosis. This causes interstitial lung illness alongside enlarged lymph hubs. It can likewise affect the heart, skin, nerves, and eyes.

Asbestosis. This is an interstitial lung infection caused by inhaling asbestos, a fiber utilized in building materials.

Interstitial Lung Disease Symptoms

The most well-known indication of all types of interstitial lung infections is shortness of breath. Nearly everybody with ILD will have breathlessness, which can deteriorate over a long time.

Other symptoms of interstitial lung disease include:

Cough, which is usually dry and does not have mucus.

Weight Loss, most often in people with COP or BOOP.

Decreased exercise tolerance

Fatigue

With most types of ILD, windedness grows shortness of breath gradually (over months). People with interstitial pneumonia or intense interstitial pneumonitis experience the side effects quickly (in hours or days).

Causes and Risks of Interstitial Lung Disease

The causes of most interstitial lung infections are obscure.

Microscopic organisms, infections, and parasites can cause interstitial pneumonia. People that inhale things that disturb their lungs can get ILD . These things include:

Asbestos

Proteins from exotic birds, chickens, or pigeons

Coal dust or various other metal dusts from working in a mining company

Grain dust from farming

Silica dust

Talc

Certain drugs can cause ILD, though it is rare. They are:

Some antibiotics, like nitrofurantoin

Some anti-inflammatory drugs, like rituximab

Chemotherapy drugs like bleomycin

Heart medications such as amiodarone

Management and Treatment

ILD treatment is intended to protect the lung's capacity to work very well and prevent the illness from deteriorating. Treatment is based on many factors , including the kind of ILD and how extreme it is. The treatment includes:

Medications: Drugs can help to further develop the lung function by diminishing irritation as well as fibrosis. Prescriptions for decreasing aggravation include steroids (prednisone) and other rheumatologic drugs, including mycophenolate (CellCept), azathioprine (Imuran), leflunomide (Arava), rituximab (Rituxan), cyclophosphamide (Cytoxan), tacrolimus (Prograf) etc. Medications used to stop further fibrosis include pirfenidone (Esbriet) and nintedanib (Ofev).

Oxygen therapy: Additional oxygen conveyed through a cylinder in the nose can make breathing simpler. This treatment raises the blood oxygen levels, so every breath is more useful.

Pulmonary and exercise therapy: Breathing activities and expanded active work can heal the lung.

Lung transplant: Certain individuals with serious instances of ILD have lung transfers to delay their death.

Complications of interstitial lung disease

Many individuals with ILD experience difficult breathing and a kind of cough that does not disappear. In more extreme cases, entanglements of the lungs can be perilous, leading to hypertension, right cardiovascular breakdown, and respiratory failure. This can occur because the lungs do not convey sufficient oxygen to the body.

Prevention of interstitial lung disease

It is basically impossible to forestall idiopathic or hereditary ILD; however, it is feasible to forestall a portion of the kinds with known causes. The risk can be diminished in the following ways:

Wearing a respirator (a veil that channels particles from the air) around unsafe substances, like asbestos, metal cleans or synthetics.

Quitting Smoking.

Receiving immunizations for flue and pneumonia to help protect the lungs.

Post-COVID conditions

Regarding CDC (2019), the vast majority of people with Coronavirus improved not long after they had the disease, but certain individuals experienced post-Coronavirus conditions. Post-Coronavirus conditions are a wide scope of new medical issues that progress or return in individuals, and they can be experienced by people for at least a month after being infected with the virus that causes Covid -19.[16]

As indicated by CDC [2019] report, individuals who do not manifest the symptoms of Coronavirus in the days or weeks after being infected can have post-Coronavirus conditions. These circumstances can present as various sorts and mixes of medical issues for various periods.

These post-Coronavirus conditions may likewise be known as long-haul COVID, post-intense Coronavirus, long haul impacts of Coronavirus, or chronic Coronavirus (ADA, 2021).[17]CDC,[16] and specialists all over the planet are attempting to look into short-and long haul wellbeing impacts related to Coronavirus, who gets it, and why.

