

One-Year Outcomes With Venovenous Extracorporeal Membrane Oxygenation Support for Severe COVID-19



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ABSTRACT

BACKGROUND Severe coronavirus disease 2019 (COVID-19) can cause acute respiratory failure requiring mechanical ventilation. Venovenous (VV) extracorporeal membrane oxygenation (ECMO) has been used in patients in whom conventional mechanical ventilatory support has failed. To date, published data have focused on survival from ECMO and survival to discharge. In addition to survival to discharge, this study reports 1-year follow-up data for patients who were successfully discharged from the hospital.

METHODS A single-institution, retrospective review of all patients with severe COVID-19 who were cannulated for VV-ECMO between March 10, 2020 and May 1, 2020 was performed. A multidisciplinary ECMO team evaluated, selected, and managed patients with ECMO support. The primary outcome of this study was survival to discharge. Available 1-year follow-up data are also reported.

RESULTS A total of 30 patients were supported with VV-ECMO, and 27 patients (90%) survived to discharge. All patients were discharged home or to acute rehabilitation on room air, except for 1 patient (3.7%), who required supplemental oxygen therapy. At a median follow-up of 10.8 months (interquartile range [IQR], 8.9-14.4 months) since ECMO cannulation, survival was 86.7%, including 1 patient who underwent lung transplantation. Of the patients discharged from the hospital, 44.4% (12/27) had pulmonary function testing, with a median percent predicted forced expiratory volume of 100% (IQR, 91%-110%). For survivors, a 6-minute walk test was performed in 59.3% (16/27), with a median value of 350 m (IQR, 286-379 m).

CONCLUSIONS A well-defined patient selection and management strategy of VV-ECMO support in patients with severe COVID-19 resulted in exceptional survival to discharge that was sustained at 1-year after ECMO cannulation.

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Coronavirus disease 2019 (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), can progress to acute respiratory distress syndrome (ARDS) with hypoxic or hypercarbic respiratory failure. Conventional mechanical ventilation in COVID-19 is associated with a mortality greater than 50%.¹⁻³ Early reports of the use of venovenous (VV) extracorporeal membrane oxygenation (ECMO) in patients with refractory ARDS caused by severe COVID-19 were discouraging because the survival outcomes were lower than those expected for

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non-COVID ARDS.⁴⁻⁶ Despite this, when the pandemic reached New York City in March 2020, we offered VV-ECMO to patients with severe COVID-19 who met specific inclusion criteria (Supplemental Text). Since the initial surge of the pandemic, a growing body of literature has emerged reporting outcomes of patients cannulated for ECMO for COVID-19.⁷⁻¹¹ To date, nearly all reports have focused on the standard ECMO outcome metrics of survival from ECMO and survival to hospital discharge. Although these are important markers for reporting standards, they are inherently limited in scope because they do not reflect overall clinical recovery. Given the lack of posthospitalization outcomes of patients who underwent VV-ECMO support for severe COVID-19, we report the final disposition status for all 30 patients from our initial experience, as well as 1-year outcomes.

PATIENTS AND METHODS

A single-institution (NYU Langone Health, New York, NY) retrospective review of all patients with severe COVID-19 who were supported with VV-ECMO between March 10, 2020 and May 1, 2020 was performed. A multidisciplinary team evaluated patients for ECMO cannulation on the basis of the development of ARDS secondary to COVID-19, underlying comorbidities, and a determination of reasonable likelihood for survival with ECMO support.⁹ The primary outcome was survival to discharge. Hospital and ECMO-related complications were also reported. As a secondary outcome, survival and clinical status at 1 year after ECMO cannulation were evaluated. This study was approved by the Institutional Review Board at NYU Langone Health (IRB #S20-00611), and a waiver of informed consent was obtained.

