

# Long COVID-19

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“Long COVID-19” refers to the existence of symptoms weeks or months after contracting the SARS-CoV-2 infection, regardless of the viral state. The long COVID-19 or post COVID-19 condition is defined as the illness that arises in patients who have a history of suspected or confirmed SARS-CoV-2 infection, usually within three months of the commencement of COVID-19, with symptoms and consequences lasting at least two months.

post COVID-19

persistent symptoms

fatigue

long COVID-19

post-acute sequalae

## 1. Introduction

The Corona virus disease or the COVID-19 outbreak that started in Wuhan in China in December 2019 shook the global healthcare system and posed a threat to the healthy survival of people worldwide. It was declared a pandemic in March 2020 and the first case of the COVID-19 virus in India was reported in 2020 January [1][2]. Over the years, many other devastating infections, such as Severe Acute Respiratory Syndrome Corona Virus (SARS-CoV) and Middle Eastern respiratory syndrome corona virus (MERS-CoV), have emerged, with SARS-CoV and MERS-CoV infections being more fatal than SARS-CoV-2. However, the COVID-19 pandemic was different and created panic among people as it showed high viral shedding and a high proportion transmission rate compared to MERS or SARS [3]. Worldwide, the Corona virus disease (COVID-19) virus has created significant risks to people's mental and physical health. Although patients and health staff receive psychological care, public mental health in general demands major attention. Furthermore, and also more generally, the prevalence of mental disorders, especially depression, increased significantly with the onset of the pandemic. This should not come as a surprise, since the pandemic is accompanied by numerous psychological stress factors: the fear of the disease, of suffering and the death of relatives and friends, the fear of job loss, social tensions due to lockdown, working from home and remote schooling [4].

Physically, patients suffer from fever, tiredness, accompanied by dry coughs without mucus or phlegm expectoration and diarrhea with muscle discomfort, disorientation, headache, sore throat, rhinorrhea, chest pain, sputum production and nausea and vomiting being among the less prevalent symptoms [5]. These signs and symptoms are distinctively different from other diseases in terms of origin, onset, duration, progression, severity and response to traditional treatment, and thus cannot be explained in terms of other diseases. Most people who develop COVID-19 fully recover, but current evidence suggests that approximately 10–20% of people experience a variety of mid- and long-term effects after they recover from their initial illness. These mid- and long-term effects are collectively known as the post COVID-19 condition or “long COVID-19”. “Long COVID-19” refers to the

existence of symptoms weeks or months after contracting the SARS-CoV-2 infection, regardless of the viral state [6]. The long COVID-19 or post COVID-19 condition is defined as the illness that arises in patients who have a history of suspected or confirmed SARS-CoV-2 infection, usually within three months of the commencement of COVID-19, with symptoms and consequences lasting at least two months [7]. Different nomenclatures as well as the timeline of defining post COVID-19 or long COVID-19 are available. A common consensus is the persistence of symptoms beyond 2 months (>8 weeks) [8][9][10]. With regards to identifying persistent symptoms, an alternative diagnosis cannot explain the signs and effects of the post COVID-19 syndrome (as per the WHO). Although such alteration is mainly reported in severe and critical disease survivors, the lasting effects also occur in individuals with a mild infection who did not require hospitalization [11].

The major symptoms of post COVID-19 illness that influence peoples' quality of work and everyday lifestyle are performance and perceived fatigue, shortness of breath, problems related to memory, sleep and concentration, constant cough, chest ache, difficulty in speaking, muscular pain, anosmia, ageusia, psychological manifestations and febrile illness. A possible way to safeguard oneself from post-COVID-19 is to be preventive towards acquiring the COVID-19 infection by adhering to all standard operating protocols. The effect of vaccination on reducing the post COVID-19 symptoms is under research. Even though transmission of post COVID-19 symptoms is improbable, one should seek immediate medical advice for managing and treating the same. Presently, specific medications or treatment strategies have not been proposed for the post COVID-19 condition. However, effective rehabilitation and holistic medical assistance are considered to be the typical symptoms management protocol for patients experiencing post COVID-19 syndrome [12]. A broad overview of all the possible longstanding effects of COVID-19 is still needed. Therefore, researchers' entry aimed to identify the prevalence of all the symptoms in post COVID-19 reported up to the month of September 2022.

