

Journal club

Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19

Commentary on:

Schmidt M, *et al.* Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19: a retrospective cohort study. *Lancet Respir Med* 2020; 8: 1121-1131.

However, data from large patient populations were missing and initial reports of COVID-19 ECMO support had high mortality rates [7, 8]. These reports were not from specialised centres and patient selection for ECMO remained uncertain. For this reason, SCHMIDT *et al.* [9] performed a retrospective cohort study in a specialised referral ECMO centre.

Cite as: Arikan H, Cordingley J. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome associated with COVID-19. *Breathe* 2021; 17: 200278.

Context

Since the first cases were reported in Wuhan, China, in December 2019, coronavirus disease 2019 (COVID-19) has become a pandemic affecting millions of people. As of November 10, 2020, over 49.7 million cases and over 1.2 million deaths have been reported globally since the start of the pandemic [1]. Early reports from China revealed that COVID-19 could range from an asymptomatic state to severe lung involvement progressing to acute respiratory distress syndrome (ARDS). Wu *et al.* [2] reported that 81% of cases were mild, 14% were severe and 5% were critical. Management of patients who developed ARDS is especially challenging. Several treatment guidelines were proposed during the pandemic [3, 4] and have been updated frequently in accordance with emerging evidence. Extracorporeal membrane oxygenation (ECMO) has already been used for ARDS resulting from other causes. At the beginning of the pandemic certain organisations recommended using ECMO on severe cases of COVID-19 [5, 6].

Methods

This study was a retrospective cohort study performed in a network of intensive care units (ICU) of the Paris Sorbonne University Hospitals. ECMO care was given in two hospitals and pre and post ECMO patients were managed in a separate hospital. ECMO referrals were evaluated by a central committee that included at least two experienced intensivists. Potential candidates for ECMO need to satisfy the Berlin definition of ARDS, and despite optimum ventilation strategy (including prone positioning and neuromuscular blockade) had at least one of the followings: arterial oxygen tension (P_{aO_2})/fraction of inspired oxygen (F_{iO_2}) <50 mmHg for at least 3 h or P_{aO_2}/F_{iO_2} <80 mmHg for at least 6 h or arterial blood pH <7.25 and arterial carbon dioxide tension (P_{aCO_2}) ≥80 mmHg for at least 6 h. Patients were defined as ineligible for ECMO if they were older than 70 years or had severe comorbidities incompatible with recovery such as metastatic malignancy, unmanageable organ

 @ERSpublications

ECMO management of severe ARDS patients with COVID-19, who are not responding to lung protective ventilation and salvage strategies like prone positioning or inhaled nitric oxide, is safe if performed in a dedicated referral centre. <https://bit.ly/3p5HOEN>



CrossMark



© ERS 2021

failure, irreversible neurological impairment and invasive ventilation duration longer than 10 days. Once a patient was accepted for ECMO the patient was put on ECMO at their bedside and transferred to the predefined ECMO hospital. Due to reports of COVID-19-associated coagulopathy, anticoagulation targets were elevated by the study team (a target of activated partial thromboplastin time to 65–75 s or anti-Xa activity of 0.3–0.5 IU·mL⁻¹). An ultraprotective mechanical ventilation strategy was used during ECMO therapy. Patients were evaluated for ECMO weaning every day according to criteria set by previous ECMO studies.

The primary outcomes were, being on ECMO, being in the ICU and weaned-off ECMO, being alive and out of ICU or death at 28, 40, 50, 60, 70, 80 and 90 days. Secondary outcomes include duration of ECMO, length of ICU stay, time of ECMO weaning, ICU and ECMO related complications. To clearly define patients' outcomes in the ICU during study period a multi-state model was utilised.

