BRIEF REPORT

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Increasing Mortality in Venovenous Extracorporeal Membrane Oxygenation for COVID-19–Associated Acute Respiratory Distress Syndrome

Jacob A. Braaten, BS[1]
Zachary R. Bergman, MD[2]
Jillian K. Wothe, BS[2]
Arianna E. Lofrano, DO[4]
Luke J. Matzek, MD[5]
Melissa Doucette, RRT, CCP[6]
Ramiro Saavedra-Romero, MD[6]
John K. Bohman, MD[5]
Matthew E. Prekker, MD, MPH[3, 4]
Elizabeth R. Lusczek, PhD[2]
Melissa E. Brunsvold, MD, FACS[2]

OBJECTIVES: Determine the factors associated with mortality in venovenous extracorporeal membrane oxygenation (V-V ECMO) patients with COVID-19 infection and provide an updated report of clinical outcomes for patients treated with V-V ECMO for COVID-19 in Minnesota.

DESIGN: Multicenter prospective observational study.

SETTING: The four adult Extracorporeal Life Support Organization–certified Centers of Excellence in Minnesota.

PATIENTS: A total of 100 patients treated with V-V ECMO for COVID-19–associated acute respiratory distress syndrome (ARDS) from March 2020 to May 2021.

INTERVENTIONS: Not applicable.

MEASUREMENTS AND MAIN RESULTS: The primary outcome was 60-day survival for patients treated with V-V ECMO for COVID-19. Outcomes of patients treated from November 2020 to May 2021(cohort 2) were compared with data from a previous cohort of patients, collected from March 2020 to October 2020 (cohort 1). The data from both cohorts were merged into a single dataset (Combined Cohort). Survival on V-V ECMO due to COVID-19–associated ARDS significantly decreased after October 2020 (63% vs 41%; $p = 0.026$). The median interval from hospital admission to V-V ECMO cannulation was significantly associated with 60-day mortality (10 d [6–14 d] in nonsurvivors vs 7 d [4–9 d] in survivors; $p = 0.001$) in the Combined Cohort and was also significantly longer in cohort 2 than cohort 1 (10 d [7–14 d] vs 6 d [4–10 d]; $p < 0.001$). In the Combined Cohort, the 60-day survival for patients who did not receive steroids was 86% ($n = 12$) versus 45% ($n = 39$) for patients who received at least one dose of steroids ($p = 0.005$).

CONCLUSIONS: There was a significant increase in mortality for patients treated with V-V ECMO for COVID-19–associated ARDS in cohort 2 compared with cohort 1. Further research is required to determine the cause of the worsening trend in mortality.

KEY WORDS: acute respiratory distress syndrome; COVID-19; mortality; pandemic; steroids; venovenous extracorporeal membrane oxygenation

Venovenous extracorporeal membrane oxygenation (V-V ECMO) has been used as treatment for acute respiratory distress syndrome (ARDS) secondary to COVID-19 in select cases that are refractory to conventional treatment. We have previously reported our experience with a survival rate of 65% in patients treated with V-V ECMO for ARDS due to COVID-19, which is in line with other studies (1). Since publishing this work, new variants

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have emerged, and therapeutic regimens have been established, both of which may affect outcomes in this population. We present an update to Minnesota's experience with V-V ECMO for ARDS due to COVID-19 by comparing 60-day mortality and patient and treatment characteristics between the first surge and the second surge of critically ill patients with this disease in our region.

MATERIALS AND METHODS

This observational study enrolled consecutive adult patients with ARDS due to COVID-19 pneumonia who received V-V ECMO during a 14-month period (from March 2020 to May 2021) at one of the four adult ECMO centers in the state of Minnesota (University of Minnesota, Hennepin County Medical Center, Abbott Northwestern Hospital, and the Mayo Clinic-Rochester). We anecdotally observed increasing short-term mortality among COVID-19 patients selected for V-V ECMO as the pandemic progressed. Therefore, for this analysis, we identified two cohorts of patients who received V-V ECMO in Minnesota: cohort 1 (n = 46) who received extracorporeal support from March 2020 to October 2020, corresponding to the first surge of COVID-19 cases in our region (and whose outcomes have been previously reported [1]), and cohort 2 (n = 54) who received ECMO from November 2020 to May 2021, corresponding to the second surge. Descriptive statistics were used to compare patient characteristics and key outcomes between the two cohorts; the outcome of interest was the difference in 60-day survival between cohorts 1 and 2, evaluated using logistic regression adjusting for the differences between groups and chi-square tests with $p < 0.05$ representing statistical significance. The institutional review board approved this study with a waiver of informed consent (University of Minnesota Internal Review Board Study 00010409: V-V ECMO in COVID). Our methodology has been published previously by Bergman et al (1, 2) and was not modified for this study.

