

# Challenges and Management of Long COVID in Individuals with Hematological Illnesses

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## Keywords

COVID-19 · Long COVID · Rehabilitation · Persistent symptoms

## Abstract

COVID-19 has impacted hundreds of millions of people globally, a relatively large proportion of whom continue to suffer from ongoing, sometime debilitating symptoms. This phenomenon, termed “long COVID,” is difficult to diagnose and manage because of a paucity of objective findings and despite the abundance of descriptive data published so far. In this review, we aimed to describe the common manifestations of long COVID, diagnostic and management challenges, and address specific aspects in hematologic patients.

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## Introduction

COVID-19 has impacted hundreds of millions of people globally [1]. Initially, authorities and healthcare systems have mainly focused on the acute phase of the disease because of its immediate life-threatening complications and mortality. This approach has underestimated

the impact of COVID-19 on survivors, a relatively large proportion of whom continue to suffer from ongoing, sometime debilitating symptoms.

Post-COVID-19, also known as “Long COVID,” a term first coined by the suffering patients themselves, is a phenomenon characterized by persistent symptoms following recovery from COVID-19 [2]. The World Health Organization defines “post COVID-19 condition” as “a history of probable or confirmed SARS-CoV-2 infection, usually 3 months from the onset of COVID-19 with symptoms that last for at least 2 months and cannot be explained by an alternative diagnosis.” [2] In this review, we will refer to this condition as long COVID.

The most common long COVID symptoms are weakness, fatigue, dyspnea, cognitive impairment, and smell and taste disturbances (Table 1) [3–5]. This is reminiscent of previously reported fatigue syndromes following other infectious diseases, such as Epstein-Barr virus, dengue virus, chikungunya, and Q fever or other syndromes with unknown pathophysiology such as chronic fatigue syndrome and fibromyalgia [6, 7].

It is imperative to discern between long COVID and specific postinfectious syndromes occurring following COVID-19. The latter relates to several distinct entities with previously established pathophysiology that associ-

**Table 1.** Typical long COVID symptoms (over 12 weeks from infection) by prevalence, data adopted from systematic review, Michelen et al. [3]

Symptom	Proportion (95% CI)	Number of studies reporting	Total number of included individuals
Weakness	41.2 (25.4–59.0)	2	513
Fatigue	31.0 (23.9–39.0)	17	6,039
Breathlessness/exertional dyspnea	25.1 (17.9–34.0)	20	5,523
Sweat/night sweats	23.7 (20.7–27.1)	2	683
Weight loss*	21.0 (8.1–44.5)	2	568
Loss of appetite	17.5 (4.1–51.0)	3	1,906
Smell disturbance	15.2 (10.8–21.0)	19	5,668
Hair loss	14.3 (5.3–33.2)	5	2,810
Taste disturbances	13.5 (9.0–19.9)	17	5,423
Myalgia	11.3 (6.2–19.8)	12	4,782
Palpitations	9.7 (6.0–15.3)	8	4,778
Arthralgia	9.4 (5.7–15.0)	9	3,960
Paresthesia	9.1 (2.2–30.9)	2	257
Cough	8.2 (4.9–13.4)	16	5,031
Nausea and vomiting	6.7 (1.6–23.6)	4	821
Chest pain	6.4 (3.2–12.4)	11	4,878
Nasal congestion	5.0 (2.7–8.9)	3	1,003
Headache	4.9 (2.3–10.1)	11	4,535
Vision disturbances	4.8 (3.3–6.8)	2	586
Flushing	4.8 (3.2–7.0)	1	538
Sore throat	4.7 (2.4–8.9)	5	2,896
Dizziness	4.5 (2.5–7.9)	5	3,141
Walking/gait abnormality	4.2 (2.0–8.5)	3	809
Diarrhea	4.0 (2.1–7.6)	10	3,925
Tremors	3.5 (0.3–30.6)	3	1,124
Skin rash	2.8 (1.0–8.2)	4	2,374
Abdominal pain	2.3 (0.5–9.4)	4	1,427
Fever	1.1 (0.2–4.7)	7	3,624
Psychosocial and neurocognitive symptoms			
Reduced quality of life	36.8 (18.4–60.0)	3	807
Concentration impairment	26.0 (21.0–31.7)	2	254
Anxiety	18.7 (8.9–35.3)	7	3,551
Sleep disorders	18.2 (9.6–31.6)	9	3,442
Memory impairment	17.9 (5.3–46.3)	5	886
PTSD	9.1 (3.7–21.0)	6	2,057
Depression	8.1 (4.1–15.1)	6	3,662
Confusion	2.7 (1.9–3.8)	2	1,218

