

Recovery after COVID-19

Persistent symptoms beyond acute infection

DAVID R. DARLEY BSc(Hons), MB BS, FRACP

GREGORY J. DORE BSc, MB BS, MPH, FRACP, PhD

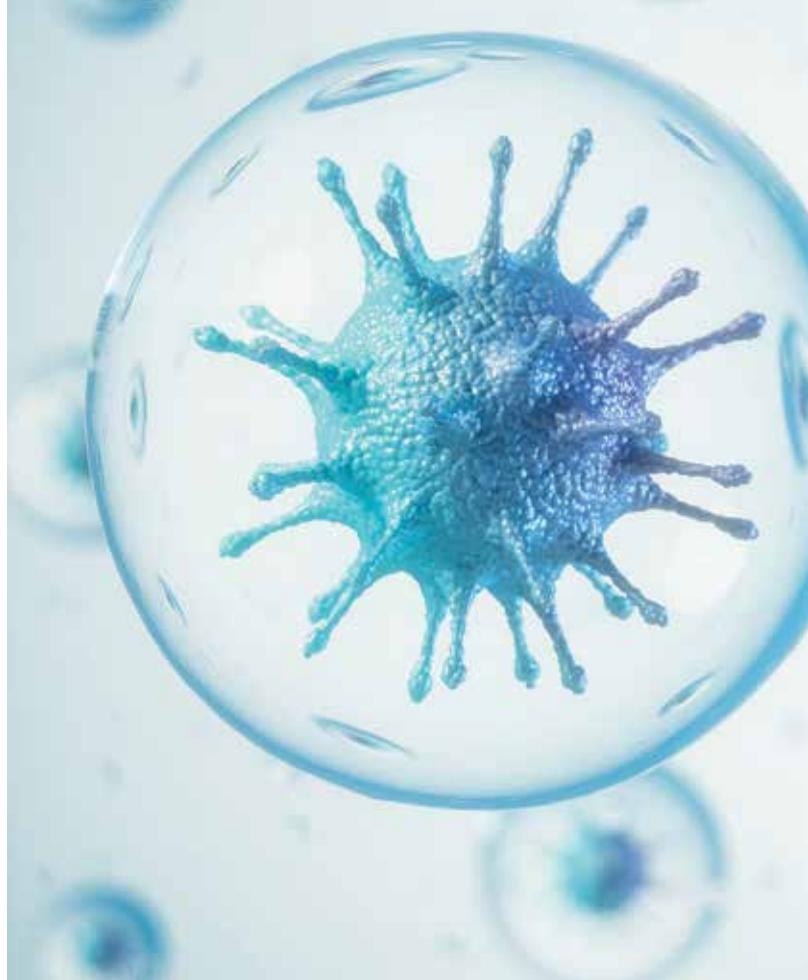
GAIL V. MATTHEWS MB ChB, MRCP(UK), FRACP, PhD

EMILY STONE MBBS, PhD, FRACP

Severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2) has caused a global pandemic with over 29,000 confirmed infections in Australia to date. A high rate of persistent symptoms several months after SARS-CoV-2 has been observed and represents a novel health concern that requires careful assessment and multidisciplinary follow up.

Key points

- A considerable proportion of patients experience persistent symptoms beyond acute phase of severe acute respiratory distress syndrome coronavirus (SARS-CoV-2) infection, known as the 'long COVID' syndrome, or post-acute sequelae of SARS-CoV-2 (PASC).
- These symptoms may impact physical function, mental health and quality of life of patients recovering from COVID-19 and other SARS infections.
- Systematic assessment is recommended to monitor recovery, assess the need for rehabilitation and detect complications.
- GPs are recommended to undertake a clinical review of patients with COVID-19 four weeks after infection.



A high rate of persistent and multiorgan symptoms, beyond the acute phase of severe acute respiratory distress syndrome coronavirus 2 (SARS-CoV-2), has been observed. Given the large number of confirmed cases of acute coronavirus disease 2019 (COVID-19) in Australia (over 29,000 confirmed infections to date)¹ being followed in the community by GPs, this represents a novel disease and health concern for which we recommend careful assessment and multidisciplinary follow up.

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Dr Darley is a Staff Specialist in the Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst, Sydney; and a PhD candidate at St Vincent's Clinical School, UNSW Sydney.

