Literature Review

Long COVID-19: Multidisciplinary Approach and Pulmonary Fibrosis Sequelae

Nidya Febrina*, Indra Yovi

Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Riau, Arifin Achmad Hospital, Pekanbaru

Corresponding Author:
Nidya Febrina | Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Riau, Arifin Achmad Hospital, Pekanbaru | unidyafebrina@gmail.com

Submitted: December 16th, 2023
Accepted: February 15th, 2023
Published: June 28th, 2024

Respir Sci. 2024; 4(3): 209-20
https://doi.org/10.36497/respirsci.v4i3.140

Abstract

COVID-19 patients may experience a persistent condition of post-COVID-19 infection, which is known as the long-COVID phenomenon or post-acute sequelae of SARS-CoV-2 infection (PASC) or post-acute COVID-19 syndrome (PACS) with long-term sequelae characteristics that stay after the convalescent period of COVID-19 disease. The most common clinical symptoms found within 5 weeks post-infection were fatigue (12.7%), cough (12.4%), headache (11.1%), loss of sense of taste or smell (10.4%), and muscle pain (8.8%). Women have a slightly higher prevalence than men, with a value of 23.6% and 20.7%, respectively, which are dominated by 35-49 years old (26.8%), 50-69 years old (26.1%), and 25-34 years old (24.9%). Pulmonary fibrosis sequelae in COVID-19 occur due to the destruction of the alveolar epithelium and the formation of active myofibroblast foci, causing excessive accumulation of extracellular matrix in lung tissue. Long COVID management requires a multidisciplinary approach, including health workers and the wider community, as well as systematic assessment management. The recommended therapy includes pharmacological (symptomatic, micronutrients, antibiotics, and anti-inflammatory) and non-pharmacological (medical and psychosocial rehabilitation). This review aims to summarize the long COVID and multidisciplinary approach to improve the patient's quality of life.

Keywords: COVID-19, fibrosis, long COVID, PACS

INTRODUCTION

Severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) is a new type of coronavirus that causes respiratory tract infections. This virus was first reported on December 31, 2019 in China. Analysis of isolates from the patient's lower respiratory tract showed the discovery of a new type of coronavirus which was named by the World Health Organization (WHO) as Coronavirus Disease 2019 (COVID-19). SARS-CoV-2 is highly contagious with transmission occurring between species.[1,2] On March 11, 2020, WHO announced that

COVID-19 had become a worldwide pandemic.[3,4]

The number of COVID-19 cases in the world on May 23, 2021, was 165,772,420 confirmed cases and 3,437,545 deaths.[5] Confirmed cases in Indonesia as of May 23, 2021, were as many as 1,736,670 with 47,967 deaths.[6] Until May 23, 2021, 1,414 people had died among the 54,254 confirmed cases in Riau province.[7]

COVID-19 can cause illnesses ranging from asymptomatic, mild, moderate, and severe, to critical symptoms. Common signs and symptoms of COVID-19 infection include fever, cough, sore throat, and shortness of breath, with an average incubation period of 5-6 days and the longest incubation period of 14 days.[8]

Globally, there were 68 million recoveries on January 19, 2021, with or without symptoms, and 2 million deaths from COVID-19. This shows that most people infected with COVID-19 can have no symptoms or recover quickly, but in some cases, clinical symptoms can persist or develop continuously.[2,3]

COVID-19 patients may experience a persistent condition of post COVID-19 infection known as the long-COVID phenomenon or post-acute sequelae of SARS-CoV-2 infection (PASC) or post-acute COVID-19 syndrome (PACS) with long-term sequelae characteristics that persist after the convalescent period of COVID-19.[2,3]

According to WHO, the long COVID syndrome is characterized by the persistence of clinical symptoms in COVID-19 patients, which lasts 4-12 weeks from the initial onset or lasts for 12 weeks or more and is referred to as the chronic post-COVID syndrome.[3] Symptoms of long COVID include fatigue, headaches, shortness of breath, anosmia, muscle weakness, and cognitive dysfunction.[2,3] Carfi et al stated that about 87.4% of COVID-19 patients who have recovered will continue to experience persistent symptoms for up to 60 days.[2,9]

This condition needs to be a concern for health workers because, with prolonged symptoms, the patient's quality of life may decrease, and the clinical deterioration can return to the patient's death.[2,9] The purpose of this literature review is to assess the prevalence, characteristics, clinical manifestations, and management in post-COVID-19 patients with long COVID syndrome and their effect on pulmonary fibrosis formation.

