The Use of Venovenous Extracorporeal Membrane Oxygenation in COVID-19 Infection: One Region's Comprehensive Experience

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Severe acute respiratory distress syndrome (ARDS) unresponsive to conventional intensive care unit (ICU) management is an accepted indication for venovenous extracorporeal membrane oxygenation (V-V ECMO) support. The frequency with which patients with coronavirus disease 2019 (COVID-19) pneumonia are selected for V-V ECMO has not been described. This was a cohort study including all patients placed on either V-V ECMO or venoarteriovenous ECMO at the four adult ECMO Centers of Excellence. Primary outcomes evaluated were survival to decannulation from the ECMO circuit, survival to discharge, and 60-day survival. Secondary outcomes were hospital length of stay (LOS), ICU LOS, length of ECMO cannulation, and length of intubation. During the study period, which corresponded to the first surge in COVID-19 hospitalizations in Minnesota, 35 patients with ARDS were selected for V-V ECMO support out of 1,849 adult ICU patients with COVID-19 infection in the state (1.9% incidence; 95% CI, 1.3–2.6%). This represents 46 (95% CI, 34–61) expected V-V ECMO patients per 100,000 confirmed positive cases of COVID-19. Twenty-six of the 35 patients (74.3%) supported with V-V ECMO survived to 60-day post-ECMO decannulation. Recent studies have demonstrated ongoing success rescuing patients with severe ARDS in COVID-19 infection. Our data add to the support of ECMO and the consideration for encouraging cooperation among regional ECMO centers to ensure access to this highest level of care. Finally, by evaluating all the patients of a single region, we estimate overall need for this resource intensive intervention based on the overall number of COVID-19 cases and ICU admissions. *ASAIO Journal* 2021; 67;503–510

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Among adults with severe respiratory failure due to the acute respiratory distress syndrome (ARDS), early extracorporeal membrane oxygenation (ECMO) support, compared with conventional management, significantly improves survival at 90 days.[1] Intensive care units (ICUs) have been inundated with patients with severe ARDS and SARS-CoV-2 infection during the current global pandemic, which has put pressure on healthcare referral networks and specialized ECMO centers to accept patients with coronavirus disease 2019 (COVID-19) and refractory hypoxemia despite optimized conventional respiratory support.[2,3] Growing literature supports ECMO use in select patients with COVID-19-associated severe ARDS, using the venovenous (V-V) configuration for respiratory support according to existing guidelines[4] with an expected hospital survival of approximately 62%; this ECMO survival rate is similar to the pre-COVID-19 experience at high-volume adult ECMO centers. Although small case series and large, international registry studies have informed ECMO practice in COVID-19-associated ARDS,[5–11] a comprehensive, statewide analysis of V-V ECMO use in the United States is lacking.

The Minnesota experience with V-V ECMO for COVID-19-associated ARDS offers a regional perspective on resource utilization and clinical outcomes. Before the COVID-19 pandemic, the four adult ECMO Centers of Excellence in the state (University of Minnesota MHealth Fairview [UMN], Hennepin County Medical Center [HCMC], Abbott Northwestern Hospital [ANW], and Mayo Hospitals and Clinics [MHC]) formed a consortium to establish uniform ECMO eligibility criteria and share resources and expertise to meet efficiently and equitably the regional demand for ECMO. A statewide plan for allocating ECMO in the case of healthcare resource scarcity, as could be the case during a respiratory pandemic, was previously created by this group[12] and an updated version specific to COVID-19 has been endorsed by the Minnesota Department of Health (MDH).[13]

In this study, we describe the epidemiology of V-V ECMO use and clinical outcomes during the first surge in COVID-19-associated severe ARDS cases in our region. We highlight

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60-day mortality with complete data on all ECMO patients. In addition, we detail the evolving use of novel therapeutics for SARS-CoV-2 infection in this cohort of ARDS patients selected for ECMO support.

Materials and Methods

Study Design and Participants

This was a retrospective, observational study of patients supported with ECMO for COVID-19-associated ARDS at one of the four adults, Extracorporeal Life Support Organization (ELSO)-certified Centers of Excellence in Minnesota (UMN, HCMC, ANW, MHC) from March 1, 2020, to September 1, 2020. Consecutive patients greater than or equal to 18 years old with SARS-CoV-2 infection confirmed by RT-PCR who were placed on V-V ECMO or venoarteriovenous (V-AV) ECMO for severe ARDS were included. COVID-19 patients placed on ECMO in the venoarterial configuration for primary cardiac support were excluded. The institutional review boards at each participating site approved this study with a waiver of informed consent. Population-level data on Minnesota SARS-CoV-2 infections as well as hospital and ICU admissions in our state were obtained from the MDH.[13]

