ARTICLE REVIEW

CURRENT APPROACH TO POST-COVID-19 PULMONARY FIBROSIS

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ABSTRAK

Jumlah pasien yang pulih dari COVID-19 terus meningkat di seluruh dunia, namun ada kekhawatiran mengenai konsekuensi jangka panjang pada organ paru pasien penyintas COVID-19. Fibrosis paru pasca-COVID-19 (post-COVID-19 pulmonary fibrosis, PCPF) telah diketahui sebagai komplikasi COVID-19, dapat terjadi pada sejumlah besar penyintas COVID-19, dan dapat bertahan berbulan-bulan setelah awitan infeksi. Patogenesis PCPF belum sepenuhnya dipahami dan kemungkinan bersifat multifaktorial, melibatkan beberapa jalur seperti inflamasi, hipoksia, dan tromboemboli. Pasien dengan penyakit yang lebih parah, usia lebih tua, dan memiliki komorbiditas berisiko lebih besar terkena PCPF. Pasien PCPF mungkin asimtomatik atau bergejala, paling sering berupa sesak napas pada berbagai tingkat keparahan, dan pemeriksaan paling baik dilakukan dengan CT resolusi tinggi. Saat ini tidak ada terapi yang sudah terbukti efektif untuk PCPF, dan banyak uji klinis sedang berlangsung. Prognosis jangka panjang PCPF juga masih perlu dipelajari lebih lanjut.

Kata kunci: COVID-19, fibrosis paru, fibrosis paru pasca-COVID-19

ABSTRACT

The number of patients recovering from COVID-19 continues to rise worldwide, but there are concerns regarding the long-term pulmonary consequences for COVID-19 survivors. Post-COVID-19 pulmonary fibrosis (PCPF) is increasingly recognized as a consequence of COVID-19, occurring in a significant number of COVID-19 survivors and might persist months after the infection. The pathogenesis is only not fully understood and is likely multifactorial, involving pathways such as inflammation, hypoxia, and thromboembolism. Patients with a more severe disease, older age, and comorbidities have a greater risk of developing PCPF. Patients with PCPF may be asymptomatic or symptomatic, most frequently dyspnea at varying severity, and the workup is best done by high-resolution CT. There are currently no well-established therapies for PCPF, and many clinical trials are ongoing. The long-term outcomes of PCPF also need to be determined.

Keywords: COVID-19, pulmonary fibrosis, post-COVID-19 pulmonary fibrosis, PCPF

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INTRODUCTION

The COVID-19 pandemic caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has made a significant global public health impact. As of early April 2022, there have been more than 489 million cases and 6 million deaths worldwide due to COVID-19.[1] However, due to enormous efforts from all fronts, currently more than 480 million people worldwide have recovered from COVID-19, but there remains concern that some organs, including the lungs, might develop long-term complications following the infection, such as pulmonary fibrosis. Although fibrosis is a physiologic response to any lung infection, there is a growing number of patients who developed post-COVID-19 pulmonary fibrosis (PCPF) after recovering from COVID-19 infection.[2]

Eradication of SARS-CoV-2 from the lungs apparently does not impede the development of PCPF. Studies have reported varying number of incidences of PCPF depending on the time of evaluation, with early analysis found that more than a third of recovered COVID-19 patients had fibrotic abnormalities on hospital discharge,[3] whereas more recent cohort study found that almost two third of COVID-19 patients had PCPF five months after the disease onset.[4] The course of PCPF will be more apparent with time, but considering millions of COVID-19 cases worldwide, even small percentage of PCPF is a concern and could amount to significant morbidity and mortality, especially in older patients who are more likely to have pre-existing lung diseases.[5] Many studies are underway to learn more about PCPF, and this review will summarize current evidence regarding PCPF.

RISK FACTORS

Several risk factors have been associated with the development of PCPF. Patient-related risk factors include older age, male, smokers, alcoholism, and the presence of comorbidities such as diabetes, hypertension, and lung or cardiovascular diseases. Among the disease-related risk factors, the severity of COVID-19 infection has consistently been linked with higher incidence of PCPF. Furthermore, features related to the acute phase of the disease, such as the presence of dyspnea, prolonged hospitalization, admission to intensive care unit (ICU), use of high-flow oxygen support, use of mechanical ventilation, development of ARDS, and certain laboratory findings such as lymphopenia, leukocytosis, and elevated lactate dehydrogenase (LDH) were associated with a higher risk of PCPF.[6]

PATHOGENESIS

The pathogenesis of PCPF is only partially known and is probably multifactorial with overlapping factors. Generally, pulmonary fibrosis indicates deposition of collagen in the lung tissue due to the impaired normal regulation of tissue repair. It is characterized by abnormal repair of the damaged alveolar epithelium, persistence of fibroblasts, increased deposition of extracellular matrix (ECM) components such as collagen, and the destruction of normal lung tissue, although the histology of PCPF is not yet well defined.[2] Various mechanisms of PCPF have been described, including the role of ACE-2 receptors, inflammation, hypoxia, and thromboembolism (Figure 1).

