Veno-venous extracorporeal membrane oxygenation support in patients with COVID-19 respiratory failure: A multicenter study

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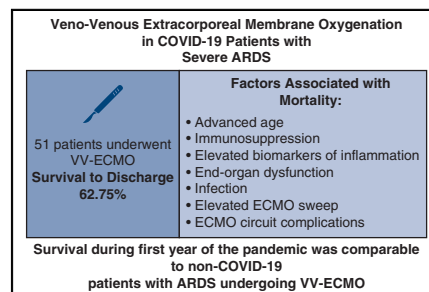
ABSTRACT

Objective: The COVID-19 pandemic presents a high mortality rate amongst patients who develop severe acute respiratory distress syndrome (ARDS). The purpose of this study was to evaluate the outcomes of veno-venous extracorporeal membrane oxygenation (VV-ECMO) in COVID–19-related ARDS and identify the patients who benefit the most from this procedure.

Methods: Adult patients with COVID-19 and severe ARDS requiring VV-ECMO support at 4 academic institutions between March and October 2020 were included. Data were collected through retrospective chart reviews. Bivariate and multivariable analyses were performed with the primary outcome of in-hospital mortality.

Results: Fifty-one consecutive patients underwent VV-ECMO with a mean age of 50.4 years; 64.7% were men. Survival to hospital discharge was 62.8%. Median intensive care unit and hospitalization duration were 27.4 days (interquartile range [IQR], 17-37 days) and 34.5 days (IQR, 23-43 days), respectively. Survivors and nonsurvivors had a median ECMO cannulation time of 11 days (IQR, 8-18) and 17 days (IQR, 12-25 days). The average postdecannulation length of stay was 17.5 days (IQR, 12.4-25 days) for survivors and 0 days for nonsurvivors (IQR, 0-6 days). Only 1 nonsurvivor was able to be decannulated. Clinical characteristics associated with mortality between nonsuriors and survivors included increasing age ($P = .0048$), hemorrhagic stroke ($P = .0014$), and postoperative dialysis ($P = .0013$) were associated with mortality in a bivariate model and retained statistical significance in a multivariable model.

Conclusions: This multicenter study confirms the effectiveness of VV-ECMO in selected critically ill patients with COVID–19-related severe ARDS. The survival of these patients is comparable to non-COVID–19-related ARDS. (JTCVS Open 2022;■:1-10)

Veno-Venous Extracorporeal Membrane Oxygenation in COVID-19 Patients with Severe ARDS

51 patients underwent VV-ECMO
Survival to Discharge 62.75%

Factors Associated with Mortality:
- Advanced age
- Immunosuppression
- Elevated biomarkers of inflammation
- End-organ dysfunction
- Infection
- Elevated ECMO sweep
- ECMO circuit complications

Survival during first year of the pandemic was comparable to non-COVID-19 patients with ARDS undergoing VV-ECMO

Venovenous extracorporeal membrane oxygenation in acute respiratory distress syndrome. The outcomes of patients with COVID-19 patients undergoing VV-ECMO are favorable, and survival is comparable to patients without COVID-19 with ARDS. Clinical markers associated with mortality may help guide patient selection for VV-ECMO cannulation and prognostication.

CENTRAL MESSAGE

The outcomes of patients with COVID-19 undergoing VV-ECMO are favorable, and survival is comparable to patients without COVID-19 with ARDS.

PERSPECTIVE

The outcomes of patients with COVID-19 undergoing VV-ECMO are favorable during the first year of pandemic. Their survival is comparable to patients without COVID-19 with ARDS. The utilization of VV-ECMO support should be considered in selected patients. Clinical markers associated with mortality may help guide patient selection for VV-ECMO cannulation and prognostication.

Abbreviations and Acronyms
ARDS   = acute respiratory distress syndrome
ELSO   = Extracorporeal Life Support
          Organization
EOLIA   = ECMO to Rescue Lung Injury in
          Severe ARDS
proBNP = B-type natriuretic peptide
VV-ECMO = veno-venous extracorporeal
          membrane oxygenation

▶ Video clip is available online.