Main results

From March 8 to May 2, 2020, 492 patients were admitted to network ICUs with a diagnosis of COVID-19. Overall, 83 patients were treated with ECMO for severe ARDS. Most of them were male (n=61; 73%). Median (interquartile range) age was 49 (41–56) years. Venovenous femoro-jugular approach was the most frequent technique for ECMO cannulation (n=79; 95%). Median (interquartile range) duration of invasive mechanical ventilation before ECMO was 4 (3–6) days. Baseline SAPS II score was 45 (29–56) and sequential organ failure assessment (SOFA) score was 12 (9–13). Most frequent comorbidities were hypertension (n=32; 39%) and diabetes (n=26; 31%). At the end of the study (July 10, 2020) median (minimum–maximum) follow-up duration was 104 (70–120) days. At the end of study period one patient was still on ECMO, four patients were weaned of ECMO but still in ICU and 48 patients were alive and discharged from ICU. Of the 48 patients alive, 34 had returned home and 14 were still hospitalised or in a rehabilitation centre. Overall, 30 (36%) patients died during study period. Up until day 60, complete follow-up data were available for all patients. Median (interquartile range) duration of ICU length of stay and ECMO support were 36 (23–60) days and 20 (10–40) days respectively. Although 20 patients were still in the ICU at day 60, the probability of death at day 60 was reported as 31% (95% CI 22–42%), probability of being on ECMO was 6% (95% CI 3–14%) and mean duration of ECMO was 24.6 days. Probability of being alive and out of ICU at day 60 was 45% (95% CI 35–56). At day 90, data from seven patients were not available. Probability of death by day 90 was reported as 36% (95% CI 27–48%), probability of being on ECMO was 1% (95% CI 0–8%) and mean duration of ECMO was 25.4 days. Probability

of being alive and out of ICU at day 90 was 56% (95% CI 46–67%).

Massive haemorrhage occurred in 35 (42%) patients mostly from the oronasal region. Of all patients treated with ECMO, 64 (77%) required more than one unit of packed red blood cell transfusion. Severe thrombocytopenia during the first 3 days of ECMO was seen in 5 (6%) patients. One patient died due to ECMO device failure. Pulmonary embolism seen in 16 (19%) patients.

Commentary

In contrast to previous reports of patients managed with ECMO for ARDS due to COVID-19, this study showed lower mortality rates compared with recent non COVID-19 ARDS studies for ECMO. The authors compared their results with the Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome (EOLIA) trial from 2018 [10]. The baseline patient characteristics indicated a worse severity of ARDS compared to EOLIA trial. However, the patient population in this study were younger than aforementioned study (median age 49 *versus* mean age 51.9). This may be associated with exclusion criteria. In EOLIA trial advanced age was not an exclusion criterion while patients older than 70 years of age were excluded in this report. Another factor that could affect outcome is duration of mechanical ventilation/intubation before ECMO. While median time since intubation to ECMO was reported as 34 h in EOLIA trial, current study showed that median time from intubation to ECMO was 8 days. Probability of dying was reported as 31% (95% CI 22–42%) which is comparable to mortality rate in EOLIA trial (35% with 44 patients in ECMO group). In this study authors reported substantially longer ICU length of stay and ECMO duration as opposed to EOLIA trial (median duration of ECMO 11 days *versus* 20 days, median ICU length of stay 23 days *versus* 36 days). In a resource limited and high demand setting like pandemic it would be difficult to sustain best care and choosing candidates properly if a patient needs to stay in ICU over 20 days. Also, generalisability of results can be challenging because it is from a high volume ECMO referral centre. However, quite similar results were obtained in another study published after this report [11]. Unfortunately, ECMO success depends on various factors but also experience [12]. ECMO related bleeding and rate of pulmonary embolism should be examined in more depth. They seemed to be higher compared to other data. Haemorrhagic complications were reported as 14% in a Chinese report [8]. But bleeding events requiring transfusion were reported in 57 (46%) patients in EOLIA trial [10]. However, one should note higher targeted anticoagulation levels in this report while interpreting bleeding complications (activated partial thromboplastin time target of 40–55 s or 0.2–0.3 IU·mL⁻¹ anti-Xa activity in the EOLIA trial). Authors reported an unusually high rate of pulmonary embolism on ECMO which

is not reported in EOLIA trial. These findings raise an important question which is whether these bleeding/thrombosis events are related to ECMO (*e.g.* circuit-associated defibrination and thrombocytopenia, disseminated intravascular coagulation, acquired von Willebrand syndrome) or related to coagulation anomalies seen in COVID-19. However, other studies regarding ECMO and thromboembolism have reported noticeably less pulmonary embolisms [13]. It may be reasonable to assume that these events were associated to COVID-19 itself.

From early days of pandemic, it has been suggested that prone positioning could have improved oxygenation and outcome. Authors reported that prone positioning utilised in 94% in the study population before initiation of ECMO. However, in EOLIA trial pre-ECMO prone positioning was reported as 56% in ECMO group. Additionally despite controversial data and recommendations against [14] using routinely, neuromuscular blocking agents were used in 96% of patients before ECMO which is again higher than EOLIA trial ECMO group (92%).

