Since January 2020 Elsevier has created a COVID-19 resource centre with free information in English and Mandarin on the novel coronavirus COVID-19. The COVID-19 resource centre is hosted on Elsevier Connect, the company's public news and information website.

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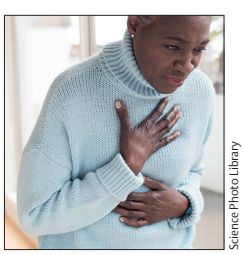
1 Waxman A, Restrepo-Jaramillo R, Thenappan T, et al. Inhaled treprostinil in pulmonary hypertension due to interstitial lung disease. *N Engl J Med* 2021; **384:** 325–34.
2 Nathan S, Waxman A, Rajagopal S, et al. Inhaled treprostinil and forced vital capacity in patients with interstitial lung disease and associated pulmonary hypertension: a post-hoc analysis of the INCREASE study. *Lancet Respir Med* 2021; published online June 29. https://doi.org/10.1016/S2213-2600(21)00165-X.
3 Lambers C, Roth M, Jaksch P, et al. Treprostinil inhibits proliferation and extracellular matrix deposition by fibroblasts through cAMP activation. *Sci Rep* 2018; **8:** 1087.
4 Nikitopoulou I, Manitsopoulos N, Kotanidou A, et al. Orotracheal treprostinil administration attenuates bleomycin-induced lung injury, vascular remodeling, and fibrosis in mice. *Pulm Circ* 2019; **9:** 2045894019881954.
5 King TE Jr, Brown KK, Raghu G, et al. BUILD-3: a randomized, controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2011; **184:** 92–99.
6 King TE Jr, Behr J, Brown KK, et al. BUILD-1: a randomized placebo-controlled trial of bosentan in idiopathic pulmonary fibrosis. *Am J Respir Crit Care Med* 2008; **177:** 75–81.
7 Kolb M, Raghu G, Wells AU, et al. Nintedanib plus sildenafil in patients with idiopathic pulmonary fibrosis. *N Engl J Med* 2018; **379:** 1722–31.
8 Behr J, Nathan SD, Wuyts WA, et al. Efficacy and safety of sildenafil added to pirfenidone in patients with advanced idiopathic pulmonary fibrosis and risk of pulmonary hypertension: a double-blind, randomised, placebo-controlled, phase 2b trial. *Lancet Respir Med* 2021; **9:** 85–95.

Surviving COVID-19: a familiar road to recovery?



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Published **Online**
October 7, 2021
https://doi.org/10.1016/S2213-2600(21)00447-1

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As health care improves, the concept of surviving well has become increasingly important. This is certainly the case in critical care, in which survivorship has been coined the defining challenge of the 21st century. Within this setting, the field now grapples with the onslaught of the COVID-19 pandemic. The initial objective globally was to manage system strain to enhance equity of provision of care. Acute services expanded care provision by increasing acute care bed numbers and stretching existing resources. For a brief period of time, the world focused only on patient survival. Consistent with the additional survivorship focus in critical care over the past 20 years, the recognition of prolonged disability in survivors of COVID-19 has stimulated a drive to understand the nature of impairments and their effects on mental and physical health, as well as return to societal roles.

In *The Lancet Respiratory Medicine*, Rachael Evans and colleagues of the PHOSP-COVID Collaborative Group present the first analyses of a UK multicentre cohort study of survivorship of hospitalised patients with COVID-19.[1] Of the 1077 patients assessed at a median of 5·9 months (IQR 4·9–6·5) after hospitalisation with COVID-19, 20% developed a new disability, 19% experienced a health-related change in occupation, and 71% described themselves as not having fully recovered. Patients described a median of nine different symptoms covering physical and mental domains, which were mirrored in both patient-reported outcome measures and in objective physical assessments.

Of note, the PHOSP-COVID group reports an inconsistent relationship between illness severity and impairments for ward-based versus intensive care-based patients with COVID-19. The four recovery phenotype clusters identified in a post-hoc clustering analysis were similarly not closely related to illness severity. The authors hypothesise that mechanisms other than index severity could be responsible for persistent symptoms. Why might patients who were not admitted to the intensive care unit (ICU) develop symptoms consistent with post-intensive care syndrome in this study? Perhaps one answer is that critically ill patients have long been managed outside the physical constraints of the ICU. During data collection, in the setting of almost overwhelmed services in the UK, the criteria for ICU admission (a threshold that has substantial international and intranational variability) would have been unusually strict.[2] In a large cohort study such as PHOSP-COVID, it is not possible to drill down to the level of detail required to substantiate this hypothesis. The fact that the recovery of non-hospitalised patients with COVID-19 follows a faster trajectory is, in some respects, supportive of a role for disease severity.[3] The extraordinary social rules of the pandemic—with numerous restrictions on mobility and lifestyle that would not normally affect discharged hospitalised patients in their recovery—might have affected mental health sequelae. Women are more likely than men to live alone in high-income countries, and are therefore less able to function without support once disabled by acute illness, which would perhaps explain the reported sexual dimorphism. In another large cohort study published in 2021, social isolation before ICU hospitalisation was associated with a greater disability burden in the year after critical illness, suggesting the

need for social isolation screening and intervention frameworks.[4] Additionally, socioeconomic position might affect health outcomes, particularly mental health, after critical illness.[5] These previously published data illustrate the important impacts of the social determinants of health.

