

## REVIEW ARTICLE

# Emergence of Long COVID: Threat to Humanity Persists!

**Kaushik Bharati**

Health Policy Consultant – UNESCO, New Delhi

**CORRESPONDING AUTHOR**

Dr. Kaushik Bharati, WZ 43-44, 3rd Floor, Om Vihar Phase 3, Uttam Nagar, New Delhi - 110059

E-mail: [dr.kaushik.bharati@gmail.com](mailto:dr.kaushik.bharati@gmail.com)**CITATION**

Bharati K. Emergence of Long COVID: Threat to Humanity Persists!. Journal of the Epidemiology Foundation of India. 2024;2(3):97-102.

DOI: <https://doi.org/10.56450/JEFI.2024.v2i03.005>**ARTICLE CYCLE**

Received: 18/05/2024; Accepted: 28/08/2024; Published: 30/09/2024

*This work is licensed under a Creative Commons Attribution 4.0 International License.**©The Author(s). 2024 Open Access***ABSTRACT**

The transition of COVID-19 from a pandemic to an endemic disease will result in the further spread of SARS-CoV-2 among the vulnerable populations, especially those who still remain unvaccinated. Thus, infections are destined to increase and the majority of humanity will become infected within a short span of time. As with most viral infections, post-infection sequelae are a reality for COVID too. In fact, it has already been observed that 10-20% of COVID patients who have fully recovered, go on to develop lingering symptoms that persist for a long period of time. This has been termed as long COVID or post-COVID condition. This underscores the fact that the danger still looms and we're not out of the woods yet. The present review article highlights the major facets of long COVID and suggests possible remedial measures that could make it a thing of the past.

**KEYWORDS**

COVID, Epidemiology, Brain Fog, Dyspnea, Fatigue, Coronavirus

**INTRODUCTION**

Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2), the etiologic agent of Coronavirus Disease 2019 (COVID-19), has wreaked havoc everywhere and devastated the lives of billions of people across the globe (1). The virus has spread to every nook-and-corner of the planet, leaving no place untouched. As of 13<sup>th</sup> April 2024, there were 704 million confirmed cases of COVID-19 and over seven million deaths worldwide (2). The pandemic has affected 231 countries in all. These figures are a gross underestimate, as only a fraction of infections have been reported. The World Health Organization (WHO), in one of its live media briefings, had put the death toll at 20 million!

The situation has been severely aggravated by microevolution of the virus due to immune pressures, brought about both by natural infections, as well as through vaccination. This has resulted in incessant emergence of new variants throughout the entire span of the pandemic, leading to intermittent waves of infection, thereby increasing the burden over time (3). Therefore, it appears that the future disease transmission scenario will unfold, based on three aspects - virus microevolution, host immunity, and vulnerability and susceptibility of individuals to SARS-CoV-2 infections (1).

With the gradual evolution of the virus, the disease pattern has also shifted - from a pandemic to an endemic state. This has

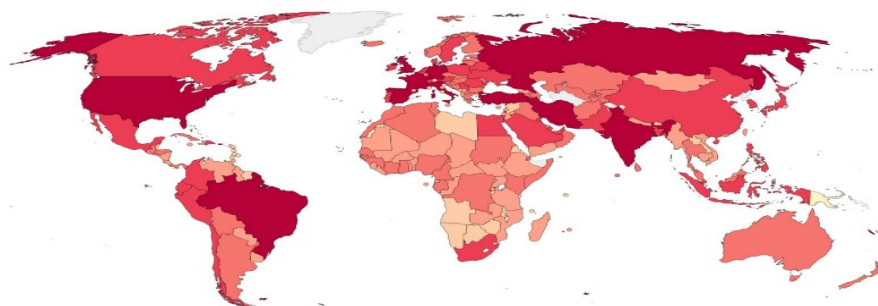
necessitated the modification and fine-tuning of the strategies to tackle the disease effectively. Therefore, the focus has shifted from disease containment, to mitigation of mortality, and eventually, prevention through mass vaccination. However, with the emergence of long COVID, the strategies need to be further tweaked to tackle this new threat. Currently, efforts are underway to understand the pathogenesis and disease kinetics of long COVID, which is also termed as post-acute COVID-19 sequelae (PACS) or post-COVID condition. Thus, in a nutshell, these terms signify the persistence or re-emergence of symptoms of COVID-19 in those individuals who have fully recovered, both clinically and microbiologically, from SARS-CoV-2 infection as certified by a negative RT-PCR test for the virus (4).

by SARS-CoV-2, with a significant number lacking a confirmed diagnosis (Figure 1). Moreover, a major proportion of survivors experience a variety of long-term sequelae and are at an increased risk of further morbidity and even mortality (5-8). Various epidemiological studies have reported that approximately 75% of critical patients, 50% of severe patients, and almost 30% of asymptomatic patients are likely to develop long COVID (9-12). However, some other epidemiological studies have reported lower estimates (13,14). Keeping the numbers aside, long COVID presents an unprecedented health crisis, having the potential to become one of the most debilitating diseases caused by an infectious agent in living memory. Notably, the uniqueness of the condition lies in its capability to damage every organ of the body, irrespective of age or gender.