ECMO Criteria and Allocation

As a consortium, leadership from each adult and pediatric ECMO center developed consensus for adult V-V ECMO eligibility criteria (Supplemental Table 1, http://links.lww.com/ASAIO/A609). Accountability to these criteria was reinforced with regular consortium operational and planning meetings attended by center leadership on approximately twice on monthly basis during the first surge of COVID-19 in the Upper Midwest. The final decision regarding ECMO candidacy was left to the individual centers. The ECMO the medical directors and program coordinators have maintained excellent and collegial working relationships before and during this pandemic so variation in clinical practice and decision-making between the centers is minimal. An ECMO center receiving a "lateral" patient transfer from another ECMO center due to resource constraints at the referring center has ultimate right to decline that patient transfer. However, this situation did not arise during the study period.

ECMO support was initiated according to the agreed-upon criteria (Supplemental Table 1, http://links.lww.com/ASAIO/A609) and established guidelines,[14] and in consultation with a specialist in critical care medicine. At the time of ECMO initiation, all patients met diagnostic criteria for severe ARDS according to the Berlin criteria[15] and were receiving invasive mechanical ventilation with a lung-protective strategy. The four ECMO centers routinely used neuromuscular blockade, prone positioning, and a trial of inhaled epoprostenol or nitric oxide before initiation of ECMO for severe ARDS, as appropriate. ECMO cannulation was preferentially performed at an ECMO center. Patients were cannulated at the referring hospital if it was deemed unsafe to transport them to an ECMO center using conventional support. In this instance, an ECMO center transport team consisting of a perfusionist, a transport RN, a pilot, and occasionally a physician responded to the referring hospital and was present to assist with cannulation and transport. Transport was provided by a helicopter or an ambulance depending on the distance and availability with a maximum distance of 240 miles. ECMO cannulation at one of the four ECMO centers was performed by an intensivist, interventional cardiologist, or emergency physician according to local protocol. Operator preference and patient factors determined if a dual-lumen jugular cannula or a two-cannula (femoral-jugular or femoral-femoral) approach was used.

ECMO Management

Following ECMO cannulation, the mechanical ventilation strategy during ECMO was comparable between the four centers: the goal was "lung rest" as defined by low mechanical power delivered by the ventilator to mitigate ventilator-induced lung injury, generally using a pressure-limited mode and a low respiratory rate. An infusion of unfractionated heparin or bivalirudin was initiated during cannulation and continued for the duration of extracorporeal support unless the patient developed a contraindication to systemic anticoagulation. Sedation goals were similar between the ECMO centers. The most common approach was deep sedation (RASS goal, –4 or –5) with paralytic usually for first 2 days until stability, then stop paralytic and target moderate sedation (RASS –2 or –3). Sedation was achieved using a combination of propofol, midazolam, fentanyl, hydromorphone, and ketamine. A comprehensive summary of the approaches taken by individual centers following ECMO cannulation is included in Supplemental Table 2 (http://links.lww.com/ASAIO/A610). Patients were assessed daily for readiness to liberate from ECMO. Decannulation from V-V support was performed at the bedside in the ICU.

There were two ECMO circuits that were utilized among all the ECMO centers: CardioHelp HLS Bioline circuit (Getinge, Göteborg, Sweden) and the Centrimaga (Abbott Cardiovascular, Plymouth, MN) with a Quadrox-i oxygenator (Getinge). Circuit change was required in the setting of clot formation and decreased efficiency. The extent of manipulation of the circuit varies between these two systems with CardioHelp circuits requiring a complete circuit change and Centrimag circuits, requiring only a replacement of the Quadrox-i oxygenator component.

Main Outcome Measures

The primary epidemiologic outcome of this study was the prevalence of ECMO support for COVID-19-associated ARDS among all critically ill COVID-19 patients in Minnesota during the study period. Critical illness was defined as admission to an ICU. The secondary epidemiologic outcome was the estimated number of ECMO cases for COVID-19-associated ARDS per 100,000 COVID-19 cases in the population, based on the observed study data for Minnesota from March to September 2020. An epidemic curve for overall adult ECMO utilization for COVID-19-associated ARDS in Minnesota was created, with daily V-V ECMO census stratified by center, using prospectively collected census data reported by ECMO program coordinators at 08:00 each day using a secure online surveillance tool.

