

## VIEWPOINT

**Carlos del Rio, MD**

Division of Infectious Diseases, Department of Internal Medicine, Emory University School of Medicine, Atlanta, Georgia.

**Lauren F. Collins, MD**

Division of Infectious Diseases, Department of Internal Medicine, Emory University School of Medicine, Atlanta, Georgia.

**Preeti Malani, MD, MSJ**

Division of Infectious Diseases, Department of Internal Medicine, University of Michigan, Ann Arbor; and Associate Editor, *JAMA*.



Audio

# Long-term Health Consequences of COVID-19

**With more than 30 million documented infections** and 1 million deaths worldwide, the coronavirus disease 2019 (COVID-19) pandemic continues unabated. The clinical spectrum of severe acute respiratory syndrome coronavirus (SARS-CoV) 2 infection ranges from asymptomatic infection to life-threatening and fatal disease. Current estimates are that approximately 20 million people globally have “recovered”; however, clinicians are observing and reading reports of patients with persistent severe symptoms and even substantial end-organ dysfunction after SARS-CoV-2 infection. Because COVID-19 is a new disease, much about the clinical course remains uncertain—in particular, the possible long-term health consequences, if any.

## Epidemiology

Currently, there is no consensus definition of postacute COVID-19. Based on the COVID Symptom Study, in which more than 4 million people in the US, UK and Sweden have entered their symptoms after a COVID-19 diagnosis, postacute COVID-19 is defined as the presence of

tion among a random sample of 292 adults ( $\geq 18$  years) who had a positive outpatient test result for SARS-CoV-2 by reverse transcriptase-polymerase chain reaction, 35% of 274 symptomatic respondents reported not having returned to their usual state of health 2 weeks or more after testing, including 26% among those aged 18-34 years ( $n = 85$ ), 32% among those aged 35-49 years ( $n = 96$ ), and 47% among those aged 50 years or older ( $n = 89$ ).<sup>4</sup> Older than 50 years and the presence of 3 or more chronic medical conditions were associated with not returning to usual health within 14 to 21 days after receiving a positive test result. Notwithstanding, 1 in 5 individuals aged 18-34 years without chronic medical conditions had not yet achieved baseline health when interviewed at a median of 16 days from the testing date.

## Manifestations

The most commonly reported symptoms after acute COVID-19 are fatigue and dyspnea. Other common symptoms include joint pain and chest pain.<sup>3</sup> In addition to these general symptoms, specific organ dysfunction has been reported, involving primarily the heart, lungs, and brain. From a pathogenesis standpoint, these complications could be the consequence of direct tissue invasion by the virus (possibly mediated by the presence of angiotensin-converting enzyme 2 receptor), profound inflammation and cytokine storm, related immune system damage, the hypercoagulable state described in association with severe COVID-19, or a combination of these factors.

**Longer-ranging longitudinal observational studies and clinical trials will be critical to elucidate the...health consequences attributable to COVID-19 and how these may compare with other serious illnesses.**

symptoms extending beyond 3 weeks from the initial onset of symptoms and chronic COVID-19 as extending beyond 12 weeks.<sup>1</sup> It is possible that individuals with symptoms were more likely to participate in this study than those without them.

Previously described, a postacute syndrome is well recognized in patients who are recovering from a serious illness, in particular an illness that required hospitalization and admission to the intensive care unit. In a 2016 study among 43 patients who had been discharged after intensive care unit stay (46% required mechanical ventilation), 36 (84%) reported impairment in cognition, mental health, or physical function that persisted for 6 to 12 months beyond hospital discharge, collectively known as post-intensive care syndrome.<sup>2</sup> In a study from Italy that assessed COVID-19 symptom persistence among 143 patients discharged from the hospital, only 18 patients (12.6%) were completely free of any COVID-19-related symptoms after a mean of 60 days after initial symptom onset.<sup>3</sup>

However, postacute COVID-19 syndrome is not just observed among patients who had severe illness and were hospitalized. In a telephone survey conducted by the Centers for Disease Control and Preven-

