Outcomes of patients with COVID-19 supported by venovenous extracorporeal membrane oxygenation for greater than 90 days

David R. Stern, MD, Lauren A. Michalak, PA-C, Allison R. Beckett, MD, Deborah R. Tabachnick, MD, and Antone J. Tatooles, MD

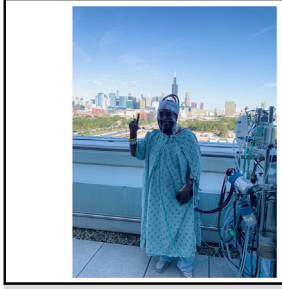
ABSTRACT

Objective: To determine the characteristics and outcomes of patients requiring prolonged (>90 days) venovenous extracorporeal membrane oxygenation (VV ECMO) support for refractory Coronavirus disease 2019 (COVID-19)-associated respiratory failure.

Methods: A retrospective, observational analysis of consecutive patients requiring VV ECMO for COVID-19–associated respiratory failure was performed at a single institution between March 2020 and January 2022. Data were collected from the medical records. Patients were predominantly cannulated and supported long-term with a single, dual-lumen cannula in the internal jugular vein with the tip positioned in the pulmonary artery. All patients were managed with an awake VV ECMO approach, emphasizing avoidance of sedatives, extubation, ambulation, physical therapy, and nutrition. Patients requiring >90 days of ECMO were identified, analyzed, and compared to those needing a shorter duration of support.

Results: A total of 44 patients were supported on VV ECMO during the study period, of whom 36 (82%) survived to discharge. Thirty-one patients were supported for <90 days, of whom 28 (90%) were discharged alive. Thirteen patients required >90 days of ECMO. All patients were extubated. Eight patients (62%) survived to discharge, with 1 patient requiring lung transplantation prior to decannulation. All survivors were free from mechanical ventilation and alive at a 6-month follow-up. Of the 4 patients who died on prolonged ECMO, 2 developed hemothorax necessitating surgery and 2 succumbed to fatal intracranial hemorrhage.

Conclusions: Patients treated with VV ECMO for COVID-19–associated respiratory failure may require prolonged support to recover. Extubation, ambulation, aggressive rehabilitation, and nutritional support while on ECMO can yield favorable outcomes. (JTCVS Open 2023;16:450-9)



Extubated, ambulatory, outdoor excursion supported on VV ECMO.

CENTRAL MESSAGE

Prolonged VV ECMO support may be necessary to facilitate pulmonary recovery in patients with refractory COVID-19–associated respiratory failure with acceptable outcomes.

PERSPECTIVE

In this retrospective observational analysis of 44 consecutive patients supported with VV ECMO for refractory COVID-19–associated respiratory failure, 13 patients required prolonged (>90 days) support. Overall survival was 82%, with 62% survival in the prolonged ECMO group. Extubation, ambulation, rehabilitation, and nutritional support can yield favorable outcomes even with prolonged ECMO.

To view the AATS Annual Meeting Webcast, see the URL next to the webcast thumbnail.

Venovenous extracorporeal membrane oxygenation (VV ECMO; hereinafter referred to as ECMO unless specified otherwise) is a viable strategy for supporting patients with respiratory failure refractory to conventional ventilator support therapies.[1,2] Early in the global COVID-19 pandemic, it was unclear whether the efficacy of ECMO for respiratory failure would extend to patients stricken with COVID-19–associated respiratory failure. However,

From the Department of Cardiovascular and Thoracic Surgery, Rush University Medical Center, Chicago, Ill.

Read at the 103rd Annual Meeting of The American Association for Thoracic Surgery, Los Angeles, California, May 6-9, 2023.

Received for publication March 6, 2023; revisions received Sept 15, 2023; accepted for publication Sept 22, 2023; available ahead of print Nov 25, 2023.

Address for reprints: David R. Stern, MD, Department of Cardiovascular and Thoracic Surgery, Rush University Medical Center, 1653 Congress Parkway, Chicago, IL 60612 (E-mail: david_stern@rush.edu).

2666-2736

https://doi.org/10.1016/j.xjon.2023.09.044

Abbreviations and Acronyms

COVID-19 = Coronavirus disease 2019
ECMO = extracorporeal membrane oxygenation
ELSO = Extracorporeal Life Support Organization
ICU = intensive care unit
LOS = length of stay
SOFA = Sequential Organ Failure Assessment
VV ECMO = venovenous extracorporeal membrane oxygenation

a recent meta-analysis that included 52 studies with 18,211 patients worldwide showed the widespread deployment of ECMO during the pandemic.[1] In addition, the Extracorporeal Life Support Organization (ELSO) published updated guidelines on the role of ECMO in patients with severe cardiopulmonary failure due to COVID-19.[2] There is also emerging evidence that prolonged ECMO support may be required for patients with COVID-19 compared to other indications for ECMO in several patient series[3-5] and case reports.[6-9]

In our institution, once cannulated for ECMO, patients with COVID-19 are managed with an awake ECMO approach emphasizing the avoidance of sedatives, extubation, ambulation, physical therapy, and nutrition. Similar to the reports referenced above,[3-9] we noted that many patients were requiring prolonged ECMO support, which translated into prolonged intensive care unit (ICU) length of stay (LOS) and prolonged use of ECMO circuits and other resources. Our awake ECMO management strategy is also labor-intensive and requires a dedicated team of physicians, nurses, physician assistants, nurse practitioners, respiratory therapists, perfusionists, ECMO specialists, physical therapists, speech therapists, occupational therapists, pharmacists, and nutritionists.

Throughout the pandemic, like much of the world, we experienced shortages of both personnel and material. These shortages limited our ability to offer ECMO to some patients who might have qualified and led to many difficult decisions. Given this milieu, we examined our outcomes in patients with COVID-19 requiring prolonged ECMO. We hypothesized that patients requiring prolonged ECMO demonstrate pulmonary recovery and outcomes similar to patients on ECMO for shorter durations. We report our outcomes in COVID-19 patients requiring >90 days of ECMO support.