The primary patient outcome was survival at 60 days after initiation of ECMO support for COVID-19-associated ARDS. Other patient outcomes of interest are inhospital mortality,

ICU and hospital length of stay (LOS), days of ECMO support, and days of endotracheal intubation and mechanical ventilation. Complications of COVID-19 and of ECMO were collected prospectively as part of local quality assurance and ELSO international registry participation by each center in this study. Complications were separated into two groups: patient complications and ECMO circuit complications. Patient complications recorded were venous or arterial thrombosis (before ECMO initiation), cardiomyopathy, renal failure, and secondary infection. ECMO circuit complications were thrombosis of any component of the extracorporeal circuit (including cannula-associated), circuit replacement, bleeding, cannula repositioning, and cannula site complications as defined by the ELSO registry.[16]

Statistical Analysis

Patient characteristics, process of care data, and outcomes were manually abstracted from the electronic medical record at each participating ECMO center. Deidentified data from each center were then merged into a complete study database using REDCap electronic data capture tools hosted by The University of Minnesota.[17] Data were analyzed and reported primarily in a descriptive fashion using the mean with standard deviation (SD) or median with interquartile range (IQR) for continuous variables and proportions for categorical variables. Inferential analysis was exploratory only and was determined using paired *t* test for continuous variables and χ^2 test or Fisher exact test for categorical variables, as appropriate. Analysis was performed using Microsoft Excel (Microsoft, Redmond WA) and R (R Core Team, 2018).[18] The threshold for statistical significance was defined by a two-tailed p value <0.05.

Results

Regional COVID-19 Epidemiology and ECMO

In Minnesota (population approximately 5.64 million[19]), the first documented case of COVID-19 occurred on March 5, 2020, and V-V ECMO was first utilized for COVID-19-associated ARDS in the state on March 11 (in a different individual). Between March 5 and September 1 of this year, 75,860 Minnesotans were diagnosed with SARS-CoV-2 infection and 6,520 (8.2%) were hospitalized; 1,849 of those COVID-19 hospitalizations (28%) required the ICU.[13] V-V ECMO was utilized in 35 of the 1,849 COVID-19 ICU admissions (1.9%; 95% CI, 1.3–2.6%) during the study period; this ECMO prevalence can be extrapolated to 46 expected V-V ECMO patients (95% CI, 34–61 patients) per 100,000 confirmed cases of SARS-CoV-2 infection in the population. Two ECMO patients were transferred from outside Minnesota. Figure 1 compares the temporal distribution of ECMO cases with the first surge in ICU admissions for COVID-19 in Minnesota. At peak case volumes between mid-May and mid-June, the four ECMO centers were concurrently managing up to 14 COVID-19 patients on extracorporeal support.

Patient Characteristics

Thirty-five adults were selected for V-V (n = 34, 97%) or V-AV (n = 1, 3%) ECMO support for COVID-19-associated severe ARDS. Characteristics of these patients, stratified by hospital survivorship, are provided in Table 1. The average age of ECMO patients with COVID-19-associated ARDS was 51 years (SD = 9.7 years), 81% were male, the average body mass index was 31.4 kg/m^2 (SD = 7.1 kg/m^2), and 37% reported Latino ethnicity (Table 1). The comorbidities most frequently present were hypertension (44%) and diabetes mellitus (41%).

The median time interval from symptom onset to hospital admission was 7.5 days (IQR, 6–10 days) and the interval from endotracheal intubation to ECMO initiation was 3 days (IQR, 1–6 days) The great majority of COVID-19-associated ARDS patients in this cohort were ventilated in the prone position (94%) and received neuromuscular blockade (97%) and inhaled pulmonary vasodilator therapy (78%) before initiating ECMO. Ventilator settings at the time of ECMO initiation included an average FiO_2 90.6% (SD = 13.8%), positive end-expiratory pressure 14.3 cm H_2O (SD = 3.1 cm H_2O), and