RESULTS

Mortality on V-V ECMO due to COVID-19–associated ARDS significantly increased after October 2020. There were 54 patients who received ECMO support after October 2020, of which 22 (41%) survived until 60-day follow-up compared with 29 (63%) in cohort 1 (p = 0.026) (1). The odds ratio of 60-day survival was 2.73 (CI, 1.21–6.15) in cohort 1 compared with cohort 2. Patient demographics, pre-ECMO clinical picture, and ICU interventions were compared between cohort 1 and cohort 2 (**Supplemental Table 1**, http://links.lww.com/CCX/A942). Patient race was significantly different between the two groups, and there was a significantly higher rate of obesity and lower rate of hypertension in cohort 2. Of note, the use of interleukin-6 inhibitors was significantly lower in cohort 2, whereas the use of steroids was significantly higher.

Patient demographics, pre-ECMO clinical picture, and ICU interventions were compared between survivors and nonsurvivors in the Combined Cohort (**Table 1**). Mortality was significantly associated with total number of blood transfusions, treatment with renal replacement therapy, and proning prior to V-V ECMO cannulation. The 60-day survival for patients who did not receive steroids was 86% (n = 12) versus 45% (n = 39) for patients who received at least one dose of steroids (p = 0.005).

In the Combined Cohort, the interval from hospital admission to V-V ECMO cannulation was significantly longer in the nonsurvivors compared with survivors (10 d [6–14 d] vs 7 d [4–9 d]; p = 0.001). The interval from hospital admission to V-V ECMO cannulation was also longer in cohort 2 than that in cohort 1 (10 d [7–14 d] vs 6 d [4–10 d]; $p < 0.001$) (**Fig. 1**). The duration on V-V ECMO was not significantly different between the cohorts, although there was a trend toward an increased V-V ECMO duration for cohort 1 compared with cohort 2 (22.5 d [13–37 d] vs 35 d [15–48 d]; p = 0.16). Of note, there was also a significant increase in the number of patients transferred from outside referral hospitals in cohort 2 (n = 44, 81%) compared with cohort 1 (n = 27, 59%) (p = 0.019).

DISCUSSION

The 60-day survival of patients on V-V ECMO for COVID-19–associated ARDS treated by our group has significantly decreased after October 2020. This trend was consistent across all four ECMO centers. Barbaro et al (3) reported worsening mortality after ECMO for COVID-associated ARDS throughout 2020, and other reports have suggested a similar global trend (4). A recent systematic review reported a pooled mortality of 46% (95% CI, 34–59%) for COVID-19 patients

TABLE 1.
Demographic, Clinical, and ICU Data for the Combined Cohort

Variables	Nonsurvivors (*n* = 49)	Survivors (*n* = 51)	*p*
Age, median (*n* [IQR])	53 (47–57)	50 (40–59)	0.36
Sex, *n* (%)			
Male	39 (80)	36 (71)	0.30
Female	10 (20)	15 (29)	
Race, *n* (%)			
White	24 (49)	18 (35)	0.15
Latino	8 (16)	17 (33)	
Black	5 (10)	10 (20)	
Native American	3 (6)	1 (2)	
Asian	8 (16)	4 (8)	
Body mass index, *n* (SD)			
Mean	31.5 (27.3–39.6)	31.5 (26.9)	0.49
Medical history, *n* (%)			
Obesity	27 (55)	23 (45)	0.32
Hypertension	19 (39)	13 (25)	0.15
Hyperlipidemia	15 (31)	13 (25)	0.57
Diabetes	17 (35)	15 (29)	0.57
Asthma/chronic obstructive pulmonary disease	5 (10)	6 (12)	0.8
Coronary artery disease	5 (10)	2 (4)	0.22
Transferred from referral hospital	39 (80)	32 (63)	0.063
Ventilator settings, average (STD)			
F_{IO_2}	90.6 (14.6)	90.8 (13.7)	0.97
Positive end-expiratory pressure	13.0 (3.1)	13.1 (3.4)	0.9
Respiratory rate	24.6 (7.0)	25.0 (7.1)	0.81
Tidal volume	320.3 (138.9)	325.2 (161.4)	0.89
Peak pressure	31.1 (4.9)	34.2 (6.3)	0.057
Arterial blood gas, average (STD)			
pH	7.3 (0.1)	7.3 (0.1)	0.66
P_{CO_2}	61.2 (20.1)	65.3 (16.6)	0.28
Pa_{O_2}	57.5 (18.8)	56.1 (14.7)	0.68
P/F ratio	70.3 (28.0)	74.2 (23.7)	0.46
Novel therapeutics, *n* (%)			
Hydroxychloroquine ± azithromycin	8 (16)	15 (29)	0.12
Remdesivir	33 (67)	26 (51)	0.096
Interleukin-6 inhibitor	18 (37)	21 (41)	0.65
Convalescent plasma	20 (41)	26 (51)	0.31
Steroids	47 (96)	39 (76)	0.005
Total steroid days, median (IQR)	10 (9–14)	9 (3–11)	0.006

