Journal of Intensive Care Medicine
2023, Vol. 38(7) 635-642

DOI: 10.1177/08850666231157286
journals.sagepub.com/home/jic
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Same but Different—ECMO in COVID-19 and ARDS of Other Etiologies. Comparison of Survival Outcomes and Management in Different ARDS Groups

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Abstract

Background: COVID-19 has led to increased numbers of patients in need of venovenous extracorporeal membrane oxygenation (ECMO) support, but knowledge on management in comparison to acute respiratory distress syndrome (ARDS) of other etiologies is still lacking. We analyzed venovenous ECMO management and survival outcomes in patients with COVID-19 in comparison to influenza ARDS and pulmonary ARDS of other origin. **Results:** Retrospective analysis of prospective venovenous ECMO registry-based data collection was performed. One hundred consecutive venovenous ECMO patients with severe ARDS were included (41 COVID-19, 24 influenza A, 35 ARDS of other etiologies). Patients with COVID-19 had higher BMI (body mass index), lower SOFA (Sequential Organ Failure Assessment) and APACHE II (Acute Physiology and Chronic Health Evaluation II) scores, lower C-reactive protein and procalcitonin levels and less vasoactive support at ECMO initiation. Significantly more patients were mechanically ventilated for more than 7 days prior to ECMO initiation in the COVID-19 group, however they were ventilated with lower tidal volumes and more often received additional rescue therapies prior to and on ECMO. COVID-19 patients had significantly more barotrauma and thrombotic events on ECMO. There were no differences in weaning of ECMO, however duration of ECMO runs and ICU length of stay was significantly longer in the COVID-19 group. The leading cause of death in the COVID-19 group was irreversible respiratory failure, while uncontrolled sepsis and multiorgan failure were leading causes in the other 2 groups. All patients who survived ICU treatment were discharged out of hospital, and there were no differences in survival among groups at 180 days. **Conclusions:** Survival outcomes of venovenous ECMO patients do not differ between COVID-19 and ARDS of other pulmonary etiologies. ARDS guidelines were in greater proportion adhered to in COVID-19 patients, with, however, longer time to ECMO initiation. COVID-19 ARDS seems specific as a more single-organ disease with longer ECMO duration and irreversible respiratory failure as a main cause of ICU mortality.

Keywords
COVID-19, ARDS, ECMO

Introduction

Exponential rise of acute respiratory distress syndrome (ARDS) patients due to the COVID-19 pandemic in recent 3 years shifted much attention to this field of intensive care. ARDS is one of the most common entities in intensive care medicine with high mortality rates,[1] despite being the focus of intensive research. Recent findings offer new insights into this syndrome, focusing not only on severity classification but on differences in etiology and types,[2] resulting in different prognostic assessments and management strategies.

Protective ventilation remains the mainstay of ARDS management,[1,3] however ventilation itself inflicts additional injury to the already damaged lung.[4] In severe ARDS protective ventilation often does not suffice to meet oxygenation and ventilatory demands of the patient. Extracorporeal membrane oxygenation (ECMO) is becoming a standard of care for the most severe ARDS patients,[5] however selection of the most appropriate patients that will benefit from this demanding and resource-consuming treatment is still difficult, especially in the recent light of understanding that ARDS encompasses very different etiological entities with different mechanisms of lung injury.[2,6] This patient and

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disease heterogeneity is probably also an important factor contributing to negative results of large prospective studies on use of ECMO in severe ARDS.[7,8]

In the past ECMO was utilized mainly in patients with severe ARDS due to influenza or bacterial pneumonia,[9] but since 2020 there is an increasing number of patients that need ECMO support due to severe coronavirus disease 2019 (COVID-19). Despite poor initial results regarding ECMO use in these patients,[10] recent reports suggest that ECMO is a feasible treatment method in these patients with survival rates comparable to other ARDS patients.[11–13] Since the disease is new, data is still emerging and is mainly retrospective. There is not much data on comparing COVID-19 ECMO management and outcomes to other groups of ARDS patients.

As a national center for ECMO support during the pandemic, as well as an ECMO teaching and referral center,[14] we analyzed our data between ECMO patients with COVID-19 ARDS etiology and 2 other most common ARDS etiologies, that is influenza and pulmonary ARDS of other origin. The aim of this study was to evaluate management of ECMO patients and survival outcomes in different ARDS groups.