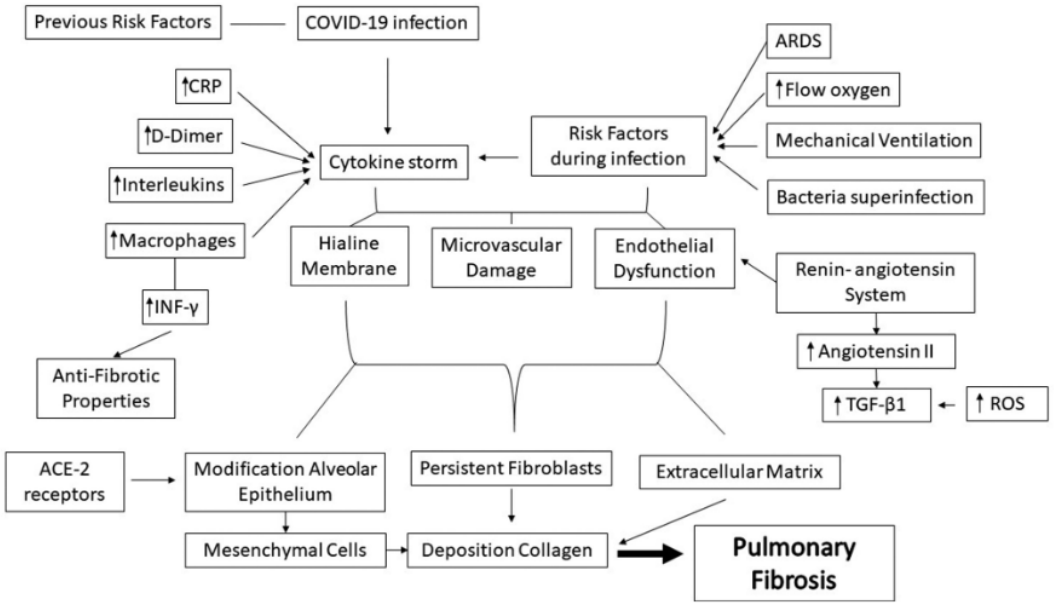

Figure 1. Proposed pathogenesis of PCPF.[6] ACE 2: angiotensin-converting enzyme receptor 2, ARDS: acute respiratory distress syndrome, CRP: C-reactive protein, INF-γ: interferon-γ, ROS: reactive oxygen species, TGF-β1: transforming growth factor-β1.

ACE-2

SARS-CoV-2 has a high affinity for receptors of angiotensin-converting enzyme 2 (ACE-2), which are present in many sites such as the endothelial cells of the respiratory tract, respiratory epithelium, immune cells, arteries, veins, arterial smooth muscle, and other epithelia which infected by the virus.[7] When the virus links to ACE-2 receptors, it can induce transition of epithelial or endothelial cells to mesenchymal cells, which will induce deposition of mesenchymal protein, a precursor to PCPF.[8] Concurrently, the renin-angiotensin system can be activated and inflict fibrosis by increasing the production of angiotensin II which will trigger transforming growth factor-β1 (TGF-β1) and mediate collagen deposition while reducing anti-fibrosis, anti-inflammatory, and anti-oxidant protection.[9]

Inflammation

Cytokine storm is one of the main causes of lung damages in COVID-19 and signifies a dysregulated inflammatory response with elevated levels of inflammatory markers such as interleukins, TNF-α, and CRP.[10] This cytokine storm is associated with higher disease severity, aggravated by other causes of secondary pulmonary injury such as bacterial superinfection and mechanical ventilation, and may induce pulmonary fibrosis by (i) impairing differentiation of epithelial cells during the repair by fibroblasts and myofibroblasts; (ii) producing matrix metalloproteinases, VEGF, and TGF-β, and (iii) increasing expression of IFN-γ which could stimulate other inflammatory cytokines, though it also has antifibrotic properties.[2, 6] Following these severe inflammatory responses, the lungs would attempt to repair the damage so that the progression to pulmonary fibrosis could be avoided, but it is still unknown why certain patients recover from such insults, while others develop progressive pulmonary fibrosis.