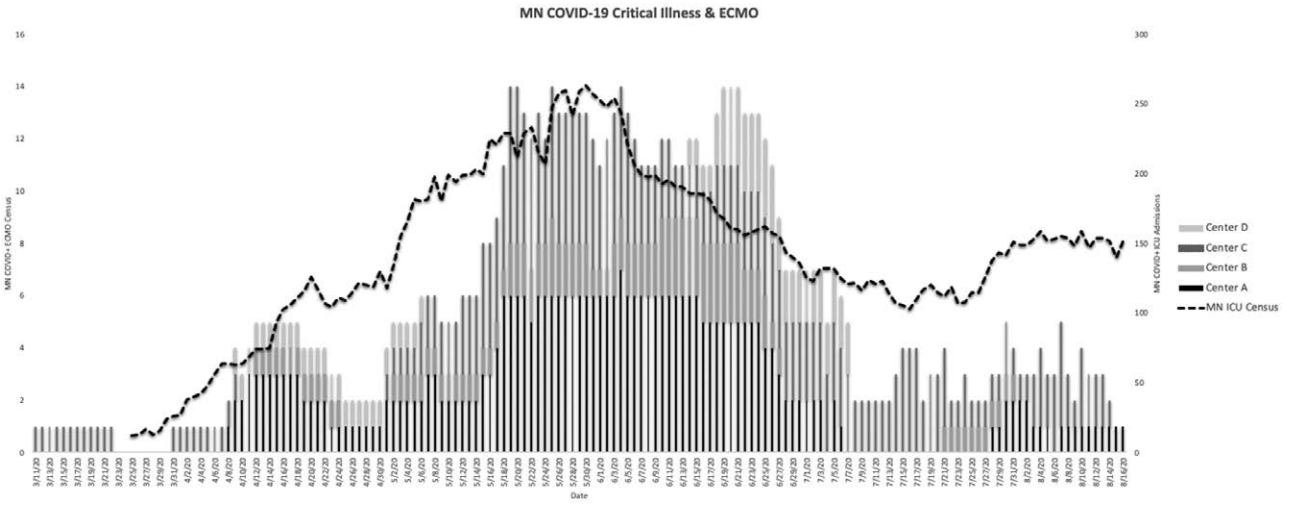

Figure 1. Number of patients receiving V-V and V-AV ECMO support by day at the 4 ECMO centers in the State of Minnesota (left *y*-axis). This is plotted against the total number of COVID-19 cases being treated in ICUs (dotted line) in the State of Minnesota (right *y*-axis). The peak in ECMO use correlated with the surge in ICU admissions in the region. COVID-19, coronavirus disease 2019; ECMO, extracorporeal membrane oxygenation; ICUs, intensive care units; V-AV, venoarteriovenous; V-V, venovenous.

Table 1. Patient Demographic Data and Clinical Data Just Before Extracorporeal Membrane Oxygenation Cannulation

Patient Demographics				
	All Patients (n = 35)	Survivors (*N* = 26)	Nonsurvivors (*N* = 9)	*p*
Age, mean (SD)	50.9 (9.7)	49.7 (9.2)	54.6 (10.7)	0.199
BMI, mean (SD)	31.4 (7.1)	30.2 (5.6)	29.0 (10.2)	0.723
Sex, n (%)				
Male	27 (77.1)	22 (84.6)	5 (55.6)	0.162
Female	8 (22.9)	4 (15.4)	4 (44.4)	
Race, n (%)				
White	7 (20.0)	6 (23.1)	1 (11.1)	0.239
Latino	13 (37.1)	11 (42.3)	2 (22.2)	
African American	7 (20.0)	5 (19.2)	2 (22.2)	
Native American	1 (2.9)	0 (0)	1 (11.1)	
Asian	5 (14.3)	3 (11.5)	2 (22.2)	
African	2 (5.7)	1 (3.8)	1 (11.1)	
Medical history, n (%)				
Obesity	14 (38.9)	10 (38.5)	4 (44.4)	0.942
Hypertension	16 (44.4)	10 (38.5)	6 (66.7)	
Hyperlipidemia	11 (30.6)	8 (30.8)	3 (33.3)	
Diabetes	15 (41.7)	11 (42.3)	4 (44.4)	
Asthma/COPD	4 (11.1)	3 (11.5)	1 (11.1)	
CAD	1 (2.8)	0 (0)	1 (11.1)	
CKD	5 (13.9)	4 (15.4)	1 (11.)	
OSA	4 (11.1)	3 (11.5)	1 (11.1)	
Pre-ECMO clinical data				
Ventilator settings, mean (SD)				
FiO2	90.6 (13.8)	87.6 (15.1)	98.9 (3.3)	0.035
PEEP (cm H_2O)	14.3 (3.1)	14.1 (3.3)	14.7 (2.8)	0.667
Respiration rate (breaths/min)	25.9 (6.2)	24.5 (6.2)	29.9 (5.0)	0.024
Tidal volume (mL)	378.8 (97.5)	395.5 (72.0)	338.2 (143.6)	0.148
Peak pressure (cm H_2O)	35.2 (4.7)	35.5 (3.8)	33.0 (11.3)	0.521
Plateau pressure (cm H_2O)	30.2 (4.8)	29.9 (5.2)	31.2 (4.1)	0.609
ABG, mean (SD)				
pH	7.30 (0.12)	7.32 (0.11)	7.23 (0.12)	0.052
PCO_2 (mm Hg)	56.2 (14.8)	53.9 (14.3)	62.7 (16.2)	0.136
PaO_2 (mm Hg)	61.1 (17.2)	64.3 (16.3)	52.2 (17.2)	0.070
PaO_2/FiO_2 ratio (average)	69.7 (23.6)	75.7 (22.7)	53.0 (17.9)	0.011
Interventions before ECMO, n (%)				
Prone positioning	31 (93.9)	22 (84.6)	9 (100)	0.691
Paralysis	32 (97.0)	24 (92.3)	8 (88.9)	0.907
Inhaled pulmonary vasodilator	26 (78.8)	18 (69.2)	8 (88.9)	0.571
Vasopressors	27 (81.8)	18 (69.2)	9 (100)	0.378
Location of ECMO cannulation, n (%)				
ECMO center	19 (54.3)	15 (57.7)	4 (44.4)	0.629
Referring hospital	16 (45.7)	11 (42.3)	5 (55.6)	0.625