Patients and Methods

Study Design

The study was conducted at the Department of Intensive Internal Medicine, University Medical Centre Ljubljana. Retrospective analysis of prospective ECMO registry-based data collection was performed. All adult (> 18 years) venovenous ECMO (VV ECMO) patients admitted from January 2016 to December 2021 were screened. Those who fulfilled ARDS criteria according to the Berlin definition[15] were included. The study was approved by the National Ethics Committee (0120-377/2020/6) and complied with the Declaration of Helsinki. Patient consent was waived due to registry-based collection of data.

Study Population and Patient Management

One hundred consecutive venovenous ECMO patients with severe ARDS of different etiologies were included in analysis. Indication for ECMO support was severe persistent hypoxemia ($PaO_2/FiO_2 < 100$ mm Hg and/or Murray score 3-4) and/or hypercapnic respiratory acidosis ($pCO_2 > 75$ mm Hg and pH <7.2) with inability to maintain protective ventilation despite optimal medical treatment, including neuromuscular blockade, prone positioning, protective ventilation, and high positive end-expiratory pressure. Contraindications for ECMO support were non-protective mechanical ventilation duration of more than 7 days (a relative contraindication in COVID-19 patients), irreversible lung failure with no option of lung transplantation, advanced-stage malignant disease and irreversible neurological damage. Relative contraindications were age >70 years, obesity with a body mass index (BMI) > 40, contraindications for anticoagulation, advanced heart failure, cirrhosis, multiorgan failure and low World Health Organization (WHO) performance status. Despite initial concerns about resource allocation, we did not change our ECMO policies during the COVID-19 pandemic.

The majority of cannulations were performed percutaneously in an intensive care unit (ICU) with transthoracic and transoesophageal echocardiography control, 2 patients were cannulated in a catheterization laboratory. Cannulas were predominantly placed in femoral and internal jugular veins, in 5 patients cannulation was bifemoral. Before the COVID-19 pandemic 11 patients were cannulated in regional hospitals by our mobile ECMO team, during the pandemic 3 patients were cannulated in regional hospitals and transferred to our unit.

Ultraprotective mechanical ventilation targeting low tidal volume (2-4 mL/kg predicted body weight [PBW]), low respiratory rate, and low driving pressure was utilized for the first days of VV ECMO initiation. Prone positioning, neuromuscular blockade, and other rescue measures were left at the physician's discretion. Anticoagulation protocol with continuous standard heparin infusion to achieve a 1.5 to 2 times upper APTT (activated partial thromboplastine time) was used in all patients except for patients with active bleeding or positive HIT antibodies. Patients with confirmed thrombotic event were put on therapeutic heparin infusion to achieve antiXa 0.3 to 0.7 IU/mL.

Data Collection and Outcome

Data were collected and analyzed retrospectively from a dedicated prospective electronic registry of ECMO patients at our department. Patients were divided into 3 groups: patients with ARDS due to COVID-19, patients with ARDS due to influenza A, and patients with ARDS due to other causes (mainly bacterial pneumonia) (Table 1). Data before VV ECMO cannulation included demographic characteristics, comorbidities, disease severity and prognostic scores, laboratory tests, mechanical ventilation parameters, and rescue treatment. Outcomes (ICU survival, 30 and 180 day survival, ECMO duration and weaning, ICU length of stay) and adverse events (ischemic stroke, haemorrhagic stroke, bleeding events, thrombotic complications, and acute kidney injury requiring renal replacement therapy) were also recorded. Six months follow-up was completed for all patients using hospital

Table 1. Causes of ARDS in VV ECMO Patients Other Than COVID 19 and Influenza.

Causes of ARDS	35
Legionella pneumonia	7
Streptococcus pneumoniae	6
Sepsis of other bacterial causes	4
Aspiration pneumonitis	4
Pneumocystis pneumonia	3
Acute pancreatitis	3
Sepsis of unknown bacterial agent	3
Leptospirosis	2
Vasculitis	1
Bleomycin pneumonitis	1
Rejection of transplanted lung	1

information system that is continuously updated from a national health system registry.