Thromboembolism

COVID-19 has been shown to result in a profoundly prothrombotic state, probably mediated by (i) inflammation-induced thrombosis, (ii) dysregulation of complement, fibrinolytic, and plasminogen systems, and (iii) viral-mediated endothelial cell injury, although the specific pathophysiology remains unclear.[11]

This hypercoagulability may lead to pulmonary embolism that may be implicated in the pathogenesis of pulmonary fibrosis by causing lung injury, as seen in a large cohort study where the incidence of interstitial lung disease (ILD) were higher in patients with a history of venous thromboembolism or pulmonary embolism.[12]

Hypoxia

Prolonged, severe hypoxia have been associated with the development of pulmonary fibrosis, probably due to the abnormal interplay between hypoxia, fibroblast formation, and ECM deposition.[13] Severe hypoxia during the acute phase of COVID-19 infection is frequently caused by ARDS, which occurs in up to 40% of patients with COVID-19,[14] and COVID-19-induced ARDS seems to be the main risk factors of PCPF, although it might be different from classical ARDS since the main site of injury is the alveolar epithelial cells, not the endothelial cells.[15] Ironically, on the other hand, hyperoxia or prolonged exposure to extremely high amount of oxygen and ventilatory support to treat lung disorder during COVID-19 infection may also induce pulmonary fibrosis through excessive production of reactive oxygen species.[16]

CLINICAL MANIFESTATIONS

PCPF may exhibit no symptom or may present with variable degrees of dyspnea, dry cough, and fatigue. Lung auscultation might reveal crackles or normal, with normal oxygen saturation or require supplemental oxygen at rest or during exercise.[6] An Austrian study that evaluated patients with COVID-19 until 100 days after infection found that these symptoms tend to lessened overtime, although symptoms remained in 41% patients by the end of the study, with dyspnea being the most common (36%), and 63% patients had persistent tomographic lung abnormalities, most frequently ground-glass opacities, consolidations, and reticulation.[17]

Patients may experience decreased exercise capacity and quality of life caused by the pulmonary dysfunction.[18] Lower diffusing capacity for carbon monoxide (DLCO) appears to be the most frequent impairment in pulmonary function tests (PFTs) despite prolonged recovery period, particularly in patients with severe pneumonia and this might be secondary to restrictive pulmonary fibrosis.[6] Persistent pulmonary dysfunction may occur months after the infection, as shown by a Chinese study which found that 20% subjects still had decreased DLCO three months after discharge, with evidence of tomographic pulmonary fibrosis in some patients.[19]

DIAGNOSIS

PCPF is diagnosed through clinical evaluation, lab tests, PFTs, and/or high-resolution CT (HRCT) in patients with previous or suspected COVID-19 infection. Changes in PFTs after COVID-19 may be indicative of PCPF, but conducting the tests are challenging during the pandemic due to high aerosol generation, as are other similar aerosolizing procedures such as bronchoscopy or lung biopsy.[2] As such, HRCT has become an important tool for screening, initial diagnosis, and assessment of severity of PCPF.

Previous studies had described the radiological features of PCPF at different stages of evaluation (Figure 2). Some authors classified PCPF radiologically based on widespread and persistent fibrotic changes, i.e. PCPF is defined as the presence of persistent fibrotic changes identified on follow-up CT scans, such as architectural distortion, parenchymal bands, ground-glass and reticular opacities, traction bronchiectasis, and honeycombing, all of which might be associated with functional impairment,[20] whereas others suggested outright extensive fibrosis on follow-up CT scans.[21] Therefore, the time of evaluation to definitively establish the presence of PCPF has not been determined, though it is necessary that these radiologic findings occur after recent COVID-19 infection.