REVIEW

According to the guidelines of the National Institute for Health and Care Excellence (NICE), the Royal College of General Practitioners (RCGP) and the Scottish Intercollegiate Guidelines Network (SIGN), long COVID is defined as a patient with signs and symptoms that continue or develop after acute infection with COVID-19, including ongoing symptomatic COVID-19 (4-12 weeks) and post-COVID syndrome (12 weeks or more) without other possible causes of illnesses.[10–13]

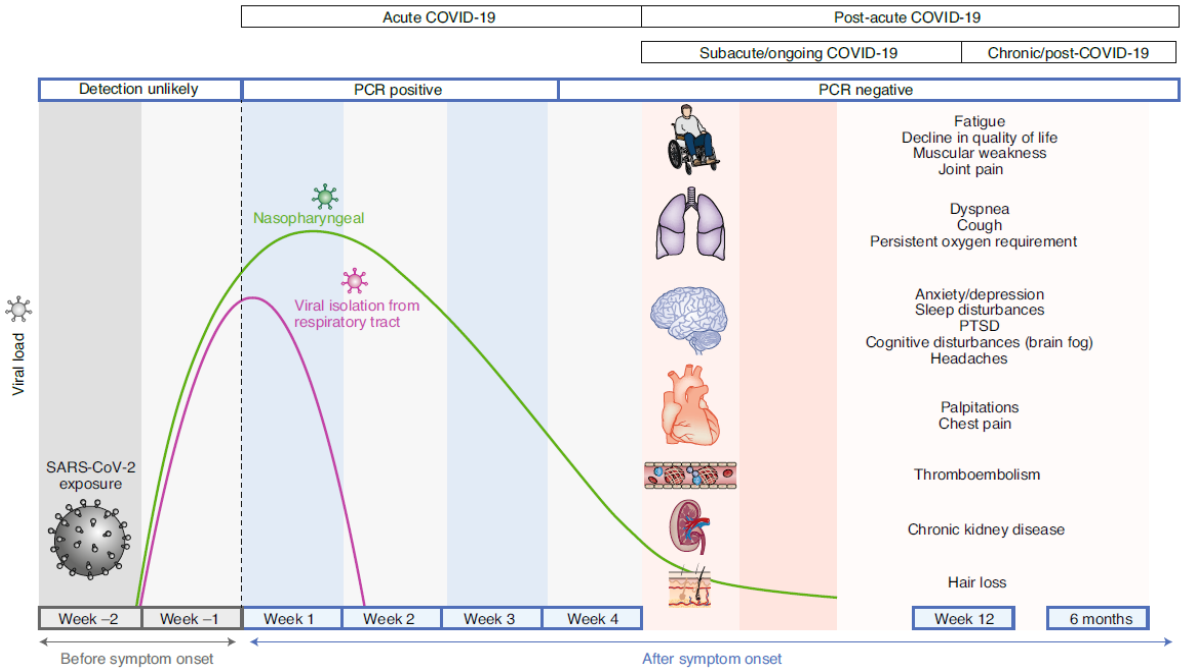

Figure 1. Timeline of COVID-19[14]

Perhimpunan Dokter Paru Indonesia (PDPI), or Indonesian Society of Respirology (ISR), in March 2021 issued clinical practice guidelines regarding post-COVID respiratory syndrome. Post-COVID-19 respiratory syndrome, according to PDPI, consists of two categories, namely post-acute COVID-19 syndrome with the onset of persistent pulmonary and respiratory symptoms ≥4 weeks from the onset of COVID-19; and chronic post-COVID-19 with the onset of persistent pulmonary and respiratory symptoms ≥12 weeks from the onset of COVID-19 symptoms.[15]

The definition and timeline of acute post-COVID-19 continue to evolve but are generally defined as persistent symptoms or the development of sequelae more than 3 or 4 weeks after the onset of acute symptoms. Based on the latest literature it is divided into two categories: (1) subacute or ongoing COVID-19 symptoms which include symptoms and abnormalities appearing from 4-12 weeks after acute COVID-19; and (2) chronic or post-COVID-19 syndromes that include symptoms and abnormalities that persist or appear after 12 weeks of the onset of acute COVID-19 and are not attributable to another diagnosis (Figure 1).[14]

