



Extracorporeal membrane oxygenation for coronavirus disease 2019-related acute respiratory distress syndrome

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Purpose of review

To understand the potential role of extracorporeal membrane oxygenation (ECMO) in coronavirus disease 2019 (COVID-19)-related acute respiratory distress syndrome (ARDS), highlighting evolving practices and outcomes.

Recent findings

The role for ECMO in COVID-19-related ARDS has evolved throughout the pandemic. Early reports of high mortality led to some to advocate for withholding ECMO in this setting. Subsequent data suggested mortality rates were on par with those from studies conducted prior to the pandemic. However, outcomes are evolving and mortality in these patients may be worsening with time.

Summary

ECMO has an established role in the treatment of severe forms of ARDS. Current data suggest adherence to the currently accepted algorithm for management of ARDS, including the use of ECMO. However, planning related to resource utilization and strain on healthcare systems are necessary to determine the feasibility of ECMO in specific regions at any given time. Utilization of national and local networks, pooling of resources and ECMO mobilization units are important to optimize access to ECMO as appropriate. Reported complications of ECMO in the setting of COVID-19-related ARDS have been predominantly similar to those reported in studies of non-COVID-19-related ARDS. Further high-quality research is needed.

Keywords

acute respiratory distress syndrome, coronavirus disease 2019, extracorporeal circulation, extracorporeal membrane oxygenation, respiratory failure

INTRODUCTION

A prominent feature of severe coronavirus disease 2019 (COVID-19) is the acute respiratory distress syndrome (ARDS). Extracorporeal membrane oxygenation (ECMO) has an established role in the management of severe forms of ARDS [1–6]. The role of ECMO in severe ARDS because of COVID-19 is less well established and has evolved throughout the pandemic. Despite preliminary data from China suggesting that ECMO was associated with prohibitively high mortality [7], the majority of evidence from the early months of the pandemic suggested that outcomes with ECMO in COVID-19-related ARDS were similar to those for non-COVID-19-related ARDS [8^{••}]. However, subsequent data suggests that mortality with ECMO for COVID-19-related ARDS may be increasing over the course of the pandemic [9[•], 10[•]].

THE ROLE OF EXTRACORPOREAL MEMBRANE OXYGENATION IN NON-CORONAVIRUS DISEASE 2019-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME

The use of venovenous ECMO for patients with ARDS is now well established [1–6, 11]. ECMO

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KEY POINTS

- Mortality trends for patients with COVID-19-related ARDS supported with ECMO are evolving and most recently suggest higher mortality than previously seen.
- The management of patients receiving ECMO for COVID-19-related ARDS should be similar to the management in patients' non-COVID-19-related ARDS until new evidence suggests otherwise.
- Resource utilization and development of regional and national networks may serve to improve availability of ECMO during the pandemic.

should be considered within the standard ARDS algorithm after providing those therapies that are fundamental to the management of ARDS, including low-volume, low-pressure ventilation and prone positioning [2,3]. ECMO is recommended at the point where all such therapies have been instituted and yet the patient still meets criteria according to the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial [2,4].

EXTRACORPOREAL MEMBRANE OXYGENATION FOR CORONAVIRUS DISEASE 2019: THE EARLY EXPERIENCE

The initial publications reporting on the use of ECMO for COVID-19-related ARDS came out of China and laid the earliest foundation for guidance in the pandemic. They reported markedly higher mortality with the use of ECMO in COVID-19 when compared to the use of ECMO for non-COVID-19-related ARDS. In a pooled analysis of four studies of 562 patients with COVID-19, with 234 having ARDS and 17 of them initiated on ECMO for refractory hypoxemia, mortality for patients receiving ECMO was 94.1%, compared with 70.9% with conventional treatment [7]. A second study reported the mortality for those receiving ECMO for COVID-19 at 82.3% [12]. Importantly, these observational data primarily reflected the difficult circumstances under which clinicians were initially practicing in and around Wuhan, China, along with considerable patient selection bias. These findings led to initial recommendations from some authors against the use of ECMO in this setting [7,12].

