



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.

Elsevier hereby grants permission to make all its COVID-19-related research that is available on the COVID-19 resource centre - including this research content - immediately available in PubMed Central and other publicly funded repositories, such as the WHO COVID database with rights for unrestricted research re-use and analyses in any form or by any means with acknowledgement of the original source. These permissions are granted for free by Elsevier for as long as the COVID-19 resource centre remains active.

# Extracorporeal Membrane Oxygenation in COVID-19



Manuel Tisminetzky, MD<sup>a</sup>, Bruno L. Ferreyro, MD<sup>a,b</sup>, Eddy Fan, PhD<sup>a,b,c,d,\*</sup>

## KEYWORDS

• ARDS • ECMO • COVID-19 • Prone positioning

## KEY POINTS

- COVID-19-related ARDS has a similar clinical presentation, course, and outcome as ARDS due to other risk factors.
- Ventilatory strategies and adjuvant therapies for COVID-19 should follow similar evidence-based principles as for non-COVID-19 ARDS.
- Extracorporeal membrane oxygenation (ECMO) is an intervention used in patients with severe ARDS that cannot achieve adequate gas exchange despite optimization of lung-protective ventilation.
- Current evidence suggests that the efficacy, clinical outcomes, and complications of ECMO in COVID-19-related ARDS are similar to non-COVID-19 ARDS.
- In this review, we summarize the rationale, evidence, and complications of venovenous ECMO support in severe ARDS secondary to COVID-19.

## INTRODUCTION

At the end of 2019 an outbreak of pneumonia caused by a novel severe acute respiratory syndrome-coronavirus 2 (SARS-CoV-2) was discovered in the city of Wuhan, China.<sup>1</sup> Although most cases of COVID-19 present with mild symptoms including fever, cough, and myalgia, a substantial number of patients develop acute hypoxemic respiratory failure and acute respiratory distress syndrome (ARDS).<sup>2,3</sup> Resembling other etiologies of ARDS, the treatment of severe presentations of COVID-19 frequently involves invasive mechanical ventilation and, in most severe cases, extracorporeal membrane oxygenation (ECMO).<sup>4</sup>

<sup>a</sup> Department of Medicine, Division of Respiriology, Sinai Health System and University Health Network, 585 University Avenue, 9-MaRS-9013, Toronto, Ontario M5G2G2, Canada; <sup>b</sup> Institute of Health Policy, Management and Evaluation, Dalla Lana School of Public Health, University of Toronto, 155 College Street, 4th Floor, Toronto, ON M5T 3M6, Canada; <sup>c</sup> Toronto General Hospital Research Institute, 200 Elizabeth Street, Toronto, ON M5G 2C4, Canada; <sup>d</sup> Interdepartmental Division of Critical Care Medicine, University of Toronto, 204 Victoria Street, 4th Floor, Room 411, Toronto, Ontario M5B 1T8, Canada

\* Corresponding author. Interdepartmental Division of Critical Care Medicine, Toronto General Hospital, 585 University Avenue, 9-MaRS-9013, Toronto, Ontario M5G2G2, Canada.

E-mail address: [eddy.fan@uhn.ca](mailto:eddy.fan@uhn.ca)

ECMO constitutes a costly and resource-intensive treatment of severe ARDS.<sup>5</sup> In the context of the COVID-19 pandemic and with an increasing number of patients requiring admission to an intensive care unit (ICU) worldwide, the appropriateness of use of such treatments as ECMO has been the focus of some discussions.<sup>6</sup> This review describes the role of venovenous (VV) ECMO in patients with COVID-19-related ARDS.

## **EXTRACORPOREAL MEMBRANE OXYGENATION FOR ACUTE RESPIRATORY DISTRESS SYNDROME: RATIONALE AND HISTORY**

ARDS is associated with high morbidity and mortality caused by direct or indirect lung injury leading to multiorgan dysfunction.<sup>7,8</sup> Mechanical ventilation remains the cornerstone of support for this syndrome, with the main goal to unload the respiratory muscles, providing adequate gas exchange while the lungs recover from the original insult.<sup>9</sup> Although mechanical ventilation is a life-saving intervention, it can also lead to ventilator-induced lung injury through different mechanisms.<sup>10</sup> The fundamental principle of lung-protective ventilation is to allow for adequate gas exchange while preventing ventilator-induced lung injury.<sup>11,12</sup> In the most severe cases, lung-protective ventilation alone may be insufficient to achieve such goals and adjuvant strategies are needed. In this setting, ECMO can provide gas exchange bypassing the lungs allowing for a reduction in the intensity of mechanical ventilation.<sup>13</sup>

The most frequent configuration used in this context (VV-ECMO) consists of a drainage cannula that withdraws deoxygenated blood from a central vein (eg, femoral vein), a mechanical pump coupled with an oxygenator, and a return cannula that restores oxygenated blood to the circulation through another central vein (eg, internal jugular vein).<sup>13</sup>

ECMO is not a novel technology and its successful application in a setting of acute respiratory failure was first described in the early 1970s. However, its use remained restricted to neonatal and pediatric patients for decades.<sup>14,15</sup> Following technological advances, a new window of opportunity for ECMO in adults with acute respiratory failure opened during the influenza A (H1N1) pandemic in 2009. During this time, ECMO was used in adults with severe ARDS as a salvage therapy.<sup>16</sup> Despite increasing enthusiasm and use, it remained unclear whether it was associated with a survival benefit.<sup>17</sup>

Also in 2009, the Conventional Ventilatory Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure (CESAR) trial compared the efficacy, safety, and cost-effectiveness of standard of care in mechanical ventilation with VV-ECMO.<sup>18</sup> There was a significant increase in survival without disability in the group randomized to referral for ECMO consideration. Importantly, only 70% of the conventional treatment group received lung-protective ventilation in this pragmatic trial. Furthermore, only 76% of the patients allocated to the ECMO group actually received ECMO. The main conclusion of this trial was that referring patients to a center of excellence capable of providing ECMO improved outcome, but it could not prove that ECMO by itself was responsible for this.<sup>19</sup>