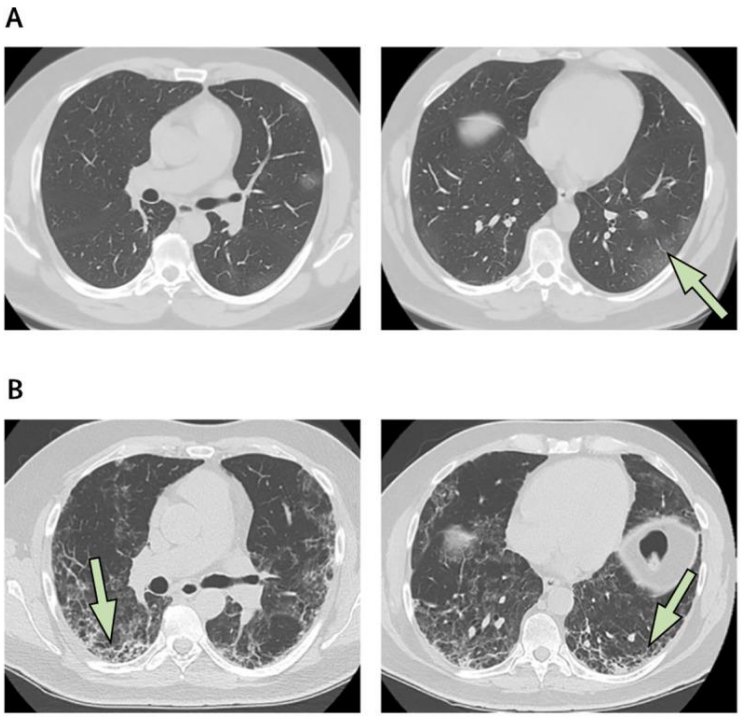

Figure 2. Tomographic findings of a patient with PCPF. (A) Mild peripheral ground glass opacities in the left lower lobe (arrow). (B) Three weeks later, the same lung zones showed progressive abnormalities and fibrotic changes (arrows).[5]

Some laboratory findings have been evaluated as potential biomarkers of PCPF progression. Increased levels of inflammatory markers such as CRP and IL-6, serum LDH, and D-dimer; reduced lymphocyte count; lower albumin; and lower plasma levels of interferon-γ were associated with increased risk of PCPF.[6, 22] However, since none of these laboratory findings are specific to PCPF, more studies are required to identify patients at high risk for PCPF.

NATURAL COURSE OF PCPF

Initially, due to limited information, studies on PCPF were compared to previous coronavirus pandemics, i.e. severe acute respiratory syndrome coronavirus (SARS) and Middle East respiratory syndrome coronavirus (MERS), since they are genetically similar to SARS-CoV-2. In SARS, post-viral lung damage and functional decline mostly recovered within two years of disease onset. CT studies of SARS patients showed pulmonary fibrosis in more than half of patients after an average of 37 days, but remained in only 5% patients after 15 years follow-up.[23, 24] Such long-term follow-up has not been investigated in MERS survivors, but in a study of patients who had recovered from MERS, chest plain radiographs taken at median 43 days after discharge showed pulmonary fibrosis in approximately a third of the patients, which were more likely to be older, had more severe initial radiographic findings, and longer ICU stay.[25]

Early studies of PCPF were limited to case reports, case series, and short-term cohort. In one of the early retrospective cohorts, follow-up CT scans found that more than half of severe COVID-19 patients had radiologic findings of PCPF at median 58 days after discharge.[20] Other earlier study performed chest CT on the last day before discharge, two weeks, and four weeks after discharge. Compared with the last chest CT before discharge, the lung abnormalities were steadily reduced in the next follow-ups and almost two third patients no longer had lung lesions at 4-week follow-up, suggesting that the lung damage was reversible for most COVID-19 patients, especially in non-severe cases.[26]

To date, there has been more studies with longer period of follow-up to evaluate the occurrence of PCPF months after the initial infection, unfortunately showing that the radiological lung abnormalities did not fully resolve in a significant number of patients, with functional impacts in some of them. A single-center cohort Chinese study comparing chest CT during hospitalization and at 150 days after discharge reported that the overall incidence of PCPF was 86.87%, and more than a third patients still had evidence of lung fibrosis at the last follow-up, with the median time of resolution of PCPF was 70.79 days.[4] Persistent pulmonary fibrosis was higher in patients with older age, higher BMI, higher severity, fever, longer viral clearance time, pre-existing disease, and delayed hospitalization. Similarly, a recent Italian prospective cohort study found that persistent tomographic lung abnormalities at 6 months after hospitalization for COVID-19 pneumonia were predominantly found in older men with worse disease impairment and longer hospital stay, although only 20% patients showed such persistence abnormalities.[27] Another prospective cohort study in China involving 114 severe COVID-19 survivors found that at 6-month follow-up, PCPF occurred in one third of them and were associated with factors such as older age, ARDS, longer hospital stay, and non-invasive mechanical ventilation.[28] Furthermore, 26% patients had abnormal DLCO by the end of the study, which more frequently occurred in patients with PCPF, suggesting that the fibrotic changes had functional impacts.