METHODS

This is a retrospective, observational analysis of consecutive patients requiring venovenous ECMO for respiratory failure due to COVID-19 refractory to conventional therapies treated at Rush University Medical Center in Chicago, Illinois between March 2020 and January 2022. Patients requiring >90 days of ECMO support were identified, and data were collected from their electronic medical records. Patient identifiers were removed prior to analysis to protect patient confidentiality. The study was approved by the local Institutional Review Board (ORA 20040401-IRB01, granted April 23, 2020), and a waiver of consent was obtained.

Survival to discharge was the primary outcome. Secondary outcomes included total ECMO days required, time from cannulation to extubation, complications, hospital LOS, ICU LOS, and discharge disposition. Patients requiring >90 days of support were compared to those requiring <90 days of support. Figure 1 provides a graphical abstract of this study.

Patient Selection and Cannulation Strategies

Criteria for ECMO cannulation were based on ELSO guidelines.[2] Patients age <70 years with a body mass index <50 kg/m^2 with single organ dysfunction demonstrating acidosis, hypoxia, or hypercarbia despite maximal ventilator support and medical therapy, including sedation, neuromuscular blockade, prone positioning, and inhaled nitric oxide, were considered for ECMO cannulation. If patients had not received maximal ventilatory and medical therapy at the time of referral, adjustments were recommended to maximize their medical therapy prior to reconsideration for ECMO. The use of low-dose vasopressors was not considered multiorgan dysfunction. Absolute contraindications included cardiac arrest without return of spontaneous circulation, severe acidosis or significantly elevated lactate levels, multisystem organ failure, projected life expectancy <5 years prior to COVID-19 infection, known severe preexisting chronic life-threatening condition, and >2 weeks of mechanical ventilation. Particularly at the height of the pandemic, institutional factors, such as critical care beds and nursing staff, were also considered.

Patients in this study were cannulated and supported with a single-access, dual-stage right atrium–to–pulmonary artery cannula (ProtekDuo; LivaNova) with access through the internal jugular vein. Owing to the need for fluoroscopy, cannulation was preferentially performed in the operating room, but bedside placement in the ICU is feasible with portable imaging. A balloon-tip catheter was floated into the pulmonary artery, and a stiff wire was placed into the pulmonary artery through this catheter. The ProtekDuo cannula was advanced into the pulmonary artery using the Seldinger technique. Six smaller patients were cannulated with 29 Fr ProtekDuo cannulas, and all other patients received 31 Fr cannulas. One patient was initially cannulated via the femoral and jugular veins but was subsequently converted to a ProtekDuo cannula. One patient supported for >90 days required conversion to a central VV ECMO because adequate flows could not be maintained with a ProtekDuo cannula. Two patients who were supported for <90 days required conversion to central venoarterial ECMO because of hemodynamic collapse following the initiation of VV ECMO.

ECMO Management

Our ECMO management approach has been described previously.[10,11] In brief, initial management involves discontinuing paralytics, weaning of intravenous sedatives, and minimizing barotrauma with the goal of extubating all patients after cannulation. Lung-protective ventilation strategies are used until extubation. Given the duration and depth of sedation encountered in many patients prior to cannulation, weaning can take several weeks. The adequacy of support is determined by optimizing the metabolic demands of the patient while ensuring end-organ perfusion, as evidenced by a normal serum lactate level. Flows are maintained at 3 to 4.5 L/min. Oxygen content and delivery are facilitated by maximizing hemoglobin concentration. Episodes of relative hypoxemia are tolerated if end-organ perfusion is not compromised. Extubation is undertaken when the patient is awake, able to cough and follow commands, has a stable ECMO flow without evidence of bleeding, and demonstrates hemodynamic stability, with a lactate level <2 mmol/L and arterial saturation >70%