**Epidemiology of Long COVID**

Currently, more than two-thirds of the population across the globe has been infected

**Figure 1: Global distribution of COVID-19**



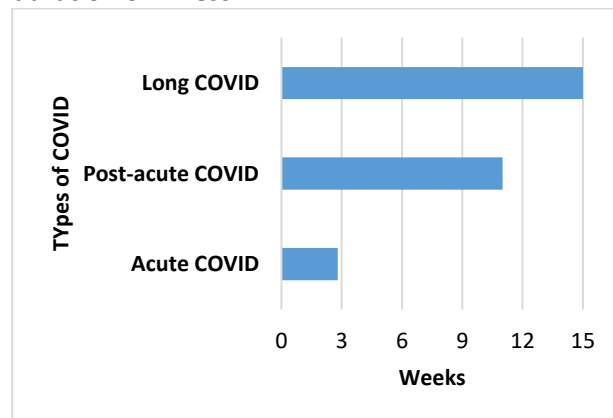
Countries Affected: 231  
 Total Cases: 704 million  
 Total Deaths: 7 million

Source: Worldometers, April 2024

**Transition from Acute COVID to Long COVID**

The transitory phase from acute COVID to long COVID is indistinct. There is considerable overlapping between the two. Hence, the timespan of this transitory phase between the acute and long forms of COVID has been termed as post-acute COVID. In this transitory phase, the symptoms go beyond three weeks, but less the 12 weeks. If the symptoms persist beyond 12 weeks, it is dubbed as long COVID. Importantly, during this phase, patients usually show biochemical, as well as radiological recovery (15) (Figure 2).

**Figure 2: Classification of COVID based on duration of illness**



### Symptoms of Long COVID

Long COVID exhibits various symptoms, even months after the initial infection, and these can occur irrespective of viral status (16). The symptoms may be continuous, relapsing or remitting in nature (17). New symptoms, other than those observed during acute COVID, may also appear. Since SARS-CoV-2 infects literally all organs of the body, the symptoms are generally multifaceted. Over 200 symptoms have been identified so far, which are often overlapping, coinciding with the simultaneous infection of several organs and organ systems.

Symptoms may include cough, fatigue, chest tightness, breathlessness, palpitations, myalgia, and absent-mindedness, among many others. Of all the diverse symptoms of long COVID, three stand out. These include cognitive dysfunction (brain fog), severe fatigue, and respiratory distress. These symptoms could arise from organ damage, post-viral syndrome, or post-critical care syndrome, among others. The various symptoms, along with their associated pathologies are highlighted in Table 1.

**Table 1: Symptoms and pathological conditions due to long COVID**

Symptoms	Pathology
<b>Heart</b>	
Chest pain	Cardiac impairment
Palpitations	Myocardial inflammation Postural Orthostatic Tachycardia Syndrome (POTS)
<b>Lungs</b>	
Cough	Abnormal gas exchange
Dyspnea	
<b>Pancreas</b>	
Not applicable	Diabetes Pancreas injury
<b>Immune System</b>	
Not applicable	Autoimmunity Mast Cell Activation Syndrome (MCAS)
<b>Gastrointestinal Tract</b>	
Abdominal pain	Gut dysbiosis
Nausea	Viral persistence
<b>Nervous System</b>	
Cognitive impairment	Dysautonomia
Fatigue	Chronic Fatigue Syndrome (CFS)
Sleep disorder	Neuroinflammation
Memory loss	Reduced cerebral blood flow
Tinnitus	Small fiber neuropathy
<b>Kidneys, Spleen, Liver</b>	
Not applicable	Organ damage
<b>Blood Vessels</b>	
Not applicable	Coagulopathy Deep Vein Thrombosis (DVT) Endothelial dysfunction Microangiopathy Micro-clot formation Pulmonary embolism Stroke
<b>Reproductive System</b>	
Erectile dysfunction	Reduced sperm count (men)
Increased severity and number of premenstrual symptoms	Reproductive problems (women)
Irregular menstruation	

