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Review

Extracorporeal membrane oxygenation in COVID-19 associated acute respiratory distress syndrome: A narrative review

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ABSTRACT

Venovenous extracorporeal membrane oxygenation (VV-ECMO) is an established rescue therapy in the management of refractory acute respiratory distress syndrome (ARDS). Although ECMO played an important role in previous respiratory viral epidemics, concerns about the benefits and usefulness of this technique were raised during the coronavirus disease 2019 (COVID-19) pandemic. Indeed, the mortality rate initially reported in small case series from China was concerning and exceeded 90%. A few months later, the critical care community published the findings from several observational cohorts on the use of extracorporeal membrane oxygenation (ECMO) in COVID-19-related ARDS. Contrary to the preliminary results, data from the first surge supported the use of ECMO in experienced centers because the mortality rate was comparable to those from the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial or other large prospective studies. However, the mortality rate of the population with severe disease evolved during the pandemic, in conjunction with changes in the management of the disease and the occurrence of new variants. The results from subsequent studies confirmed that the outcomes mainly depend on strict patient selection and center expertise. In comparison with non-COVID-related ARDS, the duration of ECMO for COVID-related ARDS was longer and increased over time. Clinicians and decision-makers must integrate this finding in the ECMO decision-making process to plan their ICU capacity and resource allocation. This narrative review summarizes the current evidence and specific considerations for ECMO use in COVID-19-associated ARDS.

Introduction

Venovenous extracorporeal membrane oxygenation (VV-ECMO) is an established rescue therapy in the management of refractory acute respiratory distress syndrome (ARDS).[1,2] During the coronavirus disease 2019 (COVID-19) pandemic, concerns were raised about the benefits and usefulness of this technique. Indeed, during a period when healthcare systems were overwhelmed worldwide and resources were limited, one could question the use of such highly resource-intensive techniques. Moreover, in comparison with the influenza pandemic, COVID-19 shows a higher likelihood of requiring mechanical ventilation and intensive care unit (ICU) stay. [3] Early in the pandemic, several observational studies reported conflicting results regarding the influence of extracorporeal membrane oxygenation (ECMO) on mortality in COVID-19-associated ARDS. Despite these negative initial results, ECMO has become a widespread treatment method for severe ARDS associated with COVID-19. To date (September 05, 2022) and according to the Extracorporeal Life Support Organization (ELSO) registry, 13,853 patients received ECMO support since the beginning of the pandemic.[4] This narrative review aims to summarize the evidence for the use of ECMO in ARDS, especially life-threatening COVID-19-associated ARDS.

History of ECMO in ARDS

The development of ECMO parallels the history of cardiac surgery and the use of cardiopulmonary bypass (CPB). In the mid-20th century, pioneers of that field hoped that the technology could be used to provide temporary life support for patients with acute cardiac or respiratory failure. However, the

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technology available in the early fifties was rudimentary, and initial attempts yielded disappointing results. The first oxygenators developed could not be used for more than a few hours before serious hematological complications occurred. During the mid-sixties, Zapol et al.[5] used newer membranes made of silicone rubber. These oxygenators lasted for days, allowing him to study ECMO-related physiological changes in animals. Concomitantly, Hill et al.[6] from the Pacific Medical Center began to use a heart–lung machine for adults presenting with cardiogenic shock and refractory hypoxic respiratory failure. However, patients who underwent implantation between 1966 and 1970 were described as moribund at the initiation of the support, and no long-term survivors were reported.

In 1972, Hill et al.[7] reported the first case of ARDS in which the patient survived after receiving ECMO support. The 24-year-old patient presented with aortic dissection and sustained multiple trauma injuries (chest, pelvis, and lower limb fractures) after a motor vehicle accident. He was successfully operated on but presented with refractory ARDS on postoperative day 4. After discussion, The Pacific Medical Center team flew in and assisted the patient with a veno-arterial extracorporeal membrane oxygenation (VA-ECMO) for 75 h. Interestingly, a trial of "protective mechanical ventilation" was provided during extracorporeal life support (ECLS). Peak airway pressure was decreased from 60 cmH_2O to 35 cmH_2O and tidal volume from 1000 mL to 800 mL. The patient was subsequently weaned-off ECMO and mechanical ventilation, transferred to an orthopedic ward, and survived.