The patients that survived to decannulation were compared with nonsurvivors to evaluate any significant factors that may have contributed to mortality.

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; ECMO, extracorporeal membrane oxygenation; OSA, obstructive sleep apnea; PEEP, positive end-expiratory pressure.

plateau pressure 30.2 cm H_2O (SD = 4.8 cm H_2O) (Table 1). Indices of oxygenation at initiation of ECMO included a mean PaO_2 of 61 mm Hg (SD = 17 mm Hg) and a PaO_2/FiO_2 (P/F) ratio of 70 (SD = 24). The mean P/F ratio at the time of ECMO initiation was significantly different between the survivors (76, SD = 23) and nonsurvivors (53, SD = 18) ($p = 0.011$) (Table 1).

Outcomes Including Complications

Twenty-six of 35 patients (74%) supported with ECMO for COVID-19-associated ARDS survived their hospitalization. There were no additional deaths from hospital discharge to 60 days from ECMO initiation in this cohort with complete outcome ascertainment at 60 days. Sixteen patients underwent tracheostomy and were discharged to acute rehabilitation settings (62% of hospital survivors); four patients were mechanically ventilated at the time of hospital discharge and the remaining 12 tracheostomy patients required only supplemental oxygen.

The median duration of ECMO support for COVID-19-associated ARDS in the overall cohort was 21.5 days (IQR = 13–33.5 days, range = 7–70 days) and was 26 days (IQR = 22–34 days) in the subgroup of patients who did not survive to hospital discharge. The median duration of endotracheal intubation was 25 days (IQR, 10–40.5 days) excluding the four patients mechanically ventilated via tracheostomy at hospital discharge. Median ICU LOS for ECMO patients was 31.5 days (IQR, 23–49 days) and overall hospital LOS was 38.5 days (IQR, 28–56 days).

Frequently observed hospital complications among ECMO patients were acute renal failure (51%) and secondary bacterial infection (63%). Ventilator-associated pneumonia (n = 16, 45%) and blood stream infections (n = 7, 20%) made up the majority of infectious complications. The most common ECMO circuit complication was ECMO cannula migration requiring repositioning (43%) and approximately one-quarter of patients required at least one ECMO circuit change during their time

on extracorporeal support (23%) (Table 2). There were nine patients (26%) cannulated with single catheter dual lumen support with an Avalon Bi-Caval Dual Lumen Catheter (Getinge) and 26 patients (74%) were cannulated with two catheter bicaval support. Cannula repositioning was more common in those cannulated with the single catheter approach (n = 5, 56%) compared with the bicaval approach (n = 10, 38%). Though this was not statistically significant ($p = 0.50$).

Novel Therapeutics

Figure 3 illustrates the cumulative use of adjunct COVID-19 treatments administered to patients with ARDS, either before or during ECMO support, from March until early August 2020. Eight ECMO patients received hydroxychloroquine (five in combination with azithromycin), all before April 26. Approximately three-quarters of patients selected for ECMO received an interleukin-6 inhibitor (72%), either tocilizumab or sarilumab, and about half of ECMO patients received the viral RNA-polymerase inhibitor remdesivir (58%) or convalescent plasma (56%). The use of these experimental treatments appeared to be relatively constant over the study period. Systemic corticosteroids were utilized in 10 patients (29%) and plasma exchange was attempted in one patient. The increase in the absolute number of patients receiving novel treatments each week mirrors the surge in the number of critically ill COVID-19 cases seen in May and June in Minnesota (Figures 1 and 3).