PATIENT SELECTION AND MANAGEMENT. The diagnosis of COVID-19 was established by nasal pharyngeal swab for reverse transcriptase polymerase chain reaction assay. Patients were evaluated, cannulated for VV-ECMO, and managed by a multidisciplinary team of cardiothoracic surgeons and critical care physicians.⁹ Patients with refractory respiratory failure during maximal mechanical ventilation were selected for VV-ECMO. No patients underwent venoarterial ECMO for COVID-related diseases during the initial pandemic surge. The primary cannulation strategy included a percutaneous right femoral venous drainage cannula and a right internal jugular venous return cannula. The details of our management strategy, including our anticoagulation strategy, early percutaneous tracheostomy, frequent bronchoscopy, and use of prone positioning during ECMO strategy, have been reported.^{12,13}

MIDTERM OUTCOMES. All alive patients had at least 1 year of follow-up. The last day of follow-up was either the last patient encounter date (if patients presented to our medical center for follow-up) or the last date of contact with the patient by telephone. Lung recovery was assessed at follow-up visits by using pulmonary function tests (PFTs) or a 6-minute walk test, or both.

STATISTICAL ANALYSIS. Descriptive analyses were used to report the following: patients' baseline characteristics; hospital course, including ECMO, COVID-19 related medical management, and ARDS-related complications; and post-ECMO outcomes. Categorical variables are reported as frequencies and percentages. Continuous variables are reported as median with interquartile range (IQR). Statistical analyses were performed with SPSS Statistics software version 26.0 (IBM Corp).

RESULTS

From March 10, 2020 through May 1, 2020, 415 patients were admitted to the intensive care unit (ICU) of the NYU Langone Health Manhattan campus with confirmed COVID-19 infection. Of these patients, 323 (77.8%) were intubated for mechanical ventilatory support. Of these ICU patients, 80 (19.3%) were evaluated for ECMO, and 30 (7.2%) were cannulated for VV-ECMO.

Demographics, baseline health characteristics, and pre-ECMO data of patients supported on VV-ECMO are reported in Table 1. The median age was 42 years (IQR, 30-47 years), and 26 patients (86.7%) were male. Patients were admitted for a median of 2.5 days (IQR, 0.75-6.5 days) before intubation and 5.5 days (IQR, 4-8.5 days) before initiation of VV-ECMO. All patients were intubated and placed on a mechanical ventilator before VV-ECMO cannulation, with a median peak inspiratory pressure of 32 cm H₂O (IQR, 28-38 cm H₂O) and a ratio of PaO₂ to fraction of inspired oxygen (FiO₂) (P/F ratio) of 80 (IQR, 61-87).

ECMO AND MEDICAL MANAGEMENT. The details of VV-ECMO cannulation strategy and concurrent interventions are outlined in Table 2. All patients were placed on VV-ECMO at the bedside in the ICU by using ultrasound-guided access. An operative intervention was required in 6 patients (20%): 3 for resection of a cystic lung with or without pneumatocele in patients with a persistent pneumothorax and air leak, 2 for evacuation of hemothorax, and 1 for lobectomy because of hemorrhagic infarction.¹⁴ Concurrent COVID-19-specific therapies are summarized in Supplemental Table 1.

ECMO AND HOSPITAL OUTCOMES. The primary end point of survival to discharge was achieved in 27 patients (90%). A total of 28 patients (93.3%) survived VV-ECMO.

TABLE 1 Demographic and Clinical Data of Patients With Severe Acute Respiratory Distress Syndrome Associated With Coronavirus Disease 2019 Before the Initiation of Venovenous Extracorporeal Membrane Oxygenation