Infection with SARS-CoV-2 causes COVID-19 and results in 15% to 20% of patients developing severe acute respiratory distress syndrome (ARDS).[1-3] In this population, in-hospital mortality has been reported up to 90%,[4] in early reports from 2020. Venovenous extracorporeal membrane oxygenation (VV-ECMO) therapy allows carbon dioxide removal and blood oxygenation in patients with severe pulmonary compromise. This temporary extracorporeal circuit serves as a bridge to gradual lung recovery, and possible lung transplantation. It has been beneficial in treating patients with ARDS without COVID-19.[5,6] Understandably, there has been significant interest in utilizing this therapy in patients with COVID-19. Early in the pandemic, data from China demonstrated poor outcomes with the implementation of VV-ECMO.[7] However, recent data from the international Extracorporeal Life Support Organization (ELSO) Registry[8] demonstrated better survival than initially reported, with a mortality rate of 38%. Given the high resource utilization of VV-ECMO in patients with COVID-19, the purpose of this multicenter study was to evaluate the outcomes of this modality with a focus on identifying the risk factors associated with in-hospital mortality. We hypothesize that mortality after VV-ECMO support in patients with COVID-19 would be comparable to mortality in patients without COVID-19 with severe ARDS.

METHODS

This study involved collaboration of 4 ECMO referral centers to develop a large prospective, observational database analyzing the outcomes of adult patients with COVID-19 with severe ARDS who underwent VV-ECMO support. VV-ECMO cannulation at each institution followed the international ELSO guidelines. Each institution contributed to the ELSO Registry. Contribution to this study was not equal between institutions with the majority of patients coming from 2 of the centers. The institutional review board at each participating institution approved the study protocol (protocol No. 20-1298; February 1, 2019). Given the observational nature of the study, informed consent was waived. Clinical data were collected through comprehensive retrospective reviews of electronic medical records. Elements of the past medical history were abstracted from the admission history and physical note. Vasopressors were defined as norepinephrine and vasopressin, whereas iotropes were defined as dobutamine, epinephrine, and milrinone. Right heart failure was diagnosed by echocardiography. Between March and October 2020, 51 consecutive adult patients with COVID-19 with ARDS were enrolled and placed on VV-ECMO.

Statistical Analysis

We performed a bivariate analysis on 272 pre-ECMO and during-ECMO clinical variables regarding their association with the primary outcome of in-hospital mortality. The χ^2 and Fisher exact tests were utilized for evaluating categorical variables, whereas t test or Wilcoxon rank-sum tests were used for continuous variables. Using the 24 statistically significant variables from the bivariate analysis, we then performed a multivariable analysis utilizing logistic regression and forward stepwise selection. All statistical tests were considered significant at a 2-sided $P < .05$. All analyses were performed using SAS software version 9.4 (SAS Institute Inc).

RESULTS

Patient Baseline Characteristics

VV-ECMO support was performed on 51 consecutive critically ill patients with COVID–19-related ARDS. The mean age was 50.4 years, and 64.7% were men. Most patients were obese (60.8%) with the average body mass index of 33.2 ± 8.6. In-hospital mortality was 37.2%, whereas 62.8% survived to hospital discharge. Significant differences existed in the baseline patient characteristics, medical history, and comorbidities among the nonsurvivors and survivors (Table 1). Patient characteristics associated with in-hospital mortality included increasing age (56.6 vs 46.7 years; $P = .0048$), pre-ECMO immunosuppression (42.1% vs 9.4%; $P = .02$), history of central nervous system dysfunction (ie, neurotrauma, stroke, encephalopathy, or seizure disorder) (21% vs 0%; $P = .02$), and essential hypertension (57.9% vs 28.1%; $P = .03$).

Clinical and Laboratory Characteristics of Patients Immediately Before VV-ECMO Cannulation

Nonsurvivors also had significant differences in their immediate pre-ECMO cannulation characteristics compared with survivors (Table 2). Inotrope requirement (52.6% vs 15.6%; $P = .01$) and steroid treatment (52.6% vs 15.6%; $P = .0014$) in the 24 hours immediately before cannulation were associated with mortality. Regarding pre-ECMO laboratory values, patients who experienced in-hospital death had higher white blood cell counts (18.9 vs 13.0; $P = .0096$). A lower minimum hemoglobin level was protective for mortality (14.3 vs 11.3; $P = .0138$). This study also evaluated several markers of inflammation such as C-reactive protein, procalcitonin, interleukin 6, and ferritin; however, only a higher pre-ECMO maximum ferritin was associated with mortality (2774 vs 1266; $P = .026$).

