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An integrated understanding of long-term sequelae after acute COVID-19

The recognition of so-called long COVID has been a great emotional relief for the many who are struggling with the aftereffects of COVID-19. Now we need to dissect this highly heterogenous syndrome; better delineate clusters of symptoms; differentiate it from other conditions and consequences of infections and hospitalisation; understand the pathophysiology, predisposing conditions, and risk factors; and indeed, learn how to better look after people with long-term complications after acute COVID-19. Dealing with such complexity requires a multidisciplinary approach and patients' involvement.[1]

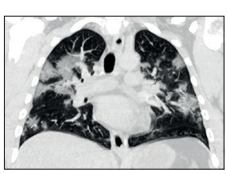
Breathlessness is one of the most common symptoms of long COVID.[2] Xiaojun Wu and colleauges[3] followed up 83 survivors of severe COVID-19 pneumonia for pulmonary functions using spirometry and diffusing capacity of the lungs for carbon monoxide (DLCO), exercise capacity, and lung imaging (high-resolution CT [HRCT]) at 3-month intervals, up to 12 months after hospital discharge.

The authors found that most patients improved over time; however, some patients had lung function and radiological alterations a year after discharge. Although pulmonary function tests improved over time, DLCO (expressing the gas exchange function of the lungs) remained low (<80% of predicted) in 27 (33%) patients at 12 months. Radiological abnormalities, such as ground-glass opacities, were still present in 20 (24%) patients, whose DLCOs and other pulmonary functions were significantly lower than in those with normal HRCT, although none had established fibrosis or progressive interstitial change.

Thus, the causes of persistently lower gas–blood exchange remain unclear in those with abnormal DLCO. Multivariate analyses found a significant association between impaired DLCO and female sex (odds ratio 8·61 [95% CI 2·83–26·2; p=0·0002) and between persistent radiological abnormalities and in-hospital radiological pneumonia scores, as has been reported elsewhere.[4] Still, these alternations did not seem to ostensibly impair daily activities because functional tests—the 6-min walk test and the Medical Research Council dyspnoea scale—showed marked improvement and were essentially normal in almost all patients 12 months post-discharge. The authors suggest that unified methodology and longer follow-up are required to study the evolution and implications of these observations—importantly, with tests that can be done routinely and with minimal inconvenience and discomfort to the patient.

Studies such as this have a dual utility: to help understand the pathophysiology of abnormalities and to direct follow-up and care in patients after acute COVID-19. At the same time, the fast pace at which reports on the lingering consequences of COVID-19 accumulate and the disparate methodologies used makes synthesising evidence difficult.[5]

For comparison, a systematic review[6] of respiratory functions in patients after hospital discharge after COVID-19 found that impaired DLCO reportedly occurred in 39% of cases overall but was twice as frequent in severe



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See **Articles** page 747

than in non-severe cases (66% *vs* 36%). Although these data are from few studies and few cases with short-term follow-up, taken together, data seem to indicate that prevalence of impaired DLCO decreases over time, as shown by Wu and colleagues. The systematic review[6] also found restrictive spirometry patterns in 15% patients and obstructive spirometry patterns in 7% patients.

Wu and colleagues focussed on respiratory manifestations of patients without comorbidities or more advanced disease, half of whom were older than 60 years and were admitted to hospital in the first quarter of 2020. The findings on lung function and how these are reflected in functional tests therefore apply to a selected population at the beginning of the pandemic and both presenting characteristics and case management have evolved since. We also do not know whether the findings are specific to COVID-19 or possibly shared by other infections with similar acute manifestations.

When reading isolated papers, we should remind ourselves that we are looking at a snapshot of one feature in a certain population, context, and timepoint while the details of complications after acute COVID-19 are still unfolding. Each piece of information increases knowledge but we need to agree on common methodologies, generate robust data, and improve our capacity to share, absorb, and process high volumes of research output more efficiently and quickly to be able to describe the novel syndrome. These steps will enable us to distinguish between transient and permanent patterns, differentiate real heterogeneity from bias and, importantly, to identify practical approaches to prevent, minimise and manage long-term COVID-19 complications.

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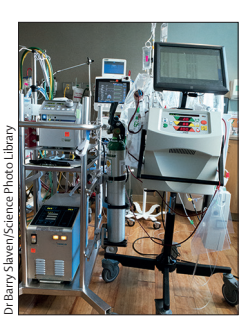
Cytokine adsorption during ECMO for COVID-19-related ARDS



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See **Articles** page 755

A syndrome of dysregulated systemic immune overactivation has been described in patients with COVID-19. Initially a cytokine storm paradigm[1] was proposed, however subsequently, it has been shown that systemic concentrations of inflammatory cytokines, although elevated in patients with severe COVID-19, are not as high as has been reported in patients with other causes of the acute respiratory distress syndrome (ARDS).[2] Despite this, data to support the use of immunomodulatory therapies, such as corticosteroids[3] and interleukin-6 (IL-6) receptor antagonists,[4] in patients critically ill with COVID-19 have emerged. With this in mind, it might seem plausible that the direct removal of circulating inflammatory mediators could offer a way to reset the cytokine milieu and provide clinical benefit.

In an important test of this hypothesis, in *The Lancet Respiratory Medicine*, Alexander Supady and colleagues[5] examined the efficiency of extracorporeal cytokine adsorption for the removal of IL-6. In their single-centre, pilot trial, the authors randomly allocated patients with COVID-19-related ARDS receiving venovenous extracorporeal membrane oxygenation (ECMO) to cytokine adsorption (n=17) for 72 h. Those not undergoing cytokine adsorption on ECMO served as controls (n=17) and the serum IL-6 concentrations were compared at 72 h. Mediator removal is concentration dependent and cytokine adsorption removes not only proinflammatory and anti-inflammatory mediators but many other biological substances (up to 55 kDa) as well.

There was no difference in the primary outcome (serum IL-6 concentrations measured at 72 h) between