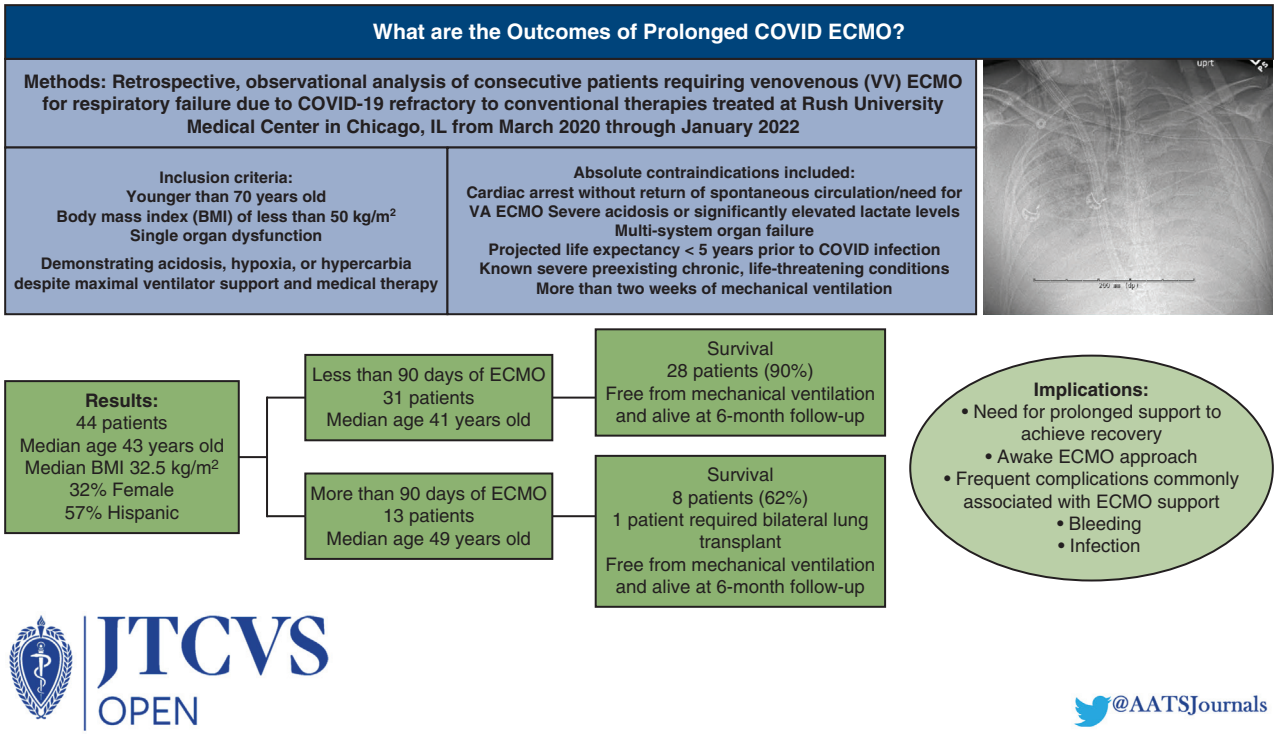


FIGURE 1. In this retrospective observational analysis of consecutive patients requiring venovenous extracorporeal membrane oxygenation (*VV ECMO*) for respiratory failure due to Coronavirus disease 2019 refractory to conventional therapies treated at Rush University Medical Center in Chicago, IL from March 2020 through January 2022, 13 patients required >90 days of ECMO support with 62% survival, highlighting the need for prolonged support to achieve recovery with favorable outcomes.

without maximal flow or sweep settings to allow for increases in support following extubation.

Following extubation, during the maintenance phase of ECMO, patients participate in physical therapy, occupational therapy, and speech therapy. Activity is increased from standing to ambulation in the ICU to excursions outside (Figure 2). Dyspnea and tachypnea are managed by increasing sweep and hemoglobin optimization. Aggressive use of incentive spirometry, ambulation, and physical therapy improves lung recruitment over time. Enteral feeds are advanced to an oral diet as tolerated. Invasive monitoring lines and central venous access are removed when the patient is hemodynamically stable. Once postcannulation hemostasis is achieved, anticoagulation with the direct thrombin inhibitor bivalirudin is initiated and continued until bleeding necessitated cessation.

Pulmonary recovery was demonstrated by improved aeration on chest radiography, appropriate blood gas values, normal arterial saturation, activity tolerance, and limited need for supplemental oxygen. When lower sweep and flows are tolerated, ECMO FiO_2 is weaned. Before decannulation, patients are trialed off sweep for a minimum of 24 hours and must ambulate without sweep. Patients are decannulated at the bedside.

Data Analysis

Categorical data are presented as percentage frequencies, and continuous data are presented as median and range. Categorical data were analyzed using the chi-square test or the Fisher exact test, as appropriate. Continuous data were analyzed by the 2-sample *t* test or Mann-Whitney *U* test, as appropriate. All tests were 2-tailed. Statistical significance was defined as $P < .05$. Analyses were performed with SAS version 9.4 (SAS Institute).

RESULTS

Patient Characteristics

Overall, 44 patients with refractory COVID-19–associated respiratory failure were supported with ECMO during the study period. The median age was 43 years, 14 (32%) patients were female, 25 (57%) were Hispanic, and the median body mass index was 32.5 kg/m^2. Thirty-one patients were on ECMO for <90 days, and 13 patients required support for >90 days. Table 1 compares baseline demographic characteristics, laboratory parameters, ventilator settings, and SOFA (Sequential Organ Failure Assessment) and Murray Scores of patients who required <90 days of ECMO support and those who were supported on ECMO for >90 days. Other than being older (49 years vs 41 years) and somewhat sicker (SOFA score 7.69 vs 6.32), patients requiring ECMO for >90 days and those supported for <90 days were similar. The lower than expected baseline median positive end-expiratory pressure can be explained by the inclusion of patients cannulated for refractory hypercarbia with not as severe hypoxemia and patients cannulated due to rapid progressive hypoxemia in the face of rising positive end-expiratory pressure. Table 2 shows a similar comparison of baseline demographics, laboratory parameters, ventilator settings, and

FIGURE 2. Awake venovenous extracorporeal membrane oxygenation (*VV ECMO*). Extubated, ambulatory, outdoor excursion supported on VV ECMO.

SOFA and Murray scores in the cohort of patients supported on ECMO for >90 days, comparing survivors and nonsurvivors. At baseline, there were no significant differences between survivors and nonsurvivors in patients requiring >90 days of ECMO.

ECMO Course and Outcomes

Of the 44 patients supported on ECMO for refractory COVID-19–associated respiratory failure in this study, 36 (82%) survived to discharge. Twenty-eight of 31 patients (90%) who were on ECMO for <90 days were discharged alive. Eight of 13 patients (62%) requiring >90 days of ECMO survived to discharge. One patient in the prolonged ECMO group required lung transplantation prior to weaning and discharge. One survivor in the <90-day cohort required tracheostomy after several trips to the operating room for hemothorax. This was the only tracheostomy in the entire group. All survivors were free of mechanical ventilation at discharge and alive at the 6-month follow-up. Table 3 characterizes the outcomes of our entire COVID-19 ECMO cohort, comparing patients supported for >90 days and <90 days. Patients on ECMO for >90 days demonstrated significantly more hemothoraces and superimposed bacteremia, pneumonia, and urinary tract infection. Approximately one-third of all survivors in both groups were discharged to home, with the remainder discharged to acute rehabilitation facilities. No patients were discharged to a long-term care facility.

Table 4 describes the outcomes of our COVID-19 ECMO patients who required >90 days of support, comparing survivors and those who died. The patients in this cohort who died sustained significantly more cannula site and intracranial bleeding, with 2 of the 4 deaths occurring during the ECMO run related to fatal intracranial hemorrhage. Although the difference in the incidence of hemothorax between prolonged ECMO survivors and nonsurvivors did not reach statistical significance, only 1 patient with a hemothorax in the survivor group required surgical intervention, whereas the other 2 patients who required surgery for hemothorax died. One patient died after decannulation prior to discharge (following 277 days of EMCO) due to recurrent respiratory failure. The longest period of support for a patient who survived to discharge was 239 days.