Early in the pandemic, there was so much uncertainty around the presentation and optimal management of COVID-19 that clinicians struggled to define the potential role ECMO might play in the management of severe COVID-19-related ARDS [13]. There were questions about the very nature of the presenting

respiratory illness and whether or not it constituted something other than ARDS [14] with the implication being that a different approach than the standard management algorithm for ARDS may be warranted. However, the lack of evidence for heterogeneity of treatment effect in COVID-19-related ARDS, as compared with non-COVID-19-related ARDS led to the tentative preservation of the standard management algorithm pending further evidence [15]. Recommendations and guidelines from major medical societies supported this approach throughout the pandemic [16–21].

EXTRACORPOREAL MEMBRANE OXYGENATION RESOURCE CONSTRAINTS AND CRISIS STANDARDS OF CARE

ECMO is a resource-intensive endeavor under the best of circumstances [22]. During the pandemic, shortages of equipment and personnel challenged the ability of many centers to provide ECMO safely if at all. Careful planning and preparation were recommended [17,23], including for adequate training of personnel and appropriate infection control measures. However, some regions experienced a rate of rise in cases or a total volume of cases that overwhelmed standard modes of operation, resulting in the need to consider triaging potentially life-saving therapies in competition with each other for similar resources, including staffing, ICU beds and equipment. Difficult decisions needed to be made about the distribution of resources to patients meeting criteria for ECMO potentially at the expense of providing competing resources to a greater number of other patients [24–27]. Given the uncertainty around outcomes with ECMO early in the pandemic, this challenge persisted until enough experience with COVID-19 allowed for recommendations for the provision of ECMO under contingency and crisis standards of care [28].

With rising caseloads and systems becoming overwhelmed, numerous groups across regions and countries created networks of ECMO referrers and providers in order to streamline the process for initiating ECMO and standardizing the criteria across geographic areas in order to avoid duplicating efforts [29,30]. In Paris, France, for example, a network of 17 hospitals centralized their resources and unified their indications and contraindications for ECMO [29]. A centralized team approved ECMO cases, mobilized retrieval teams and provided recommendations for management. Prior to the pandemic, Paris was served by one mobile ECMO team. During the pandemic, an additional five mobile ECMO units were created in order to meet

the surging demand [29[■]]. In Chile, ECMO allocation was overseen by a National Advisory Commission to improve capacity nationwide [30[■]]. Networks allowed for coordination of referrals, pooling of resources, the ability to quickly disseminate evolving recommendations and educational materials, and to have unified indications and contraindications [30[■]]. In New York, nontraditional staffing models contributed to the ability to maintain operations within an existing ECMO program [31].

Initial recommendations suggested that starting up a new ECMO center during the pandemic was not advisable [23]. One study that challenged this notion was a retrospective, multicenter, observational study of 307 patients who received ECMO for COVID-19 from 19 ECMO centers across five countries in the Middle East and India [32]. Whereas overall survival was 45%, survival at new ECMO centers was 55%, exceeding the 41% survival at established ECMO centers [odds ratio (OR) 1.65; 95% CI 0.75–3.67], albeit with a wide confidence interval and the almost certain presence of residual confounding including in patient selection [32]. Although these data suggest that centers may successfully initiate ECMO programs during a pandemic, clearly the majority of successful centers, whether new or established, should have rigorous training and education programs, quality assurance measures, well defined governance structures and appropriate support from hospital administration. Importantly, such centers are well served to collaborate within networks alongside experienced centers, as well as with societies, such as the Extracorporeal Life Support Organization (ELSO) [17,28[■],33].

EMERGING DATA

Although the preliminary data from China suggested that ECMO might offer little tangible benefit to patients with severe COVID-19-related ARDS, the experience of the Paris-Sorbonne University Hospital Network in France offered the first glimpse at well characterized data and more extended follow-up [34[■]].

Of the 492 patients included within a 2-month period, 83 required ECMO. With complete 60-day follow-up in all 83 patients, the estimated probability of mortality was 31% at 60 days and 36% at 90 days [34[■]]. Notably, 78 of 83 (94%) patients underwent prone positioning prior to the initiation of ECMO, and only 7% of patients received corticosteroids prior to ECMO, the latter reflecting the practices seen early in the pandemic [34[■]]. Hemorrhagic stroke was seen in 5% of patients and ischemic stroke in one patient.

The mortality rate seen in the Paris-Sorbonne COVID-19 ECMO cohort was seen as reassuring for understanding the place of ECMO in the algorithm for COVID-19-related ARDS, even if it did not address the issue of resource utilization. Nonetheless, additional data were clearly needed to more firmly establish the role of ECMO in this patient population [35].

