# Rehabilitation as an alternative therapy for Post COVID-19 Syndrome (PCS)

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**Abstract**

Post COVID-19 Syndrome or PCS is a group of prolonged symptoms that are experienced by COVID-19 patients and remained at least two months after the infection were healed. This condition could lower the quality of life of the patient after the infection of COVID-19. Some treatment approach has been introduced to treat PCS including conventional therapies, and non-conventional therapies such as rehabilitation were suggested to treat PCS. This narrative review will explain what is PCS, the pathophysiology of PCS, and how rehabilitation works to treat Post COVID-19 Syndrome. A literature search using online databases PubMed, and ScienceDirect using keyword: "Post COVID-19", AND "rehabilitation", OR "physical rehabilitation", OR "psychological rehabilitation", OR "neuropsychology rehabilitation", OR "medical device-based rehabilitation" OR "infectious disease", AND "efficacy" to find all studies that are relevant. The type of studies that covered in this review are experimental studies, clinical trials, and in-silico studies. Our review finds that rehabilitation have a promising potential in treating PCS. Therefore, more research on additional forms of therapy that were left out of this review but may be useful in addressing Post COVID-19 Syndrome.

*Keyword*: rehabilitation, Post COVID-19, physical rehabilitation, psychologycal rehabilitation, neuropsychology rehabilitation, infectious disease, efficacy

## 1. Introduction

A new coronavirus known as severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) was discovered in December 2019, also discovered to have a high mortality rate associated with acute respiratory distress syndrome (ARDS) (Li, 2020). Before, it was thought that a zoonotic relationship was the source of the SARS-CoV-2 pandemic, which originated in a seafood market in Wuhan, China. Later on, it was found that the outbreak was largely caused by human-to-human transmission (Zhang, 2020). More than 3 billion people, or 44% of the global population, had at least one SARS-CoV-2 infection as of November 2021 (Li, 2020, Zhang, 2020; COVID-19, 2022).

The clinical manifestations of COVID-19 infection bear similarities to those of viral pneumonia, including fever, dyspnea, sore throat, dry cough, chest pain, and extrapulmonary conditions such as thrombosis, neuropathy, cardiomyopathy, and gastrointestinal diseases (Gupta et al., 2020; Tsai et al., 2021). While the majority of treatments have been successful in helping patients recover completely from the infection, some of them continue to cause side effects even after a COVID-19 test is negative. These side effects are known as post-COVID-19 syndrome (PCS).

Post-COVID-19 Syndrome (PCS) is a group of COVID-19 symptoms that occur in people who have a history of suspected or proven SARS-CoV-2 infection. The symptoms often appear three months after the COVID-19 infection first appears and remain for at least two months, and they cannot be explained by any other diagnosis. According to WHO estimations, there are a total of 470 million cases of COVID-19 infections globally, and 200 million individuals are thought to be either experiencing or have already had long-term COVID-19-related health repercussions (Chen et al., 2022). PCS can affect multiple organs, exhibit a remission-relapse trend, and significantly decrease the quality of life (Jones et al., 2021). Mast cell activation syndrome (MCAS), which is defined by mast cell hyperactivity with an excessive and inappropriate release of chemical mediators, is linked to post-COVID-19 syndrome (PCS). PCS may arise as a result of significant effects from autoimmune mimicry, reactivation of pathogens, and inflammatory reactions in addition to modifications in the host microbiome.

In treating PCS, practitioners have given it their all. Despite the introduction of multiple PCS treatments, there are still large gaps in both clinical and practical knowledge. This does not include any recommended specific treatments. However, some alternative therapeutic approaches that are thought to be safer and more effective than the current standard pharmaceutical treatments are being investigated. such as physical therapy, exercise, and neuropsychological counselling.

## 2. Material and Methods

This review was conducted by searching for efficacy, and recommendation of using rehabilitation as an alternative therapy for Post COVID-19 Syndrome in two databases, PubMed (https//:pubmed.ncbi.nih.gov), and Science Direct ( https//:sciencedirect.com/). The keyword that used are: “Post COVID-19”, AND “rehabilitation”, OR “physical rehabilitation”, OR “psychological rehabilitation”, OR “neuropsychology rehabilitation”, OR “medical device-based rehabilitation”, AND “efficacy”.