Professor Dore is a Clinical Academic in the Department of Infectious Diseases, St Vincent's Hospital Darlinghurst, Sydney; and Head of the Viral Hepatitis Clinical Research Program at the Kirby Institute, UNSW Sydney.

Professor Matthews is a Clinical Academic in the Department of Infectious Diseases, St Vincent's Hospital Darlinghurst, Sydney; and Associate Professor at the Kirby Institute, UNSW Sydney.

Dr Stone is a Staff Specialist in the Department of Thoracic Medicine, St Vincent's Hospital Darlinghurst; and Conjoint Lecturer at St Vincent's Clinical School, UNSW Sydney, Sydney, NSW.



How and why does the patient present with this problem?

COVID-19 is characterised by symptoms such as fever, dry cough, myalgias, anosmia and gastrointestinal disturbance.²⁻⁴ Persistent symptoms, affecting multiple organ systems and lasting for months after resolution of acute infection, have been reported in a number of studies. This syndrome has been termed ‘long COVID’ or the ‘post-COVID-19 syndrome’ and refers to the long-term effects of COVID-19; however, a precise consensus definition is lacking.

As part of the ADAPT study, a prospective Australian cohort of adult patients at St Vincent’s Hospital Sydney, is being followed to characterise the long-term effects of COVID-19. At two to three months after COVID-19 infection, a considerable proportion of patients (39.7%) reported persistent symptoms including fatigue, shortness of breath and chest tightness.⁵ The proportion of patients with symptoms at initial infection and follow up are summarised in Figure 1. The proportion of individuals with persistent symptoms was highest in those hospitalised for initial infection, but a third of patients with community-managed COVID-19 reported persistent symptoms; this is of particular relevance to GPs.

In other international cohorts, fatigue is a commonly reported persistent symptom but multiple other symptoms are also described, in particular referable to the pulmonary, cardiovascular and neuropsychiatric systems.⁶⁻⁸ Ongoing research priorities include the identification of predictive factors for ‘long COVID’, defining its natural history and identifying clinically-effective interventions.⁹ Additional work is needed to understand whether long-term symptoms represent persistence of initial COVID-19 infection or a post-viral complication.

What are the likely causes of ‘long COVID’ syndrome?

Residual pulmonary radiological changes (ground-glass opacities and parenchymal bands) and abnormalities in pulmonary function testing during recovery have been reported and may explain persistent cardiothoracic symptoms in patients recovered from COVID-19.¹⁰ Figure 2 demonstrates post-viral parenchymal bands and volume loss in coronal slices of a chest CT of a recovering patient in the ADAPT study. Patients in this study showed reduced total lung capacity and abnormalities in the diffusion capacity for carbon monoxide (DLCO) on complex lung function testing, especially those requiring hospitalisation for viral pneumonia.⁵ Long-term abnormalities were also reported after severe acute respiratory distress syndrome (SARS) including reduced DLCO and exercise capacity, chronic fatigue and psychiatric morbidity.¹¹⁻¹⁵ Long-term illness has also been reported after Middle-East Respiratory Syndrome (MERS) and other viral infections including infectious mononucleosis and influenza.¹⁶⁻¹⁸

Persistent morbidity is well established after sepsis and intensive care admission.^{19,20} A wide range of cardiac complications has been observed in people with COVID-19 including fulminant myocarditis, acute heart failure and arrhythmias.^{21,22} Assessment for myocardial damage is an area for ongoing evaluation in those with persistent cardiothoracic symptoms.

Given the systemic effects of SARS-CoV-2, including reports of neurological manifestations such as large vessel stroke, encephalitis and delirium, neurocognitive impairment remains a concern.²³⁻²⁵ Abnormalities have been observed in the quality of life of people recovering from COVID-19 and include new problems in mobility, self-care and activities of daily living.²⁶ Mental health disturbances may include post-traumatic stress disorder, anxiety and depression.²⁷ Several factors could be driving these abnormalities including the

