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COVID-19 IN INTENSIVE CARE

What's new in ECMO for COVID-19?

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The first studies of coronavirus disease 2019 (COVID-19) from China reported high mortality rates in patients supported with extracorporeal membrane oxygenation (ECMO) [1]. Very little was known about the natural history of the virus, prompting both speculation about the precise role of ECMO [2] and recommendations for its use [3, 4]. Many clinicians were concerned about using high-cost, resource-intensive therapies for a small, select proportion of critically ill patients if national healthcare systems were in danger of being overwhelmed. It was unclear whether the reasons underlying these initial, apparently high mortality rates related to the pathophysiology of the virus itself or the use of ECMO by overburdened clinicians in suboptimal circumstances. Data has recently emerged outlining the potential role of ECMO for COVID-19 with greater clarity.

A multicentre French study captured the early experience with critically ill COVID-19 patients after the first wave of the pandemic hit Western Europe [5]. Eighty-three (17%) of 492 intensive care patients with COVID-19-related acute respiratory distress syndrome (ARDS) received ECMO and were ultimately assessed to have an estimated probability of 60-day mortality of 31% (95% CI 22–42). The patients were similar in many regards to those in the 'ECMO to Rescue Lung Injury in Severe ARDS' (EOLIA) trial [6], with a median partial pressure of arterial oxygen to fraction of inspired oxygen (PaO_2/FiO_2) ratio of 60 (IQR 54–68) prior to ECMO. They were also managed along similar evidence-based principles [7] to the EOLIA cohorts and 94% received prone positioning prior to ECMO. Bleeding and thrombotic events were common, with 42% of patients suffering a major bleeding episode and 19% having pulmonary emboli during ECMO. In comparison, no patients in the EOLIA trial were reported to have pulmonary emboli during ECMO. This apparent increase in the risk of life-threatening thromboembolism has also been documented in critically ill COVID-19 patients not receiving ECMO [8]. Nosocomial infections were also frequently seen. Eighty-seven percent of patients developed ventilator-associated pneumonia and 48% had bacteraemia. This report provided insights into the use of ECMO for COVID-19 in experienced centres, including those which had participated in the EOLIA trial, and had consistent protocols and standardized ARDS management practices in place prior to the pandemic.

The largest report to date from the Extracorporeal Life Support Organization (ELSO) registry included patients from 213 centres across 36 countries [9]. Data on 1035 patients with COVID-19 supported with ECMO showed an estimated cumulative incidence of in-hospital mortality 90 days after ECMO initiation of 37% (95% CI 34–40). In those who had a final disposition of death or hospital discharge, 39% had died. This report detailed patients with COVID-19 supported with ECMO regardless of clinical indication, not only those with ARDS. Six percent of patients received ECMO for mechanical circulatory support, which was associated with higher mortality (hazard ratio (HR) 1.89, 95% CI 1.2–2.97). A higher risk of mortality was also seen in those over 70 years old (HR 3.07, 95% CI 1.58–5.95). Median PaO_2/FiO_2 ratio prior to cannulation was 72 (IQR 59–94) and 60% had a trial of prone positioning prior to ECMO initiation. There were no significant differences in the rates of circuit clot or malfunction when compared to 2019 centre data from the registry, once normalized for the longer median times on ECMO in the COVID-19 patients.

Some reports highlighted the use of relatively novel management strategies consisting of bundled treatment elements, each of which had been applied in patients prior to the pandemic, but were now being trialed more systematically in patients with COVID-19. For example,

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in the multicentre French study cited earlier [5], 81% of the patients were nursed in the prone position during ECMO. It is unknown whether this practice leads to better outcomes but there is preliminary evidence suggesting that it may be associated with lower mortality [10, 11]. An American report described 40 COVID-19 patients meeting EOLIA entry criteria, 73% of whom received prone positioning prior to ECMO initiation. These patients were all cannulated for ECMO using a specific dual-lumen cannula (Protek-Duo TandemHeart cannula, CardiacAssist Inc, Pittsburgh, PA) inserted into the pulmonary artery under echocardiographic guidance, providing venovenous ECMO with right ventricular mechanical circulatory support by draining right atrial blood and returning oxygenated blood directly into the pulmonary artery [12]. Patients were able to be weaned from invasive mechanical ventilation during ECMO a mean of 13 days after ECMO initiation and physical therapy was provided thereafter. Six (15%) patients had died and 29 (73%) were discharged at the time of the report.

Despite this encouraging early signal that the majority of selected patients with COVID-19 severe enough to require ECMO survive, many uncertainties remain (Table 1). Although the tropism for severe respiratory failure is obvious, the virus can cause disease in other organ systems, the long-term effects of which are unknown [13]. In some other ECMO patient populations, there is a small but demonstrable risk of late mortality more than 90 days following initiation of ECMO, as well as risks of physical and psychological debility. Further study will be needed to ascertain the proportion of patients who suffer from these late complications after ECMO in the setting of COVID-19 and what can be done to mitigate them.

In summary, ECMO appears to have a role in the management of adult patients with COVID-19 who suffer from ARDS refractory to other management strategies. There is greater uncertainty about the role of ECMO in other populations with COVID-19, such as patients requiring mechanical circulatory support, extracorporeal cardiopulmonary resuscitation (ECPR) [14], or those with multisystem inflammatory syndrome in children. Nonetheless, preliminary data appear to support the use of ECMO in many of these conditions as well [9, 15]. The initial concerns that ECMO for COVID-19 was associated with unacceptable short-term outcomes have been assuaged, at least when ECMO is used in experienced centres. What is required now are data concerning long-term morbidity and mortality, and whether any practices—including prone positioning, optimal anticoagulation, early extubation and use of mechanical right ventricular support—during ECMO can improve these outcomes.

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GM wrote the initial draft. AC and DB critically revised the manuscript for important intellectual content. All authors read and approved the final manuscript.

Table 1 Uncertainties concerning the use of ECMO for patients with COVID-19

Timing	Question
Pre-ECMO	Does the use of a particular combination of immunomodulants (e.g. corticosteroids) ± antiviral agents (e.g. remdesivir) reduce the need for ECMO? Should the EOLIA inclusion criteria be used to decide the timing of ECMO initiation? Is there a role for ECPR and how safe is it for the treating teams?
During ECMO	Are the longer ECMO runs seen in COVID-19 associated with an increase in the risk of ECMO-related complications and morbidity, e.g. nosocomial infection? Is there an increase in bleeding or thrombotic complications despite optimal anticoagulation and is this associated with an increase in the risk of mechanical circuit problems or failure? Should we screen for DVT/PE during ECMO? Are there strategies during ECMO associated with improved long-term outcomes, such as prone positioning; full-dose anticoagulation; awake ECMO (i.e. endotracheal extubation of conscious patients while receiving ECMO); or mechanical right ventricular support during ECMO? If so, what are the mechanisms? Is tracheostomy needed in these patients? If yes, what is the optimal timing for the procedure?
After ECMO	What are the long-term outcomes of patients with COVID-19 supported with ECMO? Should we routinely and systematically screen for DVT/PE after ECMO? What is the maximum duration of ECMO where recovery is still possible and is lung transplantation an option beyond that?

COVID-19 Coronavirus Disease 2019, *ECMO* extracorporeal membrane oxygenation, *ECPR* extracorporeal cardiopulmonary resuscitation, *EOLIA* 'ECMO to Rescue Lung Injury in Severe ARDS' trial [6], *DVT/PE* deep vein thrombosis/Pulmonary embolus

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Compliance with ethical standards

Conflicts of interest
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