

Post-COVID-19 sequelae or persistent COVID-19 disease

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Abstract

The post-COVID-19 syndrome, post-acute COVID-19, long-term COVID, long-COVID, or post-sepsis syndrome terminology suggests that COVID-19 disease is frequently persistent. COVID-19 induces sequelae of variable severity and clinical significance in multiple systems and organs affected by the acute disease. The post-COVID-19 condition is an umbrella term for a complex, multisystemic disease that immediately or even after apparent recovery follows the acute phase of COVID-19, irrespective of severity. This review discusses the multiple manifestations, causes, and current treatment and evaluation recommendations in the post-COVID-19 syndrome.

Keywords: post-COVID-19 syndrome, COVID-19 long term complications, post-COVID-19 evaluation, post-COVID-19 treatment, post-COVID-19 causes.

Definition

Syndrome, sequelae or persistent disease?

A syndrome is a complex concept that is defined by an association of symptoms of a certain pathology that is induced by internal or external factors and which is characterized by altered homeostasis. It is not a symptom, nor is it a disease. The difference that separates a syndrome from a disease is that a syndrome encompasses multiple pathogenic entities without a specific cause. Toxic syndromes (toxidromes), acute respiratory distress syndrome,

irradiation syndrome, cardiovascular syndromes, cardiorenal syndromes, Down syndrome, hepatorenal syndromes, irritable bowel syndromes are pertinent examples of other well-known syndromes. Hundreds of such syndromes have been described.

This particular terminology was addressed to clarify further what defines the post-COVID syndrome. This term is, however, not generally accepted as it is not currently well substantiated. Post-COVID-19 syndrome, post-acute COVID-19, long-term COVID, long-COVID or post-sepsis syndrome imply that COVID-19 disease is frequently persistent. COVID-19 induces sequelae of variable severity and clinical significance in systems and organs affected by the acute disease such as the lung, vascular system (as a consequence of systemic endothelitis), gastrointestinal tract, and the central nervous system [1-5].

Post-COVID-19 condition is an umbrella term for a complex, multisystemic disease that immediately or even after apparent recovery follows the acute phase of COVID-19, irrespective of severity [6]. New

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or fluctuating symptoms as dyspnea, chest pain, palpitation and tachycardia, urticaria, abdominal pain, diarrhea, arthralgia, neuralgia, dysphonia, fatigue, cognition modifications, persistent fever may occur even four weeks after the initial phase of COVID-19. These symptoms have been recently grouped by the National Institute of Health Research in four particular syndromes [7].

Post-COVID-19 sequelae have been grouped in multiple syndromes such as post-intensive therapy syndrome, post-viral infection fatigue syndrome, and long COVID syndrome. All of these manifestations signify complex and unpredictable post-viral pathology, as will be further detailed.

Various authors have attempted to systematize the current post-COVID-19 knowledge, define diagnosis criteria, and clarify the need for a multidisciplinary approach in treating such patients in dedicated COVID-19 outpatient clinics.

Nalbandian *et al.* have recently described two types of clinical settings which manifest at least four weeks after the initial COVID-19 infection [4]:

- Subacute/ongoing COVID-19, which includes symptoms or abnormalities occurring four to twelve weeks after the initial acute infection;
- Chronic/post-COVID-19 which includes symptoms or abnormalities occurring twelve weeks beyond the initial acute infection and which are not attributable to other alternative diagnoses

Therefore, the most important post-COVID-19 effects in various organs and systems should be underlined [4–8]. Persistent dyspnea and hypoxia, reduced exercise capacity are commonly cited as pulmonary symptoms. Cardiovascular symptoms include dyspnea, palpitations, and chest pain. Long-term sequelae consist of myocardial fibrosis, arrhythmia, and dysautonomia [6, 9]. Thromboembolic events have been described in under 5% of patients in retrospective studies in post-COVID-19 as hematologic manifestations [5, 10, 11]. Neuropsychiatric symptoms include fatigue, myalgia, cephalalgia, dysautonomia, cognitive impairment, anxiety, depression, and sleep abnormalities. Post-traumatic stress disorders have been diagnosed in almost 30–40% of COVID-19 survivors.

The aforementioned neuropsychiatric manifestations are a consequence of not only the complex COVID-19 pathogenesis (diffuse inflammation, systemic endothelitis, immune dysfunction, microvascular thrombosis) but also of medication and the psychological and social impact of the pandemic.

A multisystemic inflammatory syndrome has been described in pediatric patients and young adults under 21 years of age, which consists of fever, elevated inflammatory markers, multiple organ dysfunction after recent or ongoing COVID-19 infection. Renal (decreased glomerular filtration rate five months after the initial infection) and endocrine

disorders (diabetes mellitus, osteoporosis, subacute thyroiditis) have been described. Various gastrointestinal, hepatic and hepatobiliary disorders have been associated with post-COVID-19 syndromes. Persistent fecal viral shedding has been observed in post-COVID-19 patients, even after COVID-19 testing has become negative in nasopharyngeal exudates. Also, hair loss has been described in up to 20% of COVID-19 survivors.