Several cases of successful neonatal respiratory insufficiency were then published. By the end of the seventies, survival among neonates receiving ECMO support was reported to be around 50%, and ECMO became an accepted therapy in neonatal critical care medicine.[8] In 1979, Zapol et al.[9] published the first randomized controlled trial (RCT) on ECMO. Their trial, which included 90 patients, compared two strategies for severe acute respiratory failure (ARF): conventional mechanical ventilation alone and a combination of VA-ECMO and conventional mechanical ventilation. The causes of ARF were mainly bacterial or viral pneumonia. The survival rate was poor in both groups (9.5% and 8.5%, respectively). The authors concluded that "ECMO can support gas exchange but did not increase the probability of long-term survival in patients with severe ARF."[9] As a result, the enthusiasm and scientific interest for ECMO declined, and decades passed before research on this topic resumed. In 1994, Morris et al.[10] published the second RCT on ECMO and ARDS. They randomized 40 patients with severe ARDS into two groups to compare extracorporeal CO_2 removal and pressure-controlled inverse ratio ventilation to conventional ventilation. The results were again disappointing, with no significant difference in survival at day 30 (33% *vs.* 42%, respectively; P=0.800). The authors concluded that extracorporeal support was not recommended as a therapy for ARDS and that its use should be restricted only to controlled clinical trials.

Contemporary evidence for VV-ECMO in ARDS Before the COVID-19 pandemic

The technical advancements in the 21st century led ECMO into a new era. Indeed, the use of a centrifugal pump in conjunction with a better membrane oxygenator improved the overall biocompatibility, whereas smaller circuits allowed better portability. However, ECMO was only used in highly specialized centers at that time.

In 2009, the H_1N_1 pandemic caused an overwhelming number of severe ARDS patients worldwide that challenged the healthcare system and the critical care community. Many of these patients were young and presented with ARDS that was refractory to conventional management. ECMO was then used as a rescue therapy and showed encouraging results in observational studies. Indeed, the Australian and New Zealand ECMO influenza investigators reported a survival rate of 71% for supported patients, with a mean age of 34.4 years and a Murray score of 3.8 at cannulation.[11] Several other national observational cohorts were published (France, United Kingdom, and Italy) and reported similar results.[12-14] In the same year, Peek et al.[15] published the CESAR trial. The authors considered that the previous RCTs[9,10] were not relevant in the modern ECMO era due to significant differences in the case selection, mechanical ventilation management, and extracorporeal circuit design. Peek et al.[15] conducted their RCT between 2001 and 2004 and included 180 adult patients with severe ARDS, a Murray score of 3 (including four components: degree of hypoxemia, respiratory system compliance, chest radiographic findings, and level of positive end-expiratory pressure) or respiratory acidosis (pH <7.20), and who were mechanically ventilated for <7 days. Patients were randomly allocated to receive conventional management in their center (90 patients) or referral to consideration for treatment by ECMO in an ECMO center (90 patients). The authors reported an increased survival rate or severe disability at 6 months for the patients referred to an expert center. Moreover, the quality adjusted life year at 6 months was also significantly better, and the strategy to transfer patients to an ECLS center was proven to be cost-effective. However, only 75% of the referred patients received ECMO; protective mechanical ventilation was applied in only 70% of the patients in the control group, and 6% died during transport (i.e., before reaching the referral center). These methodological limitations significantly limited the interpretation and the external validity of their trial.

Nearly 10 years later, the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial was published.[16] The multicenter RCT included patients who presented with severe ARDS and underwent mechanical ventilation for <7 days with one of the following criteria (partial pressure of oxygen[PaO_2]/fraction of inspired oxygen[FiO_2] ≤50 mmHg for ≥3 h, PaO_2/FiO_2 ≤80 mmHg for ≥6 h, or pH <7.25 with $PaCO_2$ >60 mmHg). Patients were randomly assigned to receive immediate VV-ECMO or undergo conventional mechanical ventilation management. Ultra-protective ventilation, including reduction of the tidal volume, respiratory rate, and plateau pressure, was protocolized in the interventional arm. Crossover to ECMO was allowed in cases showing refractory hypoxemia, defined by SpO_2 <80%, despite the use of all adjunct therapies available. The study was stopped for futility after 67 months and the inclusion of 249 patients. At 60 days, an 11% absolute mortality reduction was observed in favor of the ECMO group (35% vs. 46%), but this difference did not reach statistical significance (P=0.070). However, 28% of the patients in the control group (35 patients) required crossover and emergent cannulation in the context of refractory hypoxemia. This may have diluted the effect of ECMO on the primary outcome. Furthermore, the trial might have been underpowered

to detect a 20% absolute reduction in mortality in the ECMO group. Secondary outcomes, including renal and hemodynamic dysfunction, were also in favor of the interventional group.