To help address this gap, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial randomized patients with severe ARDS to receive treatment with VV-ECMO or conventional mechanical ventilation. The trial was stopped early for futility, with 60-day mortality of 35% in the ECMO group and 46% in the control group.<sup>20</sup> Although this difference was not statistically significant, a number of secondary outcomes and a post-hoc analyses favoured ECMO. In addition, a post hoc Bayesian analysis concluded that the posterior probability of a mortality benefit with ECMO was high even when using a strongly skeptical prior distribution.<sup>21</sup> Finally, the benefit of VV-

ECMO on mortality in patients with severe ARDS is supported by individual patient data, study level, and network meta-analyses.<sup>12,22–24</sup>

### **COVID-19-RELATED ACUTE RESPIRATORY DISTRESS SYNDROME: IS IT REALLY DIFFERENT?**

The definition of ARDS encompasses clinical and radiologic criteria along with the presence of typical risk factors for direct or indirect lung injury.<sup>25,26</sup> Clinical and biologic heterogeneity within ARDS is therefore implied and has been topic of extensive research.<sup>27–30</sup> Since the beginning of the pandemic, the overwhelming number of patients with COVID-19 admitted to ICUs around the globe allowed clinicians and researchers to appreciate this clinical heterogeneity and in consequence, treatment strategies based on different clinical features were suggested.<sup>31</sup> As more data emerged through the course of the pandemic, the characterization of COVID-19-related ARDS as a distinct entity was challenged.

Indeed, the current body of clinical, physiologic, and pathologic data seems to support the notion that this disease, although exhibiting some heterogeneity, has common features to ARDS secondary to other risk factors.<sup>32–34</sup> Accordingly, it is reasonable to apply the best evidence-based recommendations, particularly with respect to ventilatory strategies and adjuncts to mechanical ventilation.<sup>32,34</sup>

#### ***Venovenous Extracorporeal Membrane Oxygenation in COVID-19-Related Acute Respiratory Distress Syndrome: Old and New Challenges***

---

The role of VV-ECMO as a strategy for severe ARDS in the context of the COVID-19 pandemic exhibits old and new challenges. Given the increasing number of patients requiring ICU admission and ventilatory support, the role of ECMO was again brought to the attention of clinicians and the public at the same time, leading to a detailed description of patients' trajectories.<sup>35–41</sup> Furthermore, debate on whether ARDS secondary to COVID-19 is a different entity also led to questioning the role of VV-ECMO support in this context, and whether the existing evidence could be applied. Finally, increasing concerns about ICU capacity and strain led to discussions about the appropriateness of ECMO as a highly technical intervention and to whether resources should be directed toward this intervention.<sup>42,43</sup>

#### ***Extracorporeal Membrane Oxygenation in COVID-19-Related Acute Respiratory Distress Syndrome: Clinical Outcomes***

---

The literature surrounding the experience and outcomes of ECMO in patients with COVID-19 has transitioned from mainly anecdotal reports to large single and multi-center analyses (Table 1). At the beginning of the pandemic, preliminary reports from China raised concerns highlighting increased mortality of COVID-19-related ARDS when compared with ARDS secondary to other risk factors.<sup>6</sup> The appropriateness of using a treatment that requires a highly specialized and technical team and a higher level of care at the bedside in the context of increased system strain was brought to the center of discussion.<sup>6,44,45</sup>

In a pooled analysis, Henry and Lippi<sup>6</sup> described that among 17 patients that required ECMO early in the pandemic mortality was 94%. However, mortality in the non-ECMO group was also considerably high, the sample was rather small, and data regarding baseline characteristics were missing. Huang and colleagues<sup>46</sup> found similar results and suggested using ECMO only for younger patients without preexisting diseases, but these data were also derived from a small case series. Thus, these

**Table 1**  
**Studies reporting outcomes in patients on ECMO for COVID-19 ARDS**

Study	Study Design	Sample Size On ECMO (Total)	Mean Age	Mean Pao <sub>2</sub> /Fio <sub>2</sub> Ratio	Included Patients and Time Period	Mortality (%)	Median days on ECMO	Main Complications
Barbaro et al, <sup>49</sup> 2020	Cohort study	1035 (1035)	49	72	Patients included in the ELSO registry From January 16th–May 1st 2020	37.4	14	Hemorrhagic stroke 6% Hemolysis 13%
Charlton et al, 2020	Cohort study	34 (34)	46	86	Severe COVID-19 ARDS Supported with ECMO April 1st–May 31st 2020	47	13	Not reported
Cousin et al, 2020	Cohort study	30 (30)	57	69 (n = 27)	Severe COVID-19 ARDS Supported with ECMO for at least 48 h March 9th–May 6th 2020	53.3	11	Acute kidney injury 50% Deep venous thrombosis 10% Pulmonary embolism 6.7% Hemorrhagic stroke 10% Major bleeding 43% Bloodstream infection 13%
Falcoz et al, <sup>47</sup> 2020	Cohort study	17 (17)	56	71	Adults meeting EOLIA criteria March 3rd–April 1st 2020	35	9	Thrombotic 29% Bleeding 35% VAP 59% AKI 70%
Guihaire et al, 2020	Cohort study	24 (24)	49	67	Severe COVID-19 ARDS Supported with ECMO March 23rd–May 5th 2020	29	19	Pulmonary hemorrhage 17% Pulmonary embolism 25% Hemorrhagic stroke 4%