TABLE 1. Patient characteristics and demographic characteristics of 51 consecutive critically ill patients with COVID-19 and severe acute respiratory distress syndrome who underwent veno-venous extracorporeal membrane oxygenation cannulation, stratified by survivors and nonsurvivors

Characteristics	Discharge alive (n = 32)	In- hospital death (n = 19)	P value*
Demographic characteristic			
Age	46.7 ± 12.6	56.6 ± 9.4	**.0048**
Gender			
Female	12 (37.5)	6 (31.6)	.67
Male	20 (62.5)	13 (68.4)	
Body mass index	34.75 ± 9.6	30.64 ± 5.9	.10
Race/ethnicity			
African American or Black	5 (17.8)	4 (12.7)	.46
Asian	4 (12.5)	1 (5.3)	
White	7 (21.9)	7 (36.8)	
Hispanic	13 (40.6)	7 (36.8)	
Other/unknown	3 (9.4)	0 (0)	
Past medical history			
Chronic obstructive pulmonary disease	1 (3.1)	2 (10.5)	.28
Pulmonary hypertension	1 (3.1)	0 (0)	.44
Essential hypertension	9 (28.1)	11 (57.9)	**.03**
Diabetes mellitus	14 (43.75)	6 (31.6)	.39
Peripheral artery disease	7 (2.1)	19 (4.2)	.11
Stroke/transient ischemic attack	0 (0)	2 (10.5)	.06
Asthma	5 (15.6)	5 (15.6)	.98
Central Nervous System Dysfunction†	0 (0)	4 (21.1)	**.02**
Immunosuppression‡	3 (9.4)	8 (42.1)	**.02**
Substance abuse			
Tobacco use	2 (6.3)	1 (5.3)	.79
Alcohol	8 (25)	4 (21)	.65

Values are presented as n (row %) or mean ± SD. Bolded values indicate P-value <.05. *P values are either χ^2 or Fisher exact for categorical variables and t test for continuous variables. †Neurotrauma, stroke, encephalopathy, and seizure disorder. ‡Indicates treatment with immunosuppressive medications, chemotherapy, or chronic steroids.

COVID-19 Treatment Characteristics

Use of steroids <24 hours before ECMO (15.6% vs 52.6%; P = .00140) and steroid treatment in general (18.8% vs 68.4%; P = .0004) were associated with increased mortality. Hydroxychloroquine/chloroquine treatment was associated with survival (46.9% vs 15.8%; P = .025).

ECMO Cannulation Details and Post-ECMO Patient Characteristics

Patients with in-hospital mortality had a significantly higher frequency of cannulation site bleeding requiring transfusion (31.6% vs 9.4%; P = .04) and ECMO oxygenator failure (15.8% vs 0%; P = .02). Higher ECMO sweep at 4 hours postcannulation was also associated with in-hospital mortality (4.7 vs 3.28; P = .02). Furthermore, the levels of biomarkers collected 24-hours after ECMO initiation demonstrated significant differences between nonsurvivor and survivor cohorts. These included elevated C-reactive protein (290.8 vs 196.5; P = .023), D-dimer (15,724 vs 5349; P = .05), and B-type natriuretic peptide (proBNP) (16,411 vs 1185; P = .039) (Table 3).

Nonsurvivors had significantly higher rates of end-organ dysfunction such as hemorrhagic stroke (36.8% vs 3.1%; P = .0014), right heart failure (15.8% vs 0%; P = .02) and renal failure needing dialysis (63.2% vs 18.8%; P = .0013). Additionally, localized infections resulting in culture-proven infection of a body cavity (positive cultures taken from drained pleural or abdominal fluid) were also associated with in-hospital mortality (31.6% vs 6.3%; P = .014).

Patient Outcomes: Causes of Death and Complications

Among the nonsurvivors, 73.6% died from end-stage respiratory failure, 21.1% died from multisystem organ failure, and 5% died from intracranial hemorrhage. The median total ECMO cannulation time for survivors was 11 days (interquartile range [IQR], 8-18 days) and 17 days (IQR, 12-25 days) for nonsurvivors. The median postdecannulation length of stay for survivors was 17.5 days (IQR, 12.4-25 days) and 0 days (IQR, 0-6 days) for nonsurvivors. The median pre-ECMO ventilator days for survivors was 6 days (IQR, 3-8.6 days) and 4.5 days

TABLE 2. Clinical and laboratory data of 51 patients with COVID-19 immediately before initiating veno-venous extracorporeal membrane oxygenation (VV-ECMO) for severe acute respiratory distress syndrome