Main differences of this report from previous ones other than it was conducted at an expert center should be stressed. Studies reported by HENRY *et al.* [7], were observational studies. All had very small numbers of ECMO patients (1–7) and did not have specific ECMO criteria. The only study specifically designed for ECMO was a multicentre descriptive study by YANG *et al.* [8]. However, in this study population only 21 patients received ECMO (total number of patients was 59). This study had ECMO initiation criteria nearly identical to SCHMIDT *et al.* [9]. However, patient profiles of these two studies

were significantly different. SCHMIDT *et al.* [9] included younger patients (median age 49 *versus* 58 years), but more patients had organ failures according to SOFA score (median score 12 *versus* 6.5), duration of mechanical ventilation before ECMO was longer (median 4 days *versus* 36 h).

While ECMO application is a not an easy task, it will be challenging to do this under pandemic conditions. To overcome this issue, best possible practice would be referring ECMO patients to a dedicated centre as recommended by the Extracorporeal Life Support Organization (ELSO) [6]. This is perfectly achieved in this study by implementing an ICU network and a referral centre.

Implications for practice

This study provided mortality rates compared to previous non-COVID-19 ARDS studies. Its results in terms of mortality were corroborated by another report with COVID-19 patients. Despite discouraging early results from small sample sized reports, ECMO delivered through a network of ICUs proved its strength. However, longer length of stays, both in ICU and hospital, may have a significant impact on healthcare providers and limited ICU and ECMO resources. Unfortunately, it is already a challenge to design and implement a randomised clinical trial regarding ECMO because of small effect size and huge needed sample size. Although from an academic viewpoint it would be good to see a randomised trial of ECMO on severe ARDS patients with COVID-19, but it would be impractical in this extraordinary state of emergency.

Affiliations

Huseyin Arikan¹, Jeremy Cordingley²

¹Marmara University School of Medicine, Dept of Pulmonary and Critical Care Medicine, Istanbul, Turkey.

²Perioperative Medicine – Critical Care, St. Bartholomew's Hospital, Barts Health NHS Trust, London, UK.

Conflict of interest

H. Arikan has nothing to disclose. J. Cordingley has nothing to disclose.

References

- World Health Organization. Weekly epidemiological update – 10 November 2020. www.who.int/publications/m/item/weekly-epidemiological-update---10-november-2020 Date last accessed: November 14, 2020; date last updated: November 10, 2020.
- Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72 314 cases from the Chinese center for disease control and prevention. *JAMA* 2020; 323: 1239–1242.
- COVID-19 Treatment Guidelines Panel. COVID-19 Treatment Guidelines. www.covid19treatmentguidelines.nih.gov/whats-new/ Date last accessed: November 14, 2020; date last updated: November 14, 2020.
- Bai C, Chotirmall SH, Rello J, *et al.* Updated guidance on the management of COVID-19: from an American Thoracic Society/ European Respiratory Society coordinated International Task Force (29 July 2020). *Eur Respir Rev* 2020; 29.
- Alhazzani W, Møller MH, Arabi YM, *et al.* Surviving sepsis campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med* 2020; 48: e440–e469.
- 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: 707–721.
- 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: 27–28.

8. Yang X, Cai S, Luo Y, *et al.* Extracorporeal membrane oxygenation for coronavirus disease 2019-induced acute respiratory distress syndrome: a multicenter descriptive study. *Crit Care Med* 2020; 48: 1289–1295.
9. 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: 1121–1131.
10. Combes A, Hajage D, Capellier G, *et al.* Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 378: 1965–1975.
11. 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: 1071–1078.
12. Barbaro RP, Odetola FO, Kidwell KM, *et al.* Association of hospital-level volume of extracorporeal membrane oxygenation cases and mortality. Analysis of the extracorporeal life support organization registry. *Am J Respir Crit Care Med* 2015; 191: 894–901.
13. Fisser C, Reichenbacher C, Müller T, *et al.* Incidence and Risk Factors for Cannula-Related Venous Thrombosis After Venovenous Extracorporeal Membrane Oxygenation in Adult Patients With Acute Respiratory Failure. *Crit Care Med* 2019; 47: e332–e339.
14. Griffiths MJD, McAuley DF, Perkins GD, *et al.* Guidelines on the management of acute respiratory distress syndrome. *BMJ Open Respir Res* 2019; 6: e000420.