In the longest prospective cohort study to date, Liu et al. reported that most COVID-19 patients (61%) no longer had tomographic lung lesions at 7 months after discharge, whereas 29% of patients developed PCPF, particularly older patients with severe comorbidities, longer hospital stay, higher rate of mechanical ventilation, and worse laboratory findings (lower lymphocyte, higher D-dimer and LDH).[29] One Austrian multicenter cohort study, however, did not find tomographic evidence of PCPF at 100 days after disease onset as improvement occurred in most of patients, even in those with acute severe disease.[17] However, 63% patients exhibited persistent tomographic pulmonary abnormalities other than fibrosis, mainly ground-glass opacities, consolidations, and reticulation, and 41% patients still had persistent symptoms, with dyspnea being most frequent (36%). The authors suggested that the absence of PCPF was probably due to the difficulty in differentiating residual inflammation and early signs of fibrosis, especially in patients with a clear overall improvement.

MANAGEMENT

No well-established therapeutic options are available to treat PCPF currently. Many potential treatment agents are under evaluation, with antifibrotics seem to have the most attention as they have been established for the treatment of idiopathic pulmonary fibrosis (IPF).

Antifibrotics

Two available oral antifibrotics, nintedanib and pirfenidone, have recently been approved to treat IPF. Nintedanib, a tyrosine kinase inhibitor that binds on epidermal growth factor receptor, vascular endothelial growth factor receptor, and platelet-derived growth factor receptor, could inhibit pro-fibrotic signaling and reduce the proliferation, migration, and differentiation of fibroblasts and secretion of ECM components.[30] The mechanism of action of pirfenidone has not been fully defined, but it is thought to slow fibrosis by multiple pathways, such as inhibiting pro-fibrotic and pro-inflammatory cytokine cascades, including TGF-β signaling which stimulates collagen production involved in IPF pathogenesis.[31]

Despite different modes of action, both nintedanib and pirfenidone are equally effective in impeding respiratory function decline in IPF patients.[32] Both of these antifibrotics have been studied mostly in IPF patients, but a landmark trial in 2019 involving 663 patients with progressive pulmonary fibrosis caused by a wide variety of ILD found that nintedanib could attenuate FVC decline significantly, suggesting that nintedanib might inhibit fibrogenesis across a wide range of pulmonary disorders.[33] As such, this trial provided a theoretical basis for the use of antifibrotics in PCPF.

Trials using antifibrotics in COVID-19 are ongoing, and currently only limited number of trials have been completed. A small Japanese non-randomized controlled trial found that nintedanib 150 mg twice daily for 28 days markedly reduced the lung fibrosis and length of mechanical ventilation, although it did not reduce mortality.[34] A recent Chinese study involving 146 severe COVID-19 patients finds that pirfenidone (200mg three times daily for the first two days and 400mg three times daily thereafter for four weeks) significantly reduces inflammatory markers, although it does not attenuate pulmonary fibrosis at fourth week follow up, probably due to limited observation time and sample size.[35]

Immunosuppressant

The role of immunosuppressive drugs in PCPF has not been elucidated. For instance, corticosteroids might have the potential to prevent or attenuate the development of pulmonary fibrosis through their anti-inflammatory effects, and prednisone has been shown to decelerate the progression of pulmonary fibrosis in rat IPF models by decreasing inflammation in the lungs,[36] although its use in IPF patients is unproven. A randomized controlled trial is underway to evaluate the efficacy of two weeks low-dose prednisone therapy in patients recovered from COVID-19 with persistent tomographic abnormalities.[37]

Stem Cell

Mesenchymal stem cell (MSC) therapy, using non-hematopoietic cells that can be acquired from bone marrow, adipose tissues, umbilical cord, and placenta, has been proposed as a promising therapeutic option to treat PCPF as results from pre-clinical studies have shown that MSC therapy is a safe and effective method that could significantly improve the survival of pulmonary fibrosis animals by directly replacing fibrosis with normal lung cells and reducing collagen deposition and inflammation.[38] Many clinical trials are underway to confirm its benefit in COVID-19 survivors with PCPF.

Lung Transplantation

Lung transplantation (LT) could serve as a potential therapeutic option for patients with end-stage PCPF. Pulmonary fibrosis is currently the main cause of LT, and in carefully selected patients with IPF, LT offers survival benefit.[39] In cases of PCPF, LT has been successfully performed in a limited number of patients worldwide.[40] However, due to the limited knowledge about the natural course of recovery in PCPF, several concerns regarding LT exist in this scenario, such as the right time to conduct LT and the definition of end-stage lung disease in the context of PCPF, which need to be addressed in long-term studies.[6]

Pulmonary Rehabilitation

Limited data are available about the safety and benefits of pulmonary rehabilitation specifically for patients with PCPF. Previous studies in patients with IPF and other ILD, however, have demonstrated the benefits of pulmonary rehabilitation to improve lung function, exercise capacity, dyspnea, and quality of life.[41] As such, pulmonary rehabilitation in the acute and recovery stage of COVID-19 might be beneficial to help manage PCPF and future studies designed specifically in PCPF patients are necessary.