Subsequent studies demonstrated similar mortality rates in cohorts of COVID-19 patients receiving ECMO from multiple jurisdictions [30[■],36,37[■]]. One such study from the United States looked at a cohort of 5122 COVID-19 patients across 68 hospitals, of whom 190 received ECMO within 14 days of ICU admission [37[■]]. At 60 days, mortality among those receiving ECMO was 33.2% (with 17.4% of patients still hospitalized). Emulating a target trial of ECMO or no ECMO among mechanically ventilated patients within 7 days of ICU admission and with a ratio of partial pressure of arterial oxygen to fraction of inspired oxygen less than 100, mortality for patients receiving ECMO was 34.6%, compared with 47.4% without ECMO (hazard ratio 0.55; 95% CI 0.41–0.74).

The largest well characterized cohort study of COVID-19 patients receiving ECMO involved an analysis of the ELSO registry, which included 1035 adult patients from 213 hospitals across 36 countries initiated on ECMO for COVID-19 between 16 January and 1 May 2020 [38[■]]. The overall estimated cumulative incidence of in-hospital mortality 90 days after ECMO initiation was 37.4%. Factors associated with increased mortality included older age, immunocompromised state, chronic respiratory disease, acute kidney injury, pre-ECMO cardiac arrest, and receipt of venoarterial support at the time of ECMO cannulation. Central nervous system complications were relatively infrequent, with hemorrhagic stroke occurring in 6% of patients, infarct in 0.7%, and seizure in 0.6%. Mechanical complications of the circuit occurred in 28% of patients, including circuit change (15%), membrane lung failure (8%), cannula problem (6%), and pump failure (0.8%). Although several complication rates (central nervous system hemorrhage, mechanical complications) appeared to be higher than what was observed in ARDS cases in the ELSO registry in 2019 [38[■]], when complication rates were normalized to number of ECMO hours, rates were comparable with those pre-COVID. Given that this is observational data, it must be acknowledged that differences or lack thereof in complication rates may be accounted for by differences in practice between cohorts, such as any potential changes in anticoagulation practices used in patients with COVID-19 as compared with those without COVID-19.

In a prospective, voluntary survey conducted by the European chapter of ELSO (EuroELSO) that involved 177 centers across Europe and Israel between 15 March and 14 September 2020, 1531 cases of ECMO-supported COVID-19 were reported (91% venovenous ECMO), with France ($n = 385$), United Kingdom ($n = 193$), Germany ($n = 176$), Spain ($n = 166$), and Italy ($n = 136$) accounting for over two-thirds of all cases. At the time of publication, investigators reported a mortality of 44% [36].

In a systematic review and meta-analysis of 1896 patients with COVID-19 supported with ECMO (98.6% venovenous) from 22 observational studies, including the ELSO cohort, the pooled in-hospital mortality was 37.1% (35.7% for venovenous only) [8²²], which is once again comparable with the mortality reported in the intervention arm of the EOLIA trial [4]. Risk factors associated with increased mortality were older age, shorter ECMO duration, and lower BMI.

Not all reports suggested a mortality rate comparable to that seen in EOLIA. In a second multicenter observational study out of Paris, which analyzed 302 COVID-19 patients supported with ECMO, 90-day mortality was 54.3% [29²²]. Of note, mortality was associated with 2019 venovenous ECMO case volume, with a favorable volume–outcome relationship seen. Additionally, increasing age was associated with increasing mortality, and lower mortality was observed among those in whom ECMO was initiated prior to the third day of endotracheal intubation. This study reported a 12% rate of intracranial hemorrhage and 18% of patients were diagnosed with pulmonary embolism.

Perhaps one of the more provocative studies from the first year of the pandemic described a two-center experience with 40 patients who had severe COVID-19-related ARDS who received ECMO after meeting EOLIA criteria [39]. With patient characteristics and pre-ECMO treatment similar to other reported cohorts, this group nonetheless reported a very low mortality (15%) in their patients. In a follow-up letter, the final mortality after complete reporting was available on all patients was still only 17.5% [40]. Understanding the cause of these notably better outcomes than those reported elsewhere is complicated as the authors applied a package of interventions that included the use of a single-site dual-lumen cannula in a right atrium-to-pulmonary artery configuration, which provides right ventricular support; in addition, they used direct thrombin inhibitors, inhaled nitric oxide, high-dose corticosteroids [even prior to the publication of the Randomized Evaluation of COVID-19 Therapy (RECOVERY) trial] [41], and they attempted endotracheal extubation and physical rehabilitation with their patients as soon as medically

feasible [39]. Further study of this protocol is needed to determine whether individual elements (or the entire package of interventions) had a particular impact on outcomes.