CI, confidence interval; PTSD, post-traumatic stress disorder. \* Most studies do not report weight loss as a long COVID symptom. The very few studies that did consider it among the typical symptoms mostly included individuals recovered from severe disease and ICU survivors.

ate with COVID-19 and tend to appear during the postinfectious period, usually up to 12 weeks from diagnosis. These include peri-myocarditis, thyroiditis, idiopathic thrombocytopenic purpura, *Guillain-Barré* syndrome [8–12]. There is a scientific basis implying that these may appear following infectious diseases, and their association with COVID is plausible, albeit necessitating additional proof through population-based studies.

There are conflicting reports on the prevalence of long COVID, ranging from 5% and up to ~80% depending on the population surveyed, classification definitions, severity of the acute illness, and the time elapsed from the acute episode [3, 4, 13, 14]. The prevalence may be subjected to change over time, reflecting the emergence of new viral variants (e.g., delta and omicron variants) and the effect of vaccines on disease severity and potentially on long COVID itself [15].

The risk factors for long COVID established thus far include a positive association with the severity of the acute illness, and higher risk among women [4, 16, 17]. Middle-aged individuals (40–60 years old) are also at an increased risk of long COVID in comparison to younger adults [18, 19]; however, this may be confounded by disease severity and warrants further research on the subject [20, 21].

### Long COVID in Individuals Diagnosed with Hematological Diseases

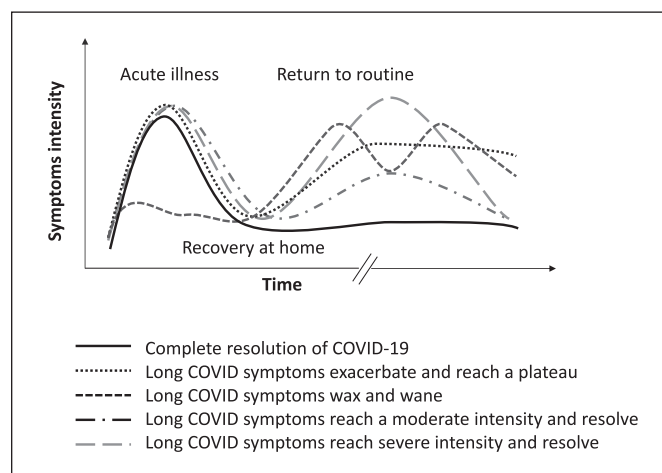
There are currently no publications reporting on the prevalence of long COVID among individuals diagnosed with hematological diseases. It is reasonable to assume that the prevalence of long COVID in this particular subpopulation is at least as high as reported for the general population. Moreover, individuals with hematological diseases are at higher risk for COVID-19 infection and its complications and are less likely to develop an adequate immune response to COVID-19 vaccines. Consequently, it is likely that their proportion among individuals with long COVID is higher than their realistic portion in the general population.

Long COVID symptoms are mostly nonspecific and multisystemic by nature. Accordingly, they share many similarities with symptoms that are suggestive of the underlying hematological disease or side effects of treatment. This is particularly relevant as fatigue and other typical long COVID symptoms are not uncommon post intensive antineoplastic therapy. The only exception is anosmia which is particularly suggestive of long COVID.

Long-term symptoms following COVID-19 in hematological patients may challenge clinical decision-making and may lead to unnecessary worries and redundant diagnostic procedures and complications; on the other hand, individuals with systemic manifestations arising from recurrence of their underlying hematological illness or opportunistic infections may be mistakenly addressed as having long COVID, delaying their diagnosis and hindering necessary treatment.

### Hematological Syndromes Post-COVID-19

Acute COVID-19 is associated with hematological complications including venous thromboembolism, disseminated intravascular coagulation, thrombocytopenia, anemia, and hemophagocytic lymphohistiocytosis [22].



**Fig. 1.** Typical courses of symptom intensity over time in individuals with long COVID.

Some of these were also reported following recovery. These include idiopathic thrombocytopenic purpura [11, 23], autoimmune hemolytic anemia [10], Evans syndrome [11], and hemophagocytic lymphohistiocytosis [24]. Further population-based studies are required in order to assert whether these associations, if exists at all, are causal or merely circumstantial. Similar to other acute illnesses, ongoing risk for post recovery venous thromboembolism is a concern [25, 26]. This topic, which justifies an in-depth consideration, is beyond the scope of the current review.