Other Therapeutic Options

Various other agents acting in different pathways are currently being investigated in clinical trials involving COVID-19 patients with PCPF, including treamid, autologous monocytes, bovhyarulonidase azoximer, anti-interleukin, and resveratrol. For instance, treamid, also known as bisamide derivative of dicarboxylic acid, has anti-inflammatory and antifibrotic effects, and could promote lung tissue regeneration in experimental pulmonary fibrosis animals by suppressing the production and deposition of collagen and by inducing endothelial progenitor cell synthesis,[42] thus could serve as a potential treatment of PCPF.

PREVENTION

Since PCPF still lacks effective therapies, it is important to try mitigate the risk of developing PCPF. Preventive measures should focus on curtailing the risk factors responsible for causing persistent lung injury, prolonged inflammatory response, and fibroproliferation.[43] Modifiable risk factors known to cause higher risk of PCPF, such as ventilator-induced lung injury, should also be mitigated. Development of COVID-19 vaccines has been a tremendous landmark in recent history and these vaccines are effective in reducing the severity of COVID-19 infection,[44] but whether this leads to reduced incidence of PCPF needs to be investigated.

PROGNOSIS

Overall, it is still too early in the course of the pandemic to determine the long-term prognosis of PCPF. Follow-up of current studies is still too short to ascertain whether PCPF would persist in the long term or improve with time. Existing studies so far have shown that the fibrotic changes tend to recover gradually with time even in those with severe COVID-19 pneumonia, but they could still remain months after the initial infection, with functional impact due to pulmonary dysfunction in some of these COVID-19 survivors.[27-29] Looking at the long-term follow up data from the SARS pandemic, it is possible that PCPF could persist for years with residual pulmonary dysfunction.[24] Future studies should also identify whether PCPF would significantly affect clinical outcome and daily function in the long term since the consequence is not only for patients' prognosis, but also for the treatment approach, i.e. which patients would likely to have benefits from therapies for PCPF.

CONCLUSION

With ongoing COVID-19 pandemic, a significant number of survivors will be at risk for long-term complications following COVID-19 and it is likely that the number of patients with pulmonary sequelae such as PCPF will markedly rise in the near future. Current understanding of PCPF remains limited, but it is increasingly becoming a priority since even a relatively minor degree of residual fibrosis could yield substantial morbidity and mortality given the huge number of COVID-19 survivors worldwide. Currently, no fully proven therapeutic options are available to treat PCPF. Further large, prospective studies in longer periods are necessary to verify the safety and effectiveness of various potential therapeutic options of PCPF.

REFERENCES

1. World Health Organization. Weekly epidemiological update on COVID-19 - 5 April 2022. WHO; 2022 [cited 10 April 2022].
   Available from: https://www.who.int/publications/m/item/weekly-epidemiological-update-on-covid-19---5-april-2022.
2. Ambardar SR, Hightower SL, Huprikar NA, Chung KK, Singhal A, Collen JF. Post-COVID-19 Pulmonary Fibrosis: Novel Sequelae of the Current Pandemic. J Clin Med. 2021;10(11):2452.

