Long COVID research: an update from the PHOSP-COVID Scientific Summit

The severity of acute SARS-CoV-2 infection has decreased with the introduction of public health policies, vaccination, improved management of acute disease, and a degree of protective immunity in those who have survived past infection. However, in the wake of the pandemic, post-acute sequelae of COVID-19—referred to as long COVID—have emerged. The UK National Institute for Health and Care Excellence (NICE) describes long COVID as a condition in which signs and symptoms continue or develop after acute COVID-19 (>4 weeks), including ongoing symptomatic COVID-19 and post-COVID-19 syndrome (≥12 weeks).

3 years since the first UK national lockdown, the Post-hospitalisation COVID-19 study (PHOSP-COVID) held a Scientific Summit in Leicester, UK (28–29 March, 2023) to review progress and address key questions related to future research. PHOSP-COVID is a UK consortium of multidisciplinary researchers and clinicians working together to understand and improve long-term health outcomes for adults who were hospitalised with COVID-19. Patients, clinicians, and scientists worked together in 2020 to agree priority research questions and, throughout the study, there has been close engagement between the consortium, patients involved in the study, and the wider public. 7935 adults who were discharged from hospital after COVID-19 between February 2020 and March 2021 were recruited into three tiers of research, which included follow-up at around 5 months and 12 months after discharge for deep phenotyping and bioresource sampling (Tier 2), and detailed immune profiling and multiorgan MRI (Tier 3). Recruitment across the four UK nations is now complete and analyses are ongoing.

The aims of PHOSP-COVID are as follows: (1) to describe the holistic impact of long COVID on people who were hospitalised with COVID-19; (2) to identify the features associated with good or poor recovery; (3) to investigate the underlying causes of long COVID; (4) to determine whether long COVID is altered by treatments given during the acute infection; and (5) to develop treatments for people with long COVID to improve recovery. PHOSP-COVID has not studied the impact of long COVID in those not hospitalised during the acute infection and does not include children, but it works closely with the other national long COVID consortia[1] and internationally with professional societies such as the European Respiratory Society.[2]

Early key findings were that, at 5 months after hospital discharge, only about 30% of participants reported that they felt fully recovered.[3] The proportion was similar after 1 year, with only marginal improvement from 5 months to 1 year.[4] Participants were less likely to have recovered if they were female, were aged 35–65 years, had a BMI of more than 30 kg/m², had multiple pre-existing, long-term conditions, or required mechanical ventilation while hospitalised for COVID-19. These risk factors and the high proportion of people with persistent symptoms after hospitalisation for COVID-19 were consistent with the findings of other studies.[5] We found that treatments given during the acute infection, such as corticosteroids, did not affect the likelihood of recovery, consistent with the 6-month follow-up of the REMAP-CAP study, which involved only critically ill participants and identified only anti-interleukin-6 (IL-6) and anti-platelet therapies as being associated with improvements in health.[6] Through unsupervised cluster analysis, we found that the severity of physical and mental health impairments largely grouped together, whereas brain fog (cognitive impairment) could occur on its own.[3] Those with the most severe health impairments had evidence of persistent inflammation.[4] In the lungs, the prevalence of interstitial lung abnormalities on thoracic CT was estimated at 8·5%.[7] Multiorgan, multimodality MRI revealed abnormalities in the brain, lungs, and kidneys, but no significant increase in cardiac or liver abnormalities compared with controls.[8] Patients with a higher burden of multiorgan injury were more likely to report poor physical and mental recovery.[8] A list of publications, including reports of key research findings, is provided in the appendix (pp 1–2), with a list of members of the PHOSP-COVID Collaborative Group (pp 3–12). PHOSP-COVID has evaluated the effectiveness of clinical care pathways and contributed to NICE and NHS England long COVID guidance.

Importantly, in view of the progress to date, the PHOSP-COVID Scientific Summit included a discussion of four key questions pertaining to future research, which were subsequently reviewed with our patient, public, and voluntary sector partners (panel). To date, efficacy has been reported in an early-phase trial of metabolic modulator therapy (AXA1125).[9] PHOSP-COVID is undertaking two proof-of-concept randomised controlled trials of rehabilitation and anti-IL-6 therapy. Other platform trials are underway, although there remains a need for further precision medicine trials that can specifically target the emerging mechanisms and phenotypes of long COVID.

Long COVID remains a major challenge for the millions of people who have persistent morbidity, for health-care systems, and for economies through loss of work. It is imperative that long COVID remains a major health-care and research priority. The planned work looking into mechanisms that drive the long-term effects of COVID-19 on all organs should help in the development of new tests, new treatments, and improved outcomes for people living with long COVID.

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1 Routen A, O'Mahoney L, Ayoubkhani D, et al. Understanding and tracking the impact of long COVID in the United Kingdom. *Nat Med* 2022; **28:** 11–15.

2 Valenzuela C, Nigro M, Chalmers JD, et al. COVID-19 follow-up programs across Europe: an ERS END-COVID CRC survey. *Eur Respir J* 2022; **60:** 2200923.

3 Evans RA, McAuley H, Harrison EM, et al. Physical, cognitive, and mental health impacts of COVID-19 after hospitalisation (PHOSP-COVID): a UK multicentre, prospective cohort study. *Lancet Respir Med* 2021; **9:** 1275–87.

4 The PHOSP-COVID Collaborative Group. Clinical characteristics with inflammation profiling of long COVID and association with 1-year recovery following hospitalisation in the UK: a prospective observational study. *Lancet Respir Med* 2022; **10:** 761–75.

5 Wu X, Liu X, Zhou Y, et al. 3-month, 6-month, 9-month, and 12-month respiratory outcomes in patients following COVID-19-related hospitalisation: a prospective study. *Lancet Respir Med* 2021; **9:** 747–54.

6 Writing Committee for the REMAP-CAP Investigators. Long-term (180-day) outcomes in critically ill patients with COVID-19 in the REMAP-CAP randomized clinical trial. *JAMA* 2023; **329:** 39–51.

7 Stewart I, Jacob J, George PM, et al. Residual lung abnormalities after COVID-19 hospitalization: interim analysis of the UKILD post-COVID-19 study. *Am J Respir Crit Care Med* 2023; **207:** 693–703.

8 The C-MORE/PHOSP-COVID Collaborative Group. Multiorgan MRI findings after hospitalisation with COVID-19 in the UK (C-MORE): a prospective, multicentre, observational cohort study. *Lancet Respir Med* 2023; published online Sept 22. https://doi.org/10.1016/S2213-2600(23)00262-X.

9 Finnigan LEM, Cassar MP, Koziel MJ, et al. Efficacy and tolerability of an endogenous metabolic modulator (AXA1125) in fatigue-predominant long COVID: a single-centre, double-blind, randomised controlled phase 2a pilot study. *eClinicalMedicine* 2023; **59:** 101946.