### Long COVID Symptoms

Long COVID is characterized by an abundance of somatic and psychosocial symptoms, while the physical examination as well as imaging and blood tests are usually unremarkable. The most frequently reported symptoms are weakness, fatigue, dyspnea, cognitive impairment, and smell and taste disturbances (Table 1) [3, 4]. These symptoms vary in their intensity and can become debilitating, impairing one's ability to regain pre-illness occupational and social functioning. The course of symptoms may also vary between individuals. While most report improvement over time, some report constant symptoms, a waxing and waning pattern or even a worsening trend (Fig. 1). The duration of long COVID is variable, and many of the afflicted individuals continue to suffer for long time periods [27, 28], and reports of symptoms lasting for 12 months and more are abundant [16, 18, 29, 30].

Several pathophysiological mechanisms have been hypothesized, primarily, immune dysregulation, and endo-theliopathy affecting the lungs, heart, and central or peripheral nervous systems. However, these hypotheses have not been established and are currently under investigation [31, 32]. Considering that longitudinal studies reported a substantial decrease in the prevalence of each of the long COVID symptoms, it is reasonable to assert that long COVID is a self-limiting medical condition. However, considering its burden, debilitating nature, and the fact that a non-negligible group of individuals may suffer for extremely long periods, effort must be taken in order to assess interventions aiming at shortening the time period for complete symptoms resolution.

### Diagnosis of Long COVID

In the absence of specific signs or other leading diagnostic clues, long COVID is diagnosed by the exclusion of other clinical conditions. The evaluation of individuals with ongoing symptoms following COVID-19 relies on meticulous history taking and physical examination. Whenever these imply an established postinfectious entity (see above), the workup should be directed at the suspected entity. In the appropriate context, after excluding signs suggesting an alternative diagnosis, in a patient who reports typical symptoms (Table 1), long COVID can be confidently assumed.

It should be emphasized that long COVID is usually not accompanied by abnormalities in vital signs, physical examination or blood parameters. Clinicians should therefore consider such abnormalities as *alarming signs*, suggesting another diagnosis. These signs include prolonged fever, night sweats, unexplained weight loss, significantly elevated markers of inflammation, and any other abnormal laboratory test. Although weight loss has been reported as a long COVID symptom in 2 studies [3], we do not consider it among the typical long COVID symptoms. Therefore, a thorough investigation is advised in these patients.

### Distinguishing between Long and Persistent/Relapsed COVID

Persistent COVID is a discrete and relatively rare entity, recognized in individuals with immune suppression, mostly reported in patients with lymphoproliferative disorders and/or treatment with anti-CD-20 monoclonal antibodies [33–35]. Although it shares clinical similari-

ties with long COVID in terms of ongoing symptoms, it involves ongoing viral replication and elevated inflammatory markers and reflects a failure of the immune system to achieve virological clearance. Relapsed COVID-19, a more controversial entity, relates to a persistent infection, in which there was documentation of virological clearance (2 consecutive negative polymerase chain reaction tests between the positive results) [36].

Distinguishing persistent COVID from long COVID in immunosuppressed individuals may be challenging, as nasopharyngeal polymerase chain reaction may be positive intermittently for a long duration even in immunocompetent individuals [36]. Ongoing fever, elevated inflammatory markers, or other alarming signs (see above) continuing into the expected recovery phase in an immunosuppressed individual are the hallmark of persistent COVID and should not be confused with long COVID.

### Management

#### *Acknowledging the Clinical Syndrome and Patient Reassurance*

In addition to the suffering arising from the debilitating symptoms, many individuals who experience long COVID withstand doubt, shame, and social stigma. One of the most important roles of physicians caring for individuals with long COVID is to acknowledge their patients' suffering. Many of the sufferers find comfort in the discovery that their harsh experience is a common phenomenon. Physicians are therefore encouraged to normalize the experience of their patients by giving it a name and to diagnose it as long COVID.

In the absence of evidence-based interventions, it is particularly important to reassure the patient. We advise physicians to share with their patients the data that has been gathered so far. It is important to convey the message that long COVID generally carries a good prognosis and tends to resolve over time. We also advise physicians to inform their patients that the duration of symptoms might be very long and that it is currently impossible to forecast the individual course of symptoms.

#### *Psychosocial Evaluation and Intervention*

Many of the individuals with long COVID experience anxiety and emotional distress (Table 1). These manifestations likely intensify other somatic and cognitive long COVID symptoms. Initial assessment should include screening for emotional distress and further referral to social workers and/or psychotherapists when necessary.