An individual patient meta-analysis of 429 patients from the EOLIA and CESAR trials was conducted,[17] and the authors reported significantly lower mortality at 90 days in the ECMO group in comparison with the control group (36% *vs.* 48%; relative risk: 0.75; 95% confidence interval [CI]: 0.60–0.94; P=0.013). Almost 50 years after the first successful case of ECLS in ARDS, ECMO became part of the standard of care in experienced centers for ARDS patients refractory to conventional management (including protective mechanical ventilation, prone position, and neuromuscular blockades).[2,18-20]

ECMO and the First Surge of COVID-19

The first data reporting the use of ECMO in COVID-19-associated ARDS were obtained from China. The mortality rate reported was concerning and exceeded 90%.[21-23] However, those studies were mainly small case series, and they included limited information about the characteristics, management, and outcomes after day 30. Some authors rushed to a premature conclusion about the lack of benefit of this technique in COVID-19 cases.[24]

Despite the rising concern from those initial reports, the World Health Organization, the ELSO, and critical care experts recommended that ECMO should be considered in the management of severe COVID-related ARDS.[25-27] They stressed in their recommendation that this technique should be provided in specialized centers with a mobile ECMO team capable of identifying selected patients and transferring them to the expert center.

In this context of uncertainty regarding the benefits of ECMO, Schmidt et al.[28] reported the characteristics and 90-day outcomes of 83 patients who received ECMO for COVID-19-related ARDS. The median pre-ECMO PaO_2/FiO_2 ratio was 60 mmHg (interquartile range [IQR]: 54–68 mmHg), and prone position and neuromuscular blockades were extensively used before ECMO onset (94% and 96%, respectively). The median age was 49 years (IQR: 41–56 years), and 73% of the patients were male. The estimated probability of death 60 days after ECMO implantation was 31% (95% CI: 22–42%), which was very similar to the mortality rate observed in the EOLIA trial. Mortality at day 90 was 36% (95% CI: 27–48%). Nonetheless, further research is needed to confirm these reassuring outcomes reported by a single experienced ECMO center [Table 1].

A subsequent multicenter observational study conducted by the ELSO [29] confirmed the results reported by Schmidt et al. That study enrolled 1035 patients from 36 countries who underwent initiation of ECMO before May 2020. The estimated cumulative incidence of death at 90 days was 37.4% (95% CI: 34.4–40.4%). Assessment of pre-ECMO characteristics showed that the median PaO_2/FiO_2 ratio was 72 mmHg (IQR: 59–94 mmHg). In comparison with the results reported by Schmidt et al.[28], prone position and neuromuscular blockades were used less frequently before ECMO initiation in the study (60% and 74%, respectively). The median patient age was 49 years (IQR: 41–57 years), and 74% of the included patients were men. Moreover, 70% of the cohort received care in another hospital before being transferred to an ELSO center and a mobile ECMO team retrieved 47% of these patients.

Table 1
Main characteristics of large retrospective cohorts of patients with COVID-19-related severe ARDS treated with ECMO.