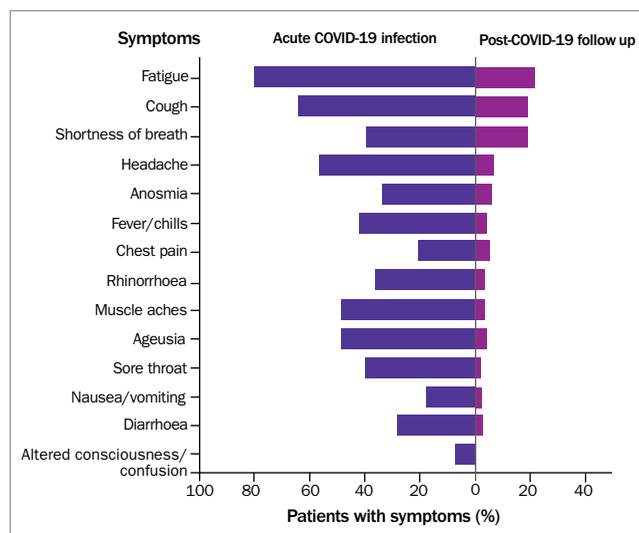


Figure 1. Symptoms at initial infection and first follow-up at two months after COVID-19.

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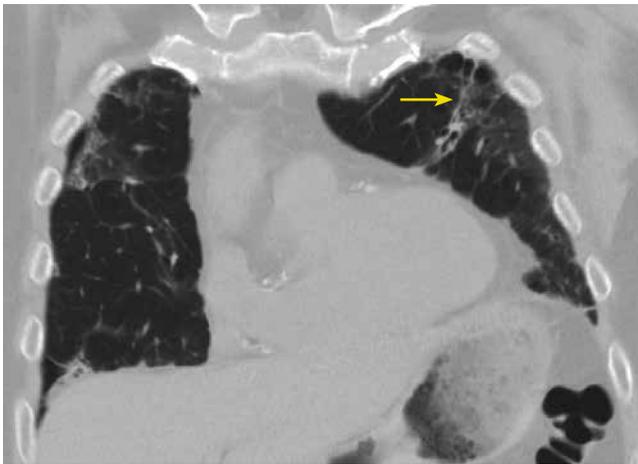


Figure 2. Coronal slice (lung window) of chest CT in a patient recovering from COVID-19 with persistent fatigue and shortness of breath. Abnormal findings of the lungs shown here include patchy, peripheral opacities with focal left upper lobe traction bronchiectasis, indicating the fibroblastic phase of viral organising pneumonia (arrow).

experience of recent illness, uncertainty of recovery, general concerns over COVID-19 and its global effects and exacerbation of pre-existing conditions. Increased mental health disturbance in the Australian community in the immediate post-COVID period has been reported, and issues around stigma and discrimination of people with or recovering from COVID-19 may also be factors contributing psychological decline.²⁸⁻³¹

Some cohorts have reported persistently elevated D-dimer, C-reactive protein, interleukin 6 (IL-6), ferritin and brain natriuretic peptide concentrations in recovering patients.³² In relation to the specific symptom of fatigue after COVID-19, there is no established association with routine laboratory markers of inflammation and cell turnover or pro-inflammatory molecules.⁶

What initial investigations should be considered if you suspect 'long COVID' in your patient?

A variety of health resources may be required to adequately manage persistent symptoms after COVID-19. We recommend a clinical review by a GP at four weeks after COVID-19 infection and we urge that GPs be aware of the potential long-term symptoms (Box). Full lung function testing and pulmonary imaging should be considered to investigate thoracic symptoms, especially in patients with oxygen desaturation or physical signs of respiratory disease by 12 weeks after acute infection. Cardiology investigations such as an echocardiogram may be required to investigate those with persistent cardiothoracic symptoms or physical signs of cardiac disease. Blood tests, including a full blood count and kidney, liver function and C-reactive protein tests, may be offered. Pulmonary rehabilitation may assist to improve exercise capacity and breathlessness.³³ Neurocognitive testing and imaging may be required to investigate cognitive symptoms. Mental health symptoms should be specifically asked about and early referral for liaison psychiatry specialist support

Symptoms of and investigations for 'long COVID' syndrome

Thoracic symptoms

- Full lung function testing
- Pulmonary imaging
- Pulmonary rehabilitation

Cardiology investigations

- Cardiac echocardiogram

Blood tests

- Full blood count
- Kidney function
- Liver function
- C-reactive protein level

Cognitive symptoms

- Neurocognitive tests
- Neurocognitive imaging

Mental health symptoms

- Investigations during consultation

may be required. Shared care by GPs and specialists is likely required to care for patients with persistent symptoms after COVID-19.