Further reported data of particular interest in the PHOSP-COVID study are those related to comorbidities. These are identified in each of the four clusters. A unifying thread in acute illnesses is the modifying effect of pre-morbid comorbidities and baseline functional states, which are greater discriminators of long-term physical and mental health outcomes than the severity of acute illness or cardiorespiratory physiology.[6] Similarly, cognitive outcomes are highly prevalent after acute illness and in older people during hospitalisation, related to the development of in-hospital delirium. The incidence of delirium in patients was not reported by the PHOSP-COVID group, but it would be interesting to investigate whether this is associated with poor cognitive outcomes. Pre-hospitalisation alcohol intake could also affect cognitive outcomes.[7]

Patients who survive a critical illness suffer from physical disability as a result of loss of skeletal muscle mass, affecting physical functional capacity. This can be due to general immobility or associated with time in the ICU (so-called ICU-acquired weakness), which is reported in patients with COVID-19.[8] There are no data provided on in-hospital or outpatient rehabilitation treatments that might have attenuated subsequent functional recovery. Furthermore, anxiety, depression, and post-traumatic stress disorder are common and often co-exist, and patients can have multiple symptoms across these domains. Return-to-work rates are low among survivors of critical illness, and this alone could affect health-related quality of life and psychological function, and many of these symptoms can persist for years.[9] Indeed, the PHOSP-COVID group offers convincing evidence that there are minimal phenotypic differences after hospitalisation for COVID-19 versus critical illness.

The findings from these high-quality data are a cause for concern. A substantial proportion of the working-age population is likely to have long-term, life-changing sequelae after COVID-19, with physical, mental, social, and fiscal effects. The good news is that the PHOSP-COVID data confirm that we have an existing prism through which to view this public health issue, with mature domains to guide research and policy: that of post-intensive care syndrome. We can view acquired disability in domains (rather than symptoms), each of which can be screened for (eg, using the Post-ICU Presentation Screen) at hospital discharge.[10] Moving forward, it will be important to use such a framework not only to capture symptomatology, but also to map symptoms to domains that could guide holistic rehabilitation and recovery interventions. Using these systematic approaches will ensure that no domains that might be affected are missed; for example, poor nutrition, dysphonia, and dysphagia are all reported in survivors of COVID-19 but are not reported by the PHOSP-COVID group. The long-term sequelae of COVID-19—similar to the persistent effects of critical illness—are unrelated to the acute diagnosis per se. Instead of developing new interventions, translation of interventions from other disease modalities offers hope for future patients, if resources are appropriately allocated.

We urgently need to build on the plethora of descriptive cohort studies examining COVID-19 sequelae with large, powered trials that examine the efficacy of individualised management options, such as pharmacological interventions, multidisciplinary inpatient and outpatient rehabilitation, or the role of targeted follow-up clinics. As with the trajectory of research over the past two decades in critical care, we need to identify responders to specific interventions, map impairments across time, and involve patients and caregivers in the process of recovery.

We declare no competing interests.

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1 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; published online Oct 7. https://doi.org/10.1016/S2213-2600(21)00383-0.

2 Martin-Loeches I, Arabi Y, Citerio G. If not now, when? A clinical perspective on the unprecedented challenges facing ICUs during the COVID-19 pandemic. *Intensive Care Med* 2021; **47:** 588–90.

3 Sudre CH, Murray B, Varsavsky T, et al. Attributes and predictors of long COVID. *Nat Med* 2021; **27:** 626–31.

4 Falvey JR, Cohen AB, O'Leary JR, Leo-Summers L, Murphy TE, Ferrante LE. Association of social isolation with disability burden and 1-year mortality among older adults with critical illness. *JAMA Intern Med* 2021; published online Sept 7. https://doi.org/10.1001/jamainternmed.2021.5022.

5 Jones JRA, Berney S, Connolly B, et al. Socioeconomic position and health outcomes following critical illness: a systematic review. *Crit Care Med* 2019; **47:** e512–21.

