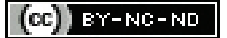# Long COVID-19 Syndrome and its Effects on Various Systems: A Narrative Review

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ABSTRACT

Since December 2019, the Coronavirus Disease-2019 (COVID-19) outbreak has led to a pandemic, causing suffering worldwide. Among the survivors of COVID-19, a second type of pandemic is observed in individuals experiencing long-term effects, known as long COVID-19 or post COVID-19 syndrome. This condition occurs when people who have recovered from COVID-19 continue to experience symptoms or develop new ones after a month or more. The exacerbation of symptoms can be attributed to various factors, including psychological, social, or biological causes, all of which contribute to the development of this condition. Although COVID-19 was first discovered a few years ago, its impact on a large population is still not fully understood. As the disease affects multiple organ systems, its effects persist even after the virus is cleared from the body, resulting in a significant number of individuals who continue to suffer from it. Therefore, this review focuses on the long-term effects of COVID-19 as post COVID-19 syndrome.

Keywords: Coronavirus disease-2019, Multiorgan failure, Psycological effect, Survivors

INTRODUCTION

Long COVID-19 syndrome is a condition characterised by long-term, multisystem, often severe health problems persisting or appearing after the typical recovery period of COVID-19 [1]. Long COVID-19 can include a wide range of symptoms, such as fatigue, breathlessness, chest pain, cognitive impairment, depression, anxiety, and Post-Traumatic Stress Disorder (PTSD). Less common symptoms like pernio, chills, flushing, ear pain, visual impairment have also been documented. It can affect anyone who has been infected with the virus that causes COVID-19, regardless of age, sex, or severity of initial illness [2]. Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) is responsible for the severe acute respiratory syndrome observed in this disease, along with symptoms like fever, fatigue, cold, cough, and in some cases Gastrointestinal (GI) symptoms [2].

The prevalence and duration of long COVID-19 are uncertain, but some studies suggest that up to 30% of people who had COVID-19 may experience long-term effects for months or years [2,3]. Long COVID-19 poses significant challenges for individuals, health systems, and society, as it may result in disability, reduced quality of life, and economic burden [2]. Many people with long COVID-19 show a negative Reverse Transcription Polymerase Chain Reaction (RT-PCR) test, indicating microbiological recovery; hence, post COVID-19 syndrome is basically a time lag between microbiological and clinical recovery.

After further research, it was found that the genetic material of the coronavirus, Ribonucleic Acid (RNA), can be observed in discharge from the nose, sputum, nasal swab, oropharyngeal swab, and blood [4]. This led us to believe that transmission of this disease could be airborne [5]. The minimum dose of the virus that can cause an infection is not clear yet, but it has been observed that the virus load can get as high as 108 viruses/mL of the swab sample [1]. Diagnosis is confirmed in most cases by performing RT-PCR on the sample taken. It is done to detect the genetic material of the virus in the sample. Other examinations done include Computed Tomography (CT) of the chest and/or X-ray of the chest to check the severity of the disease and also to confirm pneumonia. Various blood tests are also done to check for the severity of the infection such as liver function tests, bilirubin, LDH level, complete blood count, and D-dimer. For treatment and symptomatic relief of COVID-19, the drugs used are antiviral drugs such as ribavirin, ritonavir, lopinavir, remedesivir, and plasma of the patients who have recently recovered from COVID-19. Antibiotics (azithromycin), antiallergic (montelukast), and antacids (pantoprozole) are also given [6]. Studies and research from across the globe reflect that a considerable portion of recovered COVID-19 cases continues to experience multiple ill-health signs and symptoms, which are now dubbed as "long COVID-19" or "post COVID-19" syndrome [7,8], but very limited data is available regarding its effect on a larger population. Hence, this review was conducted focusing on the long-term effects of COVID-19 disease as post COVID-19 syndrome.

POST COVID-19/LONG COVID-19 SYNDROME

Patients who continue to experience symptoms of COVID-19 or develop new symptoms within a month after clinical and virological recovery are said to have long COVID-19 or post-COVID-19 syndrome [2]. Some individuals with long COVID-19 may report an exacerbation of symptoms, experiencing more severe or frequent symptoms than expected during the acute phase of COVID-19 [2]. For instance, psychological factors like stress, anxiety, depression, and PTSD can worsen the perception and expression of symptoms, as well as affect the coping and recovery process. Social factors such as isolation, stigma, discrimination, and lack of support can also worsen symptoms and impair the quality of life for people with long COVID-19 [9].