Several literatures described multiorgan inflammatory syndrome (MIS) and various organ pathological findings following the incidence of acute infection. Therefore, as standardization of knowledge regarding acute post-COVID-19, it is proposed to divide the clinical manifestations of post-acute COVID-19 into 3 categories, namely: sequelae that persist after recovering from acute infection, organ dysfunction that persists after initial recovery, and new symptoms or syndromes that develop after an initial asymptomatic or mild infection (Figure 2).[16]

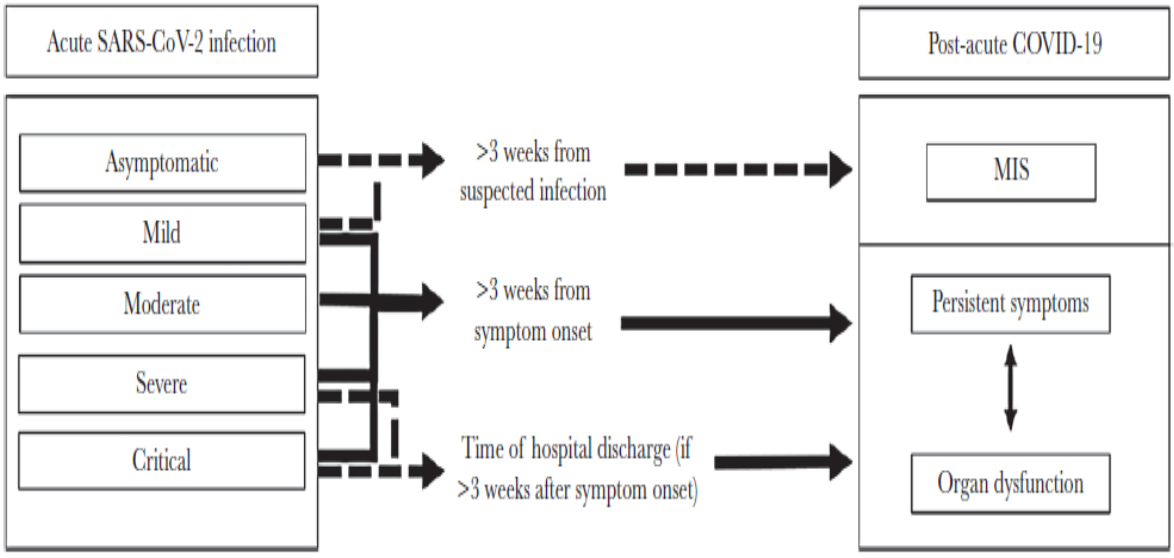

Figure 2. Phase of acute SARS-CoV-2 infection to post-acuteCOVID-19[16]

Clinical Description

The prevalence of long COVID globally is around 22.1% (95% CI: 21.2% to 23.2%) of patients with a positive test result for COVID-19 who are reported to still have at least 1 symptom within 5 weeks post COVID-19 infection, while 9.8% (7.4% to 13.1%) had symptoms for 12 weeks. The most common clinical symptoms found within 5 weeks post-infection were fatigue (12.7%), cough (12.4%), headache (11.1%), loss of sense of taste or smell (10.4%), and muscle pain (8.8%). Women have a slightly higher prevalence than men, with a value of 23.6% and 20.7%, respectively, which are dominated by the 35-49-year-old (26.8%), 50-69-year-old (26.1%), and 25-34-year-old (24.9%).[17]

Risk Factor

Epidemiological studies show that long COVID is more common in elderly patients, women, patients with comorbidities, obesity, psychiatric disorders, and those with blood type A. Patients with long COVID tend to experience more acute symptoms. The findings of symptoms such as fatigue, headache, shortness of breath, chest pain when breathing deeply, sensitive skin, hoarseness, and myalgia, as well as clinical findings of signs of the severity of the disease found on CXR during the first hospital visit in the acute phase, are also long-term risk factors for long COVID ($P<0.05$).[10]

In an epidemiological study by Belgian Health Care, the knowledge center reported that there was a statistically significant relationship between comorbidity or underlying medical conditions and clinical symptoms that appeared at the onset of infection with the occurrence of long COVID-19 ($P=0.003$).[10,17] Increased blood urea levels and D-dimer values are also independent biomarkers for the occurrence of pulmonary dysfunction in post-COVID-19 patients within 3 months after

hospitalization. The possible cause of urea and D-dimer being significant biomarkers is not only inflammation but also kidney damage and blood clotting disorders.[11]