Statistical Analysis

Numerical variables are presented as median with interquartile range (IQR). Categorical variables are presented as proportions in percentages. For overall comparison between the groups Kruskal–Wallis *H*-test was used. For comparison of categorical variables, Fischer's exact test and Chi-square test were used as appropriate. For multiple comparisons Bonferroni adjustment of statistical significance was made. Univariate and multivariate binominal logistic regression was performed to control for possible effects of variables with differences among groups on patients' outcome. The 6-month overall survival was estimated using the Kaplan–Meier method and compared by using a log-rank test. A *P*-value of <.05 was considered statistically significant. Data were analyzed by IBM SPSS Statistics (SPSS Inc. to IBM, Chicago, IL) and GraphPad Prism 7 (GraphPad Software, USA).

Results

Between January 1st, 2016 and December 31st, 2021, 100 patients (median age 53, men 72%) were supported with VV ECMO due to severe ARDS. Among them 41 with confirmed COVID-19 pneumonia, 24 with confirmed influenza A pneumonia, and 35 with ARDS of other etiologies (specified in Table 1).

Patients with COVID-19 had higher BMI than those with ARDS of other etiologies (30 kg/m^2, IQR 26-34 vs 28 kg/m^2, IQR 25-29, $P = .02$) and less patients (4.9% vs 17.1%, $P = .04$) were immunocompromised (long-term use of immunosuppressant drugs, known as immunodeficiency) in this group. Otherwise, there were no significant differences in patient characteristics and pre-ECMO comorbidities (Table 2).

Patients with COVID-19 had lower Sequential Organ Failure Assessment (SOFA) and Acute Physiology and Chronic Health Evaluation II (APACHE II) scores, 8 (IQR 4-9) and 16 (IQR 13-18), at ECMO initiation, and lower C-reactive protein (CRP) (177, IQR 102-249) and procalcitonin (PCT) levels (0.3, IQR 0.1-0.8) then other 2 cohorts. Less COVID-19 patients needed vasoactive support before ECMO cannulation (Table 2).

Although there were no significant pre-ECMO differences in PaO_2/FiO_2 ratio (overall 75 mm Hg, IQR 51-91), plato pressure (30 cmH_2O, IQR 27-32) and respiratory rate (23/min, IQR 21-25) among groups, patients in COVID-19 group had higher pH (7.34, IQR 7.26-7.38) and pCO2 levels (7.9 kPa, IQR 6.0-10.0), were ventilated with lower tidal volumes (6.3 mL/kg PBW, IQR 5.1-7.4) and more often received rescue therapies: prone positioning in 75.6% (n = 35), neuromuscular blockade in 97.6% (n = 40) and inhaled nitric oxide in 90.2% (n = 37) of patients (Table 2) than patients in the other 2 groups. Significantly more patients were mechanically ventilated for more than 7 days prior to ECMO initiation in COVID-19 group, 39% (n = 16), than in group with influenza and other etiologies, 12.5% (n = 3) and 20% (n = 7), ($P = 0.038$). COVID-19 patients also had significantly longer pre-ECMO ICU stay, 8 days (IQR 3-13) versus 2 days (IQR 1-3) in influenza group and 3 days (IQR 1-6) in group of other etiologies ($P < .001$).

After ECMO cannulation COVID-19 patients were ventilated with the lowest tidal volumes (3.8 mL/kg PBW, IQR 3.0-4.9) among groups and were proned more often, 61% (n = 25, $P < .001$). ECMO flow was similar among groups (overall 3.7 L/min, IQR 3.0-4.5) (Table 3). Only 19.5% (n = 8) of COVID-19 patients required renal replacement therapy, compared to 75% (n = 18) and 54.3% (n = 19, $P < .001$) of patients in other 2 groups. On the other hand there were more events of barotrauma requiring chest drainage and thrombotic events in COVID-19 patients, 22% (n = 9, $P = .002$) and 41.5% (n = 17, $P < .001$).

While there were no differences in weaning of ECMO with overall 56% rate of successful weaning, duration of ECMO runs and ICU length of stay was significantly longer in COVID-19 group, 15 days (IQR 9-24) and 32 days (IQR 23-46, $P < .001$), respectively. Leading cause of death in COVID-19 group was irreversible respiratory failure, 52.2% (n = 12) compared to 30.8% (n = 4) and 21.1% (n = 4) in other 2 groups. On the other hand, patients with influenza and ARDS of other etiologies more often died due to uncontrolled sepsis and multiorgan failure, 46.2% (n = 6) and 63.1% (n = 12), compared to 34.8% (n = 8) in COVID-19 group. There was no correlation between ECMO weaning success and duration of mechanical ventilation prior to ECMO.