Biological factors, including high viral load, pre-existing conditions, immune dysregulation, autoimmunity, and organ damage, may contribute to the pathophysiology and severity of long COVID-19 syndrome [2,4]. Therefore, it is important to consider the complex interplay of these variables when assessing and managing long COVID-19, as depicted in [Table/Fig-1]. Depending on the duration of symptoms, this condition can be classified into the following phases [3]:

A. **Transition phase:** Characterised by symptoms experienced during the initial infection of COVID-19, usually lasting up to the 4th-5th week.

B. **First phase:** Encompassing acute symptoms of post-COVID-19, observed from the 5th-12th week.

C. **Second phase:** Involving symptoms of the long post-COVID-19 syndrome, occurring from the 12th-24th week.

D. **Third phase:** Consisting of persistent symptoms of the long post-COVID-19 syndrome, lasting for more than 24 weeks.

[Table/Fig-1]: A Flowchart to demonstrate the phases seen in patients suffering from long/post COVID-19 syndrome [3].

Clinical Manifestation of Long COVID-19 Syndrome

Symptoms observed in patients suffering from long COVID-19 are diverse and can include fever, sore throat, difficulty breathing, cough, palpitations, muscular pain, chest pain, rashes, diarrhea, neurological symptoms, and even consistently reduced oxygen saturation [Table/Fig-2] [10]. Common pulmonary symptoms after COVID-19 include decreased exercise capacity, hypoxia, and dyspnea. Pulmonary physiology in these patients is limited by reduced lung diffusion capacities. CT scans of such patients have revealed fibrotic changes in the lungs. Other tests used to assess post COVID-19 pulmonary function include pulmonary function tests (PFTs), high-resolution CT scans, and pulmonary angiograms [11]. Long COVID-19 can also lead to various cardiovascular manifestations such as palpitations, dyspnea, chest pain, tachycardia, and arrhythmia. Echocardiograms and electrocardiograms are performed for clinical examination of these patients. Hematologic manifestations in post COVID-19 syndrome include several thromboembolic events. This is due to the prolonged hyperinflammatory state and is observed in patients with a history of coronavirus infection [11]. Common neuropsychiatric symptoms in long COVID-19 include anxiety, depression, sleep disturbances, headaches, myalgia, and PTSD [12]. Hair loss is a prominent dermatologic symptom observed in over 20% of COVID-19 survivors. Endocrine symptoms include worsening of pre-existing diabetes mellitus, thyroiditis, and bone mineral issues [11]. Gastrointestinal symptoms mainly involve gastritis and other types of stomach infections. These occur due to the depletion of beneficial gut commensals in COVID-19 survivors [11].

Systems	Clinical symptoms
Respiratory	Dyspnoea, oxygen dependence
Central nervous	Brain fog, fatigue
Psychiatric	PTSD, dysautonomia, cognitive defects
Gastrointestinal	Diarrhoea, abdominal pain
Cardiovascular system	Cardiometabolic demand increased Diastolic or systolic dysfunction
Haematological manifestation	Deep vein thrombosis, ischaemic stroke

[Table/Fig-2]: Clinical manifestations in patients of post COVID-19 [10].

PATHOPHYSIOLOGY OF LONG COVID-19 SYNDROME

COVID-19 is a disease that affects multiple organ systems, involving their infection [13]. The exact pathophysiology of long COVID-19 is still unknown, but one theory suggests that long-term inflammation may be responsible for the symptoms observed in long COVID-19 syndrome [14]. Inflammation resulting from a coronavirus infection can cause changes in Gamma-aminobutyric Acid (GABA) neurotransmitters, which can lead to neuromotor or cognitive impairments in these patients [15]. Additionally, the alteration of neuronal function due to the increased levels of circulating cytokines, particularly Interleukin-6, can penetrate the blood-brain barrier and result in central nervous system complications. On the other hand, the thrombus inflammatory pathway may contribute to the higher incidence of stroke observed in COVID-19 cases [16]. According to some theories, other factors that contribute to post COVID-19 syndrome include dysfunction of peripheral organs, viral encephalitis, and systemic inflammation [17].

What Would be the Criteria Defined for Post COVID-19?