(*Continued*)

TABLE 1. (*Continued*).
Demographic, Clinical, and ICU Data for the Combined Cohort

Variables	Nonsurvivors (*n* = 49)	Survivors (*n* = 51)	*p*
Renal failure			
Need for renal replacement, *n* (%)	29 (59)	20 (39)	0.046
Total renal replacement, d, average (STD)	22 (15.7)	21.7 (16.2)	0.94
Transfusions, average (SE)			
Total units	15 (9–25)	7 (3–17)	<0.001
Sequential Organ Failure Assessment score, average (STD)			
Prior to extracorporeal membrane oxygenation cannulation	7 (6–9)	7 (4–8)	0.14
ICU treatments, *n* (%)			
Proned	47 (96)	42 (82)	0.03
Paralyzed	45 (92)	46 (90)	0.77
Vasopressor	34 (69)	34 (67)	0.77

IQR = interquartile range, STD = standard deviation.
Patients who survived to decannulation were compared with nonsurvivors to identify significant factors that may be associated with mortality.

receiving V-V ECMO (5). This survival rate approximates 60-day survival in our study. We have identified multiple possible causes of this worsening trend in mortality.

In the Combined Cohort, mortality was significantly associated with an increased median interval from hospital admission to V-V ECMO cannulation (7 d for survivors compared with 10 d for nonsurvivors