Pathophysiology

Until now, there has not been much literature that clearly explains the pathophysiology of long COVID. In trauma or a severe primary infectious disease such as COVID-19, the systemic inflammatory response syndrome (SIRS) is dominant. This dominant systemic inflammatory response triggers the body's long-lasting compensatory anti-inflammatory response syndrome (CARS). The goal of the CARS response is to reciprocally regulate the systemic inflammatory response to reduce hyperinflammatory conditions, prevent maladaptive multiorgan dysfunction, and restore normal immunological hemostasis.[12]

This anti-inflammatory response syndrome triggers post-infectious or post-traumatic immunosuppression. The simultaneous interaction of several factors plays a role in regulating the balance of pro- and anti-inflammatory responses, namely CARS and SIRS, which determine the impact or outcome of COVID-19. The exaggerated inflammatory response that occurs is the result of (1) exposure to a virus or inoculum, (2) the presence or absence of comorbidities, and (3) an immunocompetent state, and is characterized by excessive release of inflammatory cytokines such as interleukins 1, 6, 8, 17, and 1β, monocyte chemoattractant protein-1, and tissue necrosis factor; collectively known as "cytokine storm".[12]

This process leads to the development of acute lung injury (ALI), acute respiratory distress syndrome (ARDS), coagulopathy, hypotension, hypoperfusion, organ failure (also known as multi-organ failure (MOF) or multi-organ dysfunction syndrome), and death.[12]

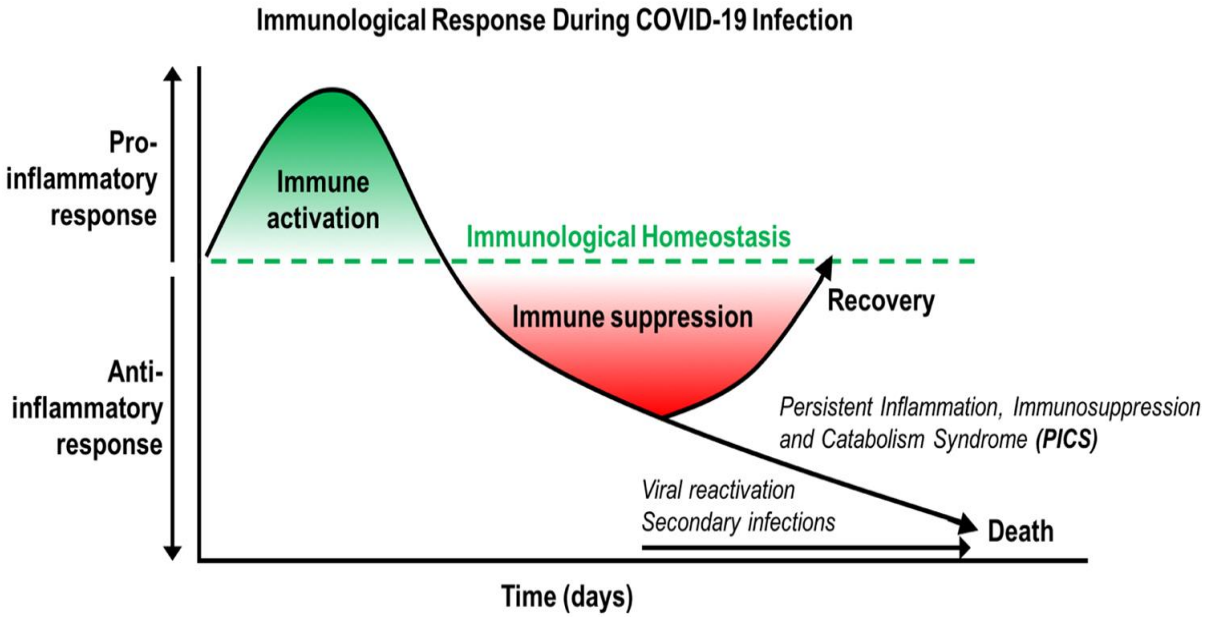

Figure 3. Immunological Respons During Covid-19 Infection[12]

On the other hand, if the inflammatory response is suppressed too far in the direction of CARS, then after the immune system has overcome the initial hyperinflammation caused by cytokine storm and progressed to ARDS, it enters a stage of prolonged immunosuppression, leading to persistent inflammation, immunosuppression, and the catabolism syndrome that becomes one of the hypotheses causing post-acute COVIDsyndrome (PACS) (Figure 3).[12]