Discussion

This study describes the combined experience in selection and management of V-V ECMO patients with COVID-19-associated severe ARDS at the four adult ECMO centers in Minnesota over the first 6 months of the SARS-CoV-2 epidemic in the Upper Midwest. Approximately 2% of critically ill adults with COVID-19 required ECMO support in our state ($n = 35$), and these patients had a 60-day survival rate of 74%, which compares favorably with both recently published COVID-19 case series and with the pre-COVID-19 V-V ECMO experience for severe pneumonia including influenza in adults.[5–11,20] This study is strengthened by the uniform and COVID-19-specific V-V ECMO eligibility criteria shared across the four ECMO centers during the study period, provision of high quality respiratory critical care at baseline (as evidenced by >90% of study patients receiving early neuromuscular blockade and prone ventilation before ECMO), complete 60-day outcome measures in all patients, and the granular utilization data for ECMO and experimental therapeutics in a geographically and temporally defined critically ill COVID-19 cohort.

The uniform ECMO eligibility criteria for COVID-19-associated ARDS adopted by our four ECMO centers were very similar to an international guideline subsequently published by ELSO,[4] and included patient- (*e.g.*, <65 years old) and disease-specific criteria (*e.g.*, P/F ratio <80 for 6 hours and high intensity mechanical ventilation for <10 days). We do acknowledge that the decision to employ V-V ECMO support for a patient with severe ARDS involves other environmental and clinical factors such as geography, referral patterns, the availability of an ICU bed, an ECMO circuit, disposable ECMO equipment including the pump and membrane oxygenator, ECMO bedside personnel, and ultimately physician judgment (with its inherent subjectivity). Anticipating a surge in COVID-19-related ECMO demand, our centers participated in the creation of a statewide framework for allocating scarce critical care resources including ECMO during a pandemic.[12,21] Fortunately, our centers were able to manage the surge in severe respiratory failure due to COVID-19 in Minnesota (and the related spike in V-V ECMO referrals) while maintaining conventional standards of care; no individual ECMO center was overwhelmed and we did not modify standard referral practices with non-ECMO centers. Frequent and transparent communication between the clinicians and administrators at the four ECMO centers helped adapt to evolving circumstances.

The results of this study are largely supportive of previous findings, which highlight the likely generalizability of our population-level estimates of ECMO utilization to other regions. These estimates may be valuable to medical and public health leaders tasked with planning for future surges in COVID-19 ARDS during the evolving pandemic. The duration of ECMO support in this study (median = 21.5 days), as well as lengths of ICU and hospital stays, are consistent with other case series[9,10] and suggest a reasonable expectation for length of intervention needed for COVID-19 patients on V-V ECMO. Of note, there was a single patient that received V-AV support, but after rapid improvement of the patient's concomitant cardiomyopathy, this patient was converted into V-V support within in 3 days. For this reason, the discussion is limited to V-V ECMO.

We observed that the 74% of patients in our ECMO case series who survived to ECMO decannulation remained alive 60 days later, which is in line with previous studies of V-V ECMO.[8–11,20] When compared with patients with COVID-19-associated

Table 2. Complication Rate and Outcomes Among the Study Population

Hospital Complications	
	n (%)
Pre-ECMO thrombosis	5 (14.3)
Cardiomyopathy	4 (11.4)
Renal failure	18 (51.4)
Infection	22 (62.8)
Other	6 (17.1)
ECMO complications	
Thrombosis	7 (20.0)
Bleeding	4 (11.4)
Cannula reposition	15 (42.9)
Cannula site complication	6 (17.1)
Circuit change	8 (22.9)
Tracheostomy	
Patients discharged with tracheostomy	16 (45.7)
On ventilator at discharge	4 (11.4)
Supplemental oxygen	12 (34.2)
Survival	
Decannulation	26 (74.3)
Discharge	26 (74.3)
60 days	26 (74.3)

Thrombosis included deep vein thrombosis, pulmonary embolism, and stroke. Given the inability to distinguish between the infection and the ECMO circuit as the etiology, thrombosis was divided between pre-ECMO cannulation and post-ECMO cannulations. Cannula site complications included hematomas and seromas. Long-term outcomes including need for tracheostomy placement and survival to ECMO decannulation, discharge, and 60 days were evaluated.

ECMO, extracorporeal membrane oxygenation.