Henry and Lippi, <sup>6</sup> 2020	Review (pooled analysis)	17 (234)	56	Not reported	Not reported	ECMO: 94 in ECMO: 71 non-ECMO	Not reported	Not reported
Jackel et al, 2020	Cohort study	15 (15)	61	64	Severe COVID-19 ARDS or influenza A/B infection Supported with ECMO October 2010 and June 2020	51.4	11	Renal-replacement therapy 33% Circuit change 33%
Jang et al, 2020	Cohort study	19 (19) 3 received VA-ECMO	63	92	Severe COVID-19 ARDS Supported with ECMO February 1st–April 30th 2020	52.6	17	Not reported
Mustafa et al, <sup>63</sup> 2020	Cohort study	40 (40)	48	69	Severe respiratory failure caused by COVID-19 March 17th–July 17th 2020	15	30	Not reported
Schmidt et al, <sup>39</sup> 2020	Cohort study	83 (492)	49	60	Adults with COVID-19 ARDS supported with VA or VV ECMO March 17th–July 17th 2020	31	20	Hemolysis 13% Pulmonary embolism 19% Massive hemorrhage 42% Hemorrhagic stroke 5% Oronasal bleeding 24% VAP 87% Cannula infection 23%
Shih et al, 2020	Cohort study	37 (37)	51	95	Severe COVID-19 ARDS March 1st–June 28th 2020	43.2	17	VAP 19% Bloodstream infection 11% Hemorrhagic stroke 8% Bleeding 32% Circuit malfunction 5%

(continued on next page)

**Table 1**  
(continued)

Study	Study Design	Sample Size On ECMO (Total)	Mean Age	Mean Pao <sub>2</sub> /Fio <sub>2</sub> Ratio	Included Patients and Time Period	Mortality (%)	Median days on ECMO	Main Complications
Takeda et al, 2020	Cohort study	26 (26)	71	70	Severe COVID-19 ARDS Supported with ECMO February 15th–March 15th 2020	38.5	Not reported	Not reported
Yang et al, 2020	Cohort study	21 (59)	58	60	Severe COVID-19 ARDS January 8th–March 31st 2020	57.1	9	Catheter site bleeding 9% Hemorrhagic stroke 4% Renal-replacement therapy 38% VAP 28%
Zayat et al, 2020	Cohort study	17 (17)	57	<100 not reported as a mean	Severe COVID-19 ARDS March 1st–April 20th 2020	47.1	Not reported	Not reported
Zhang et al, 2020	Cohort study	43 (43)	46	67	Severe COVID-19 ARDS Supported with ECMO March 3rd–May 2nd 2020	32.6	13	Acute kidney injury 50% Deep venous thrombosis 10% Pulmonary embolism 7% Hemorrhagic stroke 10% Bleeding leading to transfusion 43% Bloodstream infection 13%

Akhtar et al, 2021	Cohort study	18 (18)	47	Not reported	Severe COVID-19 ARDS Supported with ECMO	22	17	Renal-replacement therapy 56% Thromboembolic disease 56% Hemorrhagic stroke 11% Gastrointestinal bleeding 11%
Diaz et al, <sup>37</sup> 2021	Cohort study	94 (94)	48	87	Age ≥15 y COVID-19 ARDS Supported with ECMO March 3rd–August 31st 2020	38.8	16	Pulmonary embolism 2% Hemorrhagic stroke 13% Pneumothorax 14% Thromboembolic disease 22% Bleeding 39% VAP 51% Infection 71%
Lebreton et al, <sup>40</sup> 2021	Cohort study	288 (302) 11 received VA-ECMO and 3 VA-V-ECMO	52	61	Severe COVID-19 ARDS Supported with ECMO Admitted to any ICU in greater Paris March 8th–June 3rd 2020	54	14	Renal-replacement therapy 43% Pulmonary embolism 18% Hemorrhagic stroke 12% Pneumothorax 9% Bleeding 43% VAP 85%
Ramanathan et al, <sup>55</sup> 2021	Systematic review and meta-analysis	1896 (1896)	51 (n = 491)	68	Cohort study studies or randomised clinical trials examining ECMO in adults with COVID-19 ARDS December 1st 2019– January 10th 2020	35.7 (n = 1737)	16 (n = 1711)	Acute kidney injury 35% Mechanical 27% Infectious 10%

*(continued on next page)*



**Table 1**  
(continued)

Study	Study Design	Sample Size On ECMO (Total)	Mean Age	Mean Pao <sub>2</sub> /Fio <sub>2</sub> Ratio	Included Patients and Time Period	Mortality (%)	Median days on ECMO	Main Complications
Rabie et al, 2021	Cohort study	307 (307)	45	60	Adult patients of 19 ECMO centers March 1st–September 30th 2020	42	15	Infections 70% Major bleeding 24% Renal-replacement therapy 32% Pulmonary embolism 5%
Riera et al, <sup>50</sup> 2021	Cohort study	319 (319)	53	76	Severe COVID-19 ARDS Supported with ECMO	1st wave 41.1 2nd wave 60.1	17	Pneumonia 50% Acute kidney injury 26% Vascular thrombosis 16% Circuit clotting 37% Hemorrhagic shock 14%
Roedl et al, 2021	Cohort study	20 (223)	Not reported	Not reported	Adults admitted to ICU with COVID-19 February 1st– June 3rd 2020	65	Not reported	Not reported

Shaeafi et al, <sup>51</sup> 2021	Target trial	130 (1297)	49 (ECMO) 58 (non-ECMO)	80 (ECMO) 90 (non-ECMO)	Diagnosis of COVID-19 Age ≥18 y Admitted to an ICU capable of offering VV ECMO Pao <sub>2</sub> /Fio <sub>2</sub> <100 mm Hg From March 1st–July 1st 2020	34.6 Non-ECMO: 47	16	AKI 22% Pneumothorax 13% Pulmonary embolism 2% Deep vein thrombosis 18% Hemorrhagic stroke 4% Systemic bleeding 25% Bacterial pneumonia 35%
--------------------------------------	--------------	------------	----------------------------	----------------------------	--	----------------------	----	--

Search strategy: We performed a search in PubMed for articles published in English language between December 2019 and September 2021, using combinations of the terms “COVID-19,” “Extracorporeal membrane oxygenation,” and “Acute respiratory distress syndrome.” We determined relevance based on content, focusing on studies including at least 15 participants. We also manually retrieved articles from references. Finally, we also searched for relevant reports at the ELSO registry Web site: [www.else.org](http://www.else.org).