Characteristics	Discharge alive (n = 32)	In-hospital death (n = 19)	P value
Pre-ECMO characteristics			
Indication for VV-ECMO			.0629
Hypoxia Pao_2/Fio_2 <75	5 (15.6)	5 (26.3)	
Hypoxia Pao_2/Fio_2 <100	10 (31.3)	4 (21.1)	
Hypoxia Pao_2/Fio_2 100-150	8 (25)	0 (0)	
Hypercapnea pH <7.25, Pco_2 >60	0 (0)	2 (10.5)	
Hypoxia (Pao_2/Fio_2) and hypercapnia	2 (6.3)	3 (15.8)	
RESP score			.3519
I	2 (6.3)	0 (0)	
II	10 (31.3)	6 (31.6)	
III	13 (40.6)	5 (26.3)	
IV	2 (6.3)	5 (26.3)	
V	1 (3.1)	1 (5.3)	
Transported on VV-ECMO	2 (6.3)	2 (10.5)	.3530
Cannulation location			.2774
Intensive care unit bedside	31 (96.9)	17 (89.5)	
Operating room	1 (3.1)	2 (10.5)	
Inotrope <24 h before ECMO	5 (15.6)	10 (52.6)	**.01**
Vasopressors <24 h before ECMO	17 (53.1)	11 (57.9)	.44
Hyperventilation <24 h before ECMO	12 (37.5)	10 (52.63)	.4012
CPR before VV-ECMO	0 (0)	2 (10.5)	.1587
Bicarbonate infusion	2 (6.3)	1 (5.3)	.8849
Nitric oxide use	3 (9.4)	1 (5.3)	.63
Plasmapheresis <24 h before ECMO	1 (3.1)	1 (5.3)	.0603
Prone positioning <24 h before ECMO	28 (87.5)	15 (78.9)	.42
Anticoagulation before cannulation			.7294
Heparin infusion	17 (53.1)	9 (47.4)	
Bivalirudin infusion	1 (3.1)	0 (0)	
Neuromuscular blockade	29 (90.6)	17 (89.5)	.89
Nonpulmonary infection	8 (25)	2 (10.5)	.09
Steroid <24 h before ECMO	5 (15.6)	10 (52.6)	**.0014**
Ventilator days before ECMO	6.2 ± 4.5	3.9 ± 3.1	.08
Epoprostenol use <24 h before ECMO	22 (68.8)	12 (63.2)	.84
Pre-ECMO echocardiography			.1384
Right ventricular dysfunction	3 (9.4)	2 (10.5)	
Left ventricular dysfunction	0 (0)	1 (5.3)	
Acute kidney injury before ECMO	13 (40.6)	6 (31.6)	.7817
Dialysis before ECMO	1 (3.1)	0 (0)	.7278
Bacterial pneumonia	2 (6.3)	3 (15.8)	.27
Septic shock	1 (3.1)	2 (10.5)	.28
Covid-19 treatments			
Convalescent plasma	18 (56.3)	13 (68.4)	.39
Hydroxychloroquine/chloroquine	**15 (46.9)**	**3 (15.8)**	**.025**
Remdesivir	15 (46.9)	12 (63.2)	.26
Janus kinase inhibitor	1 (3.1)	0 (0)	.43
Cytokine blocker	7 (21.9)	4 (21.1)	.95
Steroids	**6 (18.8)**	**13 (68.4)**	**.0004**
Pre-ECMO laboratory values			
Absolute neutrophil count	1254.9	2028.2	.5673
Creatinine	0.94 ± 0.26	1.20 ± 1.34	.3302
Lowest pH <24 h before ECMO	7.27 ± 0.087	7.26 ± 0.12	.6004
Highest $Paco_2$ <24 h before ECMO	61.48 ± 23.2	64.64 ± 19.7	.6379
Lowest Pao_2 <24 h before ECMO	65.84 ± 18.03	64.29 ± 14.81	.7658

(Continued)