Variable	VV-ECMO (N =30)
Age, median (IQR, range), y	42 (30-47, 18-65)
Sex, n (%)	
Male	26 (87)
Female	4 (13)
Ethnicity	
Hispanic	18 (60)
White	9 (30)
Asian	3 (10)
Body mass index, median (IQR), kg/m ²	30 (25-35)
Smoking history, n (%)	
Never smoker	18 (60)
Yes, current smoker	3 (10)
Yes, former smoker	5 (16.7)
Not assessed or unknown	4 (13.3)
Comorbidities, n (%)	
Obesity, BMI, 30-35 kg/m ²	16 (53)
Overweight, BMI, 25-29 kg/m ²	9 (30)
Hypertension	7 (23)
Asthma, chronic obstructive pulmonary disease	5 (17)
Diabetes	5 (17)
Immunosuppression, steroid use	3 (10)
Known pulmonary embolism or deep venous thrombosis	3 (10)
HIV infection	2 (6.7)
Coronary artery disease	1 (3.3)
End-stage renal disease on dialysis	0 (0)
Stroke	0 (0)
Active malignant disease	0 (0)
Pre-ECMO hospital course, median (IQR)	
Days from admission to intubation	2.5 (0.75-6.5)
Days from admission to ECMO	5.5 (4-8.5)
Days from intubation to ECMO cannulation	2 (1-4)
Pre-ECMO coinfection, n (%)	
Influenza	0 (0%)
Bacterial pneumonia	4 (13.3%)
Bacteremia	2 (6.7)
Interventions before ECMO, n (%)	
Prone positioning	23 (77)
Neuromuscular blockade	24 (80)
Inhaled nitric oxide	9 (30)
Continuous renal-replacement therapy	1 (3.3)
Cardiopulmonary resuscitation	1 (3.3)
Laboratory data before ECMO, median (IQR)	
Creatinine, mg/dL	0.88 (0.73-1.2)

(Continued)

TABLE 1 Continued

Variable	VV-ECMO (N =30)
Lactate dehydrogenase, U/L	724 (550-871)
Ferritin, ng/mL	2142 (1436-2882)
D-Dimer, ng/mL	2355 (893-3483)
C-reactive protein, mg/dL	119 (68-216)
Procalcitonin, ng/mL	0.9 (0.16-2.8)
Hematocrit, %	38 (33-43)
White blood cell count, k/ μ L	11.5 (8.2-18.7)
pH median (IQR)	7.22 (7.18-7.29)
Po ₂ median (IQR), mm Hg	68 (63-73)
Pco ₂ median (IQR), mm Hg	59 (51-70)
FiO ₂ median (IQR), mm Hg	100 (75-100)
Pao ₂ /FiO ₂ (P/F ratio)	80 (61-87)
Lactate, mmol/L	1.6 (1.1-1.9)
Mechanical ventilation data, median (IQR)	
Plateau pressure, cm H ₂ O	30 (28-34)
Peak inspiratory pressure, cm H ₂ O	32 (28-38)
Positive end-expiratory pressure, cm H ₂ O	14 (12-18)
Respiratory rate, breaths/min	26 (22-28)
Tidal volume, mL	422 (363-493)
Pre-ECMO vasopressor or inotrope requirement, n (%)	13 (43)

BMI, body mass index; ECMO, extracorporeal membrane oxygenation; FiO₂, fraction of inspired oxygen; IQR, interquartile range; VV-ECMO, venovenous extracorporeal membrane oxygenation.

The cause of death for the patient who died after successful VV-ECMO decannulation, but before discharge, was progressive liver failure complicated by gastrointestinal bleeding. Patients were hospitalized for a median of 45 days (IQR, 29-80 days), with a median ICU length of stay of 40 days (IQR, 28-75 days). Patients were supported on VV-ECMO for a median of 19 days (IQR, 11-45 days; range, 0-153 days). [Supplemental Table 2](#) outlines ECMO-associated complications. Acute kidney injury, defined as a creatinine value >1.5 mg/dL, as established by the Extracorporeal Life Support Organization registry, occurred in 14 patients (46.7%), and 2 patients (6.7%) required renal replacement therapy.

