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Abstract

At the beginning of the COVID-19 pandemic, the role of extracorporeal membrane oxygenation (ECMO) was uncertain and the outcomes of ECMO-treated patients were unfavorable. During the pandemic, medical community realized that carefully selected patients may benefit from ECMO support. The goal of the study was to present the outcomes of ECMO-treated patients with severe COVID-19 ARDS referred to the respiratory ECMO hub in Croatia and to determine variables that influenced the outcome. Our study included all adult patients with confirmed COVID-19 ARDS that required ECMO treatment, in the period between February 2020 and April 2022. All ECMO circuits were veno-venous with femoro-jugular configuration, with drainage at the femoral site. A total of 112 adult patients with COVID-19 induced ARDS were included in the study. All patients had veno-venous ECMO treatment and 34 survived. Surviving patients were discharged home either from the hospital or from a designated rehabilitation facility. The mortality was associated with the incidence of nosocomial bacteremia, occurrence of heparin induced thrombocytopenia and acute renal failure. In order to reduce the mortality in COVID-19 ECMO patients, the treatment should be started as soon as criteria for ECMO are met. Furthermore, complications of the procedure should be detected as soon as possible. However, despite even the optimal approach, the mortality in COVID-19 ECMO patients will surpass that of non-COVID-19 ARDS ECMO patients, mostly due to poor resolving and long lasting ARDS with longer ECMO runs and ensuing infectious complications.

Keywords

ECMO, ARDS, COVID-19, heparin induced thrombocytopenia, acute renal failure, nosocomial bacteremia

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Introduction

Extracorporeal membrane oxygenation (ECMO) has emerged as a valuable treatment option for the most severe form of acute respiratory distress syndrome (ARDS) in the intensive care units around the world.[1–5] At the onset of COVID-19 pandemic, it was uncertain whether ECMO treatment would be beneficial, especially after discouraging outcomes were reported.[6] During the pandemic, it was elucidated that carefully selected patients may benefit from ECMO support.[7] Furthermore, with proper selection, in patients with the most severe form of COVID-19, the probability of survival improves with ECMO treatment.[8] According to current knowledge, ECMO treatment in ARDS should be applied with the "early," rather than "rescue" strategy.[9,10] Primarily in order to avoid ventilator

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Table 1. Comparison of 112 COVID-19 patients treated with ECMO according to outcome.

	Survivors (34 patients)	Non-survivors (78 patients)	*p*
Age	49 (45 to 54)	55 (43 to 57)	0.44[a]
Sex – female	9/34	19/78	0.82[b]
pO_2/FiO_2	47.0(41.0 to 54.0)	49.0 (40.0 to 55.0)	0.91[a]
RESP Score	−2(−4 to 2)	−0.5 (−3 to 1)	0.53[a]
Oxygenation Index[c]	36.0 (31.5 to 41.2)	36.8 (31.4 to 44.1)	0.90[a]
pCO_2	81.0 (70.5 to 102.7)	80.5 (69.7 to 92.7)	0.66[a]
Shock at ECMO initiation	8/34	15/78	0.62[b]
APACHE II[d] at ECMO initiation	31 (28 to 34.5)	30 (27 to 34)	0.53[a]
Acute renal failure	24/34	77/78	<0.001[b]
ECMO duration (h)	320 (210 to 490)	451 (312 to 640)	0.03[a]
Mechanical ventilation before ECMO (days)	2(1 to 5)	5 (2 to 7)	0.03[a]
Mechanical ventilation duration (days)	27 (18 to 37)	22 (15 to 32)	0.23[a]
HIT[e]	8/34	36/78	0.03[b]
Nosocomial bacteremia	13/34	58/78	<0.001[b]

[a]Mann–Whitney test.
[b]Fisher's two-tailed exact test.
[c]$FiO_2 \times$ mean airway pressure/pO_2.
[d]Acute Physiology and Chronic Health Evaluation II score.
[e]Heparin induced thrombocytopenia.

induced lung injury. In this study we present the outcomes of ECMO treatment in COVID-19 patients referred to the respiratory ECMO hub in Croatia. Furthermore, with high surge of patients requiring ECMO, even with suboptimal timing, ECMO treatment still enhances chances for survival in the most severe form of COVID-19 ARDS.