Another criterion includes individuals who have been unwell for several weeks or months after experiencing symptoms suggestive of COVID-19, regardless of whether they have tested positive or not. The National Institute of Health and Care Excellence (NICE), the Scottish Intercollegiate Guidelines Network, and the Royal College of Practitioners define COVID-19 as "signs and symptoms that occurred during COVID-19 and have persisted for more than four weeks, with no alternative diagnosis other than COVID-19" [18]. Hence, the first question in this discussion is whether a positive test or antibodies against SARS or COVID-19 are essential for diagnosis. Raveendran AV et al., discussed this topic and proposed three categories for long COVID-19 [19]:

1. Confirmed: Individuals who have tested positive for COVID-19 using RT-PCR.

2. Probable: Individuals who have symptoms of COVID-19 but test negative on RT-PCR, with or without radiological findings, and have had confirmed contact with a RT-PCR positive patient or individual within two weeks before symptom onset.

3. Possible: Individuals who have symptoms of COVID-19 but test negative on RT-PCR and have no contact with confirmed COVID-19 positive or suspected patients within two weeks before symptom onset.

Therefore, we propose that determining the link between post COVID-19 symptoms and the infection is based on two main conditions [11]:

1. There should be a connection or relationship between the symptoms and the COVID-19 infection.

2. The COVID-19 infection should precede the onset of symptoms. (It is not necessary for post COVID-19 symptoms to be present.)

These symptoms can be useful for future reference as they may persist for a long time and affect some people who have recovered from COVID-19. Hence, doctors and scientists should verify whether the symptoms are related to COVID-19 or not. It is important to perform tests that can accurately diagnose COVID-19, such as RT-PCR, CT scans, and COVID-19 antibody testing. CT scans can detect COVID-19 more easily than RT-PCR, but they are less specific. Antibody testing is not very useful in the first week of infection as they have low sensitivity in the early stage [9].

SYSTEMIC CLINICAL MANIFESTATIONS

Dyspnea and fatigue are the most commonly reported problems by the population with COVID-19. Chest pain and joint pain are other common symptoms. Additionally, patients have reported common symptoms of multiorgan dysfunction, specifically affecting the heart, lungs, and brain [11]. From a pathological perspective, these complications can be a consequence of direct tissue invasion by the COVID-19 virus (possibly due to the presence of the angiotensin-converting enzyme 2 receptor), chronic inflammation and cytokine release, decreased immune system response, and the hypercoagulable state associated with COVID-19 [16].

Cardiovascular

Raised Troponin I levels, along with thromboembolic disease, have been associated with myocardial damage in chronically affected COVID-19 patients. Myocardial damage and myocarditis with cardiac arrhythmias have also been reported following COVID-19

infection [16]. A study by South K et al., conducted on COVID-19 patients after a median of 75 days, suggested cardiac involvement in 78% of patients and myocardial infection in 60% of patients [5]. This chronic condition, its duration, and its severity are not necessarily related to the acute COVID-19 infection. The increased incidence of patients with cardiac abnormalities as a sequel of COVID-19 is concerning. It poses a potential threat to the general population, including adults with comorbidities, as well as young and healthy patients [17].

Pulmonary

In their study, Gupta A et al., found that three months after discharge, COVID-19-affected patients still had persistent symptoms and CT scan findings indicating deranged pulmonary function, including interstitial thickening and fibrosis of the alveolar tissue. There was also a decrease in the lung's diffusion capacity for carbon monoxide, as well as reduced strength of respiratory muscles. Pre-existing COVID-19 infection can increase the risk of cardiac and pulmonary problems [15].

Neurological

The COVID-19 virus can reach brain tissue by crossing the blood-brain barrier and invading the olfactory nerve, leading to anosmia [19]. Vertigo, headache, anosmia, and ageusia are the most common long-term neurological side effects of COVID-19. Stroke is a rare but serious complication of COVID-19. After 2-3 months of illness, encephalitis, seizures, and mood swings have also been observed. It has also been observed that recovered patients may experience neuropsychiatric impairments that can affect cognitive function, well-being, and day-to-day functioning [15].