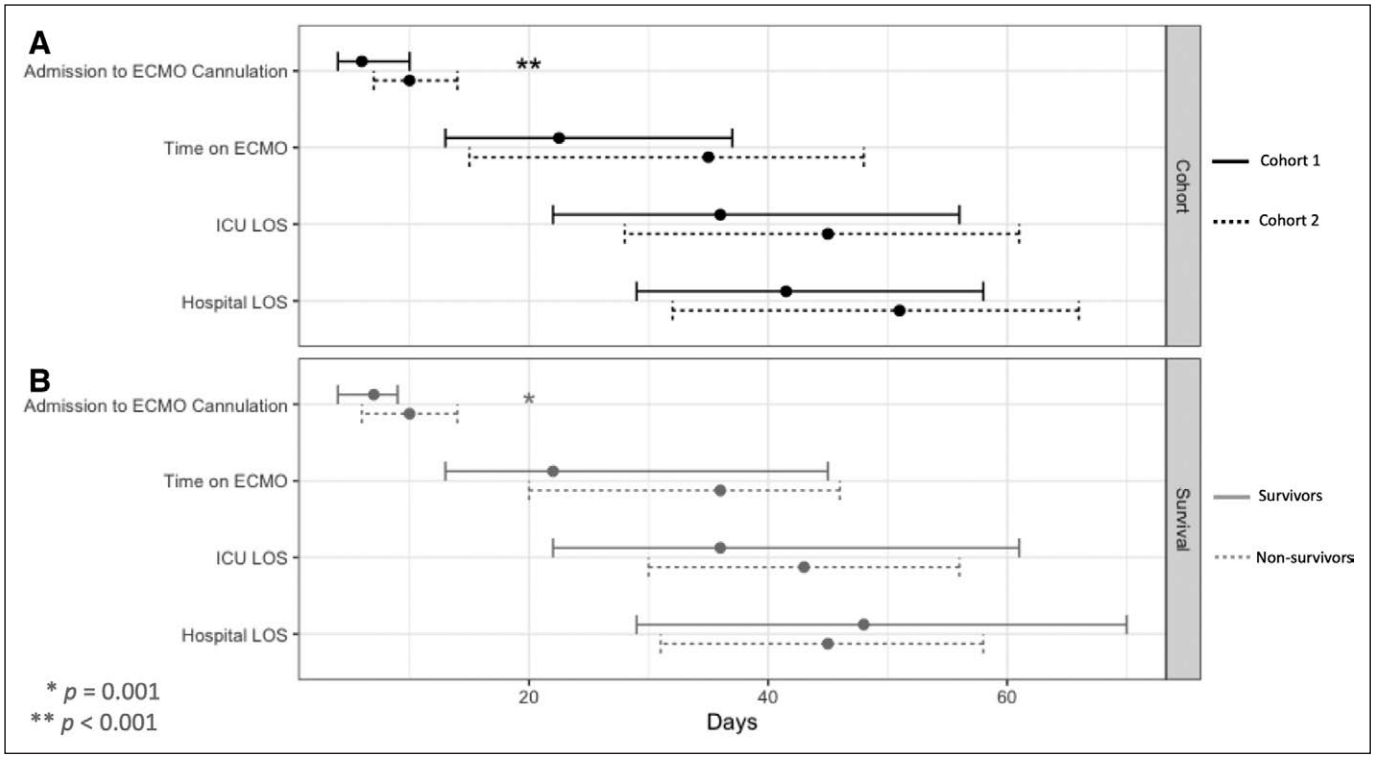

Figure 1. Hospital time course comparing survivors with nonsurvivors (**A**) and cohort 1 to cohort 2 (**B**). The times were reported as median number of days (*dot*) with interquartile range (*brackets*). The interval from admission to venovenous extracorporeal membrane oxygenation (V-V ECMO) cannulation was significantly increased for survivors versus nonsurvivors and for cohort 2 versus cohort 1. LOS = length of stay.

[$p = 0.001$]). As the pandemic has progressed, this interval has increased significantly for all patients, with a median of 6 days from admission to V-V ECMO cannulation in cohort 1 compared with 10 days in cohort 2 ($p < 0.001$). The number of patients that were initially transferred from outside referral centers was significantly higher in cohort 2 than that in cohort 1 as well.

The proportion of transferred patients, in combination with all ICUs in the state operating at near capacity during the study period, may have contributed to this increased length of the time between admission and V-V ECMO cannulation. Given that recent studies have reported a strong association between periods of increased ICU capacity and marked deterioration of COVID-19 critical care patient outcomes (6), it is plausible that the increased COVID-19 caseload and subsequent ICU strain present during the study period were an independent factor behind the increase in 60-day mortality.

Notably, a limitation of these findings is that as the pandemic continued, many clinicians became increasingly aware of the strong association between patient comorbidities and worse V-V ECMO outcomes. Although the criteria for V-V ECMO remained unchanged throughout this study, this may have affected who was offered V-V ECMO.

The increase in mortality associated with increased time of hospital admission to V-V ECMO cannulation may be driven by the tempo of disease progression. Early clinical decompensation of COVID-19 may be associated with improved outcomes compared with late decompensation. If initiated at a later stage, it is possible that V-V ECMO is unlikely to improve the substantial fibrotic lung damage that has already manifested due to severe ARDS. Although our data do not provide definitive evidence of this, other studies have reported increased survival rates when early V-V ECMO is initiated (7, 8).

The rate of treatment with steroids and duration of steroid administration were also significantly higher in the nonsurvivors. This finding is heavily confounded with the ubiquitous use of steroids in cohort 2 as 53 of 54 patients received at least one dose. This trend in steroid use has been identified in other recent studies evaluating the decreased survival in COVID-19 V-V ECMO patients (3). It is possible that the increased mortality associated with steroid use was related to some other temporal, unmeasured cause such as the increased prevalence of COVID-19 variants during the study period (9). However, previous studies have described the potentially detrimental effects of steroids on refractory (non-COVID-19) ARDS treated with V-V ECMO. In a retrospective study of 441 patients conducted prior to the COVID-19 pandemic, Kim et al (10) reported that steroid use was independently associated with increased inhospital mortality in patients successfully weaned off steroids. In addition, further analysis regarding corticosteroid use in COVID-19 remains inconclusive (11). Overall, we believe that these findings suggest that the role of steroids for COVID-19 ARDS requires additional analysis before the utilization of this therapy is confirmed in this setting.