Methods

A retrospective cohort study included 112 adult patients with confirmed COVID-19 ARDS, treated with ECMO at a teaching hospital designated as the respiratory ECMO hub in Croatia, in the period between February 2020 and April 2022.

Data

Data was compiled from a database of patients treated with ECMO for ARDS. Variables included in the analysis are presented in Table 1. Heparin induced thrombocytopenia antibodies were confirmed with ELISA testing only after the ID-PaGIA Heparin/PF4 Antibody Test was positive. Same tests to detect HIT were used in all patients.

ECMO

All ECMO circuits were veno-venous with femoro-jugular bypass and drainage at the femoral site.

Due to the high patient surge and limited possibility to provide ECMO treatment, the initiation of ECMO commenced after rescue strategies, namely proning and recruitment maneuvers, had been exhausted. The later was performed with sustained inflation technique. Persistence of pO_2/FiO_2 ratio below 60, or increased pCO_2 with pH of less than 7.2 were indications for ECMO.

Titration of heparin infusion was adjusted according to the ACT measurements. ACT values were targeted at the range between 170 and 180 s. In patients with confirmed HIT antibodies, treatment with 5 mg of fondaparinux daily was commenced.

During ECMO, the patients were ventilated in a manner to keep the plateau pressure below 30 with protective tidal volumes.

Informed consent was obtained from relatives of all patients.

Statistics

Continuous variables were presented as the median, the 25th and the 75th percentile. Categorical variables were presented as frequencies and percentages.

Univariate analysis tested the statistical significance of the difference in outcome variables between the groups.

We considered *P*-values of less than 0.05 to be statistically significant.

Statistical analysis was performed with SAS software for Windows, version 9.3. SAS Institute Inc.

Results

This single center study included 112 adult patients treated with veno-venous ECMO due to COVID-19 induced ARDS, of whom 34 survived. All surviving patients were discharged home, either from the hospital or from a rehabilitation facility.

In order to detect possible variables with significant impact on the survival, we performed univariate analysis that is presented in Table 1.

At ECMO initiation, the severity of disease was comparable regardless of the outcome. It should be stressed that overall 63% (71/112) of patients had bacteremia and 39% (44/112) developed heparin induced thrombocytopenia (HIT) while on ECMO. Furthermore, a staggering 90% of patients (101/112) acquired acute renal failure (ARF). The most common comorbidities known to affect the outcome of COVID-19 patients, such as diabetes mellitus, arterial hypertension, immunosuppression, body mass index over 30, were statistically insignificant between groups and thus omitted from the results disclosed in Table 1.

Discussion

Our study determined that the survival of COVID-19 patients on ECMO is significantly associated with the occurrence of ARF, HIT antibodies and nosocomial bacteremia.

The mortality of 74% in our patients is high, however, the inevitable provision of ECMO only after aggressive mechanical ventilation and rescue maneuvers were still hypoxemic and/or significantly hypercapnic, renders that the survival without ECMO would be negligible. To reduce the mortality in COVID-19 ECMO patients, earlier timing of ECMO treatment should be prioritized. That was clearly determined in the EOLIA trial prior to COVID-19 pandemic.[5] In that trial, crossover to rescue ECMO in MV group had a survival rate of 43%, which is similar to ours, while early ECMO group had a survival rate of 65%. To achieve that goal, a surge of COVID-19 patients to hospitals should be avoided with epidemiological measures and vaccination. Unfortunately, even with those conditions met, the mortality in COVID-19 ECMO patients will surpass that of non-COVID-19 ARDS ECMO patients, mostly due to poor resolving and long lasting ARDS with longer ECMO runs and ensuing infectious complications.[11]

Surviving patients had shorter duration of MV prior to ECMO treatment with subsequent milder ventilator induced lung injury. Longer ECMO runs in the non-survival group were probably the result of meager or absent lung function recovery. The severity of ARDS at ECMO initiation did not affect the survival, which is expected when the circumstances coerced the implementation of ECMO treatment. COVID-19 infection also independently predisposes patients for nosocomial bacteremia with probable further deterioration of the lung function and negative influence on the survival, at least in our cohort.[12]