Neuropsychiatric Effects

As the COVID-19 pandemic rapidly evolves, it has had a profound impact on the minds of people who have suffered from the coronavirus infection, as well as those who have lost their loved ones to it [16]. Neuropsychiatric symptoms are commonly observed in severely ill patients and may manifest as mood changes, obsessive-compulsive disorder, fatigue, depression, delirium, anxiety disorders, and cognitive impairment [16]. Post-traumatic stress disorder (PTSD) is seen in COVID-19 survivors, particularly in younger patients or those with a history of diabetes mellitus, autoimmune disorders, cardiovascular disorders, and obesity. It is more prevalent in female patients [17]. High rates of psychosis have also been observed in COVID-19 survivors, presenting as delusions or paranoia. This may be attributed to the stress related to the pandemic, as it has affected people on various levels [19]. Psychological effects may also stem from the side effects of treatments given during COVID-19 infection. Certain drugs, such as antiviral drugs or steroids, may increase the risk of psychosis [20]. Substance use has also increased during the COVID-19 pandemic. Many individuals have become addicted to opioids during this challenging time, and in some countries, there have been numerous deaths due to overdose [21]. Patients who use substances are now at an increased risk of COVID-19 infection. Furthermore, it has been observed that these individuals are more likely to require hospitalisation during COVID-19 infection and are more susceptible to adverse outcomes [22].

RISK FACTORS FOR LONG COVID-19 SYNDROME

Risk factors for post-COVID-19 syndrome include age, particularly those over the age of 50, obesity, patients with bronchial asthma, HIV (human immunodeficiency virus), tuberculosis, lung cancer, patients who were on steroids, and patients reporting five or more symptoms during the initial week of their illness [23]. A cohort study found that patients presenting with five or more symptoms during the initial stage of the disease may require hospitalisation and are more prone to experiencing post-COVID-19 syndrome [24]. The

presence of comorbid conditions such as asthma, ischemic heart disease, hypertension, thyroid disorders, and diabetes mellitus also increases the likelihood of post-COVID-19 syndrome [22]. Patients who were hospitalised during their initial infection, required support from the ICU during their initial infection, or experienced any complications during their infection are also at a higher risk for long COVID-19 syndrome [23].

How to Approach Patients Suffering from Post COVID-19

To diagnose a patient with long COVID-19, a thorough history taking and clinical examination are essential, especially in those who do not have a history of coronavirus infection but present with symptoms of long COVID-19 [19]. This process will also help categorise the patient as a confirmed case, a possible case of post-COVID-19, or a doubtful case of post/long COVID-19 syndrome [25-32]. The evaluation requires recording any pre-existing diseases and noting any alleviation or worsening of symptoms, as described briefly in [Table/Fig-3] [25-32].
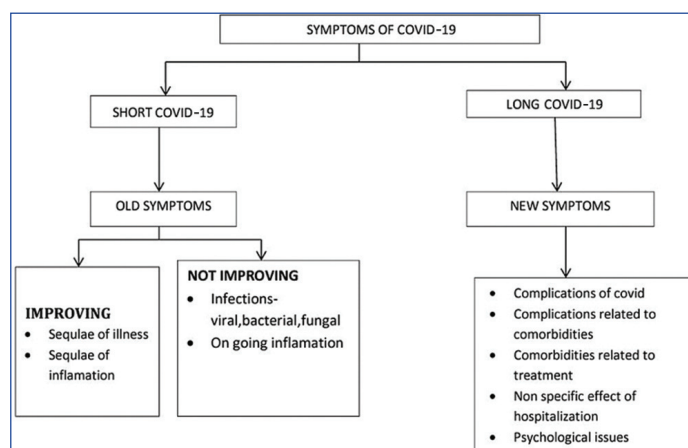
[Table/Fig-3]: Given figure gives us an idea of how to approach a patient who is suffering from post COVID-19.

MANAGEMENT OF LONG COVID-19 SYNDROME

The treatment of patients suffering from post-COVID-19 requires a comprehensive approach, including evaluating the disease, providing symptomatic treatment, addressing underlying conditions, and utilising psychological approaches [33-35]. The World Health Organisation (WHO) suggests that appropriate profiling of long/post-COVID-19 patients can facilitate the treatment process and ensure adherence to appropriate treatment protocols. Determining the patient's subgroup helps guide their treatment plan [36]. The WHO and Centres for Disease Control and Prevention (CDC) have also updated and released guidelines for the treatment of patients with long COVID-19 [36]. For the management of pulmonary symptoms, chest X-rays should be performed three months after the initial infection to monitor progress. Breathing exercises should be advised for symptom management that does not require pharmacological intervention. Antifibrotics are prescribed for patients with pulmonary fibrosis [37,38]. Beta blockers and anticoagulants have proven useful for the treatment and prevention of cardiac symptoms [39]. The use of antidepressants is not only helpful for individuals experiencing post-COVID-19 depression but has also shown improvement in the effects of post-COVID-19 syndrome by reducing inflammatory markers [40]. Numerous clinical trials are underway to explore ways to reduce inflammation in patients with post-COVID-19 syndrome [41]. Some clinical trials are investigating the use of monoclonal antibodies such as leronlimab and tocilizumab to suppress the inflammatory process observed in patients with long COVID-19 syndrome [42]. As COVID-19 infection can disrupt the normal gut microbial flora, leading to opportunistic infections, restoration of the gut microbiota with new probiotic medications is important [43]. A study by Mulangu S et al., demonstrated that antihistamines have

helped treat the pathology behind long COVID-19, and histamine antagonists have been used in clinical trials for its treatment [44]. Vitamin C supplements are also beneficial for treating long COVID-19 symptoms [45].

