



# Long-COVID, is a New Syndrome?

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## ABSTRACT

The ongoing or developing new symptoms after acute coronavirus disease-2019 (COVID-19) infection has emerged as a new clinical problem. This has become a problem facing the globally infected population and health systems. “Long-COVID” can be defined as patients with laboratory-confirmed or clinically present COVID-19 whose symptoms persist for four weeks after diagnosis. Symptoms are remarkably heterogeneous, as seen in acute COVID-19. These symptoms may remain stable or fluctuate. Controversy over its definition complicates accurate diagnosis and management of the disease. The most prominent symptoms were fatigue, sleep disturbances, chest pain, and shortness of breath. Recent reports also highlight the risk of long-term sequelae in those recovering from acute COVID-19, affecting almost all organs such as the skin, respiratory system, cardiovascular system, neuropsychiatric system, and renal system. The long-term effects of COVID-19, in hospitalized and non-hospitalized individuals, across all age groups, should be a priority for future research with standardized and controlled studies.

**Keywords:** Long-COVID, fatigue, COVID-19, sequelae of COVID-19

## Introduction

In the Coronavirus disease-2019 (COVID-19) pandemic, some patients with severe acute respiratory syndrome-coronavirus-2 (SARS-CoV-2) infection has developed a wide range of physical and mental health problems four or more weeks after acute infection. These symptoms included a wide range of ongoing or newly emerging symptoms that could not be explained by another diagnosis (1,2). Most people with acute infections recover within a few days to a few weeks after infection, so at least four weeks after infection is considered a baseline from which post-COVID conditions can be identified for the first time. Different terminology are used to describe these long-lasting symptoms, including “long-COVID”, “post-COVID syndrome”, “postacute COVID-19”, “chronic COVID-19”, “post-COVID

conditions”, and “postacute sequelae of SARS-CoV-2 infection”. Whether this set of symptoms represents a new syndrome specific to COVID-19 has yet to be determined (3,4).

Symptoms seen after COVID-19 can occur in different ways (3);

- Persistent symptoms that begin at the time of acute COVID-19 illness,
- New -onset symptoms following an asymptomatic illness or the remission period of acute illness,
- The addition of new symptoms or clinical conditions (e.g., cognitive difficulties) over time, in addition to some persistent symptoms associated with an already existing disease (e.g., shortness of breath),
- Worsening of pre-existing symptoms or conditions.

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**Received:** 03.11.2022 **Accepted:** 08.11.2022



## Symptoms

These long-lasting symptoms can occur following both mild and severe acute COVID-19 illness. These symptoms can be categorized under two different headings: physical and psychological symptoms (3,5,6,7,8,9,10).

Physical symptoms can be seen in one-third or more of the patients. Commonly reported physical symptoms include:

- Fatigue
- Cough
- Dyspnea
- Chest pain

Less common are anosmia, arthralgia, headache, rhinitis, dysgeusia, anorexia, dizziness, myalgia, insomnia, alopecia, sweating, decreased libido, and diarrhea.

Psychological and cognitive complaints may occur more frequently than in those recovering from other similar illnesses (8,10,11). It has been reported to be especially common among patients followed up in the intensive care unit (8). The main disorders seen are worsening quality of life, anxiety/depression, and persistent psychological symptoms (5,6,9). In one study, memory impairment was reported in 21% of patients with mild illness and no hospitalization (11).

At least one component of post-intensive care syndrome has been reported in at least three-quarters of COVID-19 survivors (10,12). The most common symptoms of this syndrome are physical weakness (39%), joint stiffness/pain (26%), mental/cognitive dysfunction (26%) and myalgias (21%) (10). Other psychological or cognitive complaints likely to occur are post-traumatic stress disorder, anxiety, depression, and poor memory and concentration.

Symptoms related to post-COVID conditions are summarized below (1,3);

### General symptoms

- Fever
- Disturbing fatigue
- Symptoms worsened by physical or mental effort

### Respiratory and heart symptoms

- Cough
- Difficulty breathing
- Chest pain
- Heart palpitations

### Neurological symptoms

- Headache

- Sleep difficulties
- Difficulty in thinking or concentrating (brain fog)
- Dizziness when standing up
- Depression or anxiety
- Changes in smell or taste

### Digestive symptoms

- Diarrhea

### Other symptoms

- Arthralgia and myalgia
- Changes in menstrual cycles
- Rash

Among children, although data are limited, the prevalence of persistent symptoms appears lower (1,13). The most commonly reported symptoms were fatigue (3%) and impaired concentration (2%).

The reason why there are such heterogeneous post-COVID conditions may be due to different underlying pathophysiological processes, such as (3);

- Organ damage due to acute phase disease
- Complications from uncontrolled inflammation
- Ongoing viral activity due to a possible in-host viral reservoir
- Inadequate antibody response
- Autoimmunity

## Course of Recovery

While most patients with mild acute COVID-19 illness are expected to recover quickly (e.g. two weeks), those with moderate to severe illness may take two to three months, sometimes longer. Another reason for this difference in recovery time may be the underlying premorbid risk factors (14). A longer recovery period is expected in elderly patients with comorbidities, in patients who develop complications during acute illness (e.g. secondary bacterial pneumonia, venous thromboembolism, multisystem inflammatory syndrome) and in patients with prolonged hospitalization or needed intensive care and people who did not obtain COVID-19 vaccine (1,5,8,10,15). It seems that the best way to prevent long COVID-19 in the current situation is not to obtain the disease (1,2).