DISCUSSION

At the outset of the COVID-19 global pandemic, the efficacy of ECMO in supporting critically ill patients with refractory COVID-19–associated respiratory failure was unknown. Although very few patients were included, early reports in 2020 suggested poor outcomes for ECMO in patients with COVID-19, with >90% mortality.[12] Over the past 3 years, evidence has emerged from around the world that ECMO is a viable strategy for management of COVID-19–associated respiratory failure refractory to conventional therapies. A multicenter report comprising 292 patients from 17 American ECMO centers during the first wave of the pandemic found a 42% cumulative incidence of in-hospital mortality at 90 days from ECMO cannulation.[13] This compares favorably with historical prepandemic ELSO registry VV ECMO data showing a mortality of approximately 40%.[2] Nationwide reports from Germany and Israel have shown higher mortality for patients with COVID-19 supported on ECMO (65.9% of 3875 patients and 54% of 197 patients, respectively), but both cohorts included a higher percentage of older patients, perhaps highlighting the futility of ECMO support for refractory COVID-19 in patients of advanced age.[14,15] A recent meta-analysis including 52 studies with 18,211 patients worldwide over the first 2 years of the pandemic likely provides the most complete picture of the outlook for patients with COVID-19 supported on ECMO. The pooled mortality rate was 48.8%, with advancing age a predictor of increased mortality.[1] These data have led to updated ELSO guidelines on ECMO for COVID-19, suggesting conventional selection criteria for COVID-19–related ECMO cannulation while recognizing that more stringent contraindications may be implemented when resources are limited by pandemic conditions.[2]

TABLE 1. Baseline characteristics before ECMO placement, all COVID-19 ECMO patients

Variable	All COVID-19 ECMO (N = 44)	ECMO < 90 d (N = 31)	ECMO >90 d (N = 13)	*P* value
Age, y, median (range)	43.3 (23-64)	41.0 (33-64)	48.9 (23-57)	.023
Sex, n (%)				.724
Male	30 (68.2)	22 (71.0)	8 (61.5)	
Female	14 (31.8)	9 (29.0)	5 (38.5)	
BMI, kg/m^2, median (range)	32.5 (22.9-46.5)	32.6 (22.9-46.5)	32.2 (23.4-41.9)	.905
Race, n (%)				1.000
African American	6 (13.6)	4 (12.9)	2 (15.4)	
Hispanic	25 (56.8)	17 (54.8)	8 (61.5)	
Caucasian	8 (18.2)	6 (19.4)	2 (15.4)	
Asian	4 (9.1)	3 (9.7)	1 (7.7)	
Other	1 (2.3)	1 (3.2)	0 (0.0)	
Comorbidities, n (%)				
Hypertension	13 (29.6)	7 (22.6)	6 (46.2)	.156
Diabetes	8 (18.2)	6 (19.4)	2 (15.4)	1.000
CAD	2 (4.56)	0 (0)	2 (15.4)	.083
Hyperlipidemia	7 (15.9)	3 (9.7)	4 (30.8)	.170
Asthma	8 (18.2)	5 (16.1)	3 (23.1)	.676
COPD	2 (4.56)	1 (3.2)	1 (7.7)	.509
Pulmonary fibrosis	1 (2.3)	0 (0)	1 (7.7)	.300
PE/DVT	6 (13.6)	4 (12.9)	2 (15.4)	1.000
Stroke	1 (2.3)	0 (0)	1 (7.7)	.300
HIV	0 (0)	0 (0)	0 (0)	1.000
Pregnancy	5 (11.4)	4 (12.9)	1 (7.7)	1.000
Cancer	1 (2.3)	0 (0)	1 (7.7)	.300
CKD/ESRD	0 (0)	0 (0)	0 (0)	1.000
Cirrhosis	0 (0)	0 (0)	0 (0)	1.000
Heart failure	1 (2.3)	0 (0)	1 (7.7)	.300
Laboratory parameters, median (IQR)				
Creatinine on admission, mg/dL	1.0 (0.39-1.84)	1.01 (0.39-1.84)	0.95 (0.48-1.78)	.645
Creatinine at cannulation, mg/dL	0.99 (0.50-3.81)	1.06 (0.50-3.81)	0.81 (0.53-1.64)	.297
pH	7.29 (7.07-7.47)	7.28 (7.07-7.47)	7.3 (7.17-7.47)	.502
$PaCO_2$, mm Hg	62.8 (40-105)	61.6 (40-105)	65.6 (53-78)	.294
PaO_2, mm Hg	83.7 (36-172)	84.6 (53-172)	81.6 (36-149)	.699
Ventilator settings, median (range)				
PEEP, cm H_2O	13.8 (5-22)	14.2 (8-20)	13 (5-20)	.386
FiO_2, %	94 (70-100)	94 (70-100)	94 (36-149)	.924
PaO_2/FiO_2	91.3 (36-215)	92.1 (53-215)	89.3 (36-177)	.787
SOFA score, median (range)	6.73 (3-11)	6.32 (3-11)	7.69 (4-10)	.031
Murray score, median (range)	3.63 (3-4)	3.63 (3-4)	3.62 (3-4)	.937

ECMO, Extracorporeal membrane oxygenation; *BMI*, body mass index; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *PE*, pulmonary embolism; *DVT*, deep vein thrombosis; *HIV*, human immunodeficiency virus; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *IQR*, interquartile range; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; *PEEP*, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; *SOFA*, Sequential Organ Failure Assessment; *COVID-19*, Coronavirus disease 2019.