Specific Treatment and Treatment Protocol

The best way to treat COVID-19 is to use antiviral drugs that specifically target the virus. Some of these drugs have shown effectiveness in treating COVID-19.

- **Chloroquine and hydroxychloroquine:** These drugs have been tested against the coronavirus in laboratory settings and in China during the early stages of the pandemic. The results showed that chloroquine can combat the virus and improve outcomes for COVID-19 patients. It can also reduce the length of hospital stays and the severity of symptoms [46].

- **Lopinavir:** It is a combination of boosted protease inhibitors that were previously used in the treatment of HIV infection. It was also used during the SARS COVID-19 outbreak in 2003 and showed in-vitro activity against that virus. The recommended dose is 400 mg of lopinavir with 100 mg of ritonavir, twice daily for 14 days [43].

- **Remdesivir:** It is an adenosine and RNA polymerase inhibitor and a novel drug used for the treatment of Ebola virus infection. A randomised controlled trial of remdesivir in COVID-19 did not show significant improvement [47].

- **Favipiravir:** It is an RNA polymerase inhibitor that has shown activity against the COVID-19 virus and significant cytopathy in vero culture studies.

- **Convalescent plasma from COVID-19 survivors:** It has been shown to decrease patient hospital stay and mortality [48].

- **Nasal cannula with humidified oxygen:** This is a beneficial treatment for non-critical pneumonia. Dry Venturi masks without humidified air are used to avoid aerosolisation risks. High Flow Nasal Cannula (HFNC) and Non-invasive Positive Pressure Ventilation (NPPV) should not be given to patients affected by COVID-19 [49]. Findings from previous studies are summarised in [Table/Fig-4] [5,15,50-54].

Authors name (Ref no.)	Place and year of the study	Sample size	Findings
Gupta A et al., [15]	New York, 2020	-	Deranged pulmonary function
South K et al., [5]	United Kingdom, 2020	-	Cardiac involvement in 78% of patients and myocardial infection in 60% of patients
Dennis A et al., [50]	United Kingdom, April 2020 to August 2021	536 individuals	Single- and multiorgan impairment were present in 69% and 23% of individuals
Hu Y et al., [51]	Wuhan, China, from March 2020	85 patients	45.9% symptoms of depression (45.9%) were present, 38.8% had anxiety, and 54.1% had insomnia
Perlis RH et al., [52]	Columbia, February 2021, and July 2022	16091 patients	Fatigue in (52.2%), reported either poor memory or brain fog
Ziauddeen N et al., [53]	United Kingdom, 2020	2550 patients	Cardiopulmonary (88.8%), cognitive symptoms and exhaustion, (11.2%) exhibiting more multisystem symptoms
Bull-Otterson L et al., [54]	March 2020 to November 2021	353,164 patients	Survivors (45.4%) aged ≥65 years increased risk for neurologic conditions

[Table/Fig-4]: Showing similar findings of previous studies.

CONCLUSION(S)

Long-term COVID-19 is a common, serious, and occasionally incapacitating condition. It poses a significant health concern as patients who have recovered from COVID-19 continue to experience various symptoms. This could be attributed to mechanisms such as permanent organ damage and post-viral fatigue syndrome. Therefore, it is crucial to educate the public about the risk factors associated with long-term COVID-19 and implement management strategies.

REFERENCES

[1] Wu YC, Chen CS, Chan YJ. The outbreak of COVID-19: An overview. J Chin Med Assoc. 2020;83(3):217-20. Doi: 10.1097/JCMA.0000000000000270.

[2] Mahmud R, Rahman MM, Rassel MA, Monayem FB, Sayeed SKJB, Islam MS, Islam MM. Post-COVID-19 syndrome among symptomatic COVID-19 patients: A prospective cohort study in a tertiary care center of Bangladesh. PLoS One. 2021;16(4):e0249644. Doi: 10.1371/journal.pone.0249644.