Study	Country	Number of ECMO patients	Study period (date/month/year)	SOFA score at inclusion (median [IQR])	RESP score at inclusion (median [IQR])	Prone position before ECMO (%)	Mortality (%)	Duration of support (days, median [IQR])	VAP (%)
Schmidt *et al.*[28]	France	83	08.03.2020–02.05.2020	12 (9–13)	4 (2–5)	94	31	20 (10–40)	87
Barbaro *et al.*[29]	International	1035	16.01.2020–01.05.2020	NA	NA	60	37.40	14.1 (7.9–24.1)	NA
Shaefi *et al.*[30]	USA	190	01.03.2020–01.07.2020	NA	3 (1–5)	71.1	33.20	16 (10–23)	34.70
Mustafa *et al.*[32]	USA	40	17.03.2020–17.07.2020	NA	NA	73	17.50	30 (SD 3.6)	NA
Lorusso *et al.*[34]	Europe and Israel	1531	15.03.2020–15.09.2020	NA	NA	NA	45	18 †	NA
Schmidt *et al.*[38]	France	71	01.07.2020–28.01.2021	11 (8–13)	3 (2–4)	90	48	22 (12–48)	89
Barbaro *et al.*[39]	International	3630	01.05.2020–31.12.2020	NA	NA	60 and 51 *	53 and 59*	20 (9.7–35.1)	NA
Riera *et al.*[43]	Spain and Portugal	319	01.03.2020–	NA	NA	96.6 and 100*	40.1 and 61.1*	17 (9–32)	50.4
Alhumaid *et al.*[53]	Saudi Arabia	92	01.03.2020–30.10.2020	NA	NA	28.3	48.90	15.4†	NA
Karagiannidis *et al.*[40]	Germany	3397	01.03.2020–31.05.2021	NA	NA	NA	68	17†	NA
Fanelli *et al.*[54]	Italy	146	2020–28.02.2021	7 (5–9)	NA	78	46	22 (11–38)	NA
Whebell *et al.*[44]	UK	243	03.03.2020–28.02.2021	5 (4–7)	5 (4–6)	79.4	22.9 and 26.1	NA	NA

ARDS: Acute respiratory distress syndrome; COVID-19: Coronavirus disease 2019; ECMO: Extracorporeal membrane oxygenation; IQR: Interquartile range; NA: non-applicable as results were not reported; RESP, respiratory ECMO survival prediction; SD: Standard deviation; SOFA, sequential organ failure assessment score;VAP: Ventilator-associated pneumonia.
* First and second waves.
† Mean values.

Using data from a multicenter cohort study of 5122 critically ill adults with COVID-19 admitted to 68 hospitals across the United States, Shaefi et al.[30] reported the clinical features and outcomes for 190 patients treated with ECMO within 14 days of ICU admission. To estimate the effect of ECMO on mortality, the authors emulated a target trial of ECMO receipt *vs.* no ECMO receipt within 7 days of ICU admission among mechanically ventilated patients with severe hypoxemia (PaO_2/FiO_2 <100). Among them, 190 patients were supported by ECMO during the study period. At 60 days, 33.2% of the patients had died, 49.5% were discharged from the hospital, and 17.3% remained hospitalized. Among patients eligible for the target trial emulation, 45 of the 130 (34.6%) who received ECMO died, and 553 of the 1167 (47.4%) who did not receive ECMO died. In the pre-ECMO assessments, the median PaO_2/FiO_2 ratio was 72 mmHg (IQR: 61–90 mmHg), and 71.1% of the patients underwent prone positioning while 78.4% received neuromuscular blockades before ECMO initiation. The median age was 49 years (IQR: 41–58 years), and 72.1% of the patients were men. Patients were cannulated early after intubation (median: 2 days; IQR: 0–5 days). In the primary analysis, patients who received ECMO showed lower mortality than those who did not (hazard ratio=0.55; 95% CI: 0.41–0.74). Although the study was not an RCT, its results highly suggested that ECMO may reduce mortality in select patients with severe COVID-19-associated ARDS. The above large-cohort-based studies provided a generalizable estimate of ECMO mortality during the first surge of COVID-19, which was secondarily confirmed by a meta-analysis of 22 observational studies and 1896 patients who reported a pooled mortality of 37%.[31]

Only one study reported a significantly lower mortality rate in comparison with the literature during the first wave of COVID-19. In a retrospective study of 40 patients hospitalized at two tertiary centers in Chicago, Mustafa et al.[32] reported a mortality rate of 17.5%. Moreover, at the time of the publication, 73% of the patients were discharged from the hospital while no longer receiving oxygen. Assessment of the pre-ECMO characteristics showed that the mean PaO_2/FiO_2 ratio was 68.9 mmHg, 73% of the patients underwent prone positioning, and 78% received neuromuscular blockade before ECMO initiation. The median age was 51 years (IQR: 22–64 years). Patients were cannulated early after intubation, i.e., a mean of 4 days on mechanical ventilation. Interestingly, the strategy used in this study was different from those reported in the previous cohorts: a single-access, dual-stage right atrium–to-pulmonary artery cannula (V-PA ECMO) was implanted instead of the usual configuration of VV-ECMO, and the right ventricular function before ECMO initiation was not reported. Besides, patients were extubated 11.0±1.9 days after ECMO onset, which allowed early mobilization. Nevertheless, the total ECMO duration was still long (30.0±3.6 days). While these results are impressive, they have not been replicated since this first publication. Therefore, any inferences must be made with caution, and further research is essential to evaluate the strategy used in this trial (V-PA ECMO and early extubation).