## 2. COVID Phase

In the present entry, chronic post COVID-19 studies were differentiated by their period of study and persistence of symptoms. As it is currently recognized that post COVID-19 symptomatology is more variable and more complex than predicted, which may explain why there is no unanimity in the definition of post COVID-19 [13], there exists many terminologies, a few of which are presented comprehensively by Yong et al., [14]. Researchers have used the timeline model of Fernández-De-las-peñas, C et al., where they defined the following: Phase 1, called "acute post COVID-19" symptoms, consisted of symptoms presented in between weeks 5 to 12 weeks since COVID-19 diagnosis; Phase 2, called long post COVID-19, presented symptoms from weeks 12 to 24 weeks since COVID-19 diagnosis; and Phase 3, or "persistent post COVID-19 symptoms", consisted of symptoms lasting more than 24 weeks [10].

Among all the studies, there were six studies conducted during Phase 1, eight studies during Phase 2 and seventeen studies during Phase 3. There were two studies that included mixed phases. One was conducted during Phase 2 and 3 [15] and the others were conducted during all the three phases [16]. Information on period of inclusion and follow-up helped to clearly distinguish the persistence of symptoms of COVID-19. There were a few studies that consisted of the follow-up period for variable lengths of time. Among them, a study conducted by Darcis Gilles

et al., assessed the patients post-discharge, 3 months and 6 months after COVID-19 infection [17]. Similarly, another study conducted by The PHOSP-COVID Collaborative Group (UK) assessed the patients at 5-month and one-year intervals [15]. Fernández-de-Las-Peñas, C et al., evaluated symptoms for outpatient participants at the time of acute infection, at 30 days, 60 days and 90 days [18].

## 2. Study Population

Among the 33 articles, 30 (91%) were related to the adult population (>18 years), 2 (6%) included children (one child, one child and adolescents) and 1 (3%) study was based on the elderly population. Almost all the studies included patients who were with either Reverse Transcriptase Polymerase Chain Reaction (RT- PCR) confirmed SARS-CoV-2 infection or clinically confirmed infection by physicians or laboratory tests.

In a study by Finkk et al., which was conducted on children, asymptomatic participants with the disease and those who had severe cognitive dysfunction were not included, which might have affected the study findings with regard to long-term COVID-19 symptoms that may arise in asymptomatic individuals, especially in children [19]. According to a study by Lamontagne et al., only right-handed participants (aged between 18 and 60 years) were included, and no explanation was given for the inclusion criteria. Though the proportion of right-handed individuals are high in the community, this study still fails to represent the left-handed population [20].

## 3. Signs and Symptoms

Performance and perceived fatigability/tiredness/weakness ( $n = 29$ , 87%), shortness of breath/dyspnea/breathlessness ( $n = 26$ , 78%), cough ( $n = 15$ , 45%), headache ( $n = 13$ , 39%) and insomnia ( $n = 13$ , 39%) were the most reported physiological symptoms. The least reported symptoms were sexual dysfunction, excessive sleepiness, neuropathic pain, constipation, loss of functional status, rib pain/thoracic pain, dysuria, haematuria, oliguria and glycaemia/renal problems, all of which were reported by one study each ( $n = 1$ , 3%). Among psychological symptoms reviewed, memory loss/forgetfulness was reported in nine studies (27%), followed by brain fog ( $n = 6$ , 18%), anxiety ( $n = 6$ , 18%), concentration/cognitive impairment ( $n = 6$ , 18%), confusion ( $n = 3$ , 9%), slowed down thinking ( $n = 2$ , 6%) and post-traumatic stress ( $n = 1$ , 3%). Researchers' findings in this entry are consistent with findings of other investigators, who reported symptoms affecting physical and mental health. They reported post COVID-19 psychological and neuropsychological concerns (anxiety and depression, PTSD, sleep and cognition deficits), even in people who had never had a mental health condition, which is similar to researchers' findings [21] [22]. In another study conducted by Van Kessel et al., it was found that psychological, cognitive and social symptoms were associated more with post-acute COVID-19 syndrome and less with long COVID-19 haulers. The study also mentioned that social symptoms were mainly studied in qualitative studies [23].

In a study conducted by Dennis Andrea et al., which was focused on multi-organ impairment in COVID-19 patients, there were two major findings. The first one was that in low-risk individuals, there were chronic symptoms and mild impairment found in the heart, lung, liver, kidney and pancreas compared with healthy controls. Additionally, the