All patients who survived ICU treatment were discharged out of hospital, there were no differences among groups ($P = .99$) (Table 3). To control for BMI, SOFA score, APACHE II, Murray score, and duration of mechanical ventilation before ECMO, which were different among groups, univariate and multivariate analysis were performed. None of predictor variables in univariate analysis were statistically significant, odds ratio for BMI was 1.012 (95% CI 0.94-1.088; $P = .757$), for SOFA 1.040 (95%CI 0.945-1.145; $P = .423$), for APACHE II 0.951 (95%CI 0.891-1.105, $P = .131$) for Murray score 2.00 (0.941-4.250; $P = .071$) and for duration of mechanical ventilation before ECMO 0.924 (95% CI 0.847-1.008; $P = 0.075$). In multivariate analysis we tested model with and without ARDS etiology as a predictor variable. In both cases models were not statistically significant (see Appendix Tables 4 and 5).

Six months after ECMO 41.5% (n = 17) of patients in group with COVID-19, 45.8% (n = 11) in group with influenza, and 40% of patients (n = 14) with ARDS of other etiologies were alive. Kaplan–Meier survival estimates during 180 days showed no significant difference among groups ($P = .526$) (Figure 1).

Discussion

Results of our study show no difference in survival outcomes of COVID-19 patients supported with ECMO as compared to other pulmonary ARDS groups, which is in accordance with findings of some previous studies of ECMO survival in COVID-19 patients[13,16] and supports utilization of ECMO in this group of patients. Overall ECMO survival in our study was 56% which is comparable to data from EuroELSO

Table 2. Characteristics of the Patients With Severe ARDS of Different Etiologies Before ECMO Cannulation.

	All patients n = 100	Covid-19 n = 41	Influenza n = 24	Other n = 35	*P*
Patient characteristics					
Age (years)	53 (42-60)	53 (42-58)	53 (45-61)	52 (40-62)	.72
Body mass index (kg/m^2)	29 (26-32)	30 (26-34)	29 (26-35)	28 (25-29)	**.02**‡
Men	72 (72%)	31 (75.6%)	17 (70.8%)	24 (68.6%)	.78
Pre-ECMO comorbidities					
Any	55 (55%)	20 (48.8%)	13 (54.2%)	22 (62.9%)	.47
Cancer	10 (10%)	3 (7.3%)	1 (4.2%)	6 (17.1%)	.20
Immunocompromised	8 (8%)	2 (4.9%)	0 (0%)	6 (17.1%)	**.04**
Diabetes	14 (14%)	7 (17.1%)	4 (16.7%)	3 (8.6%)	.52
Pre-existing lung disease	10 (10%)	6 (14.6%)	1 (4.2%)	3 (8.6%)	.38
Pre-existing renal insufficiency	4 (4%)	1 (2.4%)	0 (0%)	3 (8.6%)	.21
Pre-existing NYHA III/IV	4 (4%)	1 (2.4%)	1 (4.2%)	2 (5.7%)	.76
Pregnancy	3 (3%)	2 (4.9%)	1 (4.2%)	0 (0%)	.43
Condition and laboratory values at presentation					
SOFA	10 (8-13)	8 (4-9)	12.5 (12-13)	11.5 (10-14)	**<.001**†‡
APACHE II	18 (14-25)	16 (13-18)	23 (16-28)	22.5 (16-28)	**.001**†‡
Murray score	3.3 (3-3.8)	3.5 (3.3-3.8)	3.5 (3.3-4)	3.3 (3-3.3)	**.001**‡§
RESP score	2 (0-4)	1 (0-3)	3.5 (2-5)	1 (−1–3)	**.002**†§
Any vasoactive support	77 (77%)	25 (64.1%)	22 (91.7%)	30 (85.7%)	**.019**†
Lactate (mmol/L)	1.5 (1.1-2.4)	1.4 (1.1-2.1)	1.5 (1.2-3.2)	1.7 (1-3.3)	.24
CRP (mg/L)	212 (142-297)	177 (102-249)	222 (172-310)	271 (187-372)	**.006**‡
PCT (µg/L)	1.3 (0.3-10.0)	0.3 (0.1-0.8)	10.3 (1.5-57.5)	2.6 (1.2-9.7)	**<.001**†‡
Ventilation parameters					
Duration of ICU stay before intubation (days)	0 (0-1)	0 (0-4)	0 (0-1)	0 (0-0)	**.002**‡
Duration of invasive MV (days)	3 (1-7)	5 (2-10)	3 (1-3)	3 (1-6)	**.008**†
PaO_2/FiO_2 ratio (mm Hg)	75 (51-91)	73 (57-89)	80 (66-88)	76 (67-95)	.31
PCO_2 (kPa)	7.5 (6.1-9.1)	7.9 (6.0-10.0)	7.5 (6.1-9.1)	6.7 (5.5-8.5)	**.03**§
pH	7.30 (7.21-7.37)	7.34 (7.26-7.38)	7.22 (7.18-7.31)	7.28 (7.22-7.37)	**.01**†
Tidal volume (mL/kg PBW)	6.8 (5.7-8.0)	6.3 (5.1-7.4)	7.4 (6.2-8.8)	7.7 (5.8-8.6)	**.01**‡
Respiratory rate (min^{-1})	23 (21-25)	24 (21-26)	24 (20-25)	23 (20-25)	.57
Plato pressure (cmH_2O)	30 (27-32)	29 (27-32)	30 (28-37)	29 (26-32)	.19
PEEP (cmH_2O)	13 (10-15)	12 (8-14)	15 (13-17)	12 (10-14)	**.001**†§
Rescue therapies prior ECMO					
Prone positioning	47 (47%)	31 (75.6%)	7 (29.2%)	9 (25.7%)	**<.001**†‡
Neuromuscular blockade	64 (64%)	40 (97.6%)	13 (54.2%)	11 (31.4%)	**<.001**†‡
Inhaled nitric oxide	86 (86%)	37 (90.2%)	15 (62.5%)	27 (77.1%)	**.013**†