The inclusion criteria are an full-text literature, released within five years, with test subjects are patient with an Post COVID-19 Syndrome who received rehabilitation for therapies. Type of studies that included in this review are: experimental studies, clinical trials, and in-silico studies. The exclusion criteria for this article are studies without abstract, and without English version.

## 3. The pathophysiology of PCS

One possible cause of organ along with tissue dysfunction in PCS is systemic inflammatory response syndrome, also known as SIRS. MCAS and PCS are thought to be connected. SARS-CoV-2 infection-induced stressor interactions in PCS can activate mast cell genes, leading to aberrant regulation of mast cell activation (Maxwell et al., 2021). Autoantibodies are produced as a result of SARS-CoV-2 infection activating toll-like receptors (TLRs) on immune system cells. Mast cells are then activated by these autoantibodies interacting with the immunoglobulin receptors on mast cells (Mukherjee et al., 2021). Mast cells can express ACE2 in addition to producing vasoconstrictor leukotrienes (LTs), which control pulmonary RAS. Many inflammatory mediators, such as platelets-activating factor (PAF), histamine, heparin, tryptase, prostaglandins (PGs), LTs, as well as chemokines like IL-1β and IL-6, are released in response to mast cell stimulation. When infected with SARS-CoV-2, there is an increased release of cortisol, adrenaline, and corticotropic releasing factor (CRF) during stressful situations. Furthermore, the gut microbiota is altered by stress, which has an impact on neurotransmitters release, the metabolism of tryptophan, also short-chain free fatty acids (SCFAs) release. Mast cells become activated as a result of these modifications, and they release inflammatory cytokines (Fuchs et al., 2012).

A balanced anti-inflammatory response will typically be triggered by COVID-19's excessive immune response and high proinflammatory response, which will result in immunosuppression to preserve immunological homeostasis (Range, M., and Moser, 2013; Sugimoto et al., 2016). However, PCS can develop as a result of prolonged immunosuppression (Cañas, 2020). An immunosuppressive, profibrotic, and anti-inflammatory cytokine called transforming growth factor β (TGF-β) is released during and after SARS-CoV-2 infection to counteract overly proinflammatory reactions. This regulation, however, is not effective in PCS. Consequently, there is ongoing inflammation. Some studies have revealed that long-term immune stimulation is also triggered by an infection's persistence. Persistent infection induces autoreactive T cells through antigen-presenting cell presentation of antigens, leading to Multisystem Inflammatory Syndrome (MIS). (Goërtz et al., 2020; Gombar et al., 2020).

## 4. Clinical manifestation of PCS

PCS can present with a variety of clinical symptoms and organ manifestations due to the expression of the ACE2 receptor in multiple organs and the multi-organ manifestation of COVID-19. Generally speaking, though far less frequently, the primary symptoms that affect adults can also affect children and adolescents. The way the pandemic has spread thus far has demonstrated that different SARS-CoV-2 virus variants can cause different symptoms and organ manifestations and that the vaccination status of an infected individual can also affect these changes. The clinical symptoms that may appear in Post COVID-19 Syndrome are anosmia, dyspnea, persistent cough, asthma exacerbation, atypical chest pain, arrhythmia, tachycardia, sleepiness, fatigue, impaired memory/concentration, diverse psychiatric alterations, muscle weakness, myalgia, reduced glomerular filtration rate, phlebitis, nausea, diarrhea, and abdominal pain (Hallek et al., 2023).

## 5. Rehabilitation for PCS

### *5.1 Physical Therapy*

Numerous researches demonstrate that COVID-19 survivors continue to endure protracted sequelae. The most common symptom reported is fatigue. Moreover, there are symptoms like a persistent cough, dyspnea during physical activity, and muscle soreness that continues for months. It is possible to develop pulmonary fibrosis and pulmonary vascular blockage. This complication is most likely caused by acute phase inflammation (ARDS) and inflammation that results in microangiopathic changes, edema, hyaline membranes, leukocyte infiltration, and alveolar epithelial thrombosis. Furthermore, according to Esendağli et al. (2021), the kinin-kallikrein system, renin-angiotensin system, and coagulation all contribute significantly to worsening clinical outcomes. Long-term immobilization can also cause less common physical side effects such as compression injuries, myogenic, neurogenic, and iatrogenic contractures, postural instability, venous thromboembolism, muscle shortening, and cardiorespiratory deconditioning (Premraj et al., 2020; Raman et al., 2022). Physical rehabilitation, therefore, could improve functional capacity, fitness, and endurance, increase skeletal and respiratory muscle strength, improve cardiovascular function, and ultimately improve the patient's quality of life. This includes breathing exercises, aerobic exercise, resistance training, and a combination of these exercises. This includes reducing neurological and psychological symptoms, and improving sleep quality, and brain fog (Jimeno-Almazán et al., 2023). According to Maestroni et al. (2020), exercise can strengthen the immune system, decrease proinflammatory cytokines, and increase anti-inflammatory cytokines. It can even speed up the body's cells' ability to regenerate, including immune cells.