second finding was that cardiac impairment was more common in severe persistent COVID-19 syndrome [24]. According to Bellan et al., who assessed the persistence of symptoms from severe COVID-19 one year after hospital discharge, some symptoms, such as cough and arthromyalgia, were even more common at 12 than at 4 months after discharge [25]. According to Gérard et al., in a study which was conducted to assess the neglected components of long COVID-19 syndrome such as malnutrition, showed that at day 30 after COVID-19 infection, 138/288 of the patients (48%) presented with persistent malnutrition (33%) and subjective functional loss (26.3%). Furthermore, it was noted that at 6 months, 15% of the initial participants remained malnourished despite nutritional counseling and dietary guidance, oral nutritional supplements or relocation to rehabilitation centers [26]. In a study conducted by Twomey et al., the main factors associated with chronic fatigue and Post Exertional Malaise (PEM) in people living with long COVID-19 was studied. The study found that for more than 60% of those experiencing PEM in their study sample, it had been more than 40 weeks since their confirmed/suspected SARS-CoV-2 infection [27]. According to Kikkenberg et al., children who had a history of SARS-CoV-2 infection in all age groups from 0 to 14 years reported a higher prevalence of long-lasting symptoms compared with age-sex-matched controls, and, among the oldest respondents, more females than males had long-lasting symptoms [28]. In researchers' entry, the most frequent systems affected were the respiratory, systemic, neurological, mental health and dermatological health systems, with research by Moktari et al., and Subramanian et al., confirming these findings [29][30].

## 4. Risk Factors, Major Findings and Limitations

A study from researchers' entry by Naik Shivdas et al., stated the associated risk factors for long COVID symptoms were severity of the COVID-19 infection (severe/moderate) and hypothyroidism [31]. Similar findings in cross sectional studies by Burekovic et al., and Lui et al., who reported hypothyroidism as a risk factor and as a consequence of COVID-19 infection [32][33]. In patients with co morbidities such as hypothyroidism, persistent musculoskeletal and respiratory complaints were found were commonly found [30][31]. According to Dennis Andrea et al., even non-hospitalized individuals, or 10% of those infected, have had persistent symptoms related to COVID-19 [24].

According to Faten et al., persistent COVID-19 symptoms such as loss of smell/taste, shortness of breath and fatigue are persistent symptoms which mainly affected social and work-related activities [34]. According to Han et al., persistent symptoms were significantly associated with patients with poorer long-term health status, poorer quality of life and those who were experiencing severe psychological distress [35]. Persistent symptoms were found to be substantially related to poorer long-term health, lower quality of life and psychological distress. An important finding from researchers' entry is that female sex is one of the major risk factors for persistent long COVID-19 symptoms [18][28][36][37][38]. A few cross-sectional studies that report similar findings, such as a study by Peghin et al., identified female gender (OR 1.55) as a potential independent risk factor for long COVID-19; a review by Subramanian et al. and a review by Shanbehzadeh also reported the association of being female with an increased risk of reporting symptoms 12 weeks post acquiring COVID-19 [22][30][39]. Notably, fatigue was encountered more by the females compared to males. This refers to both perceived and performance fatigability. Factors such as stress,

anxiety, depression and physical pain contribute to fatigue in women. Domestic stress such as marital and family stress caused more depression and mental strain among homemakers, whereas social discrimination, need for financial stability during pandemic, safety concerns and family support caused stress and depression among working women and single women. Furthermore, increased workload, at home or in the workplace, caused physical tiredness and a greater perception of pain among women than men, which resulted in increased fatigability among women compared to men [40]. The majority of the studies mentioned limitations such as recall bias, selection bias, etc. in their study. However, this was not a major limitation in the ten (30%) multicenter studies that included various hospitals and participants from different parts of the countries and globally.

## 5. Impact of Long COVID-19 on Health and Quality of Lifestyle

It has been estimated that 2 months after the onset of COVID-19 disease, 87.1% of the patients discharged still experience at least one of the symptoms of long COVID-19, and nearly 55% experience multiple symptoms, such as difficulty in breathing, chest pain and tiredness, all of which affect their quality of life [41]. Here, it is also important to identify the cause of the symptom and confirm the underlying pathogenesis. Physicians and medical practitioners could suggest doing some biochemical and radiological tests to confirm previous infection in response to persistent symptoms. These include blood investigations monitoring blood pressure, heart rate and oxygen levels. Sometimes, a chest X-ray would be needed for a precise diagnosis. There is no standard time identified for the recovery from long COVID-19; most people return to their normal activities in less than 12 weeks, but for some people the symptoms can persist for longer periods of time, hindering their daily activities and quality of work [42]. Treatment options for long COVID-19 depend on the severity and duration of people experiencing the symptoms. Whereas people who have milder manifestations need not require any treatment, people with more severe and persistent signs should be treated by a holistic approach with health specialists for management and effective treatment options. It has been found that for most people, the health outcomes are optimal and a return to normal activities without any trace of other symptoms was reported 9 months after COVID-19 infection. However, individuals who are proficient in sports and other forms of physical exercise, individuals who are highly functioning and young individuals who are considered high performing were previously found to improve at a slower rate, which affects their ability to work exercise and socialise [43]. With these people, monitoring the signs and managing the symptoms is highly important to prevent any distressing outcomes and promote better healing [43].

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