https://doi.org/10.1038/s41581-022-00652-2

Long COVID: long-term health outcomes and implications for policy and research

Ziyad Al-Aly, Anupam Agarwal, Nisreen Alwan & Valerie A. Luyckx

Long COVID, which refers to post-acute and chronic sequelae of SARS-CoV-2 infection, can affect nearly every organ system and all demographic groups. The high and growing toll of long COVID calls for an urgent need to understand how to prevent and treat it. Governments and health systems must address the care needs of people with long COVID.

Shortly after the beginning of the COVID-19 global pandemic, reports emerged showing that some individuals infected with SARS-CoV-2 developed persistent symptoms and new health problems that arose long after the acute phase of infection and could not be explained by other factors[1]. The patient community who, to their credit, first recognized and reported this new syndrome used the term 'long COVID' to describe the post-acute and chronic sequelae of SARS-CoV-2 infection[1]. Long COVID can affect people across the lifespan — children, young adults and older adults — and across sex, race and ethnicity, and baseline health status[2]. Importantly, this syndrome not only affects patients who had severe COVID-19, but is also observed in individuals who were asymptomatic or mildly symptomatic during the acute phase of SARS-CoV-2 infection.

Long COVID often manifests as fatigue and neurocognitive impairment (also referred to as 'brain fog') and can affect nearly every organ system, with a broad array of extrapulmonary sequelae that include acute kidney injury (AKI) and chronic kidney disease[3]. Although the rates of AKI during the acute phase of SARS-CoV-2 infection have declined markedly since the early days of the pandemic, new concerns about the long-term consequences of SARS-CoV-2 infection for kidney health have since emerged. In a study from the US Department of Veteran Affairs that involved 89,216 individuals with COVID-19 and 1,637,467 non-infected control individuals, those who survived the first 30 days of SARS-CoV-2 infection had a higher risk of AKI, estimated glomerular filtration rate (eGFR) decline, kidney failure and major adverse kidney events (defined as eGFR decline ≥50%, kidney failure or all-cause mortality) than non-infected control individuals[4]. Importantly, even individuals with mild COVID-19 and without AKI during the acute infection had increased risk of adverse kidney outcomes; the risk increased gradually according to the severity of the disease during the acute phase of the infection. For example, compared with uninfected control individuals, those with COVID-19 had a greater loss of eGFR, estimated at −3.26 (−3.58 to −2.94), −5.20 (−6.24 to −4.16) and −7.69 (−8.27 to −7.12) ml/min/1.73 m^2 per year in individuals who were not hospitalized, hospitalized or admitted to intensive care, respectively, during the acute phase of SARS-CoV-2 infection[4]. Notably, in individuals with a mild SARS-CoV-2 infection who did not require hospital admission, the associated eGFR decline in the year following the infection (−3.26 ml/min/1.73 m^2) was nearly equivalent to that expected to result from approximately 4 years of normal ageing (ageing is associated with an eGFR decline of approximately −1 ml/min/1.73 m^2 per year).

The presence of AKI clearly increases the risk of post-acute COVID-19 adverse kidney outcomes[4]. A study of 1,612 patients in the first year of the pandemic showed that although individuals with AKI from causes other than COVID-19 had decline in eGFR with a mean eGFR slope of −2.7 ml/min/1.73 m^2 per year, those with COVID-19-associated AKI had much steeper declines, with a mean eGFR slope of −16.7 ml/min/1.73 m^2 per year (difference in slope −14.0 ml/min/1.73 m^2 per year)[5]. Another study followed 1,734 patients who were hospitalized for COVID-19 for nearly 1 year and showed that those with AKI during the acute phase had greater odds of reduced kidney function (defined as eGFR <60 ml/min/1.73 m^2) and proteinuria, and an 8.5% greater longitudinal decline in eGFR than individuals without AKI[6]. Collectively, current evidence suggests COVID-19 increases the risk of adverse long-term kidney events. These findings call for integration of kidney care components into post-acute COVID-19 care strategies[4].

Beyond its effect on kidney disease, SARS-CoV-2 infection can also lead to post-acute development of substantial cardiac cellular abnormalities and cardiovascular clinical sequelae including dysrhythmias, ischaemic heart disease, heart failure, pericarditis, myocarditis and thromboembolic disease[7]. Glycometabolic abnormalities are also evident in many survivors of acute COVID-19 and, in some cases, manifest as overt new-onset diabetes mellitus[8]. Analysis of neuroimaging data collected pre-infection and 4–5 months after infection further suggests that SARS-CoV-2 infection can lead to substantial structural changes in the brain, including reduction in grey matter thickness and global brain volume[9]. These alterations were evident even in individuals with mild cases of COVID-19. Moreover, experimental studies have revealed multiple biological pathways that can explain the broad array of neurological disorders experienced in the post-acute phase of SARS-CoV-2 infection, including ischaemic and haemorrhagic stroke, seizure disorders and disruptions in cognition and memory, the peripheral nervous system and mental health[10].

Of note, vaccination against SARS-CoV-2 seems to confer only partial protection against long COVID. Vaccine-associated risk reduction is most evident for pulmonary and coagulation disorders, but this protection is attenuated substantially in immunocompromised individuals. Whether the risks of long COVID differ depending on the virus variant and whether therapeutics for acute COVID-19 can reduce the risk of post-acute sequelae is not yet clear and remains under investigation.