Although there were differences between the patient populations reported in these studies, pre-cannulation management of ARDS was generally in line with best practice recommendations, including the use of prone positioning, neuromuscular blockade, and low-volume, low-pressure ventilation strategies, although rates of adherence to each of these interventions varied across studies (Tables 1 and 2).

EVOLVING PATTERNS OF MORTALITY

Data from the ELSO website, collected prospectively throughout the pandemic, suggests that mortality has increased since the initial experiences reported above [42]. A second analysis of the EuroELSO survey data, comparing the initial cohort of patients with COVID-19 who received ECMO from 12 March 2020 through 14 September 2020 with patients from 15 September 2020 through 8 March 2021, demonstrated increased mortality in the latter cohort (56 versus 47%) [9²²]. More recently, data from Germany with 768 patients with COVID-19 who received ECMO between February and December 2020 reported 73% in-hospital mortality – although mean age of 58 years was higher in this cohort than in others and age itself is clearly a risk factor for worse mortality [10²²] (Fig. 1).

Ongoing evaluation of these and other emerging data will be necessary to detect new trends and identify changing risk factors that may alter our approach to the use of ECMO, depending on how these factors influence expected outcomes. The algorithm for the use of ECMO in patients with COVID-19 will need to evolve with the data [28²²].

COMPLICATIONS

In general, COVID-19 has been associated with an increased risk of both thrombosis and bleeding [43–46], and increased rates of circuit clotting, pulmonary embolism and intracranial hemorrhage have been reported in cohorts of COVID-19 patients receiving ECMO [34²², 47–49]. Figure 2 depicts reported rates of common complications during ECMO for patients with COVID-19. Rates of other complications, including infection and severe thrombocytopenia, were similar to pre-COVID-19 data [4].

MANAGEMENT STRATEGIES

Recommendations for management strategies for ECMO in patients with COVID-19 remain similar

Table 1. Precannulation characteristics

	Schmidt, 2020	Diaz, 2020	Shaefi, 2020	Barbaro, 2020	Lebreton, 2020
Age (years) (IQR)	49 (41–56)	48 (41–55)	49 (41–58)	49 (41–57)	52 (45–58)
Male sex [n (%)]	61 (73)	71 (83.5)	137 (72.1)	764 (74)	235 (78)
BMI (IQR)	30.4 (27.9–34.1)	NR	32.7 (29.1–38)	31 (27–37)	29.7 (26.8–33.5)
Total SOFA score (IQR)	12 (9–13)	10 (7–12)	NR	NR	12 (9–14)
Time from intubation to ECMO (days) (IQR)	7 (5–10)	4 (0–7)	2 (0–5)	4.0 (1.8–6.4)	5 (3–7)
Tidal volume (ml/kg) PBW (IQR)	6.0 (5.7–6.4)	5.4 (4.7–6.0)	6 (5.3–7.1)	NR	5.6 (4.9–6.2)
Plateau pressure, cmH ₂ O (IQR or SD)	27 (27–30)	26.2 (±5.2)	30 (28–35)	NR	30 (27–32)
Driving pressure (cmH ₂ O) (IQR)	18 (16–21)	15.0 (14.0–16.0)	15 (11–18)	NR	18 (14–21)
Positive end-expiratory pressure (cmH ₂ O) (IQR or SD)	12 (12–14)	10.4 (±4.1)	15 (12–18)	14 (12–16)	12 (10–14)
PaO ₂ /FiO ₂ (IQR)	60 (54–68)	86.8 (63.7–99.2)	85 (66–120)	69 (58–85)	61 (54–70)
Prone positioning [n (%)]	78 (94)	78 (91.8)	135 (71.1)	612 (60)	285 (94)
Neuromuscular blockade [n (%)]	80 (96)	80 (94.1)	149 (78.1)	729 (72)	291 (96)