Altogether, the above data support the use of ECMO in COVID-19-associated ARDS in an experienced center because the mortality rates were similar to those reported in the CESAR and EOLIA trials.[15,16] The pre-ECMO characteristics of the patients reported by Schmidt et al.[28], Barbaro et al.[29], and Shaefi et al.[30] were comparable in terms of age, PaO_2/FiO_2 ratio, and use of adjunct therapies. Similarly, the incidence of complications was not higher in COVID-19-associated ARDS than those previously reported during ECMO for different ARDS etiologies. Lastly, the use of ECMO among critically ill patients was 3% and 8% in the USA and Europe, respectively, during the first wave of the pandemic.[30,33,34]

ECMO and sSubsequent Waves of COVID-19

New variants with different patterns of contagiousness and virulence occurred during the subsequent waves of COVID-19. Moreover, landmark publications changed the global care of patients with severe COVID-19, which may have also contributed to modifying the outcomes of the most severe patients who required ECMO.

In June 2020, the RECOVERY trial showed that dexamethasone (6 mg/day for 10 days) reduced mortality significantly in comparison with usual care.[35] Immunomodulation with monoclonal antibodies (tocilizumab and sarilumab) was also shown to be effective in improving survival and decreased the need for invasive mechanical ventilation.[36] Similarly, a paradigm shift occurred regarding the timing of intubation. Reports of a lower need for invasive mechanical ventilation with non-invasive ventilation (NIV) strategies,[26,37] vaccination of health workers, and recommendations of the international guidelines led to more frequent use of high-flow nasal oxygen and NIV in comparison with the first surge, where patients were promptly intubated. All these changes in the pre-ECMO management contributed to modifying the profile of the ECMO candidates during the pandemic.

The mortality of patients on ECMO evolved after the first wave of COVID-19 infections, and several observational cohorts reported a higher mortality rate in comparison with the previous surge.[38-40] The characteristics and outcomes of patients who received ECMO before (n=88) and after July 1, 2020 (n=71) at Sorbonne University, Paris, France were recently published.[38] In that study, patients were enrolled until January 28, 2021. Compared to the patients of the first wave, those admitted after July 1, 2020, were significantly older (median age: 54 years; IQR: 49–60 years). The time from the first symptoms to intubation (11 days; IQR: 8–17 days) as well as the time from ICU admission to ECMO onset (9 days; IQR: 4–12 days) were significantly longer than those reported during the first wave. Interestingly, the time between intubation and ECMO was similar in the two periods. The use and the duration of high-flow oxygen and NIV were respectively more frequent and longer in the second period. Despite the similar pre-ECMO PaO_2/FiO_2 ratios, organ failure rates, comorbidities, and adjunct therapies between the two periods, pneumothorax was more frequent (17% *vs.* 6%, P=0.003) and the use of high-dose steroids for non-resolving ARDS was significantly higher during the second wave (37% *vs.* 15%, P=0.001). As expected, dexamethasone was prescribed before ECMO in 82% of the patients after July 1, 2020, while only 18% received it before that date. Overall, the estimated probability of mortality at 90 days was 48% after July 1, 2020, which was significantly higher than the corresponding value during the first surge (36%). Furthermore, the median duration of ECMO significantly increased as well.