Post-COVID-19 patients' evaluation and treatment guidelines

Pulmonary sequelae consist of pulmonary fibrosis induced by viral invasion and alveolocapillary membrane penetration, which leads to protein-rich alveolar exudate formation. The fibroproliferative alveolar response is a secondary consequence that follows viral infection clearance. Micro- and macrovascular thrombosis have been described in 20–30% of COVID-19 patients, exceeding thrombotic events in critical patients suffering from other non-COVID-19 conditions. Multiple international guidelines recommend pulmonary evaluation in survivors of moderate and severe forms of acute infection during the first three months after the infection resolution, which includes chest x-rays, clinical evaluation, sputum cultures and transthoracic echocardiography. High-resolution computed tomography may also be recommended.

Hematological sequelae. Thromboprophylaxis (low-molecular-weight heparin, antiplatelets, and physical activity) is recommended up to 6 weeks after acute infection resolution, especially in the case of elevated D-dimers.

Psychiatric sequelae include post-traumatic stress disorders, depression, anxiety, insomnia, and obsessive-compulsive disorders. Psychiatric sequelae require a close evaluation and are a direct consequence of viral infection, systemic inflammation, microvascular thrombosis, and neurodegeneration. Patient-tailored treatment and close clinical monitoring are required in such manifestations [12].

Identification of the *multisystemic inflammatory syndrome*, which manifests in young adults under 21 of age by fever, elevated inflammatory markers, multiple organ dysfunction, abdominal pain, nausea and emesis, diarrhea, skin rash, arterial hypotension, and other various cardiovascular and neurological symptoms, is to be underlined.

Recent research efforts regarding post-COVID-19 have been concentrated on identifying the clinical, serological, and imaging aspects of the acute, subacute and chronic COVID-19 disease that will facilitate understanding the natural history and physiopathology of this viral infection [4].

The following clinical phenotypes at patient discharge have been described [3]:

- Chronic post-viral fatigue syndrome;
- Postcritical state syndrome;
- Post-traumatic stress disorder syndrome

As previously stated, the current definition of long-COVID is variable and inconsistent. Most studies have reported various isolated symptoms more frequently than groups of symptoms. Aldo, 4.5-89% of patients that have previously required oxygen therapy for more than 48 hours during hospitalization have reported persisting symptoms eight weeks after the acute phase of the disease. Moreover, 20% of patients that have previously tested positive for COVID-19 experience symptoms for more than five weeks after the initial infection and approximately 10% after 12 weeks or more [3]. Long COVID is more frequent in women than men and young patients aged 25-54 years.

A recent longitudinal study included compared 140 patients with a history of COVID-19 with 1160 control cases. At a median of 7.5 months after the infection, 14.3% of patients were still experiencing ongoing (2.9%, n=4) episodic symptoms (11.4%,

n=16) [13]. The authors recognize three clusters of symptoms associated with long COVID: sensory (38% – ageusia, anosmia, loss of appetite and blurred vision), neurological (42% – forgetfulness, short-term memory loss, and confusion/brain fog), and cardiorespiratory (51% – chest tightness/pain, unusual fatigue, breathlessness after minimal exertion/at rest, palpitations). While all the clusters had a strong association with post-COVID cases, the sensory cluster had the highest specificity and strength of association with persistent COVID-19. Long COVID diagnosis requires no other alternative diagnosis accounts for current symptoms [11].

Long COVID causes

Recent research has debated if the persistent manifestations and sequelae of COVID-19 constitute a newly emerging disease. Salmon-Ceron *et al.* summarize available data regarding long-COVID (Figure 1) [1]. Fatigue is a dominant symptom and appears