[3] Fernández-de-Las-Peñas C, Palacios-Ceña D, Gómez-Mayordomo V, Cuadrado ML, Florencio LL. Defining Post-COVID symptoms (Post-Acute COVID, Long COVID, Persistent Post-COVID): An integrative classification. Int J Environ Res Public Health. 2021;18(5):2621. Doi: 10.3390/ijerph18052621.

[4] Garcia-Oscos F, Salgado H, Hall S, Thomas F, Farmer GE, Bermeo J, et al. The stress-induced cytokine interleukin-6 decreases the inhibition/excitation ratio in the rat temporal cortex via trans-signaling. Biol Psychiatry. 2012;71(7):574-82. Doi: 10.1016/j.biopsych.2011.11.018.

[5] South K, McCulloch L, McColl BW, Elkind MS, Allan SM, Smith CJ. Preceding infection and risk of stroke: An old concept revived by the COVID-19 pandemic. Int J Stroke. 2020;15(7):722-32. Doi: 10.1177/1747493020943815.

[6] Gupta A, Madhavan MV, Sehgal K, Nair N, Mahajan S, Sehrawat TS, et al. Extrapulmonary manifestations of COVID-19. Nat Med. 2020;26(7):1017-32.

[7] Su Y, Yuan D, Chen DG, Ng RH, Wang K, Choi J, et al. Multiple early factors anticipate post acute COVID-19 sequelae. Cell. 2022;185(5):881-95.e20.

[8] Tenforde MW, Kim SS, Lindsell CJ, Rose EB, Shapiro NI, Files DC, et al. Symptom duration and risk factor for delayed return to usual health among outpatient with COVID-19 in a multi state health care system network, United States, March-June 2020 Mmwr-Morbid W. 2020;69(30):993-98.

[9] Lutchmansingh DD, Knauert MP, Antin-Ozerkis DE, Chupp G, Cohn L, Dela Cruz CS, et al. A clinic blueprint for post-coronavirus disease 2019 RECOVERY: Learning from the past, looking to the future. Chest. 2021;159(3):949-58.

[10] Asadi-Pooya AA, Akbari A, Emami A, Lotfi M, Rostamihosseinkhani M, Nemati H, et al. Risk factors associated with long COVID-19 syndrome. A retrospective study. Iran J Med Sci. 2021;46(6):428-36.

[11] Nalbandian A, Sehgal K, Gupta A, Madhavan MV, McGroder C, Stevens JS, et al. Post-acute COVID-19 syndrome. Nat Med. 2021;27(4):601-15.

[12] Efstathiou V, Stefanou MI, Demetriou M, Siafakas N, Makris M, Tsivgoulis G, et al. New-onset neuropsychiatric sequelae and 'long-COVID' syndrome (Review). Exp Ther Med. 2022;24(5):705.

[13] Maltezou HC, Pavli A, Tsakris A. Post COVID-19 syndrome: An insight on its pathogenesis. Vaccines (Basel). 2021;9(5):497.

[14] Stratton CW, Tang YW, Lu H. Pathogenesis-directed therapy of 2019 novel coronavirus disease. J Med Virol. 2021;93(3):1320-42.

[15] Sarkesh A, Daei Sorkhabi A, Sheykhsaran E, Alinezhad F, Mohammadzadeh N, Hemmat N, et al. Extrapulmonary clinical manifestations in COVID-19 patients. Am J Trop Med Hyg. 2020;103(5):1783-96. Doi: 10.4269/ajtmh.20-0986.

[16] Raveendran AV, Jayadevan R, Sashidharan S. Long COVID-19: An overview. Diabetes Metab Syndr. 2021;15(3):869-75.

[17] Seyed Alinaghi S, Ghadimi M, Hajiabdolbaghi M, Rasoolinejad M, Abbasian L, Nezhad MH, et al. Prevalence of COVID-19-like symptoms among people living with HIV, and using antiretroviral therapy for prevention and treatment. Curr HIV Res. 2020;18(5):373-80. Doi: 10.2174/1570162X18666200712175535.

[18] NICE SaR. COVID-19 rapid guideline: Managing the longterm effects of COVID-19 2021 [NICE, SIGN and RCGPs Rapid Guideline Managing Long term effects of C-19]. Available from: https://www.nice.org.uk/guidance/ng188/resources/covid19-rapid-guideline-managing-the-longtermeffects-of-covid19-pdf-51035515742

[19] Raveendran AV. Long COVID-19: Challenges in the diagnosis and proposed diagnostic criteria. Diabetes Metab Syndr. 2021;15(1):145-46. Doi: 10.1016/j.dsx 2020.12.025.