Muscle fiber composition can be altered, actin and myosin contractile assemblies can be synthesized, and coordination between muscles can be enhanced through low-load, high-volume strength training (Alcazar et al., 2019). Strength and endurance training combined can improve quality of life, functional capacity, and peak lung oxygen uptake while lowering oxidative stress (Pinckard, Baskin, and Stanford, 2019). Conversely, aerobic and cardio exercise improves blood vessel health (cardiac remodeling, angiogenesis, blood volume expansion), improves mitochondrial biogenesis and function, and preserves or improves cardiovascular function through myokine release from skeletal muscle (Pinckard, Baskin, and Stanford, 2019). Physical exercise also acts as a psychoactive drug. Regular physical exercise can control mood and reduce psychological stress, also prevent depression and anxiety. Physical exercise modulates brain structure and its function, additionally causes structural and neurochemical alterations in the myokine as well as brain-derived neurotrophic factor (BDNF) released during contraction, which boosts the growth of new neurons and synapses in the brain, especially in the hippocampal dentate gyrus. Moreover, it protects against cognitive dysfunction and fosters brain plasticity (Range and Moser, 2015; Jimeno-Almazán et al., 2021; Marques-Aleixo et al., 2021).

### *5.2 Psychological and Well-Being Rehabilitations*

A Meta-Analysis study shows that psychiatric manifestations such as: anxiety, sleep disturbances, and depression are common. Their prevalence increases dramatically in post-COVID-19 patients, some of these symptoms appear after three months after the acute phase and can last more than six months. This could caused by combination of an biological, and psychologic mechanism. SARS-CoV-2 RNA can stays in brain tissue for a long time, exacerbating neuronal loss over time. In addition, the influx of innate immune cells secondary to disruption of the blood-brain barrier can prolong neuroinflammation. Conversely, post-infection neuropsychiatric symptoms, especially sleep disturbances, are strongly linked to social factors like trauma throughout acute infection, confinement, isolation, as well as persistent fatigue (Najjar et al., 2020; Premraj et al., 2020; Wu et al., 2020; Generoso et al., 2021).

Neuropsychological interventions such as Othmer therapy, Cognitive Behavioral Therapy (CBT), and other interventions can control mood and prevent depression, anxiety, and psychological stress. This therapy contributes to reducing fatigue and improving sleep quality. Psychological therapy helps reduce changes in the volume and activity of the amygdala, a part of the brain that is important in emotions and feelings. Emotion processing and emotional associations in memory are altered by affecting the hippocampus. In addition, it also prevents a decrease in prefrontal cortex activity (decreased prefrontal control) (Vasile, 2020; Orendáčová, Kvašňák, and Vránová, 2022).

### *5.3 Neurophysiology Rehabilitations*

The three neurological symptoms of PCS patients that are most commonly reported are headache, ageusia, and anosmia. However, observational studies show that cerebrovascular disease (CVD), preventive encephalopathy, de novo status epilepticus, and Guillain-Barré syndrome (GBS) are highly prevalent. The underlying factor for these symptoms could be the endothelium of capillaries and neurons' ACE2/SARS-Cov-2 interaction. This is immune-mediated with markedly increased interleukin activity that directly affects every area of the brain (Nuwer, 2020; Camargo-martínez, Lozada-martínez, and Escobar-collazos, 2021).