*Abbreviations:* AKI, acute kidney injury; DVT, deep venous thrombosis; ELSO, Extracorporeal Life Support Organization; Pao<sub>2</sub>/Fio<sub>2</sub>, ratio of arterial oxygen partial pressure to fractional inspired oxygen; PE, pulmonary embolism; VAP, ventilator-associated pneumonia.

initial descriptions of ECMO for patients with severe COVID-19 were difficult to interpret and to translate into meaningful clinical recommendations.

In contrast, a prospective cohort study that included 17 patients on ECMO because of COVID-19 ARDS showed that 60-day mortality was significantly lower (35%) than the previous reports.<sup>47</sup> Schmidt and colleagues<sup>39</sup> reported a retrospective cohort of 83 patients placed on ECMO for COVID-19 ARDS comparing their results with those of the EOLIA trial. Despite having a greater severity of hypoxemia in their cohort, these patients had a similar 90-day mortality.<sup>39</sup> Based in part on these results, the Extracorporeal Life Support Organization advocated for the use of ECMO in specialized centers only.<sup>48,49</sup>

A retrospective cohort study that included 319 patients on ECMO from 24 ICUs in Spain and Portugal reported similar results (mortality 35%). This study suggested a significant higher mortality during the second wave, which may be explained by patient-level (age, time on ventilator before cannulation) and center level characteristics.<sup>40,50</sup> Finally, a systematic review and meta-analysis of 1896 patients from 22 studies reported a pooled in-hospital mortality of 37%, similar to those from randomized trials and systematic reviews in patients without COVID-19.<sup>18,22,23</sup>

Although encouraging, none of these studies had a comparative non-ECMO control group. Therefore, Shaefi and colleagues<sup>51</sup> emulated a target trial comparing mechanically ventilated patients with severe hypoxemia who received and those who did not receive ECMO within 7 days of ICU admission. Patients with severe hypoxia who received ECMO had a lower mortality compared with those who did not (35% vs 47%), similar estimates as observed in the EOLIA trial.<sup>20</sup> Despite known limitations, well-conducted observational research has an important role in understanding the efficacy of this intervention, given the lack of feasibility for another randomized trial.

### **Extracorporeal Membrane Oxygenation in COVID-19: Patient Selection**

Patient selection for VV-ECMO in patients with COVID-19 should follow the same guiding principles as for ARDS from other causes (Fig. 1).<sup>52</sup> Before initiation of ECMO is considered, referring centers should ensure conventional management has been optimized, including lung-protective ventilation, adequate level of positive end-expiratory pressure, prone positioning, and consideration of deep sedation/neuromuscular paralysis. If all these strategies fail or when lung-protective ventilation cannot be achieved (ie, a need for injurious ventilation), ECMO should be considered in

Patient Selection Criteria for ECMO Consideration			
Severity of Disease		Mechanical Ventilation Optimized	Patient Related Characteristics
<b>Oxygenation</b> PaO <sub>2</sub> /Fio <sub>2</sub> < 50 mmHg for >3 h OR PaO <sub>2</sub> /Fio <sub>2</sub> < 80 mmHg for >6 h	<b>Ventilation</b> pH < 7.25 + PaCO <sub>2</sub> ≥ 60 mmHg + RR 35/min for > 6h	Fio <sub>2</sub> ≥ 80% PEEP ≥ 10 cmH <sub>2</sub> O VT ≤ 6ml/kg (PBW) Plateau Pressure ≤ 32 cmH <sub>2</sub> O Prone positioning Neuromuscular blockade	Age ≤ 50 y Absence of comorbidities affecting short-term recovery Invasive Mechanical Ventilation ≤ 7d Adequate vascular access Absence of distributive Shock Low risk of hemorrhagic complications

**Fig. 1.** Patient selection criteria for VV-ECMO in patients with COVID-19 ARDS. Fio<sub>2</sub>, fraction of inspired oxygen; PaCO<sub>2</sub>, arterial partial pressure of carbon dioxide; PaO<sub>2</sub>/Fio<sub>2</sub> ratio of arterial oxygen partial pressure to fractional inspired oxygen; PBW, predicted body weight; PEEP, positive end-expiratory pressure; RR, respiratory rate; VT, tidal volume.

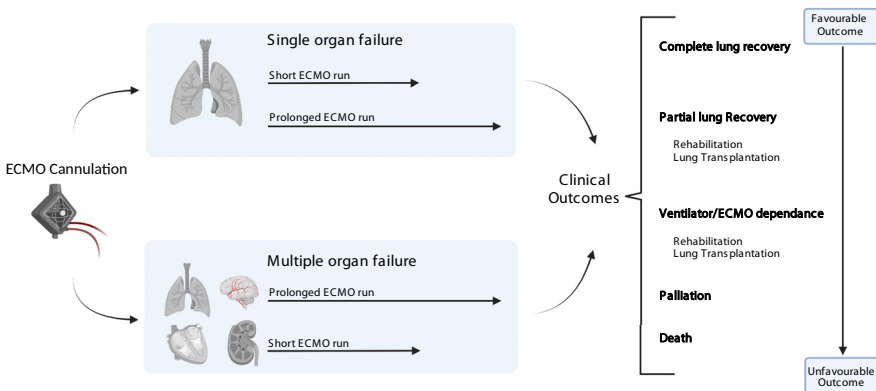
the absence of factors associated with poor benefit, such as advanced age, comorbidities, multiorgan dysfunction, and prolonged duration of invasive mechanical ventilation.<sup>52,53</sup> Although patient selection focuses on time from initiation of invasive ventilation to ECMO cannulation, increasing awareness of time on noninvasive respiratory support (eg, high-flow oxygen, noninvasive ventilation) before intubation is being raised as a potential predictor of outcome and a key parameter for adequate patient selection.<sup>37</sup>