The above results were confirmed in larger international cohorts. In the ELSO registry, 4812 patients undergoing ECMO before December 31, 2020, were analyzed.[39] The outcomes of those patients were analyzed among three groups: patients cannulated before May 2020 and after May 2020 and those cared for in new ECMO centers that started ECMO after May 1, 2020. In comparison to the patients of the first wave, patients admitted after May 2020 showed significantly greater incidences of diabetes, immunocompromised status, pre-existing heart failure, acute kidney injury (AKI), and bacterial co-infection (bacterial pneumonia and bacteremia). The use of high-flow oxygen and NIV before intubation was also more frequent. Similarly, dexamethasone and remdesivir were more commonly prescribed after May 2020 (78% *vs.* 43%; P <0.001), whereas pre-ECMO respiratory mechanics and blood gas did not change over time. Among these early adopting centers, the incidence of 90-day mortality increased significantly from 36.9% to 51.9%. The median duration of ECMO also increased from 14.1 days (7.9–24.1 days) to 20 days (9.7–35.1 days). Interestingly, 90-day mortality in patients treated in the late-adopting centers with a low ECMO case volume (9 [0–24] cases in the previous year) was 58.9% despite almost the same pre-ECMO baseline characteristics. A higher adjusted relative risk of in-hospital mortality was reported when compared to the groups treated before May 1.

The ECMOVIBER (ECMO during the COVID-19 pandemic in the Iberian peninsula) study confirmed the overall decrease in the survival of ECMO patients over the pandemic.[41] In the retrospective, observational study, which included 319 patients from 24 centers, the authors reported a significant increase in mortality during the second wave (60.1% *vs*. 41.1%, P=0.001). Patients from the second wave were older (mean age: 54.6 ± 9.9 *vs.* 51.2 ± 10.5; P=0.004) and more comorbid, and had a higher time from ICU admission to ECMO initiation. Notably, the incidence of ventilator-associated pneumonia (VAP) was significantly more frequent (58.9.1% *vs.* 41%; P=0.003), and patients from the second surge were less likely to be treated in an experienced center.

The impact of the ECMO experience level on outcomes has been highlighted during the pandemic. Karagiannidis et al.[40] reported the outcomes of 3397 COVID-19 patients supported with VV-ECMO in Germany from March 1, 2020, to May 31, 2021. Of note, the hospital mortality of these patients in Germany was 68%, which remained stable through successive surges of the pandemic. The reported rate was much higher than the mortality rates reported in France,[28,38,42] Spain, and Portugal[43] or even in international cohorts.[29,39] Mortality in that study was also considerably higher than the mortality recently reported in the United Kingdom (25%), where a centralized national referral system was established at the start of the pandemic to provide a unified pathway for hospitals in the United Kingdom to refer patients for consideration of ECMO to specialist centers.[44] Although the granularity of the data provided by Karagiannidis et al.[40] precluded a complete understanding of the reasons for such important mortality, one can argue that the liberal use of ECMO in Germany with the lack of national regulation may have played a key role.

In an emulated trial based on a nationwide COVID-19 cohort, Hajage et al.[45] found differential survival over time of an ECMO compared with a non-ECMO strategy for COVID-19. The ECMO strategy showed a higher survival probability on day 7 (87% *vs.* 83%), which decreased during follow-up on day 90 (63% *vs.* 65%). However, an ECMO strategy consistently yielded better outcomes when performed in high-volume ECMO centers or in regions where ECMO services had been organized to handle high demand. These results reinforce the need for regional ECMO networks and advocate the provision of ECMO in experienced centers to optimize the outcomes of these critically ill patients, especially at times of unprecedented strain on healthcare systems.

In summary, the mortality and the duration of ECMO increased after the first wave of COVID-19 (SARS CoV-2 wild-type). Several reasons could account for these differences. First, the patient selection seemed less strict, because, in most studies, the patients were consistently older and with more comorbidities. Older age was shown to be an independent risk factor for death in many COVID ECMO cohorts.[28-30] Second, pre-ECMO drug management markedly changed with routine use of corticosteroids and immunosuppressive agents, which may explain the higher rates of bacteremia and VAP reported after the first wave. Third, the higher use of high-flow nasal oxygen and NIV over prolonged periods could have predisposed patients to patient self-inflicted lung injury (P-SILI).[46] An increased rate of barotrauma despite similar mechanical ventilation management supports this hypothesis. Altogether, VAP and P-SILI could increase lung damage and therefore decrease the probability of lung recovery during ECMO. Moreover, the findings also suggest that ECMO candidates after the first surges were refractory to several treatments that have been shown to improve the survival of COVID-19. Fourth, the occurrence of new variants with increased virulence might have played a role, even if this hypothesis should be confirmed as an increased hospitalization risk, ICU admission, and death were reported with the delta variant (B.1.617.2).[47] Lastly, the expansion of inexperienced ECMO centers and the lack of homogeneity in ECMO management among centers is a major concern that has been highlighted during this pandemic.[29,42,45]