3. Mo X, Jian W, Su Z, Chen M, Peng H, Peng P, et al. Abnormal pulmonary function in COVID-19 patients at time of hospital discharge. Eur Respir J. 2020;55(6).
4. Li X, Shen C, Wang L, Majumder S, Zhang D, Deen MJ, et al. Pulmonary fibrosis and its related factors in discharged patients with new corona virus pneumonia: a cohort study. Respir Res. 2021;22(1):203-.
5. Spagnolo P, Balestro E, Aliberti S, Cocconcelli E, Biondini D, Casa GD, et al. Pulmonary fibrosis secondary to COVID-19: a call to arms? Lancet Respir Med. 2020;8(8):750-2.
6. Tanni SE, Fabro AT, de Albuquerque A, Ferreira EVM, Verrastro CGY, Sawamura MVY, et al. Pulmonary fibrosis secondary to COVID-19: a narrative review. Expert Rev Respir Med. 2021;15(6):791-803.
7. Renu K, Prasanna PL, Valsala Gopalakrishnan A. Coronaviruses pathogenesis, comorbidities and multi-organ damage - A review. Life sciences. 2020;255:117839-.
8. Eapen MS, Lu W, Gaikwad AV, Bhattarai P, Chia C, Hardikar A, et al. Endothelial to mesenchymal transition: a precursor to post-COVID-19 interstitial pulmonary fibrosis and vascular obliteration? Eur Respir J. 2020;56(4):2003167.
9. Xu J, Xu X, Jiang L, Dua K, Hansbro PM, Liu G. SARS-CoV-2 induces transcriptional signatures in human lung epithelial cells that promote lung fibrosis. Respir Res. 2020;21(1):182.
10. Soy M, Keser G, Atagündüz P, Tabak F, Atagündüz I, Kayhan S. Cytokine storm in COVID-19: pathogenesis and overview of anti-inflammatory agents used in treatment. Clin Rheumatol. 2020;39(7):2085-94.
11. Abou-Ismail MY, Diamond A, Kapoor S, Arafah Y, Nayak L. The hypercoagulable state in COVID-19: Incidence, pathophysiology, and management. Thromb Res. 2020;194:101-15.
12. Sode BF, Dahl M, Nielsen SF, Nordestgaard BG. Venous thromboembolism and risk of idiopathic interstitial pneumonia: a nationwide study. Am J Respir Crit Care Med. 2010;181(10):1085-92.
13. Manresa MC, Godson C, Taylor CT. Hypoxia-sensitive pathways in inflammation-driven fibrosis. Am J Physiol Regul Integr Comp Physiol. 2014;307(12):R1369-80.
14. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med. 2020;180(7):934-43.
15. Chilosi M, Poletti V, Ravaglia C, Rossi G, Dubini A, Piciucchi S, et al. The pathogenic role of epithelial and endothelial cells in early-phase COVID-19 pneumonia: victims and partners in crime. Mod Pathol. 2021;34(8):1444-55.
16. Budinger GRS, Mutlu GM. Balancing the risks and benefits of oxygen therapy in critically III adults. Chest. 2013;143(4):1151-62.
17. Sonnweber T, Sahanic S, Pizzini A, Luger A, Schwabl C, Sonnweber B, et al. Cardiopulmonary recovery after COVID-19: an observational prospective multicentre trial. Eur Respir J. 2021;57(4):2003481.
18. Strumiliene E, Zeleckiene I, Bliudzius R, Samuilis A, Zvirblis T, Zablockiene B, et al. Follow-Up Analysis of Pulmonary Function, Exercise Capacity, Radiological Changes, and Quality of Life Two Months after Recovery from SARS-CoV-2 Pneumonia. Medicina (Kaunas). 2021;57(6).
19. Liang L, Yang B, Jiang N, Fu W, He X, Zhou Y, et al. Three-month Follow-up Study of Survivors of Coronavirus Disease 2019 after Discharge. J Korean Med Sci. 2020;35(47):e418.
20. Huang W, Wu Q, Chen Z, Xiong Z, Wang K, Tian J, et al. The potential indicators for pulmonary fibrosis in survivors of severe COVID-19. J Infect. 2021;82(2):e5-e7.