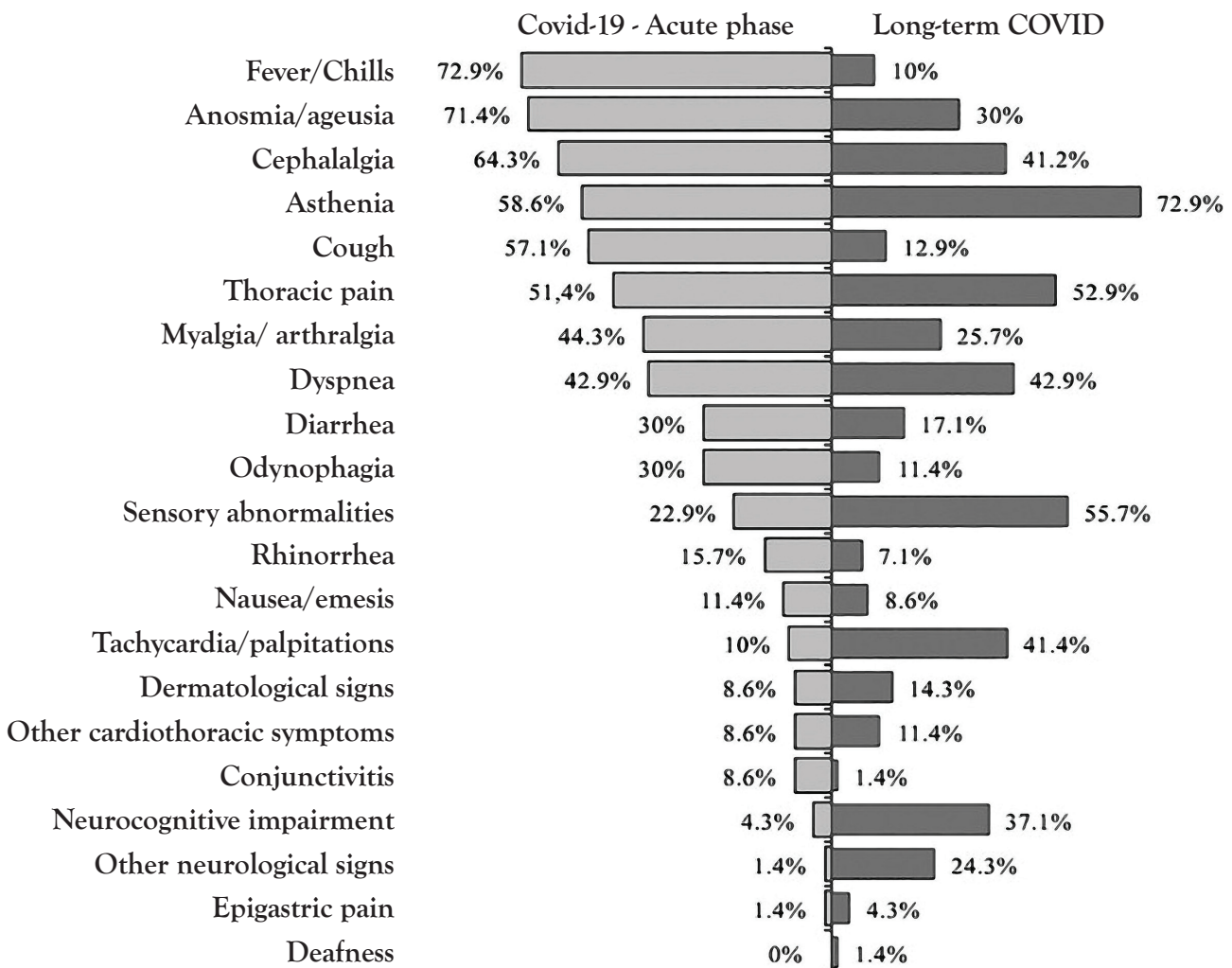


Figure 1. Comparison of acute versus long-COVID symptoms [1].

in 72% of long-COVID patients, in contrast to fever, which is more common in the acute phase.

Various theories have emerged regarding the cause of persistent COVID symptoms: viral persistence, viral reinfection (with an identical or a new variant), immune dysfunction in a proinflammatory state and/or post-traumatic stress disorder. Delayed and persistent immune and inflammatory responses may contribute to persistent COVID-19.

Asthenia is the most common post-COVID-19 symptom and is generally associated with post-viral states such as influenza, SARS, Ebola and so forth.

Salmon-Ceron *et al.* suggest that certain genetic characteristics may create the setting for auto-immune processes, which result in autoimmune diseases such as Guillain-Barré syndrome [1]. Long-COVID symptoms may be explained by immune-mediated dysautonomia, which resembles orthostatic intolerance syndrome involving postural hypotension, tachycardia, palpitations, and chest pain [9]. Reduced vasoconstriction response due to dysautonomia during postural changes leads to hypotension, presyncope, and syncope.

25% of long-COVID patients have persistent nasal or pharyngeal positive real-time polymerase chain reaction (RT-PCR results) [1]. Viral persistence may generate specific immune responses and prolonged inflammation which may be responsible for persistent symptoms [3].

Several cardiac and pulmonary abnormalities have been described. 8% of patients may exhibit myocarditis and other imagistic thoracic abnormalities 7–8 months after discharge. Singular or multiorgan dysfunction may be present four months after the acute symptomatic phase. The reversibility of the long-COVID abnormalities can not currently be attested. Thromboembolism is common in long-COVID patients. Further, neurological symptoms in long-COVID patients may resemble chronic fatigue syndrome (fatigue, myalgia) or may be severe, even life-threatening, in the case of Guillain Barré syndromes and encephalitis. “Brain fog” is frequently described in post-COVID patients. Cognitive impairment is common in long-COVID patients, especially after hospitalization.

