

Long COVID—unravelling a complex condition



Long COVID is an overarching term that was originally coined by patients and is widely used to describe ongoing symptoms after the acute phase of COVID-19, including both short-term symptoms (4–12 weeks) and longer-term sequelae (beyond 12 weeks). The term post-COVID-19 condition, developed by WHO, describes the continuation or development of new symptoms 3 months after the initial SARS-CoV-2 infection.¹ The incidence of long COVID is estimated to be 10–30% for people who are not hospitalised in the acute phase,² 50–70% for hospitalised patients,³ and 10–12% for vaccinated individuals after acute infection.⁴ Conservatively, at least 65 million individuals globally were estimated to have long COVID in 2023,² with cases increasing daily.

Long COVID is a complex, multisystem condition with the potential to have a substantial impact on individuals and society, including increased disability, increased health-care costs, and economic and productivity losses.⁵ More than 200 symptoms have been identified that can impact functioning and activities of daily living, encompassing physical, psychological, and cognitive function.² The symptoms and sequelae of long COVID can persist for weeks or months, fluctuate over time, or manifest as new-onset chronic conditions. The condition has placed an enormous burden on health-care systems. Despite some international collaboration, progress in understanding long COVID has been hindered by heterogeneous study designs, follow-up durations, and measurement methods.⁶ A global, collaborative, multidisciplinary research agenda will be essential to improve the diagnosis and treatment of long COVID.

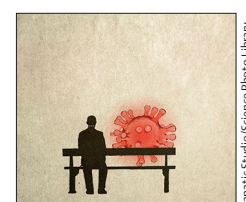
Potential mechanisms contributing to long COVID include pathophysiological changes related to the virus (eg, microclotting), immunological and inflammatory dysregulation resulting from the acute infection, viral persistence, and, in patients with severe disease, known sequelae of critical illness (post-intensive care syndrome).⁷ In a *Lancet Respiratory Medicine* Series on the post-acute sequelae of COVID-19,^{8–10} the diagnosis, treatment, and management of long COVID are discussed, with a focus on respiratory, neurocognitive, psychological, and systemic sequelae of severe acute COVID-19. Known risk factors for long COVID include severe acute disease, comorbidities (eg, diabetes and

chronic heart failure), and life-saving therapies such as invasive mechanical ventilation.

In the first Series paper, Sally J Singh and colleagues⁸ present a compelling argument for further research to understand the mechanisms that underlie long-term respiratory symptoms after COVID-19, particularly for patients who required hospital admission and received invasive mechanical ventilation. These sequelae might be due to the underlying disease or to life-saving therapies delivered in intensive care units (ICUs), such as prolonged invasive mechanical ventilation, sedation, and immobilisation, which are known to contribute to long-term morbidity in survivors. Pathological changes might be caused by SARS-CoV-2 infection or by immune-mediated injury to alveolar cells. Specific pulmonary sequelae, such as pulmonary fibrosis and thromboembolic disease, need careful assessment and management because they could lead to increased dyspnoea and physical dysfunction. Current rehabilitation strategies have been adapted from chronic respiratory disease practices and pulmonary rehabilitation programmes; however, further research is needed to establish whether these strategies are effective for long-term respiratory symptoms after COVID-19.

Frailty is well recognised as a risk factor for both COVID-19 severity and poor outcomes after critical illness.^{11,12} In some countries, frailty is routinely assessed at ICU admission to identify patients who might require additional support. In the third paper in the Series, Matteo Parotto and colleagues⁹ review research indicating that up to 30% of COVID-19 survivors are frail after hospitalisation for COVID-19. The authors describe the complex interaction between pre-existing comorbidities, frailty, socioeconomic factors, ICU support, and subsequent outcomes of long COVID for patients and caregivers. This interaction has important implications for models of health-care delivery, which include careful assessment of physical and psychological function after hospital discharge, and review of nutrition, medications, and social support. Coordinated, multidisciplinary care for people with long COVID at risk of frailty and further research for vulnerable people and groups are needed.

Some of the most commonly reported symptoms of long COVID are neuropsychological symptoms,



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including fatigue, memory loss, dizziness, loss of taste or smell, depression, and anxiety, all of which can affect activities of daily living and productivity. These sequelae have also been reported after non-COVID-19-related critical illnesses, such as acute respiratory distress syndrome and sepsis, and in survivors of prolonged mechanical ventilation. However, in a large study from the USA, in the 12 months after infection, survivors of COVID-19 had about a 40% higher risk of developing cerebrovascular or neurodegenerative disorders (eg, ischaemic and haemorrhagic stroke, or Alzheimer's disease or Parkinson's-like disease) than did controls without SARS-CoV-2 infection.¹³ In the second paper in the Series, Pratik Pandharipande and colleagues¹⁰ provide a comprehensive review of the rationale for neuropsychological sequelae, associated risk factors, and potentially modifiable targets for treatment and prevention. The authors strongly advocate the use of evidence-based clinical practice guidelines for patients receiving mechanical ventilation,¹⁴ such as limited use of neuromuscular blockade, avoidance of benzodiazepines, targeting of light sedation, regular awakening, spontaneous breathing trials, and rehabilitation.