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; CRP, C-reactive protein; ICU, intensive care unit; MV, mechanical ventilation; NYHA, New York Heart Association Functional Classification; PCT, procalcitonin; PEEP, positive end-expiratory pressure; RESP, Respiratory ECMO Survival Prediction; SOFA, Sequential Organ Failure Assessment.

Numerical variables are presented as median (25th–75th interquartile range), categorical variables are presented as number of subjects (%).

†$P < .05$ COVID-19 versus influenza.

‡$P < .05$ COVID-19 versus other.

§$P < .05$ influenza versus other.

International survey.[17] However, our analysis of COVID-19 and other ARDS groups shows some interesting differences according to ARDS etiology and patient management. These differences might give some insight into the results and provide etiology-based implementations for ECMO utilization and management in different ARDS patients.

In accordance with other registries[10,18] patients in all 3 groups in our study were predominantly men and had a high BMI index. Obesity is a known risk factor for ARDS development[19] with altered respiratory mechanics offering a reasonable pathophysiological explanation. In our analysis COVID-19 patients were significantly more obese than other ARDS patients, making obesity a possible risk factor for severe ARDS in this group of patients. Clinicians should therefore be observant of obese patients with COVID-19, especially in the light of recent findings that obesity per se is not associated with a poorer ECMO survival.[20] Male predominance in severe ARDS patients remains less understood, but was not different between COVID-19 and other ARDS groups according to our data.

In our analysis COVID-19 patients with severe ARDS had lower SOFA and APACHE II scores before ECMO implementation and also had less vasoactive support and lower laboratory markers of inflammation pre-ECMO. We might therefore conclude that COVID-19 patients had a more isolated single organ lung failure than patients in the other 2 groups, where higher scores and markers of inflammation reflect a more multiorgan injury and

Table 3. ECMO Related Data in Patients With Severe ARDS of Different Etiologies.