**THE COURSE OF EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT IN PATIENTS WITH COVID-19: PATIENT TRAJECTORIES**

During the COVID-19 pandemic, many centers experienced increased demands for ECMO, even in those with previous long-standing experience.<sup>39,40</sup> This accentuated the multiple clinical trajectories that exist among these patients once they are initially placed on ECMO (Fig. 2). Certain patients exhibit lung recovery shortly after cannulation, and liberation from ECMO is quickly and successfully achieved. This group meets the foundational criteria and expectation when starting this treatment: ECMO as a bridge to recovery. At the other end of the spectrum, certain patients undergo prolonged treatment on ECMO without significant lung recovery, introducing unique clinical and ethical challenges. For these patients, ECMO can still be a bridge to recovery, but other trajectories are also possible, including discussions about lung transplantation candidacy or transitioning to palliative care.<sup>54</sup> Decision-making by patients and families/caregivers is influenced by the spectrum of clinical trajectories. Given the prolonged time that certain patients can be on ECMO (median time up to 30 days, see Table 1), this can also lead to important challenges for decision-making by policy makers, particularly during a pandemic where ICU beds and human resources are scarce.<sup>42</sup>

**THE COURSE OF EXTRACORPOREAL MEMBRANE OXYGENATION SUPPORT IN PATIENTS WITH COVID-19: COMPLICATIONS**

During the course of ICU stay, patients on ECMO can suffer a range of complications, which can be life-threatening. These are categorized as the typical complications



**Fig. 2.** Clinical trajectories for patients on VV-ECMO with COVID-19. Patients on ECMO may present single or multiple organ failure, which affects the duration of ECMO run and consequently clinical outcomes. The spectrum of clinical outcomes varies from complete lung recovery to death.

observed because of prolonged critical illness, ECMO-specific complications, and those specific to COVID-19.

Acute renal failure with or without need for renal-replacement therapy was consistently reported as one of the most frequent complications.<sup>40,50,55</sup> Whether this is solely related to the severity of COVID-19 infection or to ECMO support is unclear. Potential mechanisms by which ECMO can contribute to kidney failure include hemolysis, secondary infections, and major bleeding.<sup>56</sup>

Major bleeding was frequently reported and often associated with worse outcome in patients with COVID-19-related ARDS supported with ECMO.<sup>57</sup> These complications are not usually associated with an identifiable coagulopathy and independent of heparin use. Clinically important bleeding in the largest cohorts was reported in 35% to 43% of the patients, with frequent sources being oronasal, cannula-related, and hemothorax.<sup>37,39,40,47</sup> In a French study, major bleeding requiring transfusions was significantly higher in patients that died but only 4% of the patients died of hemorrhagic shock.<sup>40</sup> A study conducted in Chile reported a surprisingly high rate of intracranial hemorrhage (13%), doubling what was published in the COVID-19 Extracorporeal Life Support Organization report.<sup>37,49</sup> This could be explained by the lack of protocols to control relative changes in  $P_{aCO_2}$  early after cannulation, which was shown to be associated with an increased incidence of neurologic complications.<sup>58</sup> In face of these complications, recommendations for anticoagulation strategies and target were highly variable during the pandemic.<sup>47,59</sup> Indeed, the optimal strategy for anticoagulation during ECMO remains one of the areas where further research is warranted.

Thromboembolic complications have also been described in these patients, including deep vein thrombosis, pulmonary embolism, or circuit thrombosis.<sup>60</sup> Underlying mechanisms include endothelial dysfunction, platelet activation, and disseminated intravascular coagulation.<sup>61</sup> This increased risk persists despite the use of different degrees of anticoagulation.<sup>37,40,50</sup>

Infectious complications have been reported in up to 37% of patients receiving ECMO for COVID-19.<sup>49</sup> Ventilator-associated pneumonia was the most frequent source, followed by bloodstream infections, and *Staphylococcus aureus* the most commonly cultured organism.<sup>49,55</sup> Optimization of antimicrobial therapy in the context of extracorporeal life-support poses unique challenges because of the scarce literature describing pharmacokinetic and dosing requirements during ECMO.<sup>62</sup> In the occurrence of bloodstream infections, the optimal duration of therapy and the definition of adequate source control is complicated because ECMO cannulas could be perceived as persistent infectious sources. Because one of the main reported causes of death in this population is septic shock, identifying strategies to maximize source control and appropriate treatments of infections is paramount.<sup>4</sup>

## NOVEL TECHNIQUES AND VARIATIONS IN PRACTICE

The COVID-19 pandemic was also a unique opportunity to study novel approaches, adjuvant treatments, and variations in practice. In this regard, alternative cannulation techniques, the use of prone positioning, and anticoagulation-free runs of ECMO require special attention.