Of the 27 patients discharged from the hospital, 23 patients (85.2%) were discharged to a short-term rehabilitation facility. Patients spent a median of 11 days (IQR, 8-16 days) in a short-term rehabilitation facility before discharge home. Four patients (14.8%) were discharged home directly from the hospital. Only 1 patient required daily supplemental oxygen at the time of discharge. No patients were transferred to a long-term care facility or another hospital. Thirty-day readmission occurred in 2 patients (7.4%): 1 patient was admitted for ascending cholangitis, and the other

TABLE 2 Extracorporeal Membrane Oxygenation and Medical Management Data of Patients With Severe Acute Respiratory Distress Syndrome Associated With Coronavirus Disease 2019 Who Were Initiated on Venovenous Extracorporeal Membrane Oxygenation

Variable	VV-ECMO (N=30)
VV-ECMO data, n (%)	
Right internal jugular, right femoral vein cannulation	28 (93.3)
Alternative cannulation	2 (6.7)
Cannulation at the bedside	30 (100)
Revision of cannulas	1 (3.3)
Conversion from VV-ECMO to VA-ECMO	0 (0)
Concurrent interventions during VV-ECMO, n (%)	
Cytokine hemoadsorption	10 (33)
Prone positioning	12 (40)
Tube thoracostomy	10 (33)
Bronchoscopy	29 (97)
Number performed throughout admission, median (IQR)	7 (3.8-10.5)
Tracheostomy	29 (97)
Duration from intubation to tracheostomy, d, median (IQR)	9 (5-10)
Duration from VV-ECMO to tracheostomy, d, median (IQR)	1 (1-3)
Operative intervention	6 (20)

IQR, interquartile range; VA-ECMO, venoarterial extracorporeal membrane oxygenation; VV-ECMO, venovenous extracorporeal membrane oxygenation.

patient was admitted for respiratory support requiring intermittent ventilation through a tracheostomy. Notably, the patient who was admitted for respiratory support was the same patient who was discharged with daily supplemental oxygen therapy. One patient died after discharge from the hospital as a result of end-stage liver disease and was awaiting liver transplantation at the time of death. In-hospital clinical outcomes are summarized in Table 3.

MIDTERM CLINICAL OUTCOMES. At a median follow-up of 10.8 months (IQR, 8.9-14.4 months) since ECMO cannulation, 26 patients (86.7%) were alive, and all were discharged from the hospital and at home. Of the 27 patients who survived to discharge, 25 patients (92.6%) were on room air since discharge. In 1 patient, an oxygen requirement after discharge developed from progression of post-COVID-19 pulmonary fibrosis, and this patient underwent lung transplantation 11 months after cannulation (7 months after being weaned from ECMO support). Among patients discharged from the hospital, 44.4% (12/27) underwent PFTs at a median of 5 months after cannulation (median of 4 months after decannulation). The results are summarized in Table 4. The single patient with significantly abnormal PFT results underwent lung transplantation, as described. A

TABLE 3 In-Hospital Clinical Outcomes of Patients With Severe Acute Respiratory Distress Syndrome Associated With Coronavirus Disease 2019 who were initiated on Venovenous Extracorporeal Membrane Oxygenation

Variable	VV-ECMO (N = 30)
Number of patients offered VV-ECMO, n (%)	30
Survived VV-ECMO	28 (93)
Survived to discharge	27 (90)
Duration of mechanical ventilation, d, median (IQR)	38 (27-68)
Duration of VV-ECMO, d, median (IQR)	19 (11-45)
ICU length of stay, d, median (IQR)	40 (28-75)
Hospital length of stay, d, median (IQR)	45 (29-80)
Discharge disposition of survivors, n (%)	
Home	4 (15)
Acute rehabilitation facility	23 (85)
Long-term acute care or skilled nursing facility	0 (0)
Transfer to another hospital	0 (0)
Supplemental oxygen requirement at discharge, n (%)	1 (3.7)
Acute rehabilitation length of stay, d, median (IQR)	11 (8-16)
30-day readmission, n (%)	2 (6.7)

ICU, intensive care unit; IQR, interquartile range; VV-ECMO, venovenous extracorporeal membrane oxygenation.

6-minute walk test was performed in 16 patients (59.3%). Patients walked a median of 350 m (IQR, 286-379 m), with a median Borg dyspnea index of 1 (IQR, 0-1.5). The median lowest measured oxygen saturation during the 6-minute walk was 94% (IQR, 92%-95%).