Mechanisms regarding post-COVID sequelae include virus-induced cytokine storms and dysregulation of immune responses. Competent viral replication rarely improves within 20 days of symptom onset, suggesting that symptoms are influenced by immunological phenomena. In this immunological phenomenon, the virus persists constantly in the immunological system. This makes it difficult for the virus to be destroyed by the body's immune system and causes endothelial injury and ongoing organ dysfunction, causing acute symptoms after COVID-19 infection.[12]

Mechanisms include a virus-dependent mechanism (invasion of alveolar epithelial and endothelial cells by SARS-CoV-2) and virus-independent mechanism (immunological damage and perivascular inflammation) that damage the endothelial-epithelial barrier by monocyte and neutrophil invasion and extravasation of protein-rich exudate into the alveolar space consistently and cause fibrosis, which is provoked by cytokines such as interleukin-6 (IL-6) and transforming growth factor beta (TGF-β), thus predisposing to bacterial colonization and subsequent infection. The findings in postmortem studies are that the histologic features of lung tissue are accompanied by severe endothelial injury along with the organization and foci of diffuse fibroproliferative alveolar damage, diffuse thrombosis, and microangiopathy.[11,14]

Impact of Long COVID on the Body

Patients with COVID-19 are dominated by those with mild to moderate symptoms. In total, it is estimated that 10-15% of cases develop severe symptoms, and about 5% become critical. In many patients, some symptoms can persist and occur within weeks to months after recovery. It can also occur in mild cases. In this phase, the patient is no longer infectious.[2] Symptoms after COVID-19 vary between patients. Currently, there are not many clinical studies regarding sequelae after COVID-19.[18]

Several systems or organs of the body can be affected by COVID-19. In the lungs, COVID-19 infection can cause lung tissue damage and pulmonary restriction disorders. Dyspnea, decreased exercise capacity, and hypoxia are the most common persistent symptoms. On investigation, it was found that there was a decrease in the value of the diffusion capacity, ground glass opacity, and fibrosis on radiological examination. Assessment of lung function progression or improvement can be done by checking oxygen saturation, 6-minute walk tests (6MWTs), pulmonary physiology, high-resolution CT

(HRCT) of the chest, and CT angiography if needed.[19,20]

Persistent post-COVID syndrome, also known as long COVID-19, is a pathological entity that includes physical, medical, and cognitive sequelae after COVID-19 infection. Long COVID or post COVID-19 sequelae include persistent immunosuppression and fibrosis in the lungs, heart, and blood vessels. Pathological fibrosis of organs and blood vessels refers to increased mortality and a decreased quality of life. Inhibition of TGF-β, immune modulators, and fibrosis plays a role in this post-COVID sequelae.[12]

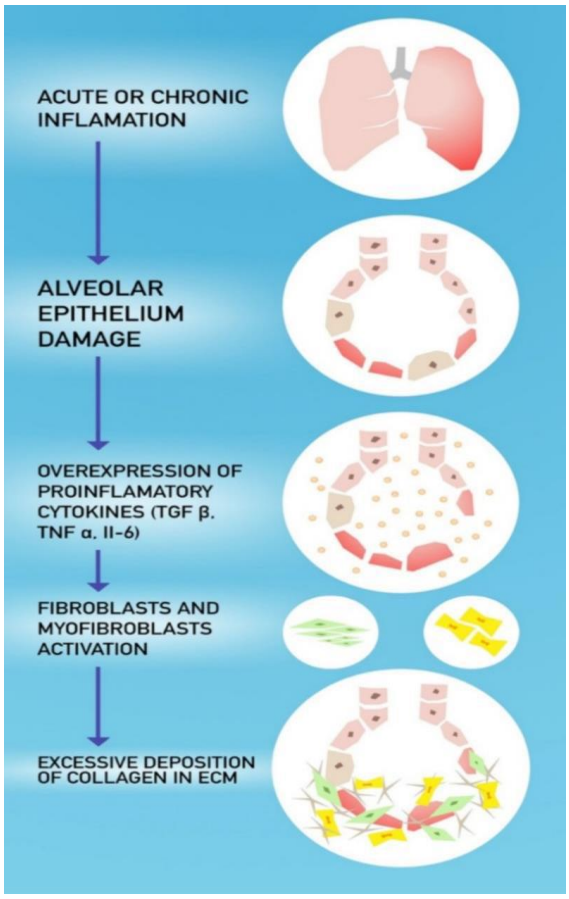

Figure 4. Lung Fibrosis Pathogenesis[19]