Mustafa and colleagues<sup>63</sup> retrospectively collected data from 40 patients with COVID-19 ARDS supported on ECMO in two hospitals in Chicago. They used a single-access, dual-stage right atrium-to-pulmonary-artery cannula, with drainage of blood from the right atrium lumen (decreasing right-sided preload), and oxygenated blood is returned into the pulmonary artery. Their strategy included a focus on earlier

discontinuation of mechanical ventilation and rehabilitation. By the time of the publication, all patients were successfully weaned off invasive mechanical ventilation, 80% had been decannulated, 73% had been discharged from hospital, and overall mortality was 15%.<sup>63</sup> These results may be associated with early mobilization, reduced need for sedation, and right ventricle support. The later might have been critical because right ventricular dysfunction is a frequently reported cause of death in patients with COVID-19 ARDS.<sup>64</sup>

The pandemic also raised awareness of the use of prone positioning, including increased use in nonintubated patients and during VV-ECMO.<sup>65–68</sup> In a report by Schmidt and colleagues,<sup>39</sup> prone positioning was used in up to 81% of patients on VV ECMO and the authors suggested that this might have contributed to improve survival rates. Similar results were reported by Guervilly and colleagues,<sup>69</sup> suggesting prone positioning while on ECMO is associated with increased liberation from ECMO and survival. Finally, a recent study reported that the rate of complications was low (6%) and only 2% of prone patients needed to be supinated to resolve the complication.<sup>70</sup> Although this finding is reassuring, prone positioning during ECMO should be performed in experienced centers.<sup>70</sup>

Titration of systemic anticoagulation to prevent clot formation while avoiding bleeding complications is one of the main challenges of ECMO management. Because of the scarce high-quality data, there is practice variation among centers particularly regarding the best method to monitor anticoagulation and the need for antithrombin supplementation.<sup>71</sup> Furthermore, an international survey from 50 different countries showed that up to 3% of the centers did not routinely prescribe anticoagulation for patients on VV ECMO.<sup>72</sup> To investigate the feasibility and safety of this approach, Kurihara and colleagues<sup>73</sup> compared 38 patients that received systemic anticoagulation with 36 patients that received thromboprophylaxis. The group of patients who received systemic anticoagulation had higher rates of gastrointestinal bleeding, received more blood transfusions, and had higher rates of oxygenator dysfunction. Although done at a single center and with a small sample size, results were consistent with previous reports.<sup>74</sup> Given that hemorrhagic complications contribute to morbidity and mortality associated to ECMO, an anticoagulation-free approach is appealing, and could be an opportunity for future research.

## SUMMARY AND FUTURE DIRECTIONS

Despite early reports suggesting COVID-19-related ARDS should warrant distinct management, current evidence suggests that similar management principles to non-COVID-19 ARDS should be applied. These include lung-protective ventilation and the use of adjuvant treatments when appropriate. Data from large cohorts and observational studies emulating clinical trials suggest that the efficacy and outcomes of ECMO in the context of severe COVID-19 is similar to ARDS because of other risk factors. The spectrum of patients' trajectories range from short ECMO runs with full lung recovery to prolonged ECMO support with significant organ dysfunction. Typical complications, such as bleeding and thromboembolic events, are frequent in patients who receive treatment with ECMO, often presenting as life-threatening. Ongoing and future research will help understand whether alternative approaches for ECMO cannulation, prone positioning, and variations in anticoagulation practices can improve the safety and efficacy of this intervention. The ongoing pandemic poses a unique opportunity to improve the understanding of the strengths and limitations of this resource-intensive intervention. Finally, enhanced collaboration among centers locally, nationally, and internationally is key for rapidly generating an important body of clinical evidence.

## CLINICS CARE POINTS

- COVID-19-related ARDS resembles ARDS caused by other risk factors in its clinical presentation and outcomes.
- Evidence-based principles of lung-protective ventilation and adjuvant therapies, such as ECMO, for the management of ARDS should be applied similarly for severe COVID-19.
- Emerging evidence in the field currently suggests that the role of ECMO in the management of COVID-19-related ARDS is comparable with non-COVID-19 ARDS, and patient selection should follow similar principles.
- Frequent complications of ECMO include acute kidney failure, major bleeding, thromboembolic events, and secondary infections.
- The dramatically high number of patients requiring ECMO worldwide for COVID-19 ARDS poses an opportunity to study variations in practice, such as different cannulation techniques, prone positioning, and alternatives in the use of anticoagulation.

## DISCLOSURE

Dr B.L. Ferreyro is supported by a Vanier Canada Graduate Scholarship. Dr E. Fan reports personal fees from ALung Technologies, Aerogen, Baxter, Boehringer-Ingelheim, GE Healthcare, MC3 Cardiopulmonary, and Vasomune outside the submitted work.

## REFERENCES

1. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet* 2020;395(10229):1054–62.
2. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet* 2020;395(10223):497–506.
3. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus–infected pneumonia in Wuhan, China. *Jama* 2020; 323(11):1061–9.
4. Blazoski C, Baram M, Hirose H. Outcomes of extracorporeal membrane oxygenation in acute respiratory distress syndrome due to COVID-19: the lessons learned from the first wave of COVID-19. *J Cardiovasc Surg* 2021;36(7):2219–24.
5. Abrams D, Ferguson ND, Brochard L, et al. ECMO for ARDS: from salvage to standard of care? *Lancet Respir Med* 2019;7(2):108–10.
6. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): pooled analysis of early reports. *J Crit Care* 2020;58:27–8.
7. Herridge MS, Chu LM, Matte A, et al. The RECOVER Program: disability risk groups and 1-year outcome after 7 or more days of mechanical ventilation. *Am J Resp Crit Care* 2016;194(7):831–44.
8. Herridge MS, Tansey CM, Matté A, et al. Functional disability 5 years after acute respiratory distress syndrome. *N Engl J Med* 2011;364(14):1293–304.
9. Goligher EC, Ferguson ND, Brochard LJ. Clinical challenges in mechanical ventilation. *Lancet* 2016;387(10030):1856–66.
10. Vasques F, Duscio E, Cipulli F, et al. Determinants and prevention of ventilator-induced lung injury. *Crit Care Clin* 2018;34(3):343–56.
11. Sorbo LD, Goligher EC, McAuley DF, et al. Mechanical ventilation in adults with acute respiratory distress syndrome. Summary of the experimental evidence