The development of long-COVID is challenging to anticipate based on the acute disease severity. There is currently a lack of scientific consensus regarding the causes and mechanisms that lead to long-COVID. Additionally, authors have debated if the aforementioned symptoms are characteristic of an already known post-viral syndrome or are part of a new, unique disease. The physical, psychological, and social impact of long-COVID may be severe [3]. The predictability of long-COVID is currently limited as there are no known risk factors that favor its development.

A recent retrospective study that included 47780 COVID-19 survivors discharged from the hospital has revealed high rates of multiorgan damage in all

age groups and ethnicities [2]. Consequently, discharged COVID-19 patients had a 3.5-fold higher risk of re-admission and a 7.7-fold higher risk of death over a follow-up interval of 140 days compared to controls. Re-admission risk was even higher in patients older than 70 years old.

Long COVID syndrome management is complex, given the lack of current data regarding its causes. After rigorous differential diagnosis, symptomatic treatment and functional rehabilitation are recommended. There are no currently published studies regarding long-COVID treatment. Treatment is currently based on intravenous immunoglobulins, corticoids, and low doses of acetylsalicylic acid.

In conclusion, long-COVID-19 symptoms and sequelae result in multiple apparently long-lasting clinical and therapeutic obstacles and are currently rising in prevalence due to the ongoing pandemic and the progressively more accurate diagnosis.

Conflict of Interest

The authors confirm that there are no conflicts of interest.

References

1. D. Salmon-Ceron *et al.*, “Clinical, virological and imaging profile in patients with prolonged forms of COVID-19: A cross-sectional study,” *The Journal of infection*, vol. 82, no. 2, pp. e1–e4, Feb-2021, doi: 10.1016/j.jinf.2020.12.002.
2. D. Ayoubkhani *et al.*, “Epidemiology of post-COVID syndrome following hospitalisation with coronavirus: a retrospective cohort study,” *medRxiv*, p. 2021.01.15.21249885, Jan. 2021, doi: 10.1101/2021.01.15.21249885.
3. E. Maxwell, “A dynamic review of the evidence around ongoing COVID-19 (often called long COVID),” *NIHR*, 2021, doi: doi:10.3310/the.med.review.45228.
4. A. Nalbandian *et al.*, “Post-acute COVID-19 syndrome,” *Nat. Med.*, vol. 27, no. 4, pp. 601–615, 2021, doi: 10.1038/s41591-021-01283-z.
5. G. Ponti, M. Maccaferri, C. Ruini, A. Tomasi, and T. Ozben, “Biomarkers associated with COVID-19 disease progression,” *Crit. Rev. Clin. Lab. Sci.*, vol. 57, no. 6, pp. 389–399, Sep. 2020, doi: 10.1080/10408363.2020.1770685.
6. M. Nurek, S. Taylor, and N. Macdermott, “Recommendations for the recognition, diagnosis, and management of patients with Post Covid-19 Condition (‘long covid’): A Delphi study,” *Lancet*, no. April, 2021, doi: 10.2139/ssrn.3822279.
7. E. Mahase, “Long covid could be four different syndromes, review suggests,” *BMJ*, vol. 371, 2020, doi: 10.1136/bmj.m3981.

8. B. Walitt and E. Bartrum, "A clinical primer for the expected and potential post-COVID-19 syndromes.," *Pain reports*, vol. 6, no. 1, p. e887, 2021, doi: 10.1097/PR9.0000000000000887.
9. M. Dani *et al.*, "Autonomic dysfunction in 'long COVID': rationale, physiology and management strategies.," *Clin. Med.*, vol. 21, no. 1, pp. e63–e67, Jan. 2021, doi: 10.7861/clinmed.2020-0896.
10. F. V. C. Machado *et al.*, "Construct validity of the Post-COVID-19 Functional Status Scale in adult subjects with COVID-19," *Health Qual. Life Outcomes*, vol. 19, no. 1, p. 40, 2021, doi: 10.1186/s12955-021-01691-2.
11. P. Venkatesan, "NICE guideline on long COVID," *Lancet Respir. Med.*, vol. 9, no. 2, p. 129, Feb. 2021, doi: 10.1016/S2213-2600(21)00031-X.
12. Z. Al-Aly, Y. Xie, and B. Bowe, "High-dimensional characterization of post-acute sequelae of COVID-19," *Nature*, vol. 594, no. 7862, pp. 259–264, 2021, doi: 10.1038/s41586-021-03553-9.
13. Z. Amin-Chowdhury *et al.*, "Characterising long COVID more than 6 months after acute infection in adults; prospective longitudinal cohort study, England," *medRxiv*, p. 2021.03.18.21253633, Jan. 2021, doi: 10.1101/2021.03.18.21253633.