The occurrence of HIT antibodies in such high proportion is probably, at least partially, due to the immune response to the virus itself, with similar pathogenesis to that of vaccine immune thrombotic thrombocytopenia. However, it is not elucidated why the occurrence of HIT antibodies affected the outcome in our cohort. Furthermore, due to the severity of illness and complex vital support it was not possible to determine if the patients with HIT antibodies had HIT itself. However, it could be carefully suggested that since the presence of HIT antibodies affected the outcome significantly, the hypercoagulable state might have been present in our patients with HIT antibodies. However, that remains to be elucidated in future studies. Nevertheless, in those patients we switched to the off-label use of fondaparinux. Whether the use of anticoagulation with fondaparinux in these circumstances had any impact on the outcome remains obscure.

Our study is limited due to its retrospective design and a sample size that precluded more robust statistical analysis. These limitations prevent the inference of results to ECMO COVID-19 patients in general. Unfortunately, mechanical ventilation data (tidal volume, positive end expiratory pressure, plateau pressure, driving pressure, etc.) were not recorded. However, our results still enhance the knowledge about the variables that might affect the outcome of COVID-19 induced ARDS that requires ECMO support.

Furthermore, our results indicate that it would be prudent to implement routine daily blood culture collection and to implement a search for HIT antibodies when the platelet count drops below the normal range. Consequently, timely antimicrobial treatment and anticoagulation with heparin alternatives could be considered readily in order to optimally mitigate the possible adverse impact of both entities.

Despite all elucidated adverse effects of the suboptimal timing of ECMO treatment in our cohort as well as published literature, we argue that even in those circumstances ECMO remains a life-saving option for substantial number of patients when exceptionally high demand for ECMO treatment during the pandemic is inevitable.

Declaration of conflicting interests

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References

1. Australia and New Zealand Extracorporeal Membrane Oxygenation (ANZ ECMO) Influenza Investigators;Davies A, Jones D, Bailey M, et al. Extracorporeal membrane oxygenation for 2009 influenza A(H1N1) acute respiratory distress syndrome. *JAMA* 2009; 302: 1888–1895.

2. Noah MA, Peek GJ, Finney SJ, et al. Referral to an extracorporeal membrane oxygenation center and mortality among patients with severe 2009 influenza A(H1N1). *JAMA* 2011; 306: 1659–1668.
3. Roch A, Hraiech S, Masson E, et al. Outcome of acute respiratory distress syndrome patients treated with extracorporeal membrane oxygenation and brought to a referral center. *Intensive Care Med* 2014; 40: 74–83.
4. Peek GJ, Clemens F, Elbourne D, et al. CESAR: conventional ventilatory support vs extracorporeal membrane oxygenation for severe adult respiratory failure. *BMC Health Serv Res* 2006; 23; 6: 163.
5. Combes A, Hajage D, Capellier G, et al; EOLIA Trial Group, REVA, and ECMONet. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med* 2018; 24; 378: 1965–1975.
6. Henry BM and 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.
7. Ramanathan K, Shekar K, Ling RR, et al. Extracorporeal membrane oxygenation for COVID-19: a systematic review and meta-analysis. *Crit Care* 2021; 14; 25: 211.
8. Whebell S, Zhang J, Lewis R, et al. Survival benefit of extracorporeal membrane oxygenation in severe COVID-19: a multi-centre-matched cohort study. *Intensive Care Med* 2022; 48: 467–478.
9. Karagiannidis C, Bein T and Welte T. ECMO during the COVID-19 pandemic: moving from rescue therapy to more reasonable indications. *Eur Respir J* 2022; 59(2): 2103262.
10. Lebreton G, Schmidt M, Ponnaiah M, et al. Paris ECMO-COVID-19 investigators. 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; 9(8): 851–862.
11. Russ M, Menk M, Graw JA, et al. COVID-19 patients require prolonged extracorporeal membrane oxygenation support for survival compared with non-COVID-19 patients. *Crit Care Explor* 2022; 29; 4(4): e0671.
12. Buetti N, Ruckly S, de Montmollin E, et al. COVID-19 increased the risk of ICU-acquired bloodstream infections: a case-cohort study from the multicentric OUTCOMEREA network. *Intensive Care Med* 2021; 47: 180–187.