Although to date no randomized study has evaluated the role of ECMO for refractory COVID-19–associated respiratory failure, the fate of those patients with COVID-19 who meet ECMO criteria but do not receive support also should be considered. The STOP-COVID Investigators analyzed data for 5122 critically ill patients with COVID-19 admitted to 68 hospitals in the United States. Of these, 1297 met the criteria for ECMO, but only 10% of these patients were actually cannulated. Mortality of patients undergoing ECMO was 34.6%, compared to 47.4% for patients who did not receive ECMO, demonstrating that patients who were cannulated for ECMO had a lower risk of death compared to those who were not.[16] Our group performed a propensity score–matched analysis of maximally ventilated patients and 80 patients supported on ECMO at 2 tertiary centers in Chicago. Mortality was 25% in patients receiving ECMO, compared to 74% in the maximally ventilated arm, representing a 3-fold improvement in

TABLE 2. Baseline characteristics before ECMO placement, COVID-19 ECMO >90 days

Variable	COVID ECMO >90 d (N = 13)	ECMO >90 d, survivors (N = 8)	ECMO >90 d, died (N = 5)	*P* value
Age, y, median (range)	48.9 (33-64)	47.3 (33-61)	51.6 (39-64)	.455
Sex, n (%)				.565
Male	8 (61.5)	4 (50.0)	4 (80.0)	
Female	5 (38.5)	4 (50.0)	1 (20.0)	
BMI, kg/m^2, median (range)	32.3 (23.4-41.9)	32.2 (25.6-41.9)	32.4 (23.4-40.6)	.957
Race, n (%)				.608
African American	2 (15.4)	1 (12.5)	1 (20.0)	
Hispanic	8 (61.5)	5 (62.5)	3 (60.0)	
Caucasian	2 (15.4)	2 (25.0)	0 (0)	
Asian	1 (7.7)	0 (0)	1 (20.0)	
Other	0 (0)	0 (0)	0 (0)	
Comorbidities, n (%)				
Hypertension	6 (46.2)	3 (37.5)	3 (60.0)	.592
Diabetes	2 (15.4)	1 (12.5)	1 (20.0)	1.000
CAD	2 (15.4)	0 (0)	2 (40.0)	.128
Hyperlipidemia	4 (30.8)	3 (37.5)	1 (20.0)	1.000
Asthma	3 (23.1)	1 (12.5)	2 (40.0)	.512
COPD	1 (7.7)	0 (0)	1 (20.0)	.385
Pulmonary fibrosis	1 (7.7)	0 (0)	1 (20.0)	.385
PE/DVT	2 (15.4)	1 (12.5)	1 (20.0)	1.000
Stroke	1 (7.7)	0 (0)	1 (20.0)	.385
HIV	0 (0)	0 (0)	0 (0)	1.000
Pregnancy	1 (7.7)	0 (0)	1 (20.0)	.385
Cancer	1 (7.7)	0 (0)	1 (20.0)	.385
CKD/ESRD	0 (0)	0 (0)	0 (0)	1.000
Cirrhosis	0 (0)	0 (0)	0 (0)	1.000
Heart failure	1 (7.7)	0 (0)	1 (20.0)	.385
Laboratory parameters, median (IQR)				
Creatinine on admission, mg/dL	0.95 (0.48-1.78)	0.98 (0.48-1.78)	0.91 (0.64-1.32)	.782
Creatinine at cannulation, mg/dL	0.81 (0.53-1.64)	0.83 (0.53-1.64)	0.79 (0.60- 0.99)	.464
pH	7.30 (7.17-7.47)	7.31 (7.19-7.47)	7.29 (7.17-7.36)	.736
$PaCO_2$, mm Hg	65.6 (53-78)	64.6 (53-74)	67.2 (60-78)	.593
PaO_2, mm Hg	81.6 (36-149)	78.7 (36-142)	86.3 (58-149)	.698
Ventilator settings, median (range)				
PEEP, cm H_2O	13 (5-20)	14.3 (8-20)	11 (5-16)	.220
FiO_2, %	94 (70-100)	94 (80-100)	94 (70-100)	.788
PaO_2/FiO_2	89.3 (36-177)	86.6 (36-177)	93.7 (58-149)	.765
SOFA score	7.69 (4-10)	7.75 (4-10)	7.6 (6-10)	.882
Murray score	3.62 (3-4)	3.7 (3-4)	3.48 (3-4)	.230

ECMO, Extracorporeal membrane oxygenation; *BMI*, body mass index; *CAD*, coronary artery disease; *COPD*, chronic obstructive pulmonary disease; *PE*, pulmonary embolism; *DVT*, deep vein thrombosis; *HIV*, human immunodeficiency virus; *CKD*, chronic kidney disease; *ESRD*, end-stage renal disease; *IQR*, interquartile range; $PaCO_2$, partial pressure of carbon dioxide; PaO_2, partial pressure of oxygen; *PEEP*, positive end-expiratory pressure; FiO_2, fraction of inspired oxygen; *SOFA*, Sequential Organ Failure Assessment; *COVID-19*, Coronavirus disease 2019.

survival with ECMO.[17] These data reinforce that although patients requiring ECMO support for refractory COVID-19–associated respiratory failure do carry a significant mortality burden, those treated with ECMO gain a demonstrable mortality benefit compared to maximal ventilatory support alone.

There is a growing body of evidence indicating that patients treated with ECMO for COVID-19 require prolonged support compared to other indications. Case reports have described ECMO treatment for 42 days,[6] 91 days,[7] and 111 days[8] with subsequent recovery and support for 207 days as a bridge to lung transplantation.[9] Several series have chronicled the need for prolonged ECMO support. Dreier and colleagues[4] reported that 7 of 11 COVID-19 ECMO survivors in their series of 16 patients required >28 days of support without identifying any significant predictive factors for the duration of ECMO support. Another series reported by Mohanka and colleagues[3] defined

