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.

Respiratory support before venovenous ECMO for COVID-19: what is the price?

The COVID-19 pandemic was an unprecedented challenge for the extracorporeal membrane oxygenation (ECMO) community. The demand for extracorporeal gas exchange markedly increased to face the surge in life-threatening respiratory failures; however, as highlighted in the Extracorporeal Life Support Organization COVID-19 guidelines,[1] the limited availability of ECMO resources (eg, consoles and circuits) and the heavy workload of health-care personnel forced a strict selection of patients for ECMO. In this context, identifying the predictors of poorer outcomes becomes essential to enable the provision of ECMO support to patients who are most likely to benefit.

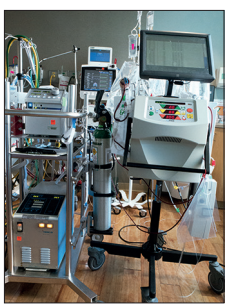
In this issue of *The Lancet Respiratory Medicine*, Alexandre Tran and colleagues[2] reported the results of a systematic review and meta-analysis of 42 observational studies, exploring the prognostic factors of mortality in adult patients with COVID-19 who were treated with venovenous ECMO. Tran and colleagues[2] used a pragmatic approach to study inclusion and grouping of variables, conducted clinically meaningful sensitivity analyses, and presented certainty using Grading of Recommendations, Assessment, Development and Evaluations methodology. Their study aimed to provide key information on prognostic factors that might identify patients who would benefit from ECMO support, and, conversely, an understanding of whether ECMO treatment might be futile and its indication inappropriate. Among different potential predictors of outcome, Tran and colleagues[2] observed that specific variables—such as patient factors (eg, older age, immunocompromised status, male sex, and chronic lung disease), pre-cannulation disease factors (eg, longer duration of symptoms and invasive mechanical ventilation, higher partial pressure of arterial carbon dioxide [$PaCO_2$] and driving pressure, and lower ratio of partial pressure of arterial oxygen to fractional concentration of oxygen in inspired air [PaO_2/FiO_2]), and centre factors (eg, less previous experience with ECMO)—were associated with mortality.

Although starting with a very large patient population (more than 17 000 patients treated with ECMO), several studies included in the meta-analysis had low-certainty evidence that was limited by serious risk of bias and imprecision. Furthermore, although prognostic centre and patient factors (with the exception of obesity) were well represented in adjusted analyses on a large sample size, pre-cannulation disease factors were mainly represented as unadjusted mean differences (eg, symptom duration) or in the presence of a limited sample size (eg, driving pressure). The conclusions of Tran and colleagues[2] should therefore be interpreted with caution. Nonetheless, we commend them for providing clinically useful findings and offering enriching data for innovative hypothesis generation.

Age and comorbidities were confirmed as patient factors with a key effect on outcomes in COVID-19-associated acute respiratory distress syndrome (ARDS), as previously reported in ARDS not related to COVID-19.[3] Regarding pre-cannulation disease factors, lower PaO_2/FiO_2, higher $PaCO_2$, and higher driving pressure were confirmed as independent predictors of mortality. Among them, driving pressure warrants careful consideration. On one hand, a high driving pressure could result from an inappropriate mechanical ventilation setting and then act as a contributor to ventilator-induced lung injury. On the other hand, driving pressure could reflect the severity of lung injury (ie, low respiratory system compliance[4]) despite a low tidal volume ventilation.

How to interpret the prognostic value of the duration of invasive mechanical ventilation is unclear, as its association with mortality was not confirmed by adjusted analysis. These conflicting results fit within current literature, as the negative prognostic value of protracted mechanical ventilation in patients with COVID-19 who are supported by ECMO is debated.[5,6] We wonder how to interpret these findings. Is prolonged mechanical ventilation in itself a contributing factor of mortality? When is prolonged mechanical ventilation sufficiently protective that the potential benefits outweigh the risks?

Another intriguing finding reported by Tran and colleagues[2] is the association of symptom duration before cannulation with mortality, a time variable that includes the duration of spontaneous breathing (with



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and without non-invasive respiratory support). Tran and colleagues[2] allow the reader to consider the potential injurious role of spontaneous breathing—recently described as patient self-inflicted lung injury[7]—among the potential contributors of mortality in COVID-19-associated ARDS. Whether patient self-inflicted lung injury might affect outcome in patients with COVID-19 who are supported by ECMO is still unclear. This potential association should be evaluated in the context of a pandemic, during which the duration of spontaneous breathing was protracted and the use of non-invasive ventilation was pushed beyond its indications because of the limited availability of ventilators and intensive care beds. The major increase in the use of non-invasive ventilation was hypothesised to be a factor influencing the increasing mortality rates of patients supported by ECMO during the first year of the COVID-19 pandemic,[8] which occurred despite the introduction of effective therapies (eg, steroids[9]).

In conclusion, the systematic review and meta-analysis by Tran and colleagues[2] identified several prognostic factors for patients with COVID-19 who are supported by ECMO, but also highlighted some knowledge gaps. Several questions remain regarding the prognostic role of spontaneous breathing, non-invasive, and mechanical ventilation before ECMO. For example, how to weight the effect of duration and method[10] of non-invasive respiratory support, how to quantify the risk of patient self-inflicted lung injury, and whether a threshold of time and intensity of ventilation before ECMO cannulation might not be protective with regards to survival remain unclear. Future studies are expected to shed light on these questions.

We declare no competing interests.

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1 Badulak J, Antonini MV, Stead CM, et al. Extracorporeal membrane oxygenation for COVID-19: updated 2021 guidelines from the Extracorporeal Life Support Organization. *ASAIO J* 2021; **67:** 485–95.
2 Tran A, Fernando SM, Rochwerg B, et al. Prognostic factors associated with mortality among patients receiving venovenous extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. *Lancet Respir Med* 2022; published online Oct 10. https://doi.org/10.1016/S2213-2600(22)00296-X.
3 Rezoagli E, McNicholas BA, Madotto F, et al. Presence of comorbidities alters management and worsens outcome of patients with acute respiratory distress syndrome: insights from the LUNG SAFE study. *Ann Intensive Care* 2022; **12:** 42.
4 Li Bassi G, Suen JY, Dalton HJ, et al. An appraisal of respiratory system compliance in mechanically ventilated COVID-19 patients. *Crit Care* 2021; **25:** 199.
5 Urner M, Barnett AG, Bassi GL, *et al.* Venovenous extracorporeal membrane oxygenation in patients with acute COVID-19 associated respiratory failure: comparative effectiveness study. *BMJ* 2022; **377:** e068723.
6 Riera J, Alcántara S, Bonilla C, et al. Risk factors for mortality in patients with COVID-19 needing extracorporeal respiratory support. *Eur Resp J* 2022; **59:** 2102463.
7 Brochard L, Slutsky A, Pesenti A. Mechanical ventilation to minimize progression of lung injury in acute respiratory failure. *Am J Respir Crit Care Med* 2016; **195:** 438–42.
8 Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation for COVID-19: evolving outcomes from the international Extracorporeal Life Support Organization Registry. *Lancet* 2021; **398:** 1230–38.
9 The RECOVERY Collaborative Group. Dexamethasone in hospitalized patients with COVID-19. *N Engl J Med* 2021; **384:** 693–704.
10 Reyes LF, Murthy S, Garcia-Gallo E, et al. Respiratory support in patients with severe COVID-19 in the International Severe Acute Respiratory and Emerging Infection (ISARIC) COVID-19 study: a prospective, multinational, observational study. *Crit Care* 2022; **26:** 276.