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.

increases the risk of COVID-19-related mortality. For the hypothesis that ICS use protects against COVID-19-related mortality, the results rule out a benefit large enough to overcome the effects of confounding factors, but do not completely exclude a smaller benefit.

Overall, the analysis is confounded and does not provide definitive answers that patients and clinicians need, although it hints that ICS use does not provide a strong protective effect. Similar to Schultze and colleagues, we believe that had the analysis taken into account clinical factors, such as disease severity and history of exacerbations, which might have influenced the choice of maintenance therapy, it might have reached different conclusions about possible harms. ICSs are used to reduce future risk of events including exacerbations and mortality;[1,2] therefore, ICS use inevitably identifies individuals with an increased disease burden associated with increased future risk. Analyses of associations between ICS use and COVID-19-related outcomes in real-life datasets cannot escape this issue, but the comprehensive analysis reported by Schultze and colleagues in a large sample of almost 1 million people is a valiant attempt to provide some clarity despite the confounding by treatment indication observed.

The analysis does not completely resolve whether regular ICS therapy for asthma or COPD either decreases or increases risk of death from COVID-19. This finding is in contrast with the very real harm patients requiring ICS therapy for their asthma or COPD might be at risk if they stop treatment because of unfounded concerns related to their effects in COVID-19. Until more information is available, patients with asthma and COPD who are stable while using ICS must continue on their treatment during the ongoing COVID-19 pandemic.

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ECMO for severe ARDS associated with COVID-19: now we know we can, but should we?

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The initial months of the COVID-19 pandemic were dominated by studies reporting poor and varied outcomes in patients who developed severe acute respiratory distress syndrome (ARDS) associated with the disease. Variable mortality could have been related to heterogeneity in patient populations and pre-pandemic intensive care infrastructure, resource constraints imposed during the pandemic, and variability in duration of follow-up. As the pandemic has evolved, lower mortality attributable to the disease has been reported. For instance, in a cohort of 742 patients with COVID-19-associated ARDS from Spain, mortality for severe ARDS was 39%,[1] similar to findings of a large epidemiological study of patients with severe ARDS who did not have COVID-19.[2]

Early reports also suggested that patients with severe ARDS associated with COVID-19 should not receive venovenous extracorporeal membrane oxygenation (ECMO) because mortality ranged from 84–100% in patients treated with ECMO. In *The Lancet Respiratory Medicine*, Matthieu Schmidt and colleagues[3] present a cohort study of 83 patients (median age 49 [IQR 41–56] years; 61 [73%] men) who received ECMO for severe ARDS associated with COVID-19 in the Paris–Sorbonne University Hospital Network intensive care units (ICUs). Their results showed an estimated 31% (95% CI 22–42) probability of death at 60 days, which is similar to that seen in studies of ECMO for severe ARDS outside the pandemic.[4] However, 24% of patients were still in the ICU on day 60. Notably, patients received outstanding pre-ECMO management with high adherence to evidence-based ARDS practices, including prone-positioning in 78 (94%) patients. During ECMO, lung-protective ventilation was achieved with median tidal volumes of 2·5 (IQR 1·8–4·2) mL/kg of predicted bodyweight, the median driving pressure decreased from 18 (IQR 16–21) cm H_2O pre-ECMO to 12 (12–14) cm H_2O on ECMO day 1, and there was an approximate 75% decrease in mechanical power (24·7 [IQR 22·0–27·3] J/min pre-ECMO to 6·1 [4·1–11·0] J/min on ECMO day 1).

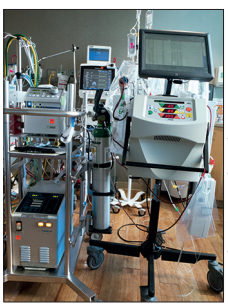
The outcome data appear impressive given that the patients represent a very severe subset of ARDS (median PaO_2/FiO_2 60 [IQR 54–68] mm Hg), while receiving a median applied positive end-expiratory pressure of 14 (IQR 12–14) cmH_2O, and were similar to or sicker than ECMO-treated patients with ARDS not associated with COVID-19 reported in the EOLIA trial in 2018.[4] However, it is difficult to draw valid conclusions from comparisons with historical data, especially given that these patients were substantially younger than previously reported patients with severe ARDS associated with COVID-19, and increased age is a well supported risk factor for mortality. Furthermore, although the data are encouraging, the results might not be generalisable, as they come primarily from one highly experienced ECMO centre, and there is a known relationship between hospital-level volume of ECMO cases and patient outcomes when using ECMO.[5]