	All patients n = 100	Covid-19 n = 41	Influenza n = 24	Other n = 35	*P*
Days from hospital admission to cannulation	5 (2-10)	10 (5-14)	2 (1-5)	4 (2-7)	**<.001**†‡
Days from ICU admission to cannulation	3 (2-9)	8 (3-13)	2 (1-3)	3 (1-6)	**<.001**†‡
Tidal volume during ECMO (mL/kg PBW)	4.5 (3.5-5.6)	3.8 (3.0-4.9)	4.4 (3.6-5.3)	5.0 (3.9-6.0)	**.036**‡
Plato pressure during ECMO (cmH_2O)	24 (21-25)	24 (21-25)	24 (20-25)	23 (22-25)	.98
Prone positioning during ECMO	36 (36%)	25 (61%)	9 (37.5%)	2 (5.7%)	**<.001**‡§
ECMO related complications					
Acute kidney injury requiring RRT	45 (45%)	8 (19.5%)	18 (75%)	19 (54.3%)	**<.001**†‡
Pneumothorax requiring chest tube placement	11 (11%)	9 (22%)	2 (8.3%)	0	**.002**‡
Thrombotic event	19 (19%)	17 (41.5%)	2 (8.3%)	0	**<.001**†‡
Pulmonary embolism	13 (13%)	13 (31.7%)	0	0	**<.001**†‡
Deep vein thrombosis	7 (7%)	6 (14.6%)	1 (4.2%)	0	.04
Ischemic stroke	1 (1%)	0	1 (4.2%)	0	.24
Bleeding complication	40 (40%)	21 (51.2%)	8 (33%)	11 (31.4%)	.07
Intracranial hemorrhage	4 (4%)	2 (4.9%)	0	2 (5.7%)	.50
Other bleeding events	39 (39%)	20 (48.8)	8 (33%)	11 (31.4%)	.27
Bacterial superinfection	64 (64%)	28 (68.3%)	17 (70.8%)	19 (54.3%)	.41
ECMO duration and outcome					
Days on ECMO	10 (6-16)	15 (9-24)	10 (7-13)	7 (6-10)	**<.001**‡
Weaning of ECMO	56 (56%)	22 (53.7%)	14 (58.3%)	23 (65.7%)	.57
ICU length of stay	20 (9-32)	32 (23-46)	14 (10-24)	13 (4-21)	**<.001**†‡
ICU survival	43 (43%)	17 (41.5%)	11 (45.8%)	15 (42.9%)	.99
Hospital survival	43 (43%)	17 (41.5%)	11 (45.8%)	15 (42.9)	.99
30-day survival	55 (55%)	25 (61.0%)	12 (50%)	18 (51.4%)	.60
90-day survival	43 (43%)	18 (43.9%)	11 (45.8%)	14 (40%)	.86
180-day survival	43 (43%)	17 (41.5%)	11 (45.8%)	14 (40%)	.90

Abbreviations: ICU, intensive care unit; RRT, renal replacement therapy.
Numerical variables are presented as median (25th–75th interquartile range), categorical variables are presented as number of subjects (%).
†$P < .05$ COVID-19 versus influenza.
‡$P < .05$ COVID-19 versus other.
§$P < .05$ influenza versus other.

systemic inflammatory involvement. This implicates that the disease process in COVID-19 ARDS is in general less systemic.

When we analyzed pre-ECMO ventilation strategies and respiratory management we found that adherence to protective ventilation and additional respiratory management such as proning, neuromuscular blockade, and inhalatory nitric oxide use was achieved in a greater proportion of COVID-19 patients than in the other 2 groups. This probably stems from the same notion that COVID-19 is primarily a single organ disease with little other organ damage to focus on. Exponential and worldwide increase in ARDS incidence during the pandemic also probably led to a higher clinicians' susceptibility to ARDS recognition and awareness of the importance of protective ventilatory strategies and rescue measures. Data on ARDS management in the pre-pandemic era show a relatively low adherence to ARDS management guidelines.[21] More strict and more protocolized ventilation strategies used during the pandemic offer a likely explanation to these between-groups differences in our analysis. The same can also be said regarding ventilation management and additional respiratory measures utilization in COVID-19 patients during ECMO support as compared to the other 2 groups.

However, despite better ventilatory management, time to ECMO initiation was significantly longer in COVID-19 group as compared to the other 2 ARDS groups. This is not a unique finding of our study[22] and raises an interesting discrepancy, that is probably multifactorial. "Silent hypoxia," an interesting feature of COVID-19,[23] may be one of the reasons, as many COVID-19 patients initially present with a relatively stable clinical performance despite low P/F ratios. Another explanation of this lag in ECMO initiation might be the previously mentioned findings that COVID-19 patients were just "less sick" according to multiorgan involvement and hemodynamics. In this case, utilization of additional respiratory measures or non-invasive ventilation as means of trying to improve patients' ventilation may be a "double-edged" sword leading to a time lag in ECMO initiation. Lack of ICU resources due to pandemic is probably not an insignificant factor as well. In our study COVID-19 patients had significantly longer times of ICU stay to cannulation as well as longer times of mechanical ventilation prior to cannulation with a mean time of 5 days of mechanical ventilation prior to ECMO. These data are consistent with findings of some recent studies.[16,22] Duration of mechanical ventilation prior to ECMO is one of the most important predictive factors with high pressure mechanical ventilation in duration of more than 7 days presenting a contraindication to ECMO initiation in many centers[24] including our center. A recent study reported a 100% mortality in COVID-19 ECMO patients supported with mechanical ventilation over 7 days prior to ECMO initiation.[13] Despite our policy, a large proportion of COVID-19 patients (39%)