The identification and treatment of severe acute respiratory COVID-19 has improved survival outcomes, but the optimum approach to management of long COVID and its sequelae remains uncertain. In the Series, considerations for the follow-up and ongoing care of patients with long COVID are discussed by international experts. Key recommendations include further research to understand the pathophysiological mechanisms of multisystem sequelae of COVID-19; approaches to care in the acute phase that mitigate the symptoms of long COVID; use of predictive biomarkers to distinguish patients who are likely to benefit from established rehabilitation therapies; further investigation into effective strategies for reducing breathlessness, including group rehabilitation, rehabilitation via telemedicine, and individual breathing exercises; dedicated multidisciplinary clinics that can provide care and support for patients and also serve as a platform for research; and efforts to develop novel preventive and therapeutic treatments for long COVID. Clinicians,

researchers, and other stakeholders need to advocate collaborative global research, with dedicated education and training for the health-care workforce and a public communication campaign to highlight ongoing challenges as a result of long COVID. Finally, patients with long COVID should be meaningfully engaged in the design and conduct of clinical trials to address key research questions aimed at improving the quality of their survival.

We declare no competing interests.

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- 1 WHO. Post COVID-19 condition (long COVID). 2022. <https://www.who.int/europe/news-room/fact-sheets/item/post-covid-19-condition> (accessed May 30, 2023).
- 2 Davis HE, McCorkell L, Vogel JM, Topol EJ. Long COVID: major findings, mechanisms and recommendations. *Nat Rev Microbiol* 2023; **21**: 133–46.
- 3 Ceban F, Ling S, Lui LMW, et al. Fatigue and cognitive impairment in post-COVID-19 syndrome: a systematic review and meta-analysis. *Brain Behav Immun* 2022; **101**: 93–135.
- 4 Al-Aly Z, Bowe B, Xie Y. Long COVID after breakthrough SARS-CoV-2 infection. *Nat Med* 2022; **28**: 1461–67.
- 5 Yang C, Tebbutt SJ. Long COVID: the next public health crisis is already on its way. *Lancet Reg Health Eur* 2023; **28**: 100612.
- 6 O'Mahoney LL, Routen A, Gillies C, et al. The prevalence and long-term health effects of long COVID among hospitalised and non-hospitalised populations: a systematic review and meta-analysis. *EClinicalMedicine* 2023; **55**: 101762.
- 7 Needham DM, Davidson J, Cohen H, et al. Improving long-term outcomes after discharge from intensive care unit: report from a stakeholders' conference. *Crit Care Med* 2012; **40**: 502–09.
- 8 Singh SJ, Baldwin MM, Daynes E, et al. Respiratory sequelae of COVID-19: pulmonary and extrapulmonary origins, and approaches to clinical care and rehabilitation. *Lancet Respir Med* 2023; published online May 19. [https://doi.org/10.1016/S2213-2600\(23\)00159-5](https://doi.org/10.1016/S2213-2600(23)00159-5).
- 9 Parotto M, Gyöngyösi M, Howe K, et al. Post-acute sequelae of COVID-19: understanding and addressing the burden of multisystem manifestations. *Lancet Respir Med* 2023; published online July 17. [https://doi.org/10.1016/S2213-2600\(23\)00239-4](https://doi.org/10.1016/S2213-2600(23)00239-4).
- 10 Pandharipande P, Williams Roberson S, Harrison FE, Wilson JE, Bastarache JA, Ely EW. Mitigating neurological, cognitive, and psychiatric sequelae of COVID-19-related critical illness. *Lancet Respir Med* 2023; published online July 17. [https://doi.org/10.1016/S2213-2600\(23\)00238-2](https://doi.org/10.1016/S2213-2600(23)00238-2).
- 11 Hodgson CL, Higgins AM, Bailey MJ, et al. The impact of COVID-19 critical illness on new disability, functional outcomes and return to work at 6 months: a prospective cohort study. *Crit Care* 2021; **25**: 382.
- 12 Ma Y, Hou L, Yang X, et al. The association between frailty and severe disease among COVID-19 patients aged over 60 years in China: a prospective cohort study. *BMC Med* 2020; **18**: 274.
- 13 Xu E, Xie Y, Al-Aly Z. Long-term neurologic outcomes of COVID-19. *Nat Med* 2022; **28**: 2406–15.
- 14 Devlin JW, Skrobik Y, Gélinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med* 2018; **46**: e825–73.