COMMENT

Our initial reports of VV-ECMO for COVID-19 were encouraging, as were the results published by other institutions; however, the final disposition and clinical status of many of these patients remained unclear.^{9,10} In this context, data published early in the pandemic were less positive. Data from the Extracorporeal Life Support Organization registry reported a mortality rate of 38%.⁷ However, a more recent review of their publicly available data found that even in the ARDS cohort, in-hospital mortality increased to 48%, with another 26% transferred to a long-term acute care hospital or another hospital.⁷ This transfer to long-term acute care hospital or another hospital represents 54.2% (691/1274) of the “survived to discharge” cohort. Only 22% of ECMO-treated patients were discharged to home or a short-term rehabilitation facility. Another large, multicenter series reported outcomes of 37 patients supported with VV-ECMO; 56.8% (21/37) survived to discharge.¹¹ Withdrawal of therapy for futility occurred in 35.1% of

TABLE 4 The 1-Year Postcannulation Clinical Outcomes of Patients With Severe Acute Respiratory Distress Syndrome Associated With Coronavirus Disease 2019 Who Were Initiated on Venovenous Extracorporeal Membrane Oxygenation

Variable	VV-ECMO (N = 30)
Survival at 1 year after cannulation, n (%)	26 (86.7)
Cause of death in patients who died during initial hospital stay, n (%)	
Cardiac arrest from ARDS secondary to COVID-19	2 (6.7)
Progressive liver failure and gastrointestinal bleeding	1 (3.3)
Cause of death in the patient who died after discharge, n (%)	
End-stage liver disease	1 (3.3)
Disposition at 1 year after cannulation, n (%)	
Home, on room air	25 (83.3)
Home, on oxygen	1 (3.3)
Died, in-hospital	3 (10)
Died, after discharge	1 (3.3)
Pulmonary function testing, n (%)	12/26 (46)
Days after cannulation, median (IQR)	218 (141-248)
Days after decannulation, median (IQR)	202 (128-214)
TLC, L, median (IQR)	6.01 (4.3-6.9)
TLC % predicted, median (IQR)	92 (88-94)
FVC, L, median (IQR)	3.44 (3.1-5.1)
FVC % predicted, median (IQR)	106 (92-116)
FEV ₁ , L, median (IQR)	2.92 (2.5-3.7)
FEV ₁ % predicted, median (IQR)	100 (89-106)
DLco % predicted, median (IQR)	86 (73-95)
6-min walk test, n (%)	16/26 (62)
Days after cannulation, median (IQR)	214 (119-240)
Days after decannulation, median (IQR)	150 (96-204)
Meters walked, median (IQR)	350 (286-379)
Borg dyspnea scale, median (IQR)	0 (0-0)
Lowest oxygen saturation, %, median (IQR)	94 (92-95)

ARDS, acute respiratory distress syndrome; COVID-19, coronavirus disease 2019; DLco, diffusing capacity for carbon monoxide; FEV₁, forced expiratory volume in 1 second; FVC, functional vital capacity; IQR, interquartile range; TLC, total lung capacity; VV-ECMO, venovenous extracorporeal membrane oxygenation.

patients (13/37). The majority of patients (38%) who survived to discharge went to another hospital, a long-term acute care hospital, or another rehabilitation facility, although the “other” rehabilitation facility was not defined. Seven patients (23%) were discharged directly home. In that study,¹¹ the number of discharged patients requiring ventilator or supplemental oxygen support was not provided. In contrast, we report a survival to discharge rate of 90% (27/30), with all patients discharged home or to short-term rehabilitation. No patients in our series left the hospital ventilator dependent, and only 1 patient required supplemental oxygen on discharge.