The authors suggest that ECMO should be considered for patients with COVID-19 with profound respiratory failure despite optimised conventional care. Although this conclusion is reasonable, much remains unknown about the role of ECMO in ARDS associated with COVID-19, including the patients who would benefit the most (or those that would be harmed), long-term outcomes, and the cost-to-benefit ratio. It is possible that going forward, fewer patients with COVID-19 will develop profound respiratory failure, given the findings from the RECOVERY trial[6] showing reduced mortality in patients with COVID-19 who were ventilated and given dexamethasone. Notably, only 12 (14%) patients in the study of Schmidt and colleagues received corticosteroids before ECMO day 8. There was a high incidence of pulmonary embolism during ECMO (16 [19%] patients) despite the authors selecting higher anticoagulation targets than would typically be used for patients with ARDS that is not associated with COVID-19. This finding highlights the importance of the coagulation system in patients with COVID-19 in general, and specifically highlights the need to investigate anticoagulation targets during ECMO in these patients.

There are substantially more extracorporeal life support organisation (ELSO) registered ECMO centres today than existed during the 2009 influenza A (H1N1) pandemic (430 centres *vs* 164 centres), and this number will probably increase. How do we ensure that quality of care is adequate on a large scale, especially during the stress of pandemics? One approach is to adopt the ELSO guidance for responsible ECMO use.[7,8] Another is to concentrate ECMO activity in dedicated high-volume centres enabled by mobile ECMO teams, a model followed by the Paris–Sorbonne University Hospital Network, which delivered comprehensive pre-ECMO management and judicious patient selection.

With the presented data in hand, is there a need for randomised trials of ECMO specific to ARDS associated with COVID-19? From a strictly academic perspective, it could be argued that they are needed. However, large randomised trials would be difficult to do during the pandemic, and although there is controversy,[9] it might be that ARDS associated with COVID-19 is similar to ARDS not associated with COVID-19 from a mechanics and gas exchange perspective[1,9] (although perhaps not from a coagulation perspective).

In the meantime, the more important question concerns the degree to which ECMO should be used in ARDS associated with COVID-19 given the resources required. In the study by Schmidt and colleagues, the median length of ECMO support (20 days) and ICU length of stay (36 days) was very high (compared with



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a median of 11 days of ECMO support and 23 days in ICU in the EOLIA trial[4]). The scale and quality of ECMO care, if replicated in other jurisdictions, might potentially save lives; however, clearly at a cost in terms of resources and potential complications.[10] Any decisions on whether and when to use ECMO for very severe COVID-19 would have to be made locally with a clear recognition of the extensive resources required (mainly human resources), the expected caseload, and the potential implications for other patients.

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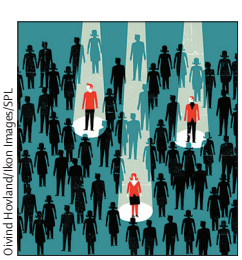
Targeting *MET* amplification in *EGFR*-mutant non-small-cell lung cancer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Activation of the hepatocyte growth factor (HGF)–MET pathway can lead to gefitinib resistance in *EGFR*-mutant non-small-cell lung cancer (NSCLC) by activating phosphoinositide 3-kinase (PI3K)–protein kinase B (AKT) signalling through two different adaptors: human epidermal growth factor receptor 3 (HER3 or ERBB2), when *MET* is triggered by genomic amplification; or Grb2-associated binder 1 (GAB1), when MET is activated by HGF. *MET* amplification has been reported in 15% of resistant tumour specimens.[1] Additionally, higher HGF expression has been detected in tumour samples from patients resistant to EGFR tyrosine kinase inhibitor (TKI) gefitinib or erlotinib than in pretreatment tumour specimens.[1]

In *The Lancet Respiratory Medicine*, Yi-Long Wu and colleagues[2] report the results of a trial of tepotinib plus gefitinib in patients with *EGFR*-mutant NSCLC who are resistant mainly to gefitinib or erlotinib and have MET overexpression or *MET* amplification (or both). MET phosphorylates a broad range of receptor tyrosine kinases in the Golgi endomembranes, which can be targeted by small-molecule inhibitors such as tepotinib. The salient findings of the randomised part of the study (phase 2) were in patients with *MET* amplification. Median progression-free survival in these patients was 16·6 months with tepotinib 500 mg plus gefitinib 250 mg once daily versus 4·2 months with chemotherapy (hazard ratio [HR] 0·13 [90% CI 0·04–0·43]); median overall survival was 37·3 months with tepotinib plus gefitinib versus 13·1 months with chemotherapy (HR 0·08 [0·01–0·51]).[2] Progression-free survival and overall survival were longer with tepotinib plus gefitinib than with chemotherapy in patients with high (immunohistochemistry [IHC]3+) MET protein