Does 'long COVID' differ from other post-viral syndromes and if so, how?

A number of viral infections have been associated with longer term symptoms after the resolution of an initial infection. SARS-CoV-1, a novel coronavirus that caused a pandemic outbreak in 2002, results in SARS illness and has been associated with pain, fatigue, psychological symptoms and disturbed sleep up to three years after infection.³⁴ Viral infection has been considered a possible causal factor for chronic fatigue/myalgic encephalomyelitis and Guillain-Barré syndrome, the neurological illness mediated by an aberrant immune response to prior infection, including viral infections.^{35,36} It is too early in the pandemic to fully establish the nature of 'long COVID'. A better understanding of this syndrome will depend on further careful clinical and research evaluation of patients after infection.

Conclusion

A considerable proportion of patients experience persistent symptoms beyond acute SARS-CoV-2 infection that may impact physical function, mental health and quality of life. Systematic assessment is recommended to monitor recovery, assess the need for rehabilitation and to detect complications. This is particularly relevant for GPs, given the significant number of patients undergoing follow up in the community.

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References

A list of references is included in the online version of this article (www.respiratorymedicinetoday.com.au).

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References

1. Coronavirus (COVID-19) current situation and case numbers. Australian Government Department of Health; Canberra; 2021. Available online at: <https://www.health.gov.au/news/health-alerts/novel-coronavirus-2019-ncov-health-alert/coronavirus-covid-19-current-situation-and-case-numbers> (accessed March 2021).
2. Docherty AB, Harrison EM, Green CA, et al. Features of 20 133 UK patients in hospital with covid-19 using the ISARIC WHO Clinical Characterisation Protocol: prospective observational cohort study. *BMJ* 2020; 369: m1985.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA* 2020; 323: 1061-1069.
4. Chary E, Carsuzaa F, Trijolet JP, et al. Prevalence and recovery from olfactory and gustatory dysfunctions in Covid-19 infection: a prospective multicenter study. *Am J Rhinol Allergy* 2020; 34: 686-693.
5. Darley DR, Dore GJ, Cysique L, et al. High rate of persistent symptoms up to 4 months after community and hospital-managed SARS-CoV-2 infection. *Med J Aust* 2021. doi: 10.5694/mja2.50963. [Online ahead of print]
6. Townsend L, Dyer AH, Jones K, et al. Persistent fatigue following SARS-CoV-2 infection is common and independent of severity of initial infection. *PLoS One* 2020; 15(11): e0240784.
7. Carfi A, Bernabei R, Landi F, Gemelli Against C-P-ACSG. Persistent symptoms in patients after acute COVID-19. *JAMA* 2020; 324: 603-605.
8. Meppiel E, Peiffer-Smadja N, Maury A, et al. Neurologic manifestations associated with COVID-19: a multicentre registry. *Clin Microbiol Infect* 2020; 27: 458-466.
9. Venkatesan P. NICE guideline on long COVID. *Lancet Respir Med* 2021; 9: 129.
10. Lerum TV, Aalokken TM, Bronstad E, et al. Dyspnoea, lung function and CT findings three months after hospital admission for COVID-19. *Eur Respir J* 2020; 2003448. doi: 10.1183/13993003.03448-2020. [Online ahead of print]
11. Lam MH, Wing YK, Yu MW, et al. Mental morbidities and chronic fatigue in severe acute respiratory syndrome survivors: long-term follow-up. *Arch Intern Med* 2009; 169: 2142-2147.
12. Ngai JC, Ko FW, Ng SS, To KW, Tong M, Hui DS. The long-term impact of severe acute respiratory syndrome on pulmonary function, exercise capacity and health status. *Respirology* 2010; 15: 543-550.
13. Hui DS, Joynt GM, Wong KT, et al. Impact of severe acute respiratory syndrome (SARS) on pulmonary function, functional capacity and quality of life in a cohort of survivors. *Thorax* 2005; 60: 401-409.