6 Ferrante LE, Pisani MA, Murphy TE, Gahbauer EA, Leo-Summers LS, Gill TM. Functional trajectories among older persons before and after critical illness. *JAMA Intern Med* 2015; **175:** 523–29.

7 Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med* 2013; **369:** 1306–16.

8 Van Aerde N, Van den Berghe G, Wilmer A, et al. Intensive care unit acquired muscle weakness in COVID-19 patients. *Intensive Care Med* 2020; **46:** 2083–85.

9 McPeake J, Mikkelsen ME, Quasim T, et al. Return to employment after critical illness and its association with psychosocial outcomes. A systematic review and meta-analysis. *Ann Am Thorac Soc* 2019; **16:** 1304–11.

10 Turner-Stokes L, Corner EJ, Siegart RJ, et al. The post-ICU presentation screen (PICUPS) and rehabilitation prescription (RP) for intensive care survivors part I: development and preliminary clinimetric evaluation. *J Intensive Care Soc* 2021; published online Feb 18. https://doi.org/10.1177/1751143720988715.

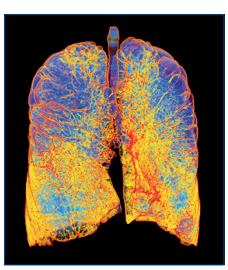
COPD exacerbations: targeting IL-33 as a new therapy

Current therapies for chronic obstructive pulmonary disease (COPD) aim to control symptoms, improve lung function, reduce acute exacerbations,[1] and decrease mortality. Despite improvements in disease management, available therapies with inhaled corticosteroids and long-acting bronchodilators have modest effects on reducing acute exacerbations of COPD and disease progression and only produce benefits in some people.[2] New and effective therapies for acute exacerbations are needed. Biological therapies that target specific pathways have been successful in several respiratory diseases and are now being assessed in COPD, albeit with little success so far.

Recent evidence highlights the potential for therapeutic blockade of IL-33 in COPD.[3] IL-33 is an alarmin and pleotropic cytokine involved in type 2 immune responses, and the activation, migration, and recruitment of immune cells that can drive disease pathogenesis.[3] IL-33 levels are increased in lung biopsy samples, epithelial and endothelial cells, serum or plasma, and sputum of patients with COPD[4–6] and correlate with reduced lung function.[5] Lung IL-33 levels are also increased in animal models of cigarette-smoke induced COPD.[7] Collectively, these data suggest that targeting IL-33 in patients with COPD might be beneficial.

In *The Lancet Respiratory Medicine*, Klaus Rabe and colleagues[8] present data from genetic analyses of gain-of-function and loss-of-function IL-33 mutations and the much anticipated results of a phase 2a randomised, placebo-controlled, clinical trial (NCT03546907) of the IL-33-targeting human IgG4 monoclonal antibody, itepekimab (SAR440340/REGN3500), in 343 patients with COPD at risk of exacerbations (mean age 63·9 years [SD 6·7], 194 [57%] men and 149 [43%] women). As a primary endpoint, this study assessed the annualised rate of moderate-to-severe acute exacerbations of COPD and as a secondary endpoint it assessed improvement in lung function measured as a change in baseline pre-bronchodilator FEV_1 in weeks 16–24 of the trial. Genetic analyses corroborated previous findings of the roles of IL-33 variants in IL-33 bioavailability and asthma risk by independently reproducing findings from two large cohorts (UK Biobank and Geisinger Health Systems) as well as the previously reported association between IL-33 variants, eosinophil counts, and asthma.[9] These confirmatory associations are the positive controls for the study, which goes on to demonstrate that a rare loss-of-function, splice-acceptor allele (rs146597587) and serum IL-33 levels are linked to reduced COPD risk. Conversely, gain-of-function mutations in *IL33* and *IL1RL1* variants are associated with increased risk. These data suggest that targeting *IL-33* might be beneficial and formed the rationale for examining the effects of IL-33 blockade in COPD. The primary outcome of reducing annualised rate of moderate-to-severe acute exacerbations of COPD was not achieved with itepekimab treatment versus placebo (relative risk [RR] 0·81 [95% CI 0·61 to 1·07], p=0·13). However, subgroup analysis identified the potential benefits of targeting *IL-33* in reducing exacerbation frequency and improving lung function versus placebo in former smokers with COPD (exacerbation frequency treatment effect RR 0·58 [95% CI 0·39 to 0·85], p=0·0061; FEV_1 least squares mean difference 0·09 L [95% CI 0·02 to 0·15], p=0·0076), who are an important clinical subset.

Some important questions remain. What role did the study's recruitment characteristics play in the testing



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Published **Online** July 21, 2021 https://doi.org/10.1016/S2213-2600(21)00182-X

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