- for the clinical practice guideline. *Ann Am Thorac Soc* 2017;14(Supplement\_4):S261–70.
12. Aoyama H, Uchida K, Aoyama K, et al. Assessment of therapeutic interventions and lung protective ventilation in patients with moderate to severe acute respiratory distress syndrome: a systematic review and network meta-analysis. *Jama Netw Open* 2019;2(7):e198116.
  13. Brodie D, Bacchetta M. Extracorporeal membrane oxygenation for ARDS in adults. *N Engl J Med* 2011;365(20):1905–14.
  14. Hill JD, O'Brien TG, Murray JJ, et al. Prolonged extracorporeal oxygenation for acute post-traumatic respiratory failure (shock-lung syndrome): use of the Bramson membrane lung. *N Engl J Med* 1972;286(12):629–34.
  15. Bartlett RH, Gazzaniga AB, Jefferies MR, et al. Extracorporeal membrane oxygenation (ECMO) cardiopulmonary support in infancy. *Trans - Am Soc Artif Intern Organs* 1976;22:80–93.
  16. Brodie D. The evolution of extracorporeal membrane oxygenation for adult respiratory failure. *Ann Am Thorac Soc* 2018;15(Supplement\_1):S57–60.
  17. Pham T, Combes A, Rozé H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome. *Am J Resp Crit Care* 2013;187(3):276–85.
  18. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet* 2009;374(9698):1351–63.
  19. Zwischenberger JB, Lynch JE. Will CESAR answer the adult ECMO debate? *Lancet* 2009;374(9698):1307–8.
  20. Combes A, Hajage D, Capellier G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018;378(21):1965–75.
  21. Goligher EC, Tomlinson G, Hajage D, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc Bayesian analysis of a randomized clinical trial. *Jama* 2018;320(21):2251.
  22. Munshi L, Walkey A, Goligher E, et al. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med* 2019;7(2):163–72.
  23. Combes A, Peek GJ, Hajage D, et al. ECMO for severe ARDS: systematic review and individual patient data meta-analysis. *Intensive Care Med* 2020;46(11):2048–57.
  24. Sud S, Friedrich JO, Adhikari NKJ, et al. Comparative effectiveness of protective ventilation strategies for moderate and severe acute respiratory distress syndrome. A network meta-analysis. *Am J Resp Crit Care* 2021;203(11):1366–77.
  25. Force ADT, Ranieri VM, Rubenfeld GD, et al. Acute respiratory distress syndrome: the Berlin definition. *Jama* 2012;307(23):2526–33.
  26. Thompson BT, Chambers RC, Liu KD. Acute respiratory distress syndrome. *N Engl J Med* 2017;377(6):562–72.
  27. Fan E, Brodie D, Slutsky AS. Acute respiratory distress syndrome: advances in diagnosis and treatment. *Jama* 2018;319(7):698–710.
  28. Sinha P, Calfee CS. Phenotypes in acute respiratory distress syndrome. *Curr Opin Crit Care* 2019;25(1):12–20.



29. Calfee CS, Delucchi K, Parsons PE, et al. Subphenotypes in acute respiratory distress syndrome: latent class analysis of data from two randomised controlled trials. *Lancet Respir Med* 2014;2(8):611–20.
30. Khan YA, Fan E, Ferguson ND. Precision medicine and heterogeneity of treatment effect in therapies for acute respiratory distress syndrome. *Chest* 2021. <https://doi.org/10.1016/j.chest.2021.07.009>.
31. Gattinoni L, Chiumello D, Caironi P, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? *Intensive Care Med* 2020;46(6):1099–102.
32. Goligher EC, Ranieri VM, Slutsky AS. Is severe COVID-19 pneumonia a typical or atypical form of ARDS? And does it matter? *Intensive Care Med* 2021;47(1):83–5.
33. Tobin MJ. Pondering the atypicality of ARDS in COVID-19 is a distraction for the bedside doctor. *Intensive Care Med* 2021;47(3):361–2.
34. Fan E, Beitler JR, Brochard L, et al. COVID-19-associated acute respiratory distress syndrome: is a different approach to management warranted? *Lancet Respir Med* 2020;8(8):816–21.
35. Hoyler MM, Kumar S, Thalappillil R, et al. VV-ECMO usage in ARDS due to COVID-19: clinical, practical and ethical considerations. *J Clin Anesth* 2020;65:109893.
36. Abrams D, Lorusso R, Vincent JL, et al. ECMO during the COVID-19 pandemic: when is it unjustified? *Crit Care* 2020;24(1):507.
37. Diaz RA, Graf J, Zambrano JM, et al. Extracorporeal membrane oxygenation for COVID-19-associated severe acute respiratory distress syndrome in Chile: a nationwide incidence and cohort study. *Am J Resp Crit Care* 2021;204(1):34–43.
38. Lorusso R, Combes A, Coco VL, et al. ECMO for COVID-19 patients in Europe and Israel. *Intensive Care Med* 2021;47(3):344–8.
39. Schmidt M, Hajage D, Lebreton G, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020;8(11):1121–31.
40. Lebreton G, Schmidt M, Ponnaiah M, et al. Extracorporeal membrane oxygenation network organisation and clinical outcomes during the COVID-19 pandemic in Greater Paris, France: a multicentre cohort study. *Lancet Respir Med* 2021. [https://doi.org/10.1016/s2213-2600\(21\)00096-5](https://doi.org/10.1016/s2213-2600(21)00096-5).
41. Fernando SM, Mathew R, Slutsky AS, et al. Media portrayals of outcomes after extracorporeal membrane oxygenation. *J Intern Med* 2021;181(3):391–4.
42. Dao B, Savulescu J, Suen JY, et al. Ethical factors determining ECMO allocation during the COVID-19 pandemic. *Bmc Med Ethics* 2021;22(1):70.
43. Enumah ZO, Carrese J, Choi CW. The ethics of extracorporeal membrane oxygenation: revisiting the principles of clinical bioethics. *Ann Thorac Surg* 2021;112(1):61–6.
44. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med* 2020;8(5):475–81.
45. MacLaren G, Fisher D, Brodie D. Preparing for the most critically ill patients with COVID-19. *Jama* 2020;323(13):1245–6.
46. Huang S, Xia H, Wu Z, et al. Clinical data of early COVID-19 cases receiving extracorporeal membrane oxygenation in Wuhan, China. *J Clin Anesth* 2020;68:110044.
47. Falcoz PE, Monnier A, Puyraveau M, et al. Extracorporeal membrane oxygenation for critically ill patients with COVID-19-related acute respiratory distress syndrome: worth the effort? *Am J Resp Crit Care* 2020;202(3):460–3.