TABLE 3. ECMO outcomes, all COVID-19 ECMO patients

Outcome	All COVID-19 ECMO (N = 44)	ECMO <90 d (N = 31)	ECMO >90 d (N = 13)	*P* value
Survival to discharge, n (%)	36 (81.8)	28 (90.3)	8 (61.5)	.038
Cannulation to extubation, d, median (IQR)	8 (2-47)	8 (2-47)	8 (2-25)	.585
ECMO days, median (IQR)	68.5 (1-277)	31 (1-85)	131 (95-277)	<.001
ICU LOS, d, median (IQR)	80 (6-299)	48 (6-99)	151 (97-299)	<.001
Hospital LOS, d, median (IQR)	81 (7-314)	56 (7-102)	154 (97-314)	<.001
Complications, n (%)				
AKI requiring RRT	6 (13.6)	5 (16.1)	1 (7.7)	.652
Stroke	3 (6.8)	1 (3.2)	2 (15.4)	.204
VTE				
Deep vein thrombosis	6 (13.6)	5 (16.1)	1 (7.7)	.652
Pulmonary embolism	1 (2.3)	0 (0)	1 (7.7)	.300
Bleeding	28 (63.6)	18 (58.1)	10 (76.9)	.314
SAH/ICH	5 (11.4)	2 (6.5)	3 (23.1)	.144
Hematomas	6 (13.6)	1 (3.2)	5 (38.5)	.006
Vaginal bleeding	3 (6.8)	2 (6.5)	1 (7.7)	1.000
Lines/cannula	12 (27.3)	5 (16.1)	7 (53.9)	.023
Hematuria	10 (22.7)	8 (25.8)	2 (15.4)	.697
Gastrointestinal	6 (13.6)	3 (9.7)	3 (23.1)	.340
Hemothorax	5 (11.4)	1 (3.2)	4 (30.8)	.022
Nasopharyngeal/oropharyngeal	20 (45.5)	11 (35.5)	9 (69.2)	.053
Other	8 (18.6)	5 (16.1)	3 (25.0)	.665
Infection	39 (88.6)	26 (83.8)	13 (100)	.301
Pneumonia	27 (61.4)	16 (51.6)	11 (84.6)	.040
Bacteremia	26 (59.1)	15 (48.4)	11 (84.6)	.026
Empyema	2 (4.6)	0 (0)	2 (15.4)	.083
Urinary tract	9 (20.5)	3 (9.7)	6 (46.2)	.012
Empiric therapy	21 (47.7)	14 (45.2)	7 (53.8)	.599
Other site	3 (6.8)	0 (0)	3 (23.1)	.022
Disposition, n (%)				
Home	14 (35)	11 (35.5)	3 (33.3)	1.000
Acute rehabilitation	22 (55)	17 (54.8)	5 (55.7)	1.000

COVID-19, Coronavirus disease 2019; *ECMO*, extracorporeal membrane oxygenation; *IQR*, interquartile range; *ICU*, intensive care unit; *LOS*, length of stay; *AKI*, acute kidney injury; *RRT*, renal replacement therapy; *VTE*, venous thromboembolism; *SAH*, subarachnoid hemorrhage; *ICH*, intracranial hemorrhage.

prolonged ECMO as >30 days of support with 10 patients in their cohort. Patients requiring prolonged support demonstrate worse pulmonary compliance and CO_2 concentrations at baseline. Seven patients were ultimately weaned, 6 with native lung recovery and 1 requiring transplantation. Russ and colleagues[5] compared the duration of support required for 16 COVID-19 ECMO survivors versus 23 surviving patients cannulated for non–COVID-19–associated respiratory failure. Patients with COVID-19 needed support for a median of 43 days, as opposed to 16 days for non–COVID-19–associated ECMO.[5]

Our own COVID-19–associated ECMO data confirm the need for prolonged support to achieve recovery. Of the 36 patients who survived to discharge after requiring ECMO for COVID-19–associated respiratory failure (out of 44 total ECMO patients with COVID-19), only 11 could be weaned with <30 days of support. In survivors, the median duration of ECMO was 63 days. Only 6 of the 36 survivors were supported for <25 days, with 1 patient requiring 239 days of support. In light of these findings, we chose to define prolonged ECMO support for this analysis as >90 days. In total, 44 patients were supported with ECMO for refractory COVID-19–associated respiratory failure at our institution with 82% survival to discharge. All patients who survived to discharge remained alive at 6-month follow-up. Survival was 90% in patients who were supported for <90 days. Thirteen patients needed prolonged ECMO, with >90 days of support, 8 of whom (62%) survived to discharge. One of these patients required lung transplantation, whereas the remainder demonstrated adequate native pulmonary recovery to separate from ECMO without mechanical ventilation. These results compare favorably with reported COVID-19 associated ECMO outcomes. To our knowledge, this is the first report of outcomes with a series of >10 patients supported on ECMO for such a prolonged duration.

TABLE 4. ECMO outcomes, COVID-19 ECMO >90 days

Outcome	COVID ECMO >90 d (N = 13)	ECMO >90 d, survivors (N = 8)	ECMO >90 d, died (N = 5)	*P* value
Time from cannulation to extubation, d, median (IQR)	8 (2-25)	6.5 (2-24)	12 (5-25)	.270
ECMO days, median (IQR)	131 (95-277)	124.5 (95-239)	154 (97-277)	.608
ICU LOS, d, median (IQR)	151 (97-299)	146 (111-261)	158 (97-299)	.706
Hospital LOS, d, median (IQR)	154 (97-314)	147.5 (111-277)	166 (97-314)	.706
Complications, n (%)				
AKI requiring RRT	1 (7.7)	0 (0)	1 (20.0)	.385
Stroke	2 (15.4)	0 (0)	2 (40.0)	.128
VTE				
Deep vein thrombosis	1 (7.7)	0 (0)	1 (20.0)	.385
Pulmonary embolism	1 (7.7)	1 (12.5)	0 (0)	1.000
Bleeding	10 (76.9)	5 (62.5)	5 (100)	.231
SAH/ICH	3 (23.1)	0 (0)	3 (60.0)	.035
Hematomas	5 (38.5)	3 (37.5)	2 (40.0)	1.000
Vaginal bleeding	1 (7.7)	0 (0)	1 (20.0)	.385
Lines/cannula	7 (53.6)	2 (25.0)	5 (100)	.021
Hematuria	2 (15.4)	1 (12.5)	1 (20.0)	1.000
Gastrointestinal	3 (23.1)	2 (25.0)	1 (20.0)	1.000
Hemothorax	4 (30.8)	2 (25.0)	2 (40.0)	1.000
Nasopharyngeal/oropharyngeal	9 (69.2)	6 (75.0)	3 (60.0)	1.000
Other	3 (23.1)	1 (12.5)	2 (40.0)	.236
Infection	13 (100)	8 (100)	5 (100)	1.000
Pneumonia	11 (84.6)	6 (75.0)	5 (100)	.487
Bacteremia	11 (84.6)	6 (75.0)	5 (100)	.487
Empyema	2 (15.4)	1 (12.5)	1 (20.0)	1.000
Urinary tract	6 (46.2)	4 (50.0)	2 (40.0)	1.000
Empiric therapy	7 (53.9)	4 (50.0)	3 (60.0)	1.000
Other site	3 (23.1)	2 (25.0)	1 (20.0)	1.000
Disposition, n (%)				
Home	3 (23.1)	3 (37.5)	0 (0)	1.000
Acute rehabilitation	5 (38.5)	5 (62.5)	0 (0)	.444