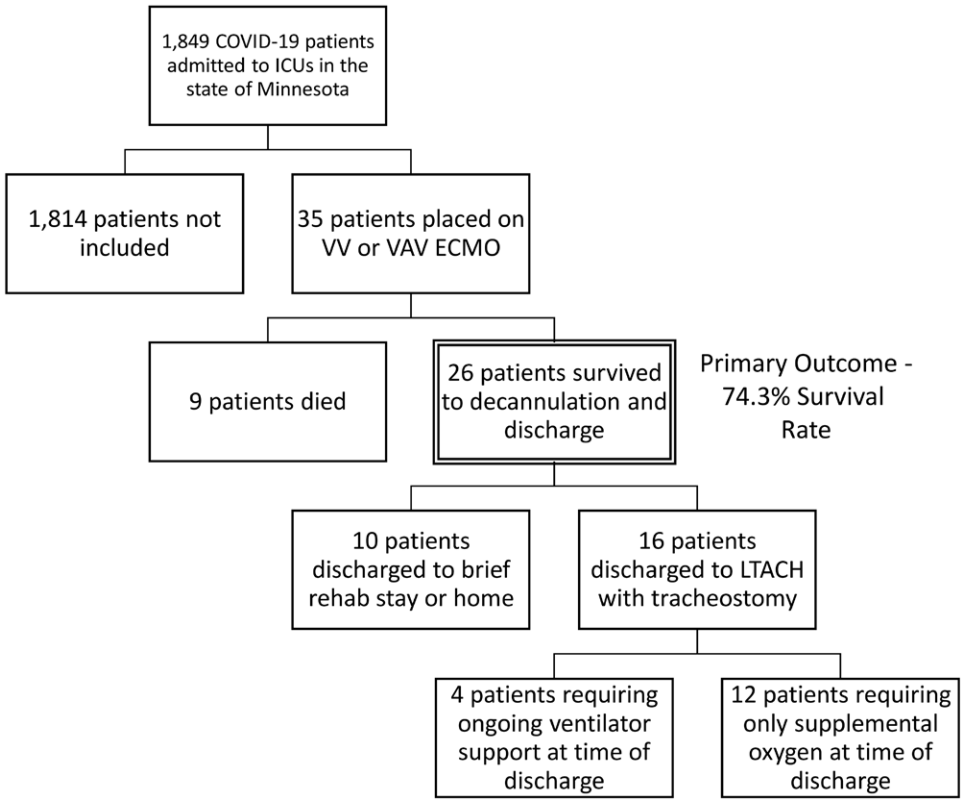

Figure 2. Flowchart establishing the study population as those patients in Minnesota ICUs receiving venovenous or V-AV ECMO. Of the surviving patients, their disposition at the time of discharge either to home/rehab or an LTACH as well as their need for tracheostomy was also evaluated. The primary outcome of survival to decannulation was reached in 26 patients (74.3%). ECMO, extracorporeal membrane oxygenation; ICUs, intensive care units; LTACH, long-term acute care hospital; V-AV, venoarteriovenous.