Compelling evidence suggests that the pandemic might lead to new-onset kidney disease (and other non-communicable diseases including diabetes, cardiovascular disease and neurological disease) in millions of people. These are chronic conditions that require lifelong care and the rise in their prevalence will have wide ramifications on

every sector of our lives, including labour participation, economic productivity and societal wellbeing. Governments and health systems must therefore be prepared to deal with the impending rise in patients in need of health care. Building health system capacity to deliver care equitably to those who need it must be prioritized.

"Compelling evidence suggests that the pandemic might lead to new-onset kidney disease … in millions of people"

More than two years into the pandemic, we still do not have systems that enable the assessment of the toll of long COVID and its myriad complications, including kidney disease. Current surveillance systems capture acute effects of infectious disease but do not account for their post-acute and long-term effects. This gap needs to be urgently addressed and thus governments and health systems must develop adequate data systems that can capture this missing information. These data will be vital to inform health system planning for post-COVID-19 care. Of note, the effects of SARS-CoV-2 infection and, more broadly, of the pandemic on the rates of non-communicable diseases, life expectancy and economic indicators should also be evaluated.

The development of large-scale clinical trial programmes to test therapeutics for long COVID is another urgent need. Experimental studies using organoid and animal models have potential to clarify the mechanisms of injury that underlie long COVID and to inform therapeutic strategies. Moreover, given that currently approved SARS-CoV-2 vaccines are limited in their ability to reduce the risk of viral transmission and of developing long COVID, vaccine strategies that can address these shortcomings are also urgently required. Finally, comparative studies that can examine differences and similarities in the biology and clinical features of long COVID and other infection-associated illnesses (for example, 'long flu' following influenza infection, and myalgic encephalomyelitis or chronic fatigue syndrome) are also urgently needed.

"Long COVID will reverberate with us for decades … long after the COVID-19 pandemic abates"

Long COVID refers to the disability and disease experienced by many people who survive the acute phase of COVID-19. Despite its name, SARS-CoV-2 not only causes acute respiratory disease but can also lead to acute and post-acute extrapulmonary sequelae in nearly every organ system (including acute and chronic kidney disease) and has affected millions of lives around the world. Given the scale and the chronic nature of several of its sequelae, long COVID will reverberate with us for decades, and will have broad and deep social, economic, political and global security implications, long after the COVID-19 pandemic abates. This pandemic provides a historic opportunity not only to understand long COVID but also other post-viral conditions and infection-associated chronic illnesses, and to increase preparedness for the next pandemic, which is certain to come. Urgent attention is needed to identify optimal care pathways to lessen the risk of further health loss and death among affected populations. These goals demand greater attention and a much needed, but so far absent, coordinated global response strategy.

Ziyad Al-Aly [1,2] ✉, Anupam Agarwal [3], Nisreen Alwan [4,5,6] & Valerie A. Luyckx [7,8,9]

[1]Clinical Epidemiology Center, Research and Development Service, VA Saint Louis Health Care System, Saint Louis, MO, USA. [2]Institute for Public Health, Washington University in Saint Louis, Saint Louis, MO, USA. [3]Division of Nephrology, Department of Medicine, University of Alabama School of Medicine, Birmingham, AL, USA. [4]School of Primary Care, Population Sciences and Medical Education, Faculty of Medicine, University of Southampton, Southampton, UK. [5]NIHR Applied Research Collaboration Wessex, Southampton, UK. [6]NIHR Southampton Biomedical Research Centre, University of Southampton and University Hospital Southampton NHS Foundation Trust, Southampton, UK. [7]Division of Paediatrics and Child Health, University of Cape Town, Cape Town, South Africa. [8]Department of Nephrology, University Children's Hospital Zurich, Zurich, Switzerland. [9]Renal Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA.

✉e-mail: zalaly@gmail.com

Published online: 1 November 2022

References

1. Alwan, N. A. The road to addressing long Covid. *Science* **373**, 491–493 (2021).
2. Xie, Y., Bowe, B. & Al-Aly, Z. Burdens of post-acute sequelae of COVID-19 by severity of acute infection, demographics and health status. *Nat. Commun.* **12**, 6571 (2021).
3. Al-Aly, Z., Xie, Y. & Bowe, B. High-dimensional characterization of post-acute sequelae of COVID-19. *Nature* **594**, 259–264 (2021).
4. Bowe, B., Xie, Y., Xu, E. & Al-Aly, Z. Kidney outcomes in long COVID. *J. Am. Soc. Nephrol.* **32**, 2851–2862 (2021).
5. Nugent, J. et al. Assessment of acute kidney injury and longitudinal kidney function after hospital discharge among patients with and without COVID-19. *JAMA Netw. Open* **4**, e211095 (2021).
6. Gu, X. et al. Association of acute kidney injury with 1-year outcome of kidney function in hospital survivors with COVID-19: a cohort study. *EBioMedicine* **76**, 103817 (2022).
7. Xie, Y., Xu, E., Bowe, B. & Al-Aly, Z. Long-term cardiovascular outcomes of COVID-19. *Nat. Med.* **28**, 583–590 (2022).
8. Xie, Y. & Al-Aly, Z. Risks and burdens of incident diabetes in long COVID: a cohort study. *Lancet Diabetes Endocrinol.* **10**, 311–321 (2022).
9. Douaud, G. et al. SARS-CoV-2 is associated with changes in brain structure in UK Biobank. *Nature* **604**, 697–707 (2022).
10. Xu, E., Xie, Y. & Al-Aly, Z. Long-term neurologic outcomes of COVID-19. *Nat. Med.* https://doi.org/10.1038/s41591-022-02001-z (2022).

Acknowledgements

The contents of this article do not represent the views of the US Department of Veterans Affairs or of the US government.

Competing interests

The authors declare no competing interests.