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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Editorial

Extracorporeal membrane oxygenation for COVID-19: Some answers and a remaining question

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The COVID-19 pandemic has created an unprecedented need for venovenous (VV) extracorporeal membrane oxygenation (ECMO) worldwide. Early data collected by the Extracorporeal Life Support Organization (ELSO) registry reported a comparable survival rate between COVID-19 patients receiving ECMO and patients receiving VV ECMO for conventional ARDS [1–3].

In the September issue of *The Lancet*, Barbaro et al. reported characteristics and outcomes of the 4812 patients of the ELSO registry who received VV ECMO for severe COVID-19-related ARDS over 2020 [4]. The study aimed to detect a change in mortality over time in these patients. Thus, they divided patients into three groups: first, patients who received VV ECMO before the 1st of May (group A1). Second, patients who received ECMO after the 1st of May at centres that had treated patients on VV ECMO before the 1st of May (group A2). Third, patients who received VV ECMO after the 1st of May at centres that had not used VV ECMO before the 1st of May (group B).

Surprisingly, mortality worsened over time with an absolute 15% increase between groups A1 and A2 (36.9% (95% CI 34.1–39.7) *versus* 51.9% (50.0–53.8)). Ninety-day mortality in group B was even higher (58.9% (55.4–62.3)). Duration of ECMO support also increased over time with a median duration of ECMO support of 14.1 days (IQR 7.9–24.1) in group A1 and 20.0 days (9.7–35.1) in group A2 ($p < 0.001$). Finally, patients treated in "high-volume centres" (*i.e.*, centres in whom more than 9 patients received VV ECMO in 2019) had a better survival rate with a relative risk reduction of nearly 50%.

These results bring us clarifications on the role of VV ECMO at the initial phase of the pandemic. The first point is the importance of specialised, high-volume ECMO centres. As already demonstrated in other specialties, and more recently in a French multicentre trial [5], exception techniques like VV ECMO should only be performed in specialised centres, by trained health care practitioners in multidisciplinary teams, with standard operating procedures, and advanced technical equipment.

Second, the duration of ECMO support in severe COVID-19-related ARDS is very high, with a quarter of the group A2 patients receiving ECMO for 5 weeks and more. This result should encourage clinicians to expect a long duration of treatments, and not attempt ECMO weaning procedures too early. Conversely, patients whose condition is not promptly improving on ECMO support have not necessarily a poor prognosis.

Third, the most recent data suggest that mortality in patients receiving VV ECMO for COVID-19-related ARDS exceeds mortality in conventional ARDS, contrary to early reports, which did not suggest significant differences [1–3]. The reason for the excess of mortality is still unknown and may be related to a more severe pulmonary injury or COVID-19 specific extrapulmonary disorders such as thromboembolism [6].

This article also raises one question. Despite accumulating knowledge on COVID-19 for one year, with evolving recommendations and practices, mortality increased significantly. The authors did not really clarify this point. They hypothesised that patients selected for VV ECMO treatment at the initial phase of the pandemic had a higher likelihood of survival than patients supported with ECMO after the 1st of May. However, the authors' model predicted a higher (not lower) mortality in patients treated at the initial phase of the pandemic.

Authors also suggested that groups A2 and B patients, who received more dexamethasone and remdesivir, had more frequently a refractory COVID-19-related ARDS. However, these treatments were simply consistent with clinical trials and evolving guidelines after the 1st of May 2020 [7–9], and did not mean that patients' ARDS were more severe. To our knowledge, the use of remdesivir and hydroxychloroquine has never been specifically studied in patients on VV ECMO and might also have influenced mortality. Furthermore, the use of prone positioning and neuromuscular blockers was similar over time in study patients, but these mean values did not reflect a probable heterogeneity in practices among centres. For example, the prone positioning rate before ECMO in the ELSO registry merely reaches 60%, compared to the more than 90% rate in a recent ECMO French multicentric study [5]. The interest of these adjunctive therapies, before and during ECMO, could be questioned in future prospective studies.

Another point that is not investigated in the article is the duration between hospital admission and endotracheal intubation. At the beginning of the pandemic, early endotracheal intubation was the most common attitude among clinicians. One of the reasons was a fear of coronavirus aerosolisation and spreading

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during non-invasive ventilation. However, further articles proved that high-flow nasal oxygen and bilevel positive airway pressure in COVID-19-related ARDS were associated with a lower rate of endotracheal intubation and could be applied without excess risk for healthcare workers. Therefore, non-invasive ventilation was recommended in international guidelines [10] and largely used after the 1st of May 2020. This clinical attitude might have decreased ventilator-associated complications and even mortality in the general population. However, the prolonged use of non-invasive ventilation may also have selected the sickest patients in whom, after the failure of non-invasive ventilation and subsequent intubation, self-inflicted lung injury worsened pre-existing COVID-19-related ARDS lesions [11]. In these patients, as in conventional ARDS patients, delayed invasive ventilation and ECMO support may have led to increased mortality [12]. In a recent monocentric study, longer duration from admission to VV ECMO tended to be associated with higher mortality [13].

Finally, COVID-19 itself evolved during the study period. Several coronavirus new variants emerged in the fall of 2020, such as B.1.1.7 (“UK variant”), B.1.351 (“South African variant”), and P1 (“Brazilian variant”). These strains seem to be more lethal than the wild-type virus [14,15]. However, these variants had not yet emerged in many countries at the end of the study, and therefore their role in the increase of mortality is probably limited. The impact of the seasonality in COVID-19 pathogenicity might also be a factor of excess mortality, but this hypothesis has never been verified.

The intense publication activity during the past year highlighted the specificities of VV ECMO support for COVID-19-related ARDS: longer duration and increased mortality compared to classic ARDS, and the need for specialised high-volume ECMO centres. Prolonged non-invasive respiratory support before ECMO is possibly a cause of excess mortality in the sickest patients and might be questioned. The role of the emerging variants in these patients should be clarified during the upcoming months.

Conflict of interest

The authors declare that they have no competing interest.

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