48. Shekar K, Badulak J, Peek G, et al. Extracorporeal Life Support Organization coronavirus disease 2019 interim guidelines: a consensus document from an international group of interdisciplinary extracorporeal membrane oxygenation providers. *Asaio J* 2020;66(7):707–21.
49. Barbaro RP, MacLaren G, Boonstra PS, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization registry. *Lancet* 2020;396(10257):1071–8.
50. Riera J, Roncon-Albuquerque R, Fuset MP, et al. Increased mortality in patients with COVID-19 receiving extracorporeal respiratory support during the second wave of the pandemic. *Intensive Care Med* 2021;1–4. <https://doi.org/10.1007/s00134-021-06517-9>.
51. Shaefi S, Brenner SK, Gupta S, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med* 2021;47(2):208–21.
52. Bullen EC, Teijeiro-Paradis R, Fan E. How I do it: how I select which ARDS patients should be treated with venovenous extracorporeal membrane oxygenation. *Chest* 2020;158(3):1036–45.
53. Bartlett RH, Ogino MT, Brodie D, et al. Initial ELSO guidance document: ECMO for COVID-19 patients with severe cardiopulmonary failure. *Asaio J* 2020;66(5):472–4.
54. Cypel M, Keshavjee S. When to consider lung transplantation for COVID-19. *Lancet Respir Med* 2020;8(10):944–6.
55. Ramanathan K, Shekar K, Ling RR, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. *Crit Care* 2021;25(1):211.
56. Legrand M, Bell S, Forni L, et al. Pathophysiology of COVID-19-associated acute kidney injury. *Nat Rev Nephrol* 2021;1–14. <https://doi.org/10.1038/s41581-021-00452-0>.
57. Cavayas YA, Sorbo L del, Fan E. Intracranial hemorrhage in adults on ECMO. *Perfusion* 2018;33(1\_suppl):42–50.
58. Cavayas YA, Munshi L, Sorbo L del, et al. The early change in PaCO<sub>2</sub> after extracorporeal membrane oxygenation initiation is associated with neurological complications. *Am J Resp Crit Care* 2020;0(ja):1525–35.
59. Gaisendrees C, Walter SG, Elderia A, et al. Adequate anticoagulation and ECMO therapy in COVID-19 patients with severe pulmonary embolism. *Perfusion* 2021;36(6):575–81.
60. Ripoll B, Rubino A, Besser M, et al. Observational study of thrombosis and bleeding in COVID-19 VV ECMO patients. *Int J Artif Organs* 2021. <https://doi.org/10.1177/0391398821989065>. 0391398821989065.
61. Asakura H, Ogawa H. Overcoming bleeding events related to extracorporeal membrane oxygenation in COVID-19. *Lancet Respir Med* 2020;8(12):e87–8.
62. Abdul-Aziz MH, Roberts JA. Antibiotic dosing during extracorporeal membrane oxygenation: does the system matter? *Curr Opin Anaesthesiol* 2020;33(1):71–82.
63. Mustafa AK, Alexander PJ, Joshi DJ, et al. Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. *Jama Surg* 2020;155(10):990–2.
64. Creel-Bulos C, Hockstein M, Amin N, et al. Acute cor pulmonale in critically ill patients with Covid-19. *N Engl J Med* 2020;382(21):e70.
65. Garcia B, Cousin N, Bourel C, et al. Prone positioning under VV-ECMO in SARS-CoV-2-induced acute respiratory distress syndrome. *Crit Care* 2020;24(1):428.
66. Oujidi Y, Bensaïd A, Melhoai I, et al. Prone position during ECMO in patients with COVID-19 in Morocco: case series. *Ann Med Surg* 2021;69:102769.

67. Talias I, Katira BH, Brochard L. Is the prone position helpful during spontaneous breathing in patients with COVID-19? *JAMA* 2020. <https://doi.org/10.1001/jama.2020.8539>.
68. Guérin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med* 2013;368(23):2159–68.
69. Guervilly C, Prud'homme E, Pauly V, et al. Prone positioning and extracorporeal membrane oxygenation for severe acute respiratory distress syndrome: time for a randomized trial? *Intensive Care Med* 2019;45(7):1040–2.
70. Giani M, Martucci G, Madotto F, et al. Prone positioning during venovenous extracorporeal membrane oxygenation in acute respiratory distress syndrome. A multicenter cohort study and propensity-matched analysis. *Ann Am Thorac Soc* 2021;18(3):495–501.
71. Chlebowski MM, Baltagi S, Carlson M, et al. Clinical controversies in anticoagulation monitoring and antithrombin supplementation for ECMO. *Crit Care* 2020; 24(1):19.
72. Protti A, Iapichino GE, Nardo MD, et al. Anticoagulation management and antithrombin supplementation practice during veno-venous extracorporeal membrane oxygenation. *Anesthesiology* 2020;132(3):562–70.
73. Kurihara C, Walter JM, Karim A, et al. Feasibility of venovenous extracorporeal membrane oxygenation without systemic anticoagulation. *Ann Thorac Surg* 2020;110(4):1209–15.
74. Krueger K, Schmutz A, Zieger B, et al. Venovenous extracorporeal membrane oxygenation with prophylactic subcutaneous anticoagulation only: an observational study in more than 60 patients. *Artif Organs* 2017;41(2):186–92.