ECMO, Extracorporeal membrane oxygenation; *IQR*, interquartile range; *ICU*, intensive care unit; *LOS*, length of stay; *AKI*, acute kidney injury; *RRT*, renal replacement therapy; *VTE*, venous thromboembolism; *SAH*, subarachnoid hemorrhage; *ICH*, intracranial hemorrhage; *COVID-19*, Coronavirus disease 2019.

We attribute our favorable outcomes, particularly with such prolonged support, to several factors. The most important factor is a consistent, committed team of providers dedicated to an awake ECMO approach. Although often challenging in patients who have been heavily sedated and are frequently paralyzed prior to cannulation, we push to extubate patients as soon as safely possible after cannulation. While we do emphasize extubation on ECMO, it is important that patients not be extubated too early on maximal support, as there needs to be capacity to increase support if metabolic demands increase postextubation. Sedation is minimized, and parenteral agents are converted to oral formulations as tolerated. The work of breathing is controlled with sweep. Following extubation, an aggressive rehabilitation program with physical, occupational, and speech therapy is initiated. Standing with progression to ambulation around the ICU is emphasized. As patients ambulate and rehabilitate, respiratory mechanics and lung recruitment with incentive spirometry improve. It was not uncommon to see that completely opacified lung fields on chest radiography begin to improve only after patients began ambulating. Enteral nutrition is also a priority. Rehabilitation while on support facilitates the best opportunity for the patient to separate from ECMO and thrive afterward. Only 1 patient who was weaned died prior to discharge, following 277 days of ECMO support, as a result of recurrent respiratory failure. Owing to the emphasis on rehabilitation while on ECMO, one-third of our survivors could be discharged to home, and the remainder were discharged to acute rehabilitation facilities where they could continue an aggressive rehabilitation program. No surviving patients were discharged to long-term care facilities, and all survivors were free of mechanical ventilation at discharge and alive at the 6-month follow-up, demonstrating the utility of this aggressive rehabilitation on ECMO approach.

Facilitating this awake ECMO approach influences our cannulation strategy. Patients are supported long-term with the ProtekDuo, single-access dual-lumen cannula in the internal jugular vein (or rarely, subclavian vein), with the tip positioned in the pulmonary artery. We favor this approach for several reasons. This configuration provides a stable platform with long-term cannula stability without malposition and a single access point that minimizes recirculation. The right ventricular support provided by this cannula with direct flow into the pulmonary artery is also of potential benefit, as we frequently encountered elevated central venous pressure and pulmonary hypertension, leading to right ventricular failure in patients with severe COVID-19. Data are emerging to support our approach. A multicenter, retrospective study in which our group participated supports our conclusion regarding the benefits of ProtekDuo cannulation. Among 435 patients with COVID-19 supported with ECMO from 17 centers, 99 patients received ProtekDuo support. At 90 days, in-hospital mortality was 41% for patients cannulated with a ProtekDuo versus 60% with dual-site cannulation and 61% with a single-site dual-lumen cannula in the internal jugular vein with the tip positioned in the inferior vena cava.[18] A recent review of 5 studies comprising 194 patients cannulated with the ProtekDuo for COVID-19 associated respiratory failure suggests similar conclusions. Survival rates were between 59% and 89% across the studies and significant survival benefit was demonstrated when compared to other cannulation configurations.[19]

Despite this approach, our patients did experience the frequent complications commonly associated with ECMO support, with bleeding and infection the most prevalent. Of patients on ECMO for >90 days, 77% suffered at least 1 bleeding complication, and 100% demonstrated superimposed infection. We believe that our focus on aggressive rehabilitation and nutrition while on support gives patients the best opportunity to tolerate these complications and proceed toward recovery. Ultimately, all 4 patients who died while on ECMO after >90 days of support succumbed to major bleeding complications, 2 from hemothorax and 2 from intracranial hemorrhage, highlighting bleeding as the Achilles heel of ECMO therapy.

This study has several limitations. This was a retrospective review with data collection limited to chart review and outside hospital records. In addition, the sample size was small, and there was no control group.

Conclusions

We have demonstrated that a subset of patients treated with ECMO for refractory COVID-19–associated respiratory failure require prolonged support to achieve pulmonary recovery with outcomes comparable to patients supported on ECMO for shorter durations. Eight of 13 patients (62%) supported for >90 days survived to discharge and were alive at the 6-month follow-up without the need for mechanical ventilation. Only 1 patient required lung transplantation. Although early outcomes of lung transplantation for COVID-19–associated respiratory failure appear to be similar to those of lung transplantation for other indications,[20] the long-term trajectory of transplanted versus COVID-19–recovered native lungs remains unknown. Even if survivors of prolonged COVID-19 ECMO eventually progress to transplantation, delaying lung transplantation to a more elective setting at a later date likely will extend patients' overall lifespan. Long-term follow-up of our patients with COVID-19 supported with prolonged ECMO will be important to answer this question.

Webcast

You can watch a Webcast of this AATS meeting presentation by going to: https://www.aats.org/resources/outcomes-of-patients-with-covid-19-supported-by-vv-ecmo-for-greater-than-ninety-days.