Specificity of COVID-19 in ECMO sSupport

Several specific aspects regarding the care of these patients should be noted. In comparison with ARDS attributable to other etiologies, COVID-19-related ARDS requires longer periods of ECMO, which seems to have increased over the pandemic. This important point is crucial to planning ICU capacity in the context of resource constraints. For instance, the median ECMO days in 90-day survivors in the French and the international cohorts was 20 (9.7–35.1) days and 14.1 (7.9–24.1) days, respectively, whereas it was 9 (6–16) days in the CESAR trial[15] and 15 ±13 days in the EOLIA trial.[16] The risk of superinfection in these patients is a matter of concern. Schmidt et al.[38] reported that 89% of the patients were treated for VAP during their ICU stay. Among a cohort of 50 COVID-19 patients who received ECMO, 86% had VAP, which recurred in 79% of the patients, and most recurrences were relapses despite adequate antimicrobial treatment.[48] The increasing number of reports on COVID-19-associated invasive pulmonary aspergillosis (CAPA) has raised concerns regarding the possibility that CAPA is a factor contributing to mortality. However, the exact incidence of CAPA is variable worldwide, and the distinc-

tion between colonization and invasive fungal infection remains challenging.[49,50] Interestingly, the estimated cumulative incidence of VAP was significantly higher in COVID-19 patients than in influenza patients treated with ECMO (P=0.002). Notably, these data were collected during the first wave where steroids and other immunotherapies were not used as a standard of care. Further research should be conducted to determine if the incidence of infections, recurrences, and relapses increased with the current medical management and whether antimicrobial therapy should be adapted in the context of COVID-19-related ARDS (dual therapy instead of single therapy, particularly for non-fermenting Gram-negative bacteria; a combination of intravenous and aerosolized antibiotics; or prolonged antibiotic duration).

COVID-19 also shows some vascular tropism and exposes patients to a higher risk of thromboembolic and bleeding events, which are frequent and dreaded complications of ECMO.[51] Recently, Mansour et al.[52] provided important insights regarding these complications in COVID-19 patients treated with ECMO. In a large, prospective, multicenter cohort study including 620 patients from February 2020 to March 2022, the incidence of bleeding was greater than that of thrombosis (49% *vs.* 36%). In contrast to the complications of thrombosis, bleeding was independently associated with in-hospital mortality, with intracranial hemorrhage carrying the highest risk of death. Although that study has obvious limitations, it highlights the challenges in determining the optimal dose of anticoagulants in these patients. Increasing the anticoagulation regimen for COVID-19 patients beyond the limits mentioned in existing guidelines may be associated with harm and unclear benefits.

Lastly, the ECMO experience of the centers is of utmost importance because it strongly influences the outcomes.[29,42,45] Indeed, guidelines and experts' opinions advised against the initiation of new ECMO programs during the pandemic, and centers with >30 cases of VV-ECMO in the previous year had consistently better outcomes.[42,45]

Conclusions

Two and a half years after the beginning of the pandemic, several large cohort studies have highlighted the benefits of ECMO in severe COVID-19-related ARDS. Despite scarce resources and overwhelmed healthcare systems, ECMO has been used frequently worldwide. However, the mortality rate has evolved during the pandemic, in conjunction with changes in the pre-ECMO management of the disease and the occurrence of new variants. The findings for large cohorts confirmed that outcomes mainly depend on patient selection and center expertise, reinforcing the need to strictly apply EOLIA inclusion criteria in experienced ECMO centers with trained medical and nursing staff. While planning for ICU and ECMO capacity, physicians and decision-makers must consider the prolonged duration of ECMO, ICU, and hospital stays of patients with severe diseases. Further research is now warranted to improve patient selection and the treatment of VAP on ECMO. Lastly, because the disease will likely continue to evolve in the future, surveillance of the outcomes with new variants and reassessment of the ECMO selection criteria may be required in a near future.

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Conflicts of Interest

Matthieu Schmidt reports lecture fees from Getinge, Drager, and Xenios outside the submitted work. Alain Combes reports grants from Getinge, and personal fees from Getinge, Baxter, and Xenios outside the submitted work. The other author declares that he has no conflict of interest related to this manuscript.

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