Post-COVID Pulmonary Fibrosis

The most widely recognized lung issue that is looked at for in a post-Covid patient is lung fibrosis. Clinical recovery is by and large complete in mild-to-moderately severe COVID-19 cases; however very few patients with extreme infection might proceed to lung fibrosis. The groups of patients at very high risk of migrating to lung fibrosis are the older, particularly those requiring ICU stay and mechanical ventilation. There is no definitive treatment that can be used for this pulmonary fibrosis till date, even though different options are being investigated.

An analysis of PCPF ought to be found in clinical, radiologic, and pathologic data. Lab tests, pulmonary function tests (PFTs), as well as high-resolution CT (HRCT) done for a patient who had Coronavirus infection or is suspected of having it might give proof to help determine PCPF. Considering current conditions (deficiencies of individual defensive gear personal protective equipment (PPE), clinical suppliers, and procedural space), it is hard to legally look for high-hazard, spraying systems, for example, bronchoscopy or careful lung biopsy, particularly since these would not change the management in the acute setting.[18,19] Until this point in time, there were no solid information on the recurrence and seriousness of PF related to Coronavirus.

Few recent studies on Coronavirus have portrayed patients with lingering radiographic anomalies with steady pulmonary fibrosis[20,21]and corresponding discoveries of

fibrotic highlights on histopathology.[22] Among 90 Coronavirus patients that were hospitalized, the larger part had residual mild to significant pulmonary changes on CT when they were discharged, a median of 24 days after manifestation onset.[20] A few authors have classified PCPF diagnosed radiologically as broad and persistent fibrotic changes, including parenchymal bands, unpredictable points of interaction, reticular opacities, and foothold bronchiectasis with or without honeycombing.[23] Different studies demonstrated that some subsequent CTs showed broad fibrosis altogether.[21] Since there is no single test that demonstrates the conclusion, it might be that these radiologic changes happened transiently alongside the ongoing Coronavirus infection. There are a few varieties in presentation and severity, yet cases commonly present with reciprocal GGOs,[24] later advancing to fibrosis with negative Covid-19 tests. In a methodical survey of 131 pneumonic samples from Coronavirus patients, three histologic examples of lung injury were distinguished and frequently observed to cover: epithelial, vascular, and fibrotic changes. In a post-mortem examination study, the fibrosing DAD design was seen most normally and ordinarily showed either alveolar conduit fibrosis or diffuse thickening of alveolar walls.[25]

Etiology and Pathophysiology

Expected contributing etiologies for PCPF involve viral pneumonia and pneumonitis[26-29]; ARDS from Coronavirus pneumonia and Coronavirus related sepsis[27-31]; injury (delayed mechanical ventilation (MV)[26,31-33]; thromboembolism[28]; hyperoxia[28,34,35]; and dysregulations in the immune response[26-31](Figure 2). These variables might cover injury from MV that is not required for PCPF to happen.[29] There has been some conversation on P-SILI (patient-self-instigated lung injury), a type of lung injury that is thought to happen from early ARDS, in which strong unconstrained breathing exertion might add to lung damage. It is assumed that this can influence the timing of intubation.[36,37]

Patterns of Progression of PCPF

One case series archived the requirement for lung transplantation for presenting ARDS fibrosis, which is Coronavirus option. However, these patients had serious ARDS and delayed MV (>3 weeks). Indeed, even after various negative virology tests, these patients showed an