### Long COVID: Some Prominent Studies

An Italian study reported that around 87% of recovered COVID-19 patients exhibited at least one persistent symptom even after two months. Out of these patients, 32% exhibited one or two symptoms, while 55% exhibited three or more. None of the individuals showed any signs of febrile illness. Common symptoms included fatigue (53%), reduced quality of life (44%), dyspnea (43%), joint pain (27%), and chest pain (22%). Other symptoms included skin rashes, cough, headache, palpitations, diarrhea, and 'pins-and-needles' sensation. Notably, the patients couldn't perform routine daily activities. Additionally, there were also psychiatric problems, such as anxiety, depression, and post-traumatic stress disorder (PTSD) (18). COVID-19 patients have been found to experience breathing difficulties and extreme fatigue, even after three months of discharge from hospital (19). It has also been reported that residual symptoms occur in 35% of outpatients, but as high as 87% in case of inpatients undergoing treatment for COVID-19 (18,20).

One study found that approximately 35% patients failed to return to work even three weeks after testing COVID-positive. This was more prominent in older age groups than younger ones (26% in 18-34 years, 32% in 35-49 years, and 47% in 50 years and above). Absenteeism from work was also more with increasing number of comorbidities (28% in case of one comorbidity, 46% with two, and 57% with three or more comorbidities). This was also true for obese individuals (BMI>30) and in those suffering from psychiatric disorders (anxiety, depression, PTSD, paranoia, schizophrenia, and obsessive-compulsive disorder) (20).

With the onset of long COVID, fever and chills that were present during acute COVID completely resolved in 97% and 96% of patients, respectively. However, cough, fatigue, and breathing problems didn't resolve in 43%, 35%, and 29% patients, respectively. Also, anosmia (loss of smell) and ageusia (loss of taste) took longer to resolve, which on average was eight days. Also, it was found that the five most common characteristics of long COVID were fatigue (58%), headache (44%),

attention deficit disorder (27%), hair fall (25%), and dyspnea (24%) (21).

### Risk Factors for Long COVID

Studies have identified several risk factors that increase the chances of developing long COVID. For example, long COVID is more common in women than men. Age is another risk factor. Long COVID patients have been found to be four years older than those who don't suffer from it (17). Those who have more than five symptoms during acute COVID, are much more likely to develop long COVID. Presence of comorbidities also increase the risk of developing long COVID, even in those who had mild disease during the acute stage (22).

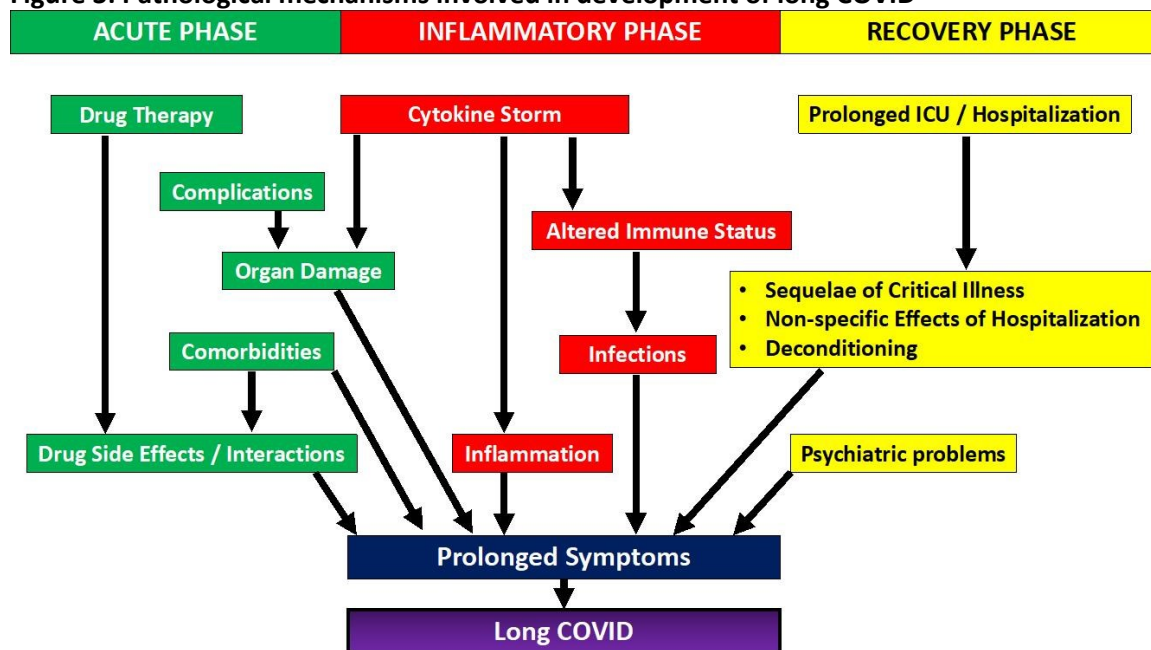
### Pathogenesis of Long COVID

There are many reasons that could explain the persistence of symptoms in long COVID patients. Some of these are highlighted below:

- Sequelae of organ damage
- Sequelae of critical illness
- Extent of tissue injury
- Recovery time required for each organ system
- Persistence of chronic inflammation
- Dysregulated immune response leading to autoimmunity
- Viral persistence
- Non-specific effect of hospitalization
- Post-intensive care syndrome
- Complications of SARS-CoV-2 infection
- Complications of comorbid conditions
- Adverse effects of medications

It should be noted that altered immunity, reinfection, relapse, persistent inflammation, and medical interventions could influence viral persistence (23,24). Psychiatric conditions and deconditioning can also contribute to persistent symptoms. These in turn, especially psychological issues can be influenced by the financial and social impact of COVID-19. Thus, it is clearly evident that multiple mechanisms contribute to the pathogenesis of long COVID, therefore requiring a multi-disciplinary approach to tackle the problem (25) (Figure 3).

**Figure 3: Pathological mechanisms involved in development of long COVID**



**Management of Long COVID**

Since the pathophysiology of long COVID is multifaceted, management also needs to utilize a multipronged approach. Multiple disciplines of the medical sciences need to be involved in the overall management strategy. This involves a thorough evaluation, treatment of underlying problems, occupational therapy, physiotherapy, as well as psychological and emotional support. Minor complaints, such as fever, cough, pain, and body ache, can be treated symptomatically with over-the-counter (OTC) drugs. However, prescription medications, such as antibiotics may be required in case of nasty infections. The etiology behind the symptoms need to be traced and treated as per standard protocol. Long COVID patients who have sequelae affecting the respiratory or nervous systems may require chest physiotherapy and neuro-rehabilitation. Treatment of physical ailments will not suffice. The mental and psychological issues must also be addressed to promote overall health. Optimization of treatment strategies may be required for established comorbid conditions, such as diabetes, cardiovascular diseases, cancer, hypertension, and immunodeficiency disorders, as the degree of severity may be altered due to exposure to the virus. Moreover, efforts

should be made to address the social and financial aspects associated with long COVID, as these are likely to affect mankind for years to come (15).

**Concluding Remarks**

COVID-19 and its associated long COVID have taken the world by storm, with the virus infecting the lion’s share of the global population within a span of just three years. With the transition from a pandemic to an endemic disease, it is very likely that long COVID cases will continue to rise in the foreseeable future. Thus, it is of utmost importance to fully understand the causes and associated post-viral syndromes of long COVID with a sense of urgency. Importantly, it should be kept in mind that there will be enormous socioeconomic connotations, as long COVID continues to spread. Going forward, more and more people will require health care support, which is likely to overburden the fragile health systems, especially in resource-poor countries. Treatment guidelines and actionable policies are urgently needed for optimal utilization of scarce resources for the benefit of humanity as a whole.

**CONFLICT OF INTEREST**

There are no conflicts of interest.

## DECLARATION OF GENERATIVE AI AND AI ASSISTED TECHNOLOGIES IN THE WRITING PROCESS

The authors haven't used any generative AI/AI assisted technologies in the writing process