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; NR, not reported; PaO₂/FiO₂, ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen; PBW, predicted body weight; SD, standard deviation; SOFA, sequential organ failure assessment.

to those for other disease processes for which ECMO may be indicated [28^a], including mechanical ventilation strategies, anticoagulation, and the role of sedation and analgesia [50,51]. Criteria for ECMO initiation remain similar to prior recommendations [33] and include a ratio of partial pressure of oxygen in arterial blood to fraction of inspired oxygen (PaO₂:FIO₂) less than 80 mmHg for more than 6 h, PaO₂:FIO₂ less than 50 mmHg for greater than 3 h, or pH less than 7.25 with partial pressure of carbon dioxide in arterial blood (PaCO₂) at least 60 mmHg for more than 6 h [28^a]. Absent evidence to the contrary, deviation from accepted strategies is discouraged [28^a]. The role of prone positioning during ECMO – for either COVID-19 or

non-COVID-19-related ARDS [52] – and whether ECMO should ever be considered instead of invasive mechanical ventilation [53,54] remain to be determined.

CONCLUSION

The treatment of COVID-19-related ARDS, including the use of ECMO, should follow the current management algorithm for non-COVID-19-related ARDS patients based on data suggesting comparable mortality rates in these settings. However, more recent data suggests that mortality may be rising over time in patients supported with ECMO for COVID-19-related ARDS and this should prompt

Table 2. Extracorporeal Membrane Oxygenation - Postcannulation data

	Schmidt, 2020	Diaz, 2020	Shaefi, 2020	Barbaro, 2020	Lebreton, 2020
ECMO days [median (IQR)]	20 (10–40)	NR	16 (10–23)	13.9 (7.8–23.3)	14 (8–26)
ICU LOS days [median (IQR)]	36 (23–60)	40 (21–57)	31 (20–43)	NR ^a	30 (17–47)
Mortality (%)	31.0 ^b	38.8 ^c	33.2 ^b	37.4 ^d	54.0 ^c

ECMO, extracorporeal membrane oxygenation; IQR, interquartile range; LOS, length of stay; NR, not reported.

^aMedian duration of hospital stay was 26.9 days (IQR 15.7–43.0)

^b60-day mortality.

^c90-day mortality.

^d90-day in-hospital mortality.

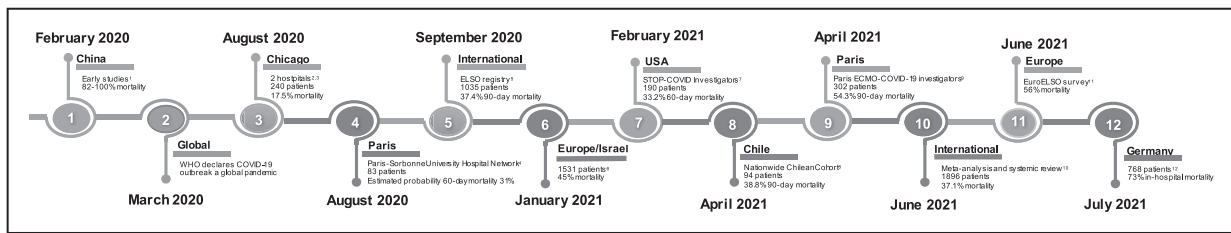


FIGURE 1. Extracorporeal membrane oxygenation for coronavirus disease 2019-related acute respiratory distress syndrome mortality highlights. Timeline placing studies discussed in body of article highlighting size of study and reported mortality. Placed in sequential order by date of online publication. ¹Henry 2020; ²Mustafa 2020; ³Mustafa 2021; ⁴Schmidt 2020; ⁵Barbaro 2020; ⁶Lorusso 2021; ⁷Shaefi 2021; ⁸Diaz 2021; ⁹Lebreton 2021; ¹⁰Ramanathan 2021; ¹¹Broman 2021; ¹²Karagiannidis 2021. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ELSO, extracorporeal life support organization; EuroELSO, European extracorporeal life support organization; STOP-COVID, The Study of the Treatment and Outcomes in Critically Ill Patients With COVID-19; WHO, World Health Organization.

reconsideration of the threshold for initiating ECMO, particularly when resources are limited. During the pandemic, any application of a high intensity resource, such as ECMO, must take into consideration not only the potential benefit to an individual patient but also its impact on other patients and the broader healthcare system. The