CONCLUSIONS

We posit multiple factors affected the outcomes associated with V-V ECMO for COVID-19 ARDS including access to care and the increased prevalence of COVID variants. Nearly all hospitals were at maximum capacity, limiting transfers and increasing the time to V-V ECMO cannulation and use of steroids. The results of our review allow us to propose hypotheses regarding potential causes for the decreased survival experienced by our group. Further research is required to establish conclusions regarding the increase in mortality.

Despite the decreased reported rate of survival, V-V ECMO remains a reasonable treatment for patients with COVID-19–associated ARDS. Many patients placed on V-V ECMO are severely critically ill, refractory to conventional mechanical ventilation. Withholding V-V ECMO may produce even higher mortality rates than reported here. Although mortality appears to have increased from initial reports earlier in the pandemic, V-V ECMO still provides a benefit for these patients.

1 *University of Minnesota, Medical School, Minneapolis, MN.*

2 *Department of Surgery, University of Minnesota, Minneapolis, MN.*

3 *Department of Internal Medicine, Hennepin Healthcare, Minneapolis, MN.*

4 *Department of Anesthesiology and Perioperative Medicine, Mayo Clinic, Rochester, MN.*

5 *Department of Critical Care Medicine, Abbott Northwestern Hospital, Minneapolis, MN.*

6 *Department of Emergency Medicine, Hennepin Healthcare, Minneapolis, MN.*

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For information regarding this article, E-mail: mbrunsvo@umn.edu

REFERENCES

1. Bergman ZR, Wothe JK, Alwan FS, et al: Risk factors of mortality for patients receiving venovenous extracorporeal membrane oxygenation for COVID-19 acute respiratory distress syndrome. *Surg Infect (Larchmt)* 2021; 22:1086–1092
2. Bergman ZR, Wothe JK, Alwan FS, et al: The use of venovenous extracorporeal membrane oxygenation in COVID-19 infection: One region's comprehensive experience. *ASAIO J* 2021; 67:503–510
3. Barbaro RP, MacLaren G, Boonstra PS, et al; Extracorporeal Life Support Organization: Extracorporeal membrane oxygenation for COVID-19: Evolving outcomes from the international extracorporeal life support organization registry. *Lancet* 2021; 398:1230–1238
4. Reddy R, Dovidio J, Baram M, et al. Outcomes of extracorporeal membrane oxygenation in ARDS due to COVID-19: Comparison of the first and the second wave. *Chest* 2021; 160:A1065
5. Melhuish TM, Vlok R, Thang C, et al: Outcomes of extracorporeal membrane oxygenation support for patients with COVID-19: A pooled analysis of 331 cases. *Am J Emerg Med* 2021; 39:245–246
6. Dennis JM, McGovern AP, Thomas NJ, et al: Trends in 28-day mortality of critical care patients with coronavirus disease 2019 in the United Kingdom: A national cohort study, March 2020 to January 2021. *Crit Care Med* 2021; 49:1895–1900
7. Li X, Hu M, Zheng R, et al: Delayed initiation of ECMO is associated with poor outcomes in patients with severe COVID-19: A multicenter retrospective cohort study. Original research. *Front Med* 2021; 8:716086
8. Mustafa AK, Alexander PJ, Joshi DJ, et al: Extracorporeal membrane oxygenation for patients with COVID-19 in severe respiratory failure. *JAMA Surg* 2020; 155:990–992
9. Challen R, Brooks-Pollock E, Read JM, et al: Risk of mortality in patients infected with SARS-CoV-2 variant of concern 202012/1: Matched cohort study. *BMJ* 2021; 372:n579
10. Kim T, Noh J-H, Chung JH, et al: Steroid is associated with death after successful weaning of ECMO in acute respiratory failure: Analysis of a multicenter registry. *Eur Respir J* 2019; 54(Suppl 63):PA2186
11. Sahilu T, Sheleme T, Melaku T: Severity and mortality associated with steroid use among patients with COVID-19: A systematic review and meta-analysis. *Interdiscip Perspect Infect Dis* 2021; 2021:6650469