Neurological therapy, such as the use of Transcutaneous auricular vagus nerve stimulation, Neurofeedback Othmer Therapy, transcranial brain microcurrent stimulation (NIBS), and other modalities, can improve vascular dysregulation. Vascular autoregulation fails to work where dilation of the central arteries and veins is at or below the lower limit of the normal range, while the smaller peripheral vessels, arteries, and veins, are even lower. This indicates the failure of blood vessels to dilate, which reduces blood flow far below the average level of perfusion in the brain and causes stress on the brain (Lamontagne et al., 2021; Miskowiak et al., 2021). For example, NIBS can enhance peripheral artery and vein dilatation and narrowing capacity by over 300% in multiple dimensions. The normal reference range is exceeded by peripheral venous dilatation. Retinal microangiopathy or viral residues may cause ocular symptoms like follicular conjunctivitis, redness, discharge, and pain in the eyes. Improved microvascular function in the eye and a decrease in visual complaints are possible with NIBS therapy (Sabel et al., 2021). Transcutaneous auricular vagus nerve stimulation has been shown to have an anti-inflammatory effect. which reduces levels of C-reactive protein (CRP) and cortisol. Although there was no significant increase in IL-6 and IL-10, however, clinically it had a positive effect on memory and attention (Laura et al., 2022).

*5.4 Medical Device-Based Rehabilitation*

Various rehabilitation modalities are utilized in treating symptoms and inflammation after acute infection. For example, the use of brain microcurrent stimulation to suppress certain neurological functions, such as locomotor behavior, depression, or attention, improves visual and cognitive dysfunction (Teselink et al. 2021). The mechanisms of this transcranial stimulation include blood flow stimulation, disturbance of brain oscillations, changes in functional connectivity in the brain networks, and alterations in the excitability of neural networks (excitation or inhibition) (Sabel et al., 2020; Teselink et al., 2021). According to Konieczka et al. (2014), this modality can reactivate hypometabolic "silent neurons," boost the expression of neurotrophic factors that safeguard synaptic and neuronal plasticity, improve brain tissue transformation, and improve blood flow and vascular autoregulation. These effects can be felt in various organs, particularly the brain, inner ear, and eyes.

Other modalities involving electrical stimulation, such as Functional Electrical Stimulation (FES) and VEST High-Frequency Chest Wall oscillation devices (HFCWO), have been used in chronic lung disease patients, muscle weakness, also spinal cord injury. The use of HFCWO can also significantly reduce daily sputum counts and improve chest radiographic images. Histopathological observations of bronchial epithelial cells, squamous cells, and alveolar histiocytes from sputum samples suggest that rehabilitation with HFCWO can contribute to effective expectoration (Çelik et al., 2022). Another electrical modality, Neuromuscular Electrical Stimulation (NMES), applies tiny electrical impulses to the nerves that innervate the muscles. The main goal of administering electrical stimulation is to induce intermittent muscle contractions to minimize loss of muscle mass, strengthen these muscles, and improve mobility recovery during and after acute care for COVID-19. Increasing muscle strength, especially skeletal muscles in breathing increases respiratory capacity (Burgess et al., 2021). Hyperbaric oxygen therapy (HBOT), a type of oxygenation therapy, can help with fatigue disorders, pain symptoms, psychiatric symptoms (such as depression, anxiety, and somatization), and dysexecutive function or brain fog. The frontal, parietal, and limbic regions of the brain that are linked to cognitive and psychiatric functions have altered microstructurally, and these alterations are linked to an increase in CBF. An increasing amount of clinical research has also demonstrated how effective HBOT is at reducing fibromyalgia patients' pain and improving their quality of life (Atzeni et al., 2019). Fibromyalgia has been linked in the past to reduced cerebral perfusion in the insula, hippocampus, putamen, prefrontal cortex, and cingulate. Blood perfusion in these areas is increased by HBOT (De Paepe et al., 2020; Zilberman-Itskovich et al., 2022).

## 6. Conclusion

Research on rehabilitation as a substitute treatment for post-COVID-19 syndrome (PCS) has demonstrated positive outcomes in managing conditions that affect PCS patients. This is demonstrated by the patients' improved clinical conditions without any unfavorable side effects. Because of this, rehabilitation presents a viable alternative treatment option for PCS patients. When choosing alternative therapies for PCS patients, a number of factors should be taken into account, such as the patients' psychosocial state, the alternative therapies' cost-effectiveness, and the clinical conditions that manifest in the patients. It must be taken into account in order for medical professionals to identify and offer appropriate alternative therapies in order to treat PCS patients' symptoms as effectively as possible.

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