[20] Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID-19. Nat Med. 2021;27(4):626-31.

[21] Hu Y, Ma J, Huang H, Vermund SH. Coinfection with HIV and SARS-CoV-2 in Wuhan, China: A 12-person case series. J Acquir Immune Defic Syndr. 2020;85(1):01-05. Doi: 10.1097/QAI.0000000000002424.

[22] Del Amo J, Polo R, Moreno S, Díaz A, Martínez E, Arribas JR, et al. Incidence and severity of COVID-19 in HIV-positive persons receiving antiretroviral therapy: A cohort study. Ann Intern Med. 2020;173(7):536-41. Doi: 10.7326/M20-3689.

[23] Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. BMJ. 2020;370:m3026.

[24] Lan L, Xu D, Ye G, Xia C, Wang S, Li Y, et al. Positive RT-PCR test results in patients recovered from COVID-19. J Am Med Assoc. 2020;323(15):1502-03.

[25] Garg P, Arora U, Kumar A, Wig N. The "post COVID-19" syndrome: How deep is the damage?. J Med Virol. 2021;93(2):673-74. Doi: 10.1002/jmv.26465.

[26] Van Elslande J, Vermeersch P, Vandervoort K, Wawina-Bokalanga T, Vanmechelen B, Wollants E, et al. Symptomatic Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Reinfection by a Phylogenetically Distinct Strain. Clin Infect Dis. 2021;73(2):354-56. Doi: 10.1093/cid/ciaa1330.

[27] Falahi S, Kenarkoohi A. COVID-19 reinfection: Prolonged shedding or true reinfection? New Microbes New Infect. 2020;38:100812. Doi: 10.1016/j.nmni. 2020.100812.

[28] Becker RC. Toward understanding the 2019 Coronavirus and its impact on the heart. J Thromb Thrombolysis. 2020;50(1):33-42. Doi: 1007/s11239-020-02107-6.

[29] Gerwyn M, Maes M. Mechanisms explaining muscle fatigue and muscle pain in patients with myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS): A review of recent findings. Curr Rheumatol Rep. 2017;19(1):1. Doi: 10.1007/s11926-017-0628-x.

[30] Biehl M, Sese D. Post-intensive care syndrome and COVID-19-Implications post pandemic. Cleve Clin J Med. 2020. Doi: 10.3949/ccjm.87a.ccc055.

[31] Forte G, Favieri F, Tambelli R, Casagrande M. COVID-19 pandemic in the Italian population: Validation of a post-traumatic stress disorder questionnaire and prevalence of PTSD symptomatology. Int J Environ Res Public Health. 2020;17(11):4151.

[32] Lopez-Leon S, Wegman-Ostrosky T, Perelman C, Sepulveda R, Rebolledo PA, Cuapio A, et al. More than 50 long-term effects of COVID-19: A systematic review and meta-analysis. Sci Rep. 2021;11(1):16144. Doi: 10.1038/s41598-021-95565-8.

[33] Rodriguez-Morales AJ, Cardona-Ospina JA, Gutiérrez-Ocampo E, Villamizar-Peña R, Holguin-Rivera Y, Escalera-Antezana JP, et al. Clinical, laboratory and imaging features of COVID-19: A systematic review and meta-analysis. Travel Med Infect Dis. 2020;34:101623. Doi: 10.1016/j.tmaid.2020.101623. 32179124.

[34] Zheng KI, Feng G, Liu WY, Targher G, Byrne CD, Zheng MH. Extrapulmonary complications of COVID-19- A multisystem disease? J Med Virol. 2021;93(1):323-35. Doi: 10.1002/jmv.26294.

[35] Maley JH, Brewster I, Mayoral I, Siruckova R, Adams S, McGraw KA, et al. Resilience in survivors of critical illness in the context of the survivors' experience and recovery. Ann Am Thorac Soc. 2016;13(8):1351-60. Doi: 10.1513/annalsats.201511-782oc.

[36] "Post COVID-19 Condition." Accessed May 27, 2023. https://www.who.int/teams/health-care-readiness/post COVID-19-condition.

[37] Del Rio C, Collins LF, Malani P. Long-term health consequences of COVID-19. JAMA. 2020;324(17):1723-24. Doi: 10.1001/jama.2020.19719.