## General Evaluation

There are several guidelines for COVID-19 follow-up after acute illness developed by several organizations

(3,4,16,17,18,19,20). The severity of the previous illness should be taken into account when deciding whether to follow-up the patient. Patients with mild-to-moderate illness that has not required hospitalization do not need to routinely schedule a COVID-19 follow-up visit unless the patient requests one or has progressive or new symptoms. Patients with more severe acute COVID-19 disease who had been hospitalized would be offered a follow-up examination within 2 to 3 weeks at the latest (2). When the patient presents for a follow-up examination, a comprehensive history of COVID-19 should be taken, including the length of hospitalization, complications, treatments given, etc. Physical examination must be performed in detail in patients who have had COVID-19 (3,4,21).

Patients presenting with persistent or increasing respiratory symptoms, fatigue, or weakness should undergo detailed assessment, such as ambulatory pulse-oximetry, in addition to standard vital signs (e.g. blood pressure, heart rate, respiratory rate, pulse-oximetry, body temperature). Orthostatic vital signs may be important for individuals reporting postural symptoms, dizziness, fatigue, cognitive impairment, or weakness (4,21).

The laboratory tests must be ordered on the basis of abnormal tests during the illness and the present symptoms. For most patients recovering from mild acute COVID-19, laboratory testing is not necessary. For patients with ongoing symptoms, it is reasonable to do the basic panel of laboratory tests (2,4,21):

- Complete blood count
- Blood chemistry, including electrolytes and renal function
- Liver function studies, including serum albumin
- Inflammatory markers, C-reactive protein, erythrocyte sedimentation rate, and ferritin

For selected patients:

- Brain natriuretic peptide and troponin, (in patients with heart failure or complicated by myocarditis or with possible cardiac symptoms such as dyspnea, chest discomfort, edema)
- D-dimer (in patients with unexplained persistent or new dyspnea or in any patient with suspected of thromboembolic disease)
- Thyroid function tests in patients with unexplained and persistent fatigue or malaise
- Creatinine kinase in patients with weakness or muscle tenderness

- Antinuclear antibody, rheumatoid factor, anti-cardiolipin, etc. for rheumatological conditions

COVID-19 testing and serology does not need to be routinely retested to establish a diagnosis of post COVID conditions. Serologic testing may be performed for recovering plasma donation or for evaluation of unexplained symptoms in patients with no prior positive COVID-19 serology (2,21).

## Management

The primary goal of medical management in these patients is to optimize the quality of life. And these patients should be consulted or referred to relevant specialists for a comprehensive management plan based on their current symptoms and underlying physical and psychiatric conditions (4).

For example; for the following cardiopulmonary problems, the patient would be referred to cardiology or pulmonology if necessary. Ongoing dyspnea, cough, chest discomfort, pleuritic pain, wheezing, orthopnea, chest pain, peripheral edema, palpitations, dizziness, orthostasis, and pre-syncope or syncope are questioned in detail. A comprehensive cardiopulmonary evaluation should be performed based on the basis of their clinical history and findings. Follow-up chest imaging, typically chest radiography at 12 weeks, is recommended for all patients in whom a pulmonary infiltrate or other abnormality is detected on imaging during the acute course of COVID-19. Imaging should be performed without delay, particularly in patients with new or progressive respiratory symptoms. Chest computed tomography (CT) may be preferred if malignancy is suspected, or high-resolution CT may be an appropriate imaging study for patients with suspected interstitial lung disease such as acute respiratory distress syndrome (ARDS). Pulmonary function tests may be a good choice in patients with persistent, progressive, or emerging respiratory symptoms and in patients recovering from ARDS (22,23).

Referral to neurology and psychiatry departments for ongoing or progressive or new neurologic or neurocognitive problems is appropriate. Neurological imaging is typically not recommended unless there is concern for an unexplained neurological deficit or focal lesion or other conditions (4).

It is recommended that all patients be evaluated for signs and symptoms of deep venous thrombosis, pulmonary embolism, or arterial thrombosis (e.g. digital ischemia) in the upper and lower extremities. Patients with documented thromboses are treated similarly to thromboses in non-COVID-19 patients (2).

In addition to these symptoms, note that invasive fungal infections such as rhino-orbital mucormycosis, have been reported in patients recovering from COVID-19. As known, treatment with corticosteroids and poorly controlled diabetes mellitus are the main risk factors for mucormycosis (24,25). In acute COVID-19 patients with these risk factors, mucormycosis should be suspected if sinus congestion, blackish or colorless nasal discharge, facial or eye pain, or visual symptoms are detected following the acute period (26). Other infectious complications have also been observed in COVID-19 patients with these risk factors, including pulmonary aspergillosis (27) and strongyloides hyperinfection (28). Although these infectious complications are generally considered a late complication of acute illness, note that they can also occur late in patients recovering from moderate to severe COVID-19.

Patients with persistent taste and/or olfactory disturbances may benefit from further evaluation and management, and should be referred to an otolaryngologist (2). Adequate

rest, good sleep hygiene, and specific fatigue management strategies may be recommended for patients with persistent fatigue (2).

Additionally, it is good and necessary to be transparent with the patient for the process of goal setting and make it clear that post COVID conditions are not yet well understood, so well as the type, duration, severity, and recovery of post COVID conditions differ among patients.

It would not be wrong to say that the challenging pandemic period we have experienced in the last two years has given us doctors a lot to learn professionally, but considering current knowledge, we can easily say that we still have a long way to go.

### Ethics

**Peer-review:** Externally and internally peer-reviewed.

**Financial Disclosure:** The author declared that this study received no financial support.

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