These discordant outcomes likely reflect differences in patient selection, patient management, and a willingness to continue support in the setting of single-organ dysfunction. Our selection philosophy was that VV-ECMO was not salvage therapy, to be used in the absence of other options. Instead, VV-ECMO support was offered to patients that the team believed had a reasonable chance for survival if these patients were offered support. Accordingly, we aimed to initiate support early in the clinical course, thereby limiting the amount of time the lungs were subjected to the recognized deleterious effects of high airway pressure, respiratory rates, and levels of oxygenation. Although patient selection was important, a standardized, aggressive approach to the management of these patients was equally valuable. This included not deviating from lung-protective ventilation strategies, nearly universal early tracheostomy and frequent bronchoscopy, treatment of coinfection, and standardization of an anticoagulation regimen. Finally, our team, with the endorsement of hospital leadership, continued support of patients with VV-ECMO with single-organ dysfunction. Consequently, 3 patients were supported with VV-ECMO for longer than 100 days (Supplemental Figure); all 3 patients have been discharged from the hospital.

At 1 year after cannulation, the reported midterm outcomes for the cohort generally reflect clinical pulmonary recovery. Although available data thus far are limited to approximately one-half of the cohort, a median 6-minute walk test of 350 m is encouraging. Similarly, with the exception of the patient with progressive post-COVID-19 pulmonary fibrosis, the remaining patients who underwent PFTs demonstrated normal lung function, with a median percent predicted forced expiratory volume in 1 second (FEV₁) of 100%. Despite a normalized FEV₁ and forced vital capacity, the majority of patients had a diffusing capacity for carbon monoxide level at the lower end of normal, thus indicating some residual pulmonary damage, the clinical significance of which is unknown.

In 1 patient, an oxygen requirement developed after discharge, and this patient was found to have progression of post-COVID-19 interstitial fibrosis. This patient eventually underwent lung transplantation, had an uncomplicated postoperative course, and was discharged home on room air on postoperative day 7.

Another notable finding is that all patients in our cohort either had enough lung recovery to be weaned from ECMO support or died of nonrespiratory causes. This is important because some centers have moved on to lung transplantation after as little as 1 to 2 months of ECMO support. Thus, our data support maintaining patients with single-organ dysfunction on ECMO for COVID-19 ARDS and permitting sufficient time to recover, for 2 reasons. First, not all patients supported

with ECMO for COVID-19 ARDS will ultimately require lung transplantation. Second, in those patients who ultimately require lung transplantation, a period of rehabilitation, even if these patients are oxygen dependent, may result in more rapid recovery from their eventual transplantation.

The limitations of this study are inherent in its retrospective, observational design. Selection bias is unavoidable and acknowledged; similar bias exists in all available COVID-19 ECMO data. To date, patients with severe COVID-19 have not been randomized to ECMO vs medical therapy. In our opinion, it is the role of the ECMO team to select appropriate patients for this strategy. ECMO is a potentially lifesaving resource that is time intensive and costly. Allocation of such resources was even more complex at the beginning of this global pandemic. The need to avoid futile procedures was

heightened by limited resources, including trained staff and health care providers and personal protective equipment. Similarly, the risk to the providers of these procedures was unknown. With this in mind, we chose to avoid offering ECMO as only salvage therapy.

In conclusion, with appropriately selected patients and aggressive management strategies, the use of ECMO support in patients with severe COVID-19 can result in exceptional early survival that, in this cohort, was sustained at 1 year after ECMO cannulation.

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ECMO in COVID-19: Continued Variable Outcomes



INVITED COMMENTARY:

In this issue of *The Annals of Thoracic Surgery*, Smith and colleagues¹ present a mid-term follow up for patients cannulated for venovenous extracorporeal membrane oxygenation (VV-ECMO) during the first wave of the COVID-19 pandemic. The authors seek to expand our

understanding of outcomes post-discharge, a topic that has not been clearly addressed. The present analysis includes 30 patients cannulated over 3 months at a single institution, and demonstrates impressive survival—86.7% at a median follow-up of 10.8 months. Significantly, all surviving patients were home, most (25 of 26) required no supplemental oxygen, and pulmonary function tests had generally returned to baseline. These data are in sharp contrast to much of the initial