Lung tissue analysis of five cases with severe COVID-19-associated pneumonia, including two autopsy specimens and three specimens from the lungs of explored lung transplant recipients, showed histopathology and single-cell ribonucleic acid (RNA) expression patterns similar to those of end-stage pulmonary fibrosis without SARS-CoV infection. This suggests that the majority of individuals infected with COVID-19 develop pulmonary fibrosis, and this occurrence occurs more rapidly in the phase after the resolution of the acute infection.[14]

It has been reported that SARS-CoV-2 uses angiotensin-converting enzyme-2 (ACE-2) as a receptor on the human endothelium, causing lung damage and parenchymal lesions. Research on the distribution of ACE-2 in tissues shows that the viral receptor is very broad and expressed in human tissues such as the lungs, digestive tract, kidneys, testes, and other organs. Pulmonary fibrosis is a pathological consequence of acute and chronic interstitial lung disease characterized by damaged alveolar epithelial reconstruction, persistence of fibroblasts, and excessive deposition of collagen and other extracellular matrix (ECM) components with damage to normal lung architecture.[19]

When lung tissue damage occurs, it triggers cells to release excessive growth factors and cytokines, including monocyte chemoattractant protein-1 (MCP-1), transforming growth factor-β (TGF-β), tumor necrosis factor-α (TNF-α), FGF, PDGF, interleukin-1b (IL-1b), and interleukin-6 (IL-6). Through several studies and scientific literature, serum

levels of these cytokines have greatly increased in COVID-19 patients.[13,19]

This dysregulation of matrix metalloproteinase release causes epithelial and endothelial damage and uncontrolled fibroproliferation. TGF-β regulates fibrosis and, together with VEGF, Il-6, TNF, and vascular dysfunction, participates in the progression to fibrosis due to the differentiation and activation of fibroblasts into active myofibroblast foci that are responsible for the excessive accumulation of extracellular matrix in the basement membrane and interstitial tissue.[13,19]

In the heart, COVID-19 can cause palpitation, dyspnea, chest pain, heart muscle damage, and heart failure. Other sequelae found were myocardial fibrosis, arrhythmias, tachycardia, and autonomic dysfunction due to excessive inflammation of the heart.[21–23] Research conducted by the University of London in 2020 found that of 2739 respondents consisting of post-COVID-19 patients aged >18 years, 86% experienced cardiovascular symptoms, with the percentage of symptoms of palpitations, tachycardia, and chest pain is 68.8%, 61.4%, and 53.1%, respectively.[23]

The impact of COVID-19 on the brain and nervous system is anosmia, venous thromboembolism (pulmonary embolism, heart attack, and stroke), and cognitive disorders such as impaired memory and concentration. In the field of neuropsychiatry, COVID-19 can cause fatigue, myalgia, headaches, anxiety, depression, post-traumatic stress disorder, and sleep disturbances, which are reported to occur in 30-40% of COVID-19 sufferers.[14]

According to data from 2739 respondents in the 2020 of long COVID symptom study by the University of London, which was conducted for 7 months post-acute COVID-19 infection, 72.8% of respondents experienced memory disorders, with short-term and long-term memory disorders of 64.8% and 36.12%, respectively. In addition, other neuropsychiatric impacts were observed, namely 78.6% of respondents experienced sleep disturbances, 57.9% experienced anxiety, 47.3% experienced depression, and 37.6% experienced emotional control difficulties.[23]

This neuropsychiatric disorder is associated with inflammation that occurs in microglia nerve fibers, which causes multisystem disorders ranging from physical to psychological disorders of the nervous system. In the musculoskeletal system, COVID-19 can cause joint and muscle pain and fatigue. This was found in the same study, with a percentage of musculoskeletal disorders as high as 93.9%, with symptoms of chest tightness at 74.8%, followed by myalgia at 69.1%, and joint pain at 52.2%.[23]

Management

Long COVID management includes a holistic and multidisciplinary approach. Assessment of disease history and symptoms is very helpful in the diagnosis and management of long COVID. Long COVID management requires repeated assessment and evaluation. Management

includes psychological support, supportive investigations, oxygenation therapy if needed, nutritional management, pharmacological therapy, medical rehabilitation, and hospitalization if indicated.[14,15]