14. Hui DS, Wong KT, Ko FW, et al. The 1-year impact of severe acute respiratory syndrome on pulmonary function, exercise capacity, and quality of life in a cohort of survivors. *Chest* 2005; 128: 2247-2261.
15. Ahmed H, Patel K, Greenwood DC, et al. Long-term clinical outcomes in survivors of severe acute respiratory syndrome and Middle East respiratory syndrome coronavirus outbreaks after hospitalisation or ICU admission: a systematic review and meta-analysis. *J Rehabil Med* 2020; 52(5): jrm00063.
16. Batawi S, Tarazan N, Al-Raddadi R, et al. Quality of life reported by survivors after hospitalization for Middle East respiratory syndrome (MERS). *Health Qual Life Outcomes* 2019; 17: 101.
17. Fugl A, Andersen CL. Epstein-Barr virus and its association with disease – a review of relevance to general practice. *BMC Fam Pract* 2019; 20: 62.
18. Sellers SA, Hagan RS, Hayden FG, Fischer WA, 2nd. The hidden burden of influenza: a review of the extra-pulmonary complications of influenza infection. *Influenza Other Respir Viruses* 2017; 11: 372-393.
19. 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: 502-509.
20. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA* 2010; 304: 1787-1794.
21. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol* 2020; 5: 802-810.
22. 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* 2020; 5: 1265-1273.
23. Oxley TJ, Mocco J, Majidi S, Kellner CP, et al. Large-vessel stroke as a presenting feature of Covid-19 in the young. *N Engl J Med* 2020; 382: e60.
24. Ye M, Ren Y, Lv T. Encephalitis as a clinical manifestation of COVID-19. *Brain Behav Immun* 2020; 88: 945-946.
25. Cipriani G, Danti S, Nuti A, Carlesi C, Lucetti C, Di Fiorino M. A complication of coronavirus disease 2019: delirium. *Acta Neurol Belg* 2020; 120: 927-932.
26. Halpin SJ, McIvor C, Whyatt G, et al. Postdischarge symptoms and rehabilitation needs in survivors of COVID-19 infection: a cross-sectional evaluation. *J Med Virol* 2021; 93: 1013-1022.
27. Rogers JP, Chesney E, Oliver D, et al. Psychiatric and neuropsychiatric presentations associated with severe coronavirus infections: a systematic review and meta-analysis with comparison to the COVID-19 pandemic. *Lancet Psychiatry* 2020; 7: 611-627.
28. Cao W, Fang Z, Hou G, et al. The psychological impact of the COVID-19 epidemic on college students in China. *Psychiatry Res* 2020; 287: 112934.
29. Gonzalez-Sanguino C, Ausin B, Castellanos MA, et al. Mental health consequences during the initial stage of the 2020 Coronavirus pandemic (COVID-19) in Spain. *Brain Behav Immun* 2020; 87: 172-176.
30. Wang C, Pan R, Wan X, et al. Immediate psychological responses and associated factors during the initial stage of the 2019 coronavirus disease (COVID-19) epidemic among the general population in China. *Int J Environ Res Public Health* 2020; 17: 1729.
31. Stanton R, To QG, Khalesi S, et al. Depression, anxiety and stress during COVID-19: associations with changes in physical activity, sleep, tobacco and alcohol use in Australian adults. *Int J Environ Res Public Health* 2020; 17: 4065.
32. Mandal S, Barnett J, Brill SE, et al. 'Long-COVID': a cross-sectional study of persisting symptoms, biomarker and imaging abnormalities following hospitalisation for COVID-19. *Thorax* 2020. doi: 10.1136/thoraxjnl-2020-215818. [Online ahead of print]
33. Wootton SL, King M, Alison JA, Mahadev S, Chan ASL. COVID-19 rehabilitation delivered via a telehealth pulmonary rehabilitation model: a case series. *Respirol Case Rep* 2020; 8: e00669.
34. Moldofsky H, Patcai J. Chronic widespread musculoskeletal pain, fatigue, depression and disordered sleep in chronic post-SARS syndrome; a case-controlled study. *BMC Neurol* 2011; 11: 37.
35. Muller AE, Tveito K, Bakken IJ, Flottorp SA, Mjaaland S, Larun L. Potential causal factors of CFS/ME: a concise and systematic scoping review of factors researched. *J Transl Med* 2020; 18: 484.
36. Willison HJ, Jacobs BC, van Doorn PA. Guillain-Barre syndrome. *Lancet* 2016; 388: 717-727.