## Cardiovascular

Myocardial injury, as defined by an increased troponin level, has been described in patients with severe acute COVID-19, along with thromboembolic disease. Myocardial inflammation and myocarditis, as well as cardiac arrhythmias, have been described after SARS-CoV-2 infection. In a German study of 100 patients who recently recovered from COVID-19, cardiac magnetic resonance imaging (performed a median of 71 days after COVID-19 diagnosis) revealed cardiac involvement in 78% and ongoing myocardial inflammation in 60%.<sup>5</sup> The presence of chronic comorbidities, duration and severity of acute COVID-19 illness, and time since original diagnosis did not correlate with these findings. However, the sample was not random and likely biased toward patients with cardiac findings. Nevertheless, among 26 competitive college athletes who received a diagnosis of COVID-19 by reverse transcriptase-polymerase chain reaction, none of whom required hospitalization and the majority without reported symptoms, 12 (46%) had evidence of myocarditis or

**Corresponding**

**Author:** Carlos del Rio, MD, Department of Medicine, Emory University School of Medicine, 49 Jesse Hill Jr Dr SE, FOB Room 201, Atlanta, GA 30303 (cdelrio@emory.edu).

prior myocardial injury by cardiac magnetic resonance imaging routinely performed for positive testing results (range, 12-53 days later).<sup>6</sup> The durability and consequences of such imaging findings are not yet known and longer follow-up is needed. However, an increased incidence of heart failure as a major sequela of COVID-19 is of concern, with considerable potential implications for the general population of older adults with multimorbidity, as well as for younger previously healthy patients, including athletes.

### Pulmonary

In a study of 55 patients with COVID-19, at 3 months after discharge, 35 (64%) had persistent symptoms and 39 (71%) had radiologic abnormalities consistent with pulmonary dysfunction such as interstitial thickening and evidence of fibrosis.<sup>7</sup> Three months after discharge, 25% of patients had decreased diffusion capacity for carbon monoxide. In another study of 57 patients, abnormalities in pulmonary function test results obtained 30 days after discharge, including decreased diffusion capacity for carbon monoxide and diminished respiratory muscle strength, were common and occurred in 30 patients (53%) and 28 patients (49%), respectively.<sup>8</sup> If compounded on cardiovascular comorbidity, either preexisting or incident from COVID-19, persistent decline in lung function could have major adverse cardiopulmonary consequences.

### Neurologic

SARS-CoV-2 can penetrate brain tissue via viremia and also by direct invasion of the olfactory nerve, leading to anosmia. To date, the most common long-term neurologic symptoms after COVID-19 are headache, vertigo, and chemosensory dysfunction (eg, anosmia and ageusia). Although stroke is a serious albeit uncommon consequence of acute COVID-19, encephalitis, seizures, and other conditions such as major mood swings and "brain fog" have been reported up to 2 to 3 months after initial illness onset.<sup>9</sup> Past pandemics involving viral pathogens (such as SARS-CoV-1, Middle East respiratory syndrome coronavirus [MERS], and influenza) have involved neuropsychiatric sequelae that could linger for months in "recovered" patients, which can seriously threaten cognitive health, overall well-being, and day-to-day functional status.

### Emotional Health and Well-being

In addition to symptom persistence and clinical sequelae that may last far beyond the initial COVID-19 illness, the extent of emotional and behavioral concerns and general distress for those affected has yet to be determined. A diagnosis of COVID-19, and subsequent need for physical distancing, has been associated with feelings of isolation and loneliness.<sup>10</sup> COVID-19-related stigma has also become pervasive and can result in a sense of hopelessness. Increasing reports of lingering malaise and exhaustion akin to chronic fatigue syndrome may leave patients with physical debility and emotional disturbance. Compounded by the psychological toll of the pandemic experienced population wide, individuals recovering from COVID-19 may be at even greater risk of depression, anxiety, posttraumatic stress disorder, and substance use disorder. These combined effects have the potential to result in a global health crisis, considering the sheer number of COVID-19 cases worldwide.