The multidisciplinary team in long COVID-19 management includes first-level care in first-rate primary care facilities, pulmonology, cardiology, infectious diseases, neuropsychiatry, pharmacy, occupational health, and health care management, but the involvement of each of these fields varies according to indications.[20] Supportive examinations carried out for long COVID-19 include laboratory tests, oxygen saturation, radiology, lung function, electrocardiography, and quality of life assessment using a questionnaire.[15,21]

Laboratory tests performed include a complete blood count, CRP, ferritin, liver function, kidney function, blood glucose, blood gas and electrolyte analysis, blood coagulation factor, and PCR swab examination. Radiological examination includes CXR and/or thoracic ultrasonography and/or CT scan, and lung perfusion scan if indicated. Lung function tests were also carried out to assess lung physiological disorders.[15,21]

Rintatolimod is the first successful immunomodulatory drug for the treatment of phase II/III encephalomyelitis/chronic fatigue syndrome (ME/CFS). This therapy has the potential to improve the symptoms as well as therapy in long COVID-19 so that it can improve the patient's quality of life. Another therapy recommended for long COVID is an agonist against mast cell activation syndrome (MCAS).[11]

Mast cell activation syndrome causes multisystem inflammatory and allergic disorders, and triggers the activation of fibroblast factors that could lead to pulmonary fibrosis, which is often found in COVID-19 patients. The SARS-CoV2 virus has been reported to trigger mast cell responses along with other immune cells, given that MCAS and COVID have a similar underlying mechanism and range of therapeutic choices. Managing mast cell-mediated hyperinflammation states and reducing symptoms further may be advantageous for patients' long-term control and recovery.[11]

Other pharmacological treatment options include antiallergic antihistamines (olopatadine and ketotifen), anti-inflammatory antibiotics (clarithromycin), and corticosteroids (hydrocortisone and dexamethasone). The persistence of SARS-CoV-2 is one factor that contributes to the occurrence of long COVID. A pilot clinical trial project on long COVID therapy in 2020 in India reported that vitamin D3 therapy in the oral form of cholecalciferol could increase viral clearance, which shortened the duration of SARS-CoV-2 infection.[11]

Oral cholecalciferol also decreased fibrinogen levels in infected individuals, thereby improving pulmonary fibrosis. Following the results of this study, antifibrotic therapy (nintedanib and pirfenidone) became the recommended potent therapeutic option to treat the long-term effects of pulmonary fibrosis in COVID-19. Another therapeutic option is

probiotics. Probiotics and prebiotics have been recommended as supplements in COVID-19 patients, referring to their safety and benefits as systemic immunomodulators in the regulation of the lung-digestive tract axis.[11]

Non-pharmacological therapy in the field of pulmonology includes pulmonary rehabilitation, oxygen therapy, psychotherapy, adequate nutrition, and hospitalization, as indicated.[15] Functional rehabilitation is one of the recommendations that has proven to be meaningful in the management of long COVID. In rehabilitation, patients are encouraged to perform light aerobic movements that depend on each individual's capacity.[2,11]

The difficulty level of rehabilitation is increased according to the level of tolerance until clinical improvement is seen (4-6 weeks). The rehabilitation carried out includes breathing exercises to increase the efficiency of the respiratory muscles and diaphragm. This exercise is done for 5-10 minutes per day. This rehabilitation exercise is good for patients with chronic obstructive pulmonary disease, acute respiratory depression syndrome, and COVID-19. These medically modifiable and supportive capabilities can help maintain quality of life and mental health.[2,11]

CONCLUSION

Pulmonary fibrosis in COVID-19 occurs due to the destruction of the alveolar epithelium and the formation of foci of active myofibroblasts, causing excessive accumulation of extracellular matrix in lung tissue. Long COVID management requires a multidisciplinary approach, including health workers and the wider community, as well as systematic assessment management. Referrals to specialists are recommended as indicated. The recommended therapy includes pharmacological (symptomatic, micronutrients, antibiotics, and anti-inflammatory) and non-pharmacological (medical and psychosocial rehabilitation).