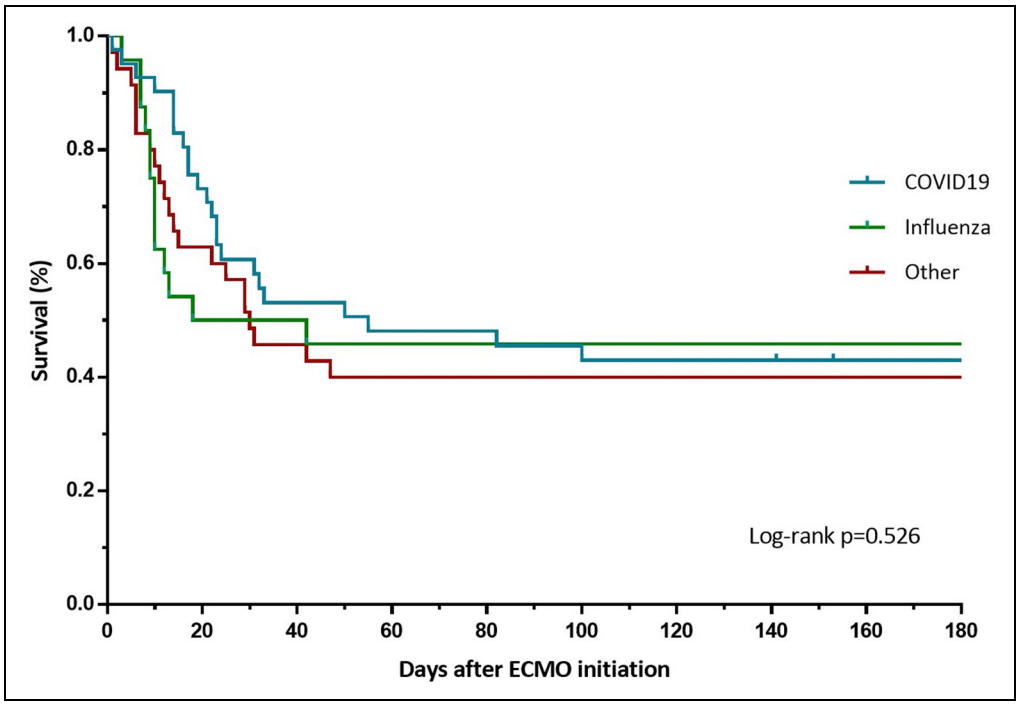

Figure 1. Patient survival during 180 days after ECMO initiation. Kaplan–Meier survival estimates during 180 days after ECMO initiation for patients with ARDS due to COVID-19, influenza A, and other causes.
Abbreviations: COVID-19, patients with ARDS due to COVID-19; Influenza, patients with ARDS due to influenza A; Other, patients with ARDS due to other causes.

received ECMO after a 7 day-limit of mechanical ventilation as the disease was new and the decision was often left at the discretion of physician in charge. However, our data do not show a significant difference in ECMO survival regarding pre-ECMO mechanical ventilation duration in these patients.

Regarding complications on ECMO, we found that COVID-19 patients had more thrombotic events (pulmonary embolism, deep venous thrombosis) despite the same anticoagulation protocol utilized in all ARDS groups. However, we did not observe more bleeding events compared to the other 2 groups as was reported in a recent study.[13] Barotrauma events were much higher in COVID-19 group despite more protective ventilation strategies during ECMO compared to the other 2 groups. Renal replacement therapy was significantly higher in the other 2 groups. Leading cause of death on ECMO was irreversible lung damage in COVID-19 patients, while other patients predominantly died due to uncontrolled sepsis or multiorgan failure. This suggests again that COVID-19 ARDS is a more single organ entity with severe lung injury, while other ARDS groups have more multiorgan and systemic involvement.