### Conclusions

Granted that no long-term data of substantial numbers of patients with various presenting symptoms exist and with comparison groups, and that it is still early in the COVID-19 pandemic, it is possible that large numbers of patients will experience long-term sequelae. Outpatient post-COVID-19 clinics are opening in many localities where large outbreaks have occurred, and the term "long-haulers" has been suggested to refer to these patients. It is imperative that the care of this vulnerable patient population take a multidisciplinary approach, with a thoughtfully integrated research agenda, to avoid health system fragmentation and to allow the comprehensive study of long-term health consequences of COVID-19 on multiple organ systems and overall health and well-being. Furthermore, such an approach will provide the opportunity to efficiently and systematically conduct studies of therapeutic interventions to mitigate the adverse physical and mental health effects among hundreds of thousands, if not millions, of people who recover from COVID-19. Longer-ranging longitudinal observational studies and clinical trials will be critical to elucidate the durability and depth of health consequences attributable to COVID-19 and how these may compare with other serious illnesses.

### ARTICLE INFORMATION

**Published Online:** October 5, 2020.

doi:[10.1001/jama.2020.19719](https://doi.org/10.1001/jama.2020.19719)

**Conflict of Interest Disclosures:** None reported.

### REFERENCES

- Greenhalgh T, Knight M, A'Court C, Buxton M, Husain L. Management of post-acute Covid-19 in primary care. *BMJ*. 2020;370:m3026. doi:[10.1136/bmj.m3026](https://doi.org/10.1136/bmj.m3026)
- Maley JH, Brewster I, Mayoral I, et al. Resilience in survivors of critical illness in the context of the survivors' experience and recovery. *Ann Am Thorac Soc*. 2016;13(8):1351-1360. doi:[10.1513/AnnalsATS.201511-782OC](https://doi.org/10.1513/AnnalsATS.201511-782OC)
- Carfi A, Bernabei R, Landi F; Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. doi:[10.1001/jama.2020.12603](https://doi.org/10.1001/jama.2020.12603)
- Tenforde MW, Kim SS, Lindsell CJ, et al; IVY Network Investigators; CDC COVID-19 Response Team; IVY Network Investigators. Symptom duration and risk factors for delayed return to usual health among outpatients with COVID-19 in a multistate health care systems network: United States, March-June 2020. *MMWR Morb Mortal Wkly Rep*. 2020;69(30):993-998. doi:[10.15585/mmwr.mm6930e1](https://doi.org/10.15585/mmwr.mm6930e1)
- Puntmann VO, Carerj ML, Wieters I, et al. Outcomes of cardiovascular magnetic resonance imaging in patients recently recovered from coronavirus disease 2019 (COVID-19). *JAMA Cardiol*. Published online July 27, 2020. doi:[10.1001/jamacardio.2020.3557](https://doi.org/10.1001/jamacardio.2020.3557)
- Rajpal S, Tong MS, Borchers J, et al. Cardiovascular magnetic resonance findings in competitive athletes recovering from COVID-19 infection. *JAMA Cardiol*. Published online September 11, 2020. doi:[10.1001/jamacardio.2020.4916](https://doi.org/10.1001/jamacardio.2020.4916)
- Zhao YM, Shang YM, Song WB, et al. Follow-up study of the pulmonary function and related physiological characteristics of COVID-19 survivors three months after recovery. *EClinicalMedicine*. 2020;25:100463. doi:[10.1016/j.eclinm.2020.100463](https://doi.org/10.1016/j.eclinm.2020.100463)
- Huang Y, Tan C, Wu J, et al. Impact of coronavirus disease 2019 on pulmonary function in early convalescence phase. *Respir Res*. 2020;21(1):163. doi:[10.1186/s12931-020-01429-6](https://doi.org/10.1186/s12931-020-01429-6)
- Zubair AS, McAlpine LS, Gardin T, Farhadian S, Kuruvilla DE, Spudich S. Neuropathogenesis and neurologic manifestations of the coronaviruses in the age of coronavirus disease 2019: a review. *JAMA Neurol*. 2020;77(8):1018-1027. doi:[10.1001/jamaneurol.2020.2065](https://doi.org/10.1001/jamaneurol.2020.2065)
- Galea S, Merchant RM, Lurie N. The mental health consequences of COVID-19 and physical distancing: the need for prevention and early intervention. *JAMA Intern Med*. 2020;180(6):817-818. doi:[10.1001/jamainternmed.2020.1562](https://doi.org/10.1001/jamainternmed.2020.1562)