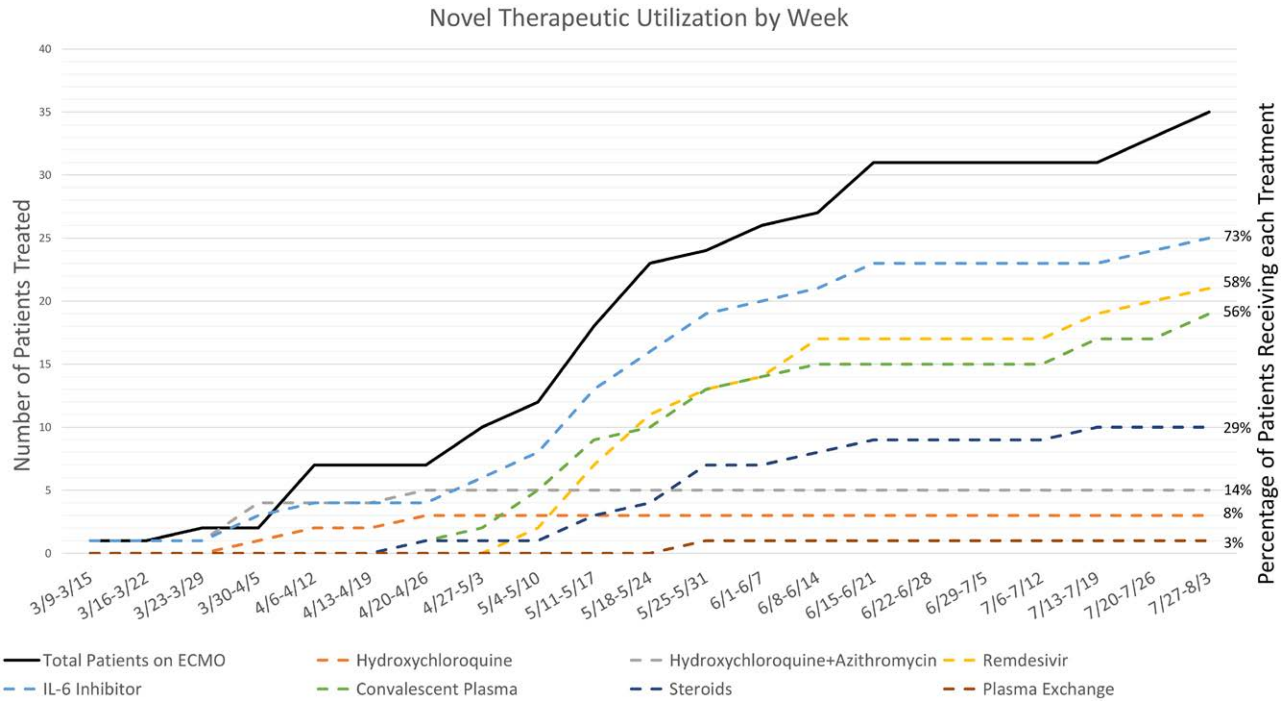

Figure 3. The accumulation of ECMO cases and the utilization of novel therapeutics are illustrated cumulatively over the study period. Many of the patients received the novel therapeutics before ECMO cannulation, which explains the week of 3/30–4/5 when there are more treatments that are given than total patients. The total portion of the patient population that received each treatment was included as well. ECMO, extracorporeal membrane oxygenation. full color online

ARDS in a large ECMO registry study by Barbaro *et al.*,[11] this study had comparable survival (74% *vs.* 63%, respectively) with a similar pre-ECMO clinical picture. Part of the absolute 11% improvement in survival between the studies may be due to refinement in COVID management practices over time; the registry study reported outcomes from January to May 2020 and this study reflected our regional surge in critically ill COVID-19 patients from March to September. The RECOVERY trial, published online on July 17, 2020 during the latter half of our study period, established the efficacy of dexamethasone in severe COVID-19 pneumonia.[22] This timing could explain the relatively small proportion of patients (29%) who received corticosteroid therapy in this series. A single ECMO patient in our series received plasma exchange due to multiorgan failure and ongoing secondary pneumonia; there was concern for treatment with antiinflammatory medications in this setting. This patient later died of gram-negative septic shock.

As expected, we found associations between certain patient characteristics (older age, female sex, and lower pre-ECMO indices of oxygenation [P/F ratio]) and hospital mortality. We did not control for potential confounders in this analysis due to the relatively small number of cases/outcomes and their exploratory, or hypothesis-generating, nature. Interestingly, females made up the minority of our study cohort (23%) but accounted for 44% of total deaths ($p = 0.16$). This is a surprising trend as previous studies have suggested males have worse outcomes in COVID-19 infection.[23] However, Barbaro *et al*[11] also demonstrated a trend toward increased hospital mortality with increasing age and female sex among ECMO patients with COVID-19 in a large study.

This study has several important limitations. First, the modest size of this ECMO cohort with COVID-19-associated ARDS limits our ability to establish statistical significance of outcome differences between the survivors and nonsurvivors. The magnitude or direction of associations between the patient factors and mortality could be influenced by confounding in this retrospective case series or by the selection bias inherent in ECMO use; missing data were minimized by prospective data collection for epidemiologic measures and for patient and circuit complications. Additionally, the estimated incidence of ECMO use is based on the initial wave of COVID-19 infections and multiple factors may affect this estimation as the pandemic progresses. As the portion of the population that has contracted and subsequently recovered from the infection increases, the immunity within the community will likely decrease the overall incidence of the disease. With the introduction of a vaccine as well, the number of cases and severity of disease will hopefully decrease resulting in a decreased need for V-V ECMO support. Finally, we present the frequency of novel therapeutics in this cohort and do not assess their efficacy. In fact, several of the treatments are currently approved under emergency use authorization only and have limited safety and efficacy data informing their use.[24]

In conclusion, we report favorable patient outcomes in a cohort of adults with severe COVID-19-associated ARDS failing conventional ICU support who were rescued with V-V ECMO in Minnesota. Extracorporeal life support is expensive and resource-intensive and therefore limited to regional referral centers with adequate volume and experience managing this technology. Regional coordination and disciplined patient selection during the first surge of COVID-19 in Minnesota contributed to these results. ECMO utilization, estimated here as a proportion of ICU admissions for COVID-19 or on a per-infected population basis, may inform ongoing U.S. regional planning for surges in the demand for critical care resources during the evolving COVID-19 pandemic.

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