REFERENCES

1. Iqbal A, Iqbal K, Arshad Ali S, Azim D, Farid E, Baig MD, et al. The COVID-19 Sequelae: A Cross-Sectional Evaluation of Post-recovery Symptoms and the Need for Rehabilitation of COVID-19 Survivors. Cureus. 2021;13(2):e13080.
2. Nabavi N. Long covid: How to define it and how to manage it. BMJ. 2020;370:m3489.
3. Department of Communications (DCO). Post COVID-19 condition [Internet]. WHO. 2021. Available from: https://www.who.int/podcasts/episode/science-in-5/episode--47---post-covid-19-condition
4. Gorna R, MacDermott N, Rayner C, O'Hara M, Evans S, Agyen L, et al. Long COVID guidelines need to reflect lived experience. The Lancet. 2021;397(10273):455–7.
5. WHO. Number of COVID-19 cases reported to WHO [Internet]. WHO.

2021 [cited 2021 May 23]. Available from: https://data.who.int/dashboards/covid19/cases?n=c

6. Kementrian Kesehatan RI. Situasi COVID-19 di Indonesia [Internet]. Kementrian Kesehatan RI. 2021 [cited 2021 May 23]. Available from: https://covid19.go.id/peta-sebaran-covid19.%20Diakses%2023%20Mei%202021
7. Dinas Kesehatan Provinsi Riau. Riau Province COVID-19 update [Internet]. Dinas Kesehatan Provinsi Riau. 2021 [cited 2021 May 23]. Available from: https://corona.riau.go.id
8. Kementrian Kesehatan Republik Indonesia (Kemenkes RI). Pedoman Pencegahan dan Pengendalian Coronavirus Disease (Covid-19) Revisi Ke-5. Jakarta; 2020.
9. PDPI, PERKI, PAPDI, PERDATIN, IDAI. Pedoman tatalaksana COVID-19 Edisi 3 Desember 2020. Pedoman Tatalaksana COVID-19. 2020. 36–37 p.
10. Zapatero DC, Hanquet G, Heede K Van Den. COVID-19–KCE CONTRIBUTIONS - Epidemiology of Long Covid: A Pragmatic Review of the Literature. Belgium: Belgian Health Care Knowledge Center; 2021.
11. Yong SJ. Long COVID or post-COVID-19 syndrome: putative pathophysiology, risk factors, and treatments. Infect Dis. 2021;53(10):737–54.
12. Oronsky B, Larson C, Hammond TC, Oronsky A, Kesari S, Lybeck M, et al. A Review of Persistent Post-COVID Syndrome (PPCS). Clin Rev Allergy Immunol. 2021;64(1):66–74.
13. Dani M, Dirksen A, Taraborrelli P, Torocastro M, Panagopoulos D, Sutton R, et al. Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies. Clinical Medicine. 2021;21(1):e63–7.
14. Nalbandian A, Sehgal K, Gupta A, Madhavan M V., McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601–15.
15. PDPI. Panduan Umum Praktik Klini Penyakit Paru dan Pernapasan. Jakarta: PDPI; 2021.
16. Amenta EM, Spallone A, Rodriguez-Barradas MC, El Sahly HM, Atmar RL, Kulkarni PA. Postacute COVID-19: An Overview and Approach to Classification. Open Forum Infect Dis. 2020;7(12):ofaa509.
17. Ayoubkhani D, Gaughan C, Jenkins J. Update on long COVID prevalence estimate. ONS. 2021.
18. Carfì A, Bernabei R, Landi F. Persistent Symptoms in Patients After Acute COVID-19. JAMA. 2020;324(6):603–5.
19. Lechowicz K, Drożdżal S, Machaj F, Rosik J, Szostak B, Zegan-Barańska M, et al. COVID-19: The Potential Treatment of Pulmonary Fibrosis Associated with SARS-CoV-2 Infection. J Clin Med. 2020;9(6):1917.
20. Vehar S, Boushra M, Ntiamoah P, Biehl M. Post-acute sequelae of SARS-CoV-2 infection: Caring for the 'long-

haulers.' Cleve Clin J Med. 2021;88(5):267–72.

21. Knight SR, Ho A, Pius R, Buchan I, Carson G, Drake TM, et al. Risk stratification of patients admitted to hospital with COVID-19 using the ISARIC WHO Clinical Characterisation Protocol: development and validation of the 4C Mortality Score. BMJ. 2020;370:m3339.
22. 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.
23. Davis HE, Assaf GS, McCorkell L, Wei H, Low RJ, Re'em Y, et al. Characterizing long COVID in an international cohort: 7 months of symptoms and their impact. EClinicalMedicine. 2021;38:101019.