COVID-19 pandemic has highlighted the importance of coordinated approaches by healthcare networks and adherence to established practices in order to optimize the provision of ECMO during a crisis. This experience has also called attention to the role medical societies and research networks may play in collating experiences from ECMO

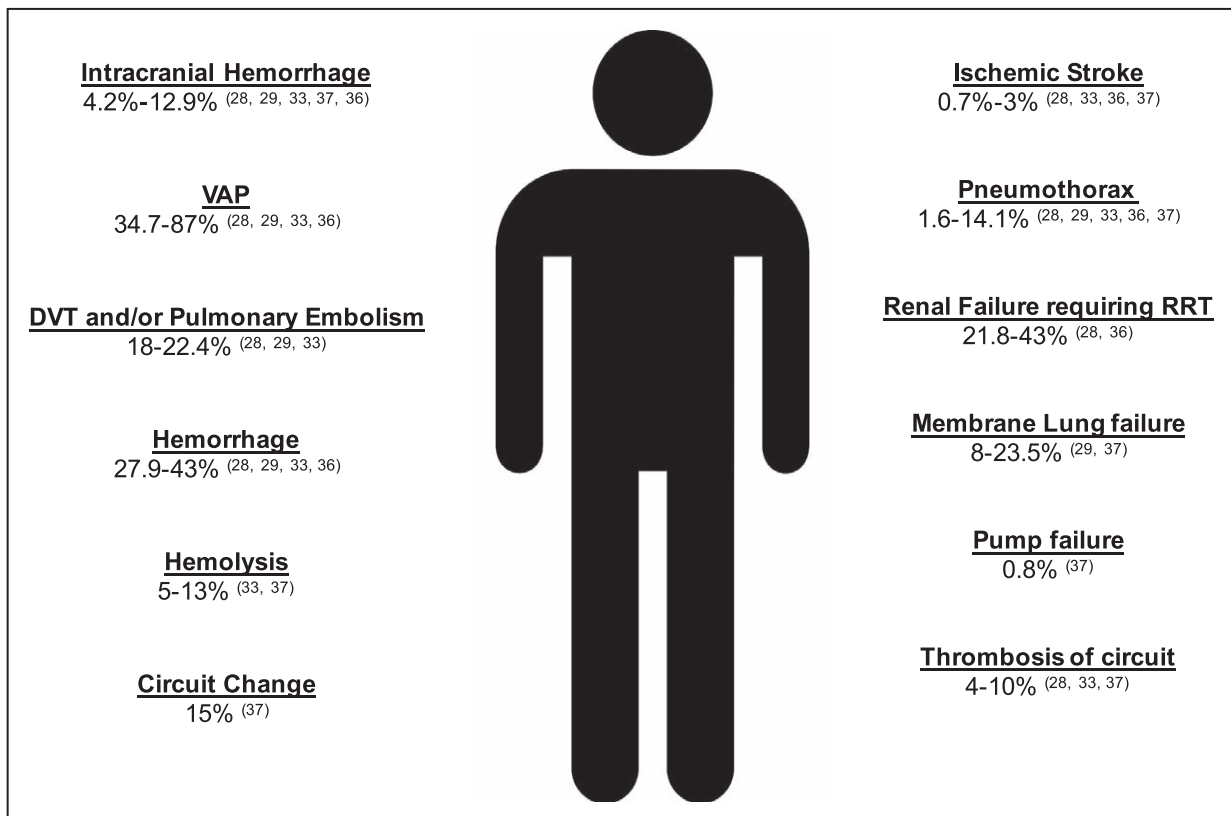


FIGURE 2. Complications during extracorporeal membrane oxygenation for coronavirus disease 2019-related acute respiratory distress syndrome. Selected ECMO-related complications for patients with severe COVID-19-related ARDS requiring ECMO. Superscript numbers refer to references from the text. ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DVT, deep vein thrombosis; ECMO, extracorporeal membrane oxygenation; RRT, renal replacement therapy; VAP, ventilator associated pneumonia.

centers around the world to better inform the broader ECMO community, particularly during a time of great uncertainty.

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Conflicts of interest

D.B. receives research support from ALung Technologies. He has been on the medical advisory boards for Baxter, Abiomed, Xenios and Hemovent, and is the President-elect of the Extracorporeal Life Support Organization (ELSO).

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