Conflict of Interest Statement

A.J.T. has served as a consultant for Abbott Laboratories, Medtronic, and Livanova outside of the submitted work. All other authors reported no conflicts of interest.

The *Journal* policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they may have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

We thank the nurses, physician assistants, nurse practitioners, respiratory therapists, perfusionists, ECMO specialists, physical therapists, speech therapists, occupational therapists, pharmacists, nutritionists, residents, fellows, and everybody else who cared for the patients in our cohort.

References

1. Ling RR, Ramanathan K, Sim JJL, Wong SN, Chen Y, Amin F, et al. Evolving outcomes of extracorporeal membrane oxygenation during the first 2 years of the COVID-19 pandemic: a systematic review and meta-analysis. *Crit Care*. 2022;26:147.
2. Badulak J, Antonini MV, Stead CM, Shekerdemian L, Raman L, Paden ML, et al. Extracorporeal membrane oxygenation for COVID-19: updated 2021 guidelines from the extracorporeal life support organization. *ASAIO J*. 2021;67:485-95.
3. Mohanka MR, Joerns J, Lawrence A, Bollineni S, Kaza V, Cheruku S, et al. ECMO long haulers: a distinct phenotype of COVID-19-associated ARDS with implications for lung transplant candidacy. *Transplantation*. 2022;106:e202-11.
4. Dreier E, Malfertheiner MV, Dienemann T, Fisser C, Foltan M, Geismann F, et al. ECMO in COVID-19-prolonged therapy needed? A retrospective analysis of outcome and prognostic factors. *Perfusion*. 2021;36:582-91.

5. Russ M, Menk M, Graw JA, Skrypnikov V, Hunsicker O, Rudat K, et al. COVID-19 patients require prolonged extracorporeal membrane oxygenation support for survival compared with non-COVID-19 patients. *Crit Care Explor*. 2022; 4:e0671.
6. Fitzgerald AL, Vachharajani HH, Davidson BP, Kruit NJ, Eslick AT. The prolonged use of VV ECMO support in COVID-19: a case report. *J Crit Care Med (Targu Mures)*. 2020;6:224-30.
7. Biblowitz K, Mullin M, McDermott L, Sykuta A, Baram M, Hirose H. A multidisciplinary approach to prolonged extracorporeal membrane oxygenation for acute respiratory distress syndrome due to coronavirus 2019-case report. *AME Case Rep*. 2022;6:8.
8. Xu Z, Xu Y, Liu D, Liu X, Zhou L, Huang Y, et al. Case report: prolonged VV-ECMO (111 days) support in a patient with severe COVID-19. *Front Med*. 2021; 8:681548.
9. Naar J, Kruger A, Vondrakova D, Janotka M, Kubele J, Lischke R, et al. A total of 207 days of veno-venous extracorporeal membrane oxygenation support for severe COVID-19 prior to successful lung transplantation: a case report. *J Pers Med*. 2022;12:2028.
10. Gurnani PK, Michalak LA, Tabachnick D, Kotwas M, Tatooles AJ. Outcomes of extubated COVID and non-COVID patients receiving awake venovenous extracorporeal membrane oxygenation. *ASAIO J*. 2022;68:478-85.
11. Tatooles AJ, Mustafa AK, Joshi DJ, Pappas PS. Extracorporeal membrane oxygenation with right ventricular support in COVID-19 patients with severe acute respiratory distress syndrome. *JTCVS Open*. 2021;8:90-6.
12. Henry BM, Lippi G. Poor survival with extracorporeal membrane oxygenation in acute respiratory distress syndrome (ARDS) due to coronavirus disease 2019 (COVID-19): pooled analysis of early reports. *J Crit Care*. 2020; 58:27-8.
13. Saeed O, Tatooles AJ, Farooq M, Schwartz G, Pham DT, Mustafa AK, et al. Characteristics and outcomes of patients with COVID-19 supported by extracorporeal membrane oxygenation: a retrospective multicenter study. *J Thorac Cardiovasc Surg Tech*. 2022;163:2107-16.e6.
14. Friedrichson B, Kloka JA, Neef V, Mutlak H, Old O, Zacharowski K, et al. Extracorporeal membrane oxygenation in coronavirus disease 2019: a nationwide cohort analysis of 4279 runs from Germany. *Eur J Anaesthesiol*. 2022;39:445-51.
15. Makhoul M, Keizman E, Carmi U, Galante O, Ilgiyaev E, Matan M, et al. Outcomes of extracorporeal membrane oxygenation (ECMO) for COVID-19 patients: a multi-institutional analysis. *Vaccines (Basel)*. 2023;11:108.
16. Shaefi S, Brenner SK, Gupta S, O'Gara BP, Krajewski ML, Charytan DM, et al. Extracorporeal membrane oxygenation in patients with severe respiratory failure from COVID-19. *Intensive Care Med*. 2021;47:208-21.
17. Mustafa AK, Joshi DJ, Alexander PJ, Tabachnick DR, Cross CA, Jweied EE, et al. Comparative propensity matched outcomes in severe COVID-19 respiratory failure-extracorporeal membrane oxygenation or maximum ventilation alone. *Ann Surg*. 2021;274:e388-94.
18. Saeed O, Stein LH, Cavarocchi N, Tatooles AJ, Mustafa A, Jorde UP, et al. Outcomes by cannulation methods for venovenous extracorporeal membrane oxygenation during COVID-19: a multicenter retrospective study. *Artif Organs*. 2022;46:1659-68.
19. Maybauer MO, Capoccia M, Maybauer DM, Lorusso R, Swol J, Brewer JM. The ProtekDuo in ECMO configuration for ARDS secondary to COVID-19: a systematic review. *Int J Artif Organs*. 2023;46:93-8.
20. Roach A, Chikwe J, Catarino P, Rampolla R, Noble PW, Megna D, et al. Lung transplantation for Covid-19-related respiratory failure in the United States. *N Engl J Med*. 2022;386:1187-8.

Key Words: COVID-19, respiratory failure, ECMO, VV ECMO, prolonged ECMO