[38] Lechien JR, Chiesa-Estomba CM, Place S, Van Laethem Y, Cabaraux P, Mat Q, et al; COVID-19 Task Force of YO-IFOS. Clinical and epidemiological characteristics of 1420 European patients with mild-to-moderate coronavirus disease 2019. J Intern Med. 2020;288(3):335-44.

[39] Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ. COVID-19: Consider cytokine storm syndromes and immunosuppression. Lancet. 2020;395(10229):1033-34. Doi: 10.1016/S0140-6736(20)30628-0.

[40] Zhao YM, Shang YM, Song WB, Li QQ, Xie H, Xu QF, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. E Clinical Medicine. 2020;25:100463. Doi: 10.1016/j.eclinm.2020.100463.

[41] Gong J, Ou J, Qiu X, Jie Y, Chen Y, Yuan L, et al. A tool to early predict severe corona virus disease 2019 (COVID-19): A multicenter study using the risk nomogram in Wuhan and Guangdong, China. Clin Infect Dis. 2020;71(15):833-40. Doi:10.1093%2Fcid%2Fciaa443.

[42] Holshue ML, DeBolt C, Lindquist S, Lofy KH, Wiesman J, Bruce H, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382(10):929-36. Doi:10.1056/nejmoa2001191.

[43] Phan LT, Nguyen TV, Luong QC, Nguyen TV, Nguyen HT, Le HQ, et al. Importation and human-to-human transmission of a novel coronavirus in Vietnam. N Engl J Med. 2020;382(9):872-74. Doi:10.1056/NEJMc2001272.

[44] Mulangu S, Dodd LE, Davey RT Jr, Tshiani Mbaya O, Proschan M, Mukadi D, et al. A randomized, controlled trial of ebola virus disease therapeutics. N Engl J Med. 2019;381(24):2293-2303. Doi: 10.1056/NEJMoa1910993.

[45] Zhu N, Zhang D, Wang W, Li X, Yang B, Song J, et al. A novel coronavirus from patients with pneumonia in China, 2019. N Engl J Med. 2020;382(8):727-33. Doi: 10.1056/NEJMoa2001017.

[46] Wong G, Liu W, Liu Y, Zhou B, Bi Y, Gao GF. MERS, SARS, and Ebola: The role of super-spreaders in infectious disease. Cell Host Microbe. 2015;18(4):398-401. Doi:10.1016/j.chom.2015.09.013.

[47] Tan W, Zhao X, Ma X, Wang W, Niu P, Xu W, et al. A novel coronavirus genome identified in a cluster of pneumonia cases- Wuhan, China 2019-2020. China CDC Wkly. 2020;2(4):61-62.

[48] Liu GS, Li H, Zhao SC, Lu RJ, Niu PH, Tan WJ. Viral and bacterial etiology of acute febrile respiratory syndrome among patients in Qinghai, China. Biomed Environ Sci. 2019;32(6):438-45. Doi: 10.3967/bes2019.058.

[49] Shakoory B, Carcillo JA, Chatham WW, Amdur RL, Zhao H, Dinarello CA, et al. Interleukin-1 receptor blockade is associated with reduced mortality in sepsis patients with features of macrophage activation syndrome: Reanalysis of a prior phase III trial. Crit Care Med. 2016;44(2):275-81.

[50] Dennis A, Cuthbertson DJ, Wootton D, Crooks M, Gabbay M, Eichert N, et al. Multi-organ impairment and long COVID-19: A 1-year prospective, longitudinal cohort study. J R Soc Med. 2023;116(3):97-112.

[51] Hu Y, Chen Y, Zheng Y, You C, Tan J, Hu L, et al. Factors related to mental health of inpatients with COVID-19 in Wuhan, China. Brain Behav Immun. 2020;89:587-93.

[52] Perlis RH, Santillana M, Ognyanova K, Safarpour A, Trujillo KL, Simonson MD, et al. Prevalence and correlates of long COVID-19 symptoms among US adults. JAMA Netw Open. 2022;5(10):e2238804.

[53] Ziauddeen N, Gurdasani D, O'Hara ME, Hastie C, Roderick P, Yao G, et al. Characteristics and impact of long COVID-19: Findings from an online survey. Plos One. 2022;17(3):e0264331.

[54] Bull-Otterson L, Baca S, Saydah S, Boehmer TK, Adjei S, Gray S, et al. Post-COVID-19 conditions among adult COVID-19 survivors aged 18-64 and ≥65 Years- United States, March 2020-November 2021. MMWR Morb Mortal Wkly Rep. 2022;71(21):713-17.

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