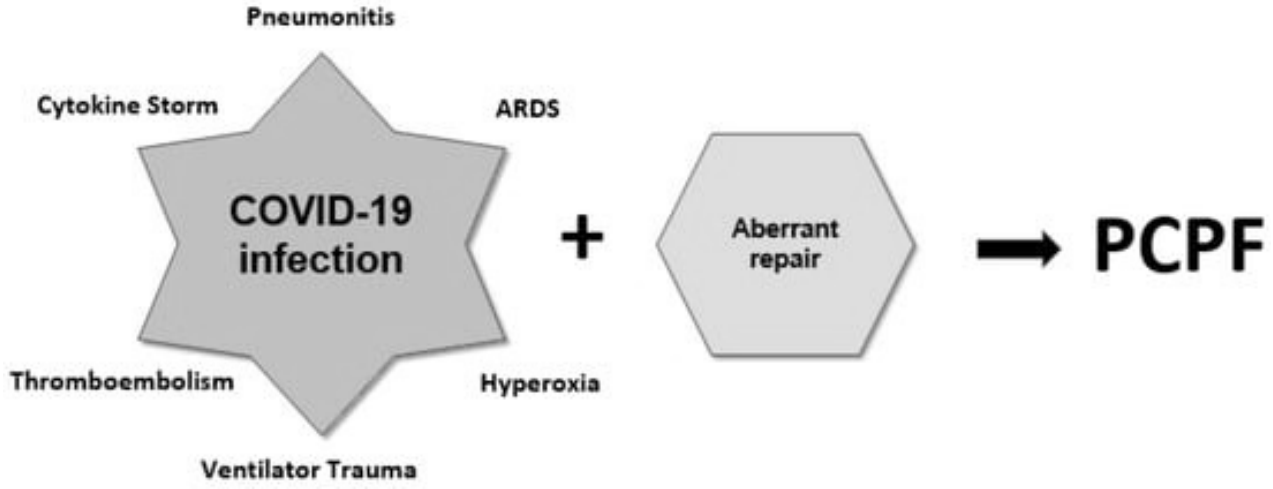

Figure 2. Injury → Inflammatory response → Repair → Fibrosis. Source:[26-31]

irreversible decrease in lung work despite having maximal help with MV and ECMO.[38]

PCPF's course could be like other very much recorded types of post-viral PF; like those happening after SARS/MERS/H1N1 infection. In SARS patients, post-viral parenchymal harm and patients' functional decrease generally recuperated at the beginning of two years of infection. CT investigations of SARS-CoV-1 showed radiologic highlights reminiscent of fibrosis in the greater part of patients following a normal 37 days[39]; but there were interstitial irregularities in just 5% of the patients after 15 years of the disease development.[40] It is unclear if the change in findings over the long haul addresses determination or survival inclination rather than the goal of fibrotic imaging discoveries in certain patients. Essentially, post-ARDS fibrotic changes are not believed to advance when the etiology of ARDS is due to viral respiratory infections. Whether they are moderate or not, non-reversible fibrotic changes could essentially affect patients' personal satisfaction and lead to other sickness-related morbidity and mortality.[34] Be that as it may, there is still a lot of vulnerability concerning how PCPF might advance. As more information becomes accessible, we

desire to acquire information on this.

The lack of solid information on the recurrence and seriousness of PCPF might be connected with the difficulty in diagnosing PCPF in the current pandemic conditions. One observational study utilized subsequent CT examination and analyzed PF based on broad radiologic proof. Out of 81 survivors of extreme Coronavirus pneumonia who had been hospitalized, more than half had radiologic proof of PF at follow-up.[23] Radiologic highlights of fibrosis have likewise been seen in 44% of patients discharged after receiving Coronavirus treatment.[41] Another review showed that there was a high pace of lung function anomalies on pneumonic capacity testing, proposing PF on discharge. In this review, 47% patients had impeded gas move and 25% had diminished absolute lung capacity.[42] Finally, in the autopsies of thirty patients who died from Coronavirus, histopathological progression of DAD to fibrosing design was seen in 43% of the samples.[25]

Types of Post-COVID Conditions

New or Ongoing Symptoms

Certain individuals experience a scope of new or progressing manifestations that can last weeks or months after first being infected with the virus that causes Coronavirus. Dissimilar to a portion of different sorts of post-Coronavirus conditions that tend just to happen in individuals who have had a serious ailment, these side effects can happen to any individual who has had Coronavirus, regardless of whether the disease was mild, or they had no underlying manifestations. People commonly report experiencing different combinations of the following symptoms:

- Difficulty breathing or shortness of breath
- Tiredness or fatigue
- Symptoms that get worse after physical or mental activities (also known as post-exertional malaise)
- Difficulty thinking or concentrating (sometimes referred to as “brain fog”)
- Cough
- Chest or stomach pain
- Headache
- Fast-beating or pounding heart (also known as heart palpitations)
- Joint or muscle pain
- Pins-and-needles feeling
- Diarrhea
- Sleep problems
- Fever
- Dizziness on standing (lightheadedness)
- Rash
- Mood changes
- Change in smell or taste
- Changes in menstrual period cycles

Multiorgan Effects of COVID-19

Individuals who had extreme sickness with Coronavirus symptoms experienced multiorgan impacts or immune system conditions for a long time with manifestations lasting weeks or months after the Coronavirus disease. Multiorgan impacts can influence many, while possibly not all, body frameworks, including heart, lung, kidney, skin, and body functions (Figure 3).[11] Autoimmune system conditions that happen to a person's system attack healthy cells in his/her body unintentionally, causing aggravation (enlarging) or tissue harm in the impacted parts of the body.

While it is exceptionally interesting, certain individuals, generally children, experience multisystem inflammatory syndrome (MIS) during or after having Coronavirus disease. MIS is a circumstance where various body parts can become inflamed. MIS can prompt post-Coronavirus conditions if an individual keeps encountering multiorgan impacts or different side effects.

Impact of angiotensin-2-converting enzyme (ACE-2) on interstitial lung disease

The etiology of post-Coronavirus pulmonary fibrosis is multifactorial and relies upon age, smoking, viral infection, drug susceptibility, and hereditary inclination. SARS-CoV-2 uses angiotensin-2-converting enzyme (ACE-2) receptor, a cell receptor in people for cell passage, and causes interstitial lung harm. Chronic inflammation which might bring about epithelial harm and fibroblast actuation is considered as the primary driver of pulmonary fibrosis or causes interstitial lung harm as displayed in Figure 4.

Human ACE2 is a laid-out useful receptor by which SARS-CoV enters and targets cells (Figure 5).[23,24] The transmembrane spike glycoprotein (S protein) of SARS-CoV joins to the cell layer ACE2; SARS-CoV then, at that point, connects to the objective cells, trailed by SARS-CoV-S protein prepared by cell surface proteases, for example, transmembrane protease serine 2 (TMPRSS2). This permits the combination of viral and cell membrane bringing about SARS-CoV entry and replication in the objective cells. In addition, ACE2 knockout extraordinarily decreases viral disease and replication in mice after

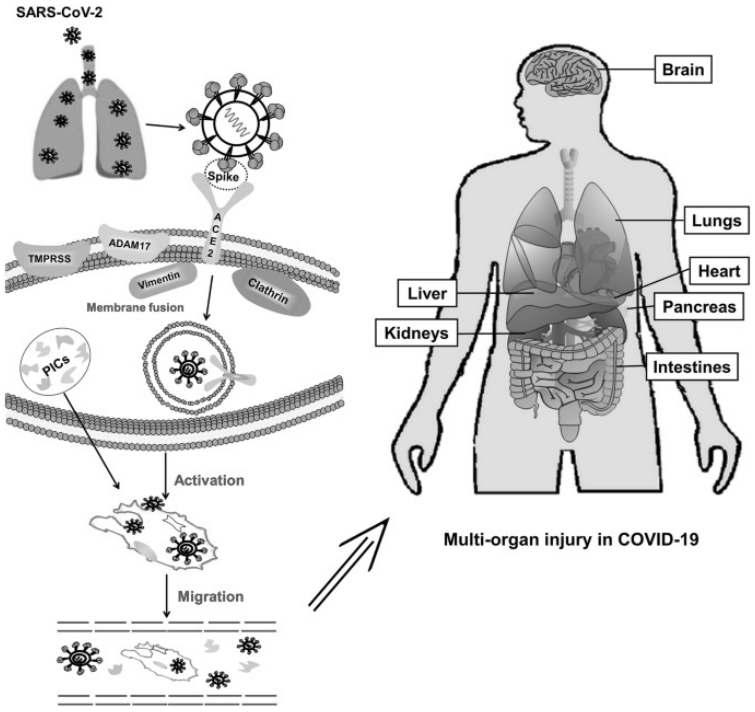

Figure 3. Impact of SARS-CoV-2 Multiorgan. SARS-CoV-2 enters lung cells through the ACE2 receptor. The without cell and macrophage-phagocytosed infection can spread to different organs and taint ACE2-communicating cells at the local site, causing multi-organ injury. Source[11]