This may also be the explanation for the observed difference in ECMO support duration. In accordance with previous reports,[12,13,25] COVID-19 patients in our analysis had much longer duration of ECMO support with a mean duration of 15 days. This suggests that the process of lung damage and restoration is very different in COVID-19 than in influenza or ARDS of other etiology and poses one of the major and most important differences in clinical approach to these patients. However, once COVID-19 patients were weaned off ECMO, their out-of-hospital and 6-month survival rates did not differ from other groups despite longer ECMO runs.

There are several limitations to our study. It is a retrospective data analysis of a relatively small groups of patients. As a lot of patients were transferred to our center from other regional hospitals, there was no control in pre-ECMO patient management. Policies on ECMO contraindication criteria were not strictly adhered to, especially in COVID-19 patients. ECMO and ventilation management was more protocolized during the pandemic due to a large volume of patients. Management of ARDS patients due to other causes and ARDS due to COVID-19 were not contemporaneous and familiarity and experience with ECMO management could not be excluded for. All these factors might have affected outcomes of this analysis.

Conclusions

In conclusion, results of our study show that survival outcomes of ECMO patients do not differ between COVID-19 and ARDS of other pulmonary etiologies, suggesting that ECMO is a feasible method in this group of patients. COVID-19 ARDS differs from other pulmonary ARDS groups in that it is a more single-organ disease with less systemic involvement and that the process of lung restoration is much longer and requires longer extracorporeal support duration. Protective ventilatory strategies and other rescue respiratory measures were much more adhered to in COVID-19 patients pre- and during ECMO in our study, however time to ECMO initiation was much longer. This latter finding opens a question of whether long ECMO runs observed in these patients result

from disease process itself or whether additional ventilation-induced lung injury is the primary cause. Timely recognition of severe COVID-19 ARDS therefore remains a crucial step in management of these patients. Survival outcomes do not differ between COVID-19 and other ARDS groups in spite of longer ECMO runs suggesting that COVID-19 is not a prognostically unfavorable ARDS etiology for ECMO utilization compared to other causes of ARDS.

Author Contributions

AG, JB, and VG designed the study. The acquisition, analysis, and interpretation of data were done by JB, IZ, and AG. AG and JB drafted the manuscript. AG, JB, IZ, and VG revised the manuscript. All authors read and approved the final manuscript.

Declaration of Conflicting Interests

The authors declared no potential conflicts of interest with respect to the research, authorship, and/or publication of this article.

Funding

The authors received no financial support for the research, authorship, and/or publication of this article.

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Appendix

Table 4. Logistic Regression Predicting Likelihood of ICU Survival Based on BMI, SOFA, APACHE II, Murray score and Duration of Mechanical Ventilation Prior to ECMO.

	B	SE	*P*	Odds ratio	95% CI for odds ratio	
					Lower	**Upper**
BMI	−0.029	0.048	.542	0.971	0.884	1.067
SOFA	0.083	0.067	.216	1.087	0.952	1.240
APACHE II	−0.087	0.041	.034	0.917	0.847	0.993
Murray score	0.835	0.487	.086	2.305	0.888	5.986
MV duration before ECMO	−0.083	0.057	.144	0.921	0.824	1.029

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment.
The logistic regression model was not statistically significant, $\chi 2(4) = 10.46$, $P = .063$.

Table 5. Logistic Regression Predicting Likelihood of ICU Survival Based on BMI, SOFA, APACHE II, Murray score, Duration of Mechanical Ventilation Prior to ECMO and ARDS Etiology.

	B	SE	*P*	Odds ratio	95% CI for odds ratio	
					Lower	**Upper**
BMI	−0.021	0.049	.670	0.979	0.890	1.077
SOFA	0.080	0.073	.269	1.084	0.940	1.249
APACHE II	−0.093	0.043	.028	0.911	0.838	0.990
Murray score	1.072	0.552	.052	2.921	0.990	8.620
MV duration before ECMO	−0.082	0.059	.162	0.921	0.821	1.034
COVID 19			.548			
Influenza	−0.110	0.757	.884	0.895	0.203	3.944
Other	0.594	0.728	.415	1.810	0.435	7.538

Abbreviations: APACHE II, Acute Physiology and Chronic Health Evaluation; BMI, body mass index; MV, mechanical ventilation; SOFA, Sequential Organ Failure Assessment.
The logistic regression model was not statistically significant, $\chi 2(4) = 11.691$, $P = .111$.