Whenever appropriate, physicians and psychotherapists can conduct the clinical visits together. This holistic approach of multidisciplinary care is beneficent.

#### *Physical and Pulmonary Rehabilitation*

Patients following severe or critical disease tend to suffer significant deconditioning and most require rehabilitation, be it in-hospital or at an outpatient facility. Post-discharge rehabilitation has been shown to be beneficial for survivors of severe or critical COVID-19 [37–39]. However, decreased exercise capacity also occurs in individuals with long COVID following mild or moderate acute disease. Most of these do not require additional evaluation, but patients with severe dyspnea, dyspnea at rest, chest pain on exercise and any abnormal physical finding on examination may need referral for additional studies such as pulmonary function testing, echocardiography, and cardiopulmonary exercise testing [40, 41].

No comparative interventional studies have been published thus far for managing long COVID in the medium-long term. We recommend that all patients be encouraged to gradually resume or take up low-intensity physical activity such as walking or swimming. Patients with a sedentary lifestyle prior to COVID-19 should try to begin a regular albeit very light exercise program (even a few minutes at a time) and increase gradually [42]. Patients with prior active lifestyle should be advised avoiding an abrupt return to their previous exercise schedule. Gradual increase of exercise intensity and duration should be adjusted to patients' ability and postexercise recovery rate. Recommendations for professional athletes have been proposed by several authors [42, 43]. Even in the absence of evidence in mild-moderate recoverees, it is plausible to offer physiotherapy or hydrotherapy to patients unable to return to their occupational or recreational pre-illness routine.

#### *Cognitive Assessment and Rehabilitation*

Long COVID cognitive symptoms usually include impaired executive functions such as working memory, concentration, and attention [3, 44]. This may severely impair the quality of life and daily functioning of the sufferers. At the extreme of the spectrum, working individuals sometimes find themselves unable to implement their occupational duties and maintain their employment. Retired or elderly individuals may encounter decline in their quality of life, as they feel unable to conduct recreational or leisure activities as was prior to COVID-19.

For individuals with mild cognitive symptoms and no overt influence on their quality of life, we recommend re-

turning to premorbid occupational and recreational routine as early as possible. Daily reading, solving crossword puzzles, Sudoku, or any other cognition challenging activities are also recommended. It is advised to reserve assessment by occupational therapist and neurologist for those with severe functional impairment or diminished quality of life. Cognitive rehabilitation by a trained occupational therapist could provide coping strategies to limit impact on daily life and may accelerate the rate of improvement [45].

#### *Olfactory Training*

Individuals recovering from COVID-19 often experience anosmia, dysgeusia, parosmia, and phantosmia. Many of them describe these symptoms as devastating, impairing their quality of life. For long COVID symptoms involving changes in taste and smell, we suggest olfactory training. This protocol was developed for cases of postinfectious olfactory dysfunction and was proven effective in several randomized control trials [46, 47] prior to COVID-19. A single randomized control trial has examined use of nasal corticosteroids with olfactory training versus training alone and has shown both interventions as equally effective in long COVID patients, with no added benefit for the corticosteroid group [48]. Considering that olfactory training carries no potential harms or side effects (as opposed to corticosteroids), it is recommended for long COVID, whereas it is advised to avoid addition of corticosteroids [47].

#### *Summary*

Long COVID is a debilitating entity that affects the life of millions of sufferers worldwide. Since its pathophysiology is yet to be understood, interventions aimed at improving quality of life and hasten symptoms' resolution rate are still lacking. Physicians caring for these patients should focus their efforts on three main aspects: rule out other entities; patient reassurance; and referral for rehabilitation whenever appropriate.

Individuals with hematological illnesses, most notably those with malignancies, constitute a particular subpopulation in several ways. They are more susceptible to COVID-19 and possibly to long COVID as well. Moreover, their nonspecific and systemic long COVID symptoms mimic disease progression or recurrence and therefore may pose diagnostic dilemmas. Hematologists should be aware of this phenomenon and be familiar with the typical symptoms as well as alarming signs implying other diagnoses. This approach will spare patients unnecessary distress and diagnostic procedures. Furthermore, a holis-



tic approach, reassurance, and rehabilitation programs may provide these individuals with comfort and hope, merits that potentially have therapeutic value, which is of particular need at times of no proven directed treatments.

### Conflict of Interest Statement

The authors report no conflict of interest.

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