## REFERENCES

- Estrada LV, Levasseur JL, Maxim A, Benavidez GA, Porter KMP. Structural racism, place, and COVID-19: A narrative review describing how we prepare for an endemic COVID-19 future. *Health Equity*. 2022; 6(1): 356-66.
- Worldometer Coronavirus Tracker. Available at: <https://www.worldometers.info/coronavirus/>; Accessed on: 16.05.2024.
- Reese H, Luliano AD, Patel NN, Garg S, Kim L, Silk BJ, et al. Estimated incidence of coronavirus disease 2019 (COVID-19) illness and hospitalization - United States, February-September 2020. *Clin Infect Dis*. 2021; 72(12): e1010-e1017.
- Garg P, Arora U, Kumar A, Wig N. The "post-COVID" syndrome: How deep is the damage? *J Med Virol*. 2021; 93(2): 673-4.
- Katsoularis I, Fonseca-Rodriguez O, Farrington P, Jerndal H, Lundevaller EH, Sund M, et al. Risks of deep vein thrombosis, pulmonary embolism, and bleeding after COVID-19: Nationwide self-controlled cases series and matched cohort study. *BMJ*. 2022; 377.
- Xie Y, Xu E, Bowe B, Al-Aly Z. Long-term cardiovascular outcomes of COVID-19. *Nat Med*. 2022; 28: 583-60.
- Bhaskaran K, Rentsch CT, Hickman G, Hulme WJ, Schultze A, Curtis HJ, et al. Overall and cause-specific hospitalisation and death after COVID-19 hospitalisation in England: A cohort study using linked primary care, secondary care, and death registration data in the OpenSAFELY platform. *PLoS Med*. 2022; 19: e1003871.
- Roca-Fernandez A, Wamil M, Telford A, Carapella V, Borlotti A, Monteiro D, et al. Cardiac abnormalities in Long COVID 1-year post-SARS-CoV-2 infection. *Open Heart*. 2023; 10(1): e002241.
- Malkova A, Kudryavtsev I, Starshinova A, Kudlay D, Zinchenko Y, Glushkova A, et al. Post COVID-19 syndrome in patients with asymptomatic/mild form. *Pathogens*. 2021; 10: 1408.
- Groff D, Sun A, Ssentongo AE, Ba DM, Parsons N, Poudel GR, et al. Short-term and long-term rates of postacute sequelae of SARS-CoV-2 infection: A systematic review. *JAMA Netw Open*. 2021; 4(10): e2128568.
- Huang L, Yao Q, Gu X, Wang Q, Ren L, Wang Y, et al. 1-year outcomes in hospital survivors with COVID-19: A longitudinal cohort study. *Lancet*. 2021; 398: 747-58.
- Ayoubkhani D, Khunti K, Nafilyan V, Maddox T, Humberstone B, Diamond I, et al. Post-COVID syndrome in individuals admitted to hospital with COVID-19: Retrospective cohort study. *BMJ*. 2021; 372: n693.
- Ayoubkhani D, Pawelek P, Gaughan C. Technical article: Updated estimates of the prevalence of post-acute symptoms among people with coronavirus (COVID-19) in the UK: 26 April 2020 to 1 August 2021 - Office for National Statistics, 2021.
- Ballering AV, van Zon SKR, Hartman TCO, Rosmalen JGM; Lifelines Corona Research Initiative. Persistence of somatic symptoms after COVID-19 in the Netherlands: An observational cohort study. *Lancet*. 2022; 400(10350): 452-61.
- Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute COVID-19 in primary care. *BMJ*. 2020; 370: m3026.
- Geddes L. Why strange and debilitating coronavirus symptoms can last for months. *New Sci*. 2020. Available at: <https://www.newscientist.com/article/mg24632881-400-why-strange-and-debilitatingcoronavirus-symptoms-can-last-for-months/>; Accessed on 17.05.2024.
- Nabavi N. Long COVID: How to define it and how to manage it. *BMJ*. 2020; 370: m3489.
- Carfi A, Bernabei R, Landi F. Persistent symptoms in patients after acute COVID-19. *J Am Med Assoc*. 2020; 324(6): 603-5.
- Arnold DT, Hamilton FW, Milne A, Morley AJ, Viner J, Attwood M, et al. Patient outcomes after hospitalization with COVID-19 and implications for follow-up: Results from a prospective UK cohort. *Thorax*. 2021; 76(4): 399-401.
- Tenforde MW, Kim SS, Lindsell CJ, Rose EB, Shapiro NI, Files DC, et al. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network - United States, March-June 2020. *MMWR Morb Mortal Wkly Rep*. 2020; 69(30): 993-8.
- 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.
- Sudre CH, Murray B, Varsavsky T, Graham MS, Penfold RS, Bowyer RC, et al. Attributes and predictors of long COVID. *Nat Med*. 2021; 27(4): 626-31.
- Tay MZ, Poh CM, Renia L, MacAry PA, Ng LFP. The trinity of COVID-19: Immunity, inflammation and intervention. *Nat Rev Immunol*. 2020; 20(6): 363-74.
- Biehl M, Sese D. Post-intensive care syndrome and COVID-19 - Implications post pandemic. *Cleve Clin J Med*. August 5, 2020 (ahead of print).
- Gemelli Against COVID-19 Post-Acute Care Study Group. Post-COVID-19 global health strategies: The need for an interdisciplinary approach. *Aging Clin Exp Res*. 2020; 32: 1613-20.