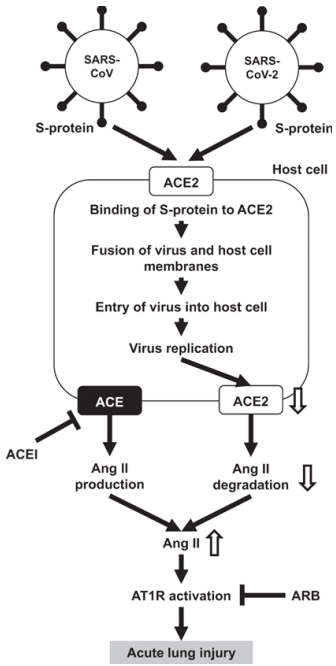

Figure 4. A possible plan of the relationship of ACE2, angiotensin II, and AT1R and intense lung injury of SARS and Coronavirus. Ang II, angiotensin II; Pro, angiotensin-changing over chemical; ACE2, angiotensin-changing over compound 2; ACEI, angiotensin-changing over catalyst inhibitor; AT1R, angiotensin II sort 1 receptor; ARB, angiotensin II sort 1 receptor blocker; SARS-CoV, severe acute respiratory condition Covid; SARS-CoV-2, severe acute respiratory disorder Covid 2; S-protein, spike-glycoprotein. Source: [23,24]

exploratory SARS-CoV infection. Accordingly, it is proposed that reducing SARS-CoV-S protein to ACE2 is vital for SARS-CoV disease.

Prevention of Post Covid conditions

The most effective way to forestall present Coronavirus conditions is to forestall Coronavirus sickness. For healthy individuals , they were advised to get immunized against Covid-19 . It ias simply the most effective way to prevent serious Coronavirus sickness and it also protects everybody around us.People were also told to take note of their general wellbeing and use social measures even after being immunized against the virus.

The capacity of a immunization to forestall post-Coronavirus conditions relies upon its capacity to forestall infection in any case. The antibodies available then pointed toward forestalling extreme infection and death. They were not active against the infection; however, they still had some defensive impact. It was speculated that patients that have being immunized against Coronavirus and still developed the infection would be more averse to have manifestations for over a month.

Post Covid-19 condition can be considered a multi-framework disorder showing regularly with respiratory, cardiovascular, hematologic, and neuropsychiatry symptoms either alone or in combination. The treatment ought to be individualized and ought to be an interprofessional approach coordinated towards both the clinical and psychological parts of this disorder.

Vaccination and Post Covid-19

CDC suggested that individuals be immunized whether or not they previously had Covid-19. Also, there were recounted proofs that being completely inoculated against Covid-19 would further improve Post-Coronavirus Disorder symptoms.

Conclusion

The most well-known lung issue looked out for in post-Coronavirus patients is lung fibrosis. Considering the tremendous overall weight of Coronavirus, even for a little case to advance to lung fibrosis is a genuine concern. The danger of fibrosis advancement is most noteworthy for the elderly patients with extreme infection and needing ventilatory help. During the period of this study, authoritative and experimentally demonstrated preventive or treatment choices for this condition did not exist, despite the broad examination that was in progress.

Post-Coronavirus pneumonic fibrosis is as of now restricted to symptomatic treatment, which is generally a neglected viewpoint. While confronting this lethal infection, research and clinical perceptions need to be completed in order to draw the attention to the impending danger of post-Coronavirus interstitial lung Disease (PC-ILD) in Coronavirus survivors.

Long time follow-up of mild- seriously impacted patients should be highly considered in Coronavirus treatment. Distinguishing predominance and examples of long-lasting lung damage is central in forestalling and treating Coronavirus instigated fibrotic lung disease.

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