21. Deng L, Khan A, Zhou W, Dai Y, Md E, Chen R, et al. Follow-up study of clinical and chest CT scans in confirmed COVID-19 patients. Radiol Infect Dis. 2020;7(3):106-13.
22. Zou J-N, Sun L, Wang B-R, Zou Y, Xu S, Ding Y-J, et al. The characteristics and evolution of pulmonary fibrosis in COVID-19 patients as assessed by AI-assisted chest HRCT. PLoS One. 2021;16(3):e0248957-e.
23. Antonio GE, Wong KT, Hui DS, Wu A, Lee N, Yuen EH, et al. Thin-section CT in patients with severe acute respiratory syndrome following hospital discharge: preliminary experience. Radiology. 2003;228(3):810-5.
24. Zhang P, Li J, Liu H, Han N, Ju J, Kou Y, et al. Long-term bone and lung consequences associated with hospital-acquired severe acute respiratory syndrome: a 15-year follow-up from a prospective cohort study. Bone Res. 2020;8:8.
25. Das KM, Lee EY, Singh R, Enani MA, Al Dossari K, Van Gorkom K, et al. Follow-up chest radiographic findings in patients with MERS-CoV after recovery. Indian J Radiol Imaging. 2017;27(3):342-9.
26. Liu C, Ye L, Xia R, Zheng X, Yuan C, Wang Z, et al. Chest Computed Tomography and Clinical Follow-Up of Discharged Patients with COVID-19 in Wenzhou City, Zhejiang, China. Annals of the American Thoracic Society. 2020;17(10):1231-7.
27. Cocconcelli E, Bernardinello N, Giraudo C, Castelli G, Giorgino A, Leoni D, et al. Characteristics and Prognostic Factors of Pulmonary Fibrosis After COVID-19 Pneumonia. Frontiers in medicine. 2022;8:823600-.
28. Han X, Fan Y, Alwalid O, Li N, Jia X, Yuan M, et al. Six-month Follow-up Chest CT Findings after Severe COVID-19 Pneumonia. Radiology. 2021;299(1):E177-E86.
29. Liu M, Lv F, Huang Y, Xiao K. Follow-Up Study of the Chest CT Characteristics of COVID-19 Survivors Seven Months After Recovery. Frontiers in medicine. 2021;8:636298-.
30. Wollin L, Wex E, Pautsch A, Schnapp G, Hostettler KE, Stowasser S, et al. Mode of action of nintedanib in the treatment of idiopathic pulmonary fibrosis. Eur Respir J. 2015;45(5):1434-45.
31. Margaritopoulos GA, Vasarmidi E, Antoniou KM. Pirfenidone in the treatment of idiopathic pulmonary fibrosis: an evidence-based review of its place in therapy. Core Evid. 2016;11:11-22.
32. Finnerty JP, Ponnuswamy A, Dutta P, Abdelaziz A, Kamil H. Efficacy of antifibrotic drugs, nintedanib and pirfenidone, in treatment of progressive pulmonary fibrosis in both idiopathic pulmonary fibrosis (IPF) and non-IPF: a systematic review and meta-analysis. BMC Pulmonary Medicine. 2021;21(1):411.
33. Flaherty KR, Wells AU, Cottin V, Devaraj A, Walsh SLF, Inoue Y, et al. Nintedanib in Progressive Fibrosing Interstitial Lung Diseases. N Engl J Med. 2019;381(18):1718-27.
34. Umemura Y, Mitsuyama Y, Minami K, Nishida T, Watanabe A, Okada N, et al. Efficacy and safety of nintedanib for pulmonary fibrosis in severe pneumonia induced by COVID-19: An interventional study. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;108:454-60.
35. Zhang F, Wei Y, He L, Zhang H, Hu Q, Yue H, et al. A trial of pirfenidone in hospitalized adult patients with severe coronavirus disease 2019. Chin Med J (Engl). 2021;135(3):368-70.
36. Yu W, Guo F, Song X. Effects and mechanisms of pirfenidone, prednisone and acetylcysteine on pulmonary fibrosis in rat idiopathic pulmonary fibrosis models. Pharm Biol. 2017;55(1):450-5.
37. ClinicalTrials.gov. Short Term Low Dose Corticosteroids for Management of Post COVID-19 Pulmonary Fibrosis. U.S. National Library of Medicine; 2020

[cited 10 April 2022]. Available from: https://clinicaltrials.gov/ct2/show/NCT04551781.
38. Li X, Yue S, Luo Z. Mesenchymal stem cells in idiopathic pulmonary fibrosis. Oncotarget. 2017;8(60):102600-16.
39. Laporta Hernandez R, Aguilar Perez M, Lázaro Carrasco MT, Ussetti Gil P. Lung Transplantation in Idiopathic Pulmonary Fibrosis. Med Sci (Basel). 2018;6(3):68.
40. King CS, Mannem H, Kukreja J, Aryal S, Tang D, Singer JP, et al. Lung Transplantation for Patients With COVID-19. Chest. 2022;161(1):169-78.
41. Reina-Gutiérrez S, Torres-Costoso A, Martínez-Vizcaíno V, Núñez de Arenas-Arroyo S, Fernández-Rodríguez R, Pozuelo-Carrascosa DP. Effectiveness of Pulmonary Rehabilitation in Interstitial Lung Disease, Including Coronavirus Diseases: A Systematic Review and Meta-analysis. Arch Phys Med Rehabil. 2021;102(10):1989-97.e3.
42. Skurikhin E, Nebolsin V, Widera D, Ermakova N, Pershina O, Pakhomova A, et al. Antifibrotic and Regenerative Effects of Treamid in Pulmonary Fibrosis. Int J Mol Sci. 2020;21(21).
43. Ojo AS, Balogun SA, Williams OT, Ojo OS. Pulmonary Fibrosis in COVID-19 Survivors: Predictive Factors and Risk Reduction Strategies. Pulm Med. 2020;2020:6175964.
44. Huang YZ, Kuan CC. Vaccination to reduce severe COVID-19 and mortality in COVID-19 patients: a systematic review and meta-analysis. Eur Rev Med Pharmacol Sci. 2022;26(5):1770-6.