TABLE 2. Continued

Characteristics	Discharge alive (n = 32)	In-hospital death (n = 19)	P value
Lowest bicarbonate <24 h before ECMO	27.83 ± 7.2	26.87 ± 5.8	.6456
Lowest Sao_2 <24 h before ECMO	85.32 ± 13.6	81.47 ± 23.4	.4883
Creatinine, maximum <24 h before ECMO	2.42 ± 5.1	1.53 ± 1.51	.4933
Lactate, maximum (mmol/L)	24.2 ± 105.3	3.69 ± 4.4	.4897
Total bilirubin, maximum	1.38 ± 1.37	0.88 ± 0.62	.1487
Platelets, minimum <24 h before ECMO	73,806 ± 180,151	13,454 ± 51,053	.2129
White blood cells, maximum <24 h before ECMO	**13.0 ± 6.9**	**18.9 ± 7.5**	**.0096**
Hemoglobin, minimum, <24 h before ECMO	**11.3 ± 2.0**	**14.3 ± 5.6**	**.0138**
proBNP, maximum	161.3 ± 208.4	5779.6 ± 14,888.9	.2016
Pre-ECMO markers of inflammation			
C-Reactive protein, maximum	245.6 ± 154.6	224.6 ± 140.6	.6554
Procalcitonin, maximum	4.65 ± 9.22	7.55 ± 18.1	.5836
Interleukin 6, maximum	99.67 ± 91.2	17.9 ± 11.1	.5192
Ferritin, maximum	**1266.9 ± 1085.9**	**2774 ± 2757.6**	**.0260**
Pre-ECMO ventilator settings			
Respiratory rate	29.6 (11.0)	28.9 (8.0)	.83
Tidal volume, maximum	382.8 (136.1)	425.7 (99.6)	.35
Mean airway pressure, maximum	24.3 (3.9)	25.5 (3.8)	.49
Positive end expiratory pressure, maximum	16.1 (3.0)	14.7 (2.8)	.15
Plateau pressure, maximum	30.7 (6.4)	32.0	.85

Values are presented as n (%) or mean ± SD. Bold values indicate *P*-value <.05. *Pao₂*, partial pressure of oxygen; *Fio₂*, inspired oxygen fraction; *RESP*, respiratory extracorporeal membrane oxygenation survival prediction; *CPR*, cardiopulmonary resuscitation; *Paco₂*, partial pressure of carbon dioxide; *Sao₂*, oxygen saturation; *proBNP*, B-type natriuretic peptide.

(IQR, 1-6 days) for nonsurvivors. The median hospital length of stay at the time for ECMO cannulation was 7 days (IQR, 1-9 days) for survivors, and 5 days (IQR, 0-7 days) for nonsurvivors. The median total hospitalization days for survivors were 37 days (IQR, 28-47 days) and 23 days (IQR, 16-37 days) for nonsurvivors. Median intensive care unit days for survivors was 26 days (IQR, 19-38 days) and 22 days (IQR, 16-37 days) for nonsurvivors (Table 4). Among survivors, 14 were discharged home, 8 were discharged to long-term acute care, and 9 were discharged to an acute rehabilitation facility (Table 4). Utilizing a multivariable model, increasing age (odds ratio [OR], 1.156; 95% CI, 1.028-1.3; P = .0157), postoperative dialysis requirement (OR, 20.015; 95% CI, 2.837-141.17; P = .0026) and postoperative hemorrhagic stroke (OR, 58.265; 95% CI, 3.809-891.47; P = .0035) were predictive of in-hospital mortality.

DISCUSSION

This study reports the experience of VV-ECMO support for COVID–19-related ARDS at 4 major academic centers in the United States during the first year of pandemic. Fifty-one consecutive patients received VV-ECMO support. Among them, 32 patients were weaned from VV-ECMO and discharged from the hospital alive, whereas 19 patients died. The in-hospital mortality rate of patients who received ECMO therapy during this study was 37.2%.

Early data during the pandemic reported dismal outcomes after VV-ECMO implementation in patients with COVID-19,[4] which resulted in hesitancy in the utilization of VV-ECMO support in this population.[9] As the pandemic progressed, the medical community regained confidence in the utility of VV-ECMO. The recent publication of the international ELSO Registry cited a 38% in-hospital mortality consistent with the mortality rate reported in our study and with previously published reports of VV-ECMO use in patients without COVID-19 with ARDS.[5,10]

In our study, essential hypertension was a significant risk factor for in-hospital mortality in patients receiving VV-ECMO. Essential hypertension has been recognized as a risk factor for worsened severity of COVID-19 infection.[11] In a study by Guan and colleagues,[12] hypertension was the most common comorbidity among patients with COVID-19 who developed severe complications and required intubation. In a meta-analysis based on 6 studies, patients with COVID-19 with severe respiratory complications were 2-fold more likely to have primary hypertension.[13] Multiple explanations for the association between hypertension and COVID-19 severity have been proposed, with the most common being accumulated end-organ damage caused by long-standing hypertension.[11] Unfortunately, primary hypertension is a complex variable to quantify. In many of these retrospective studies, including our own, there are significant uncertainties about the severity of hypertension, the timing of hypertension diagnoses, and antihypertensive medication adherence.

In this report, we also noted that the use of inotropic drugs and steroids within 24 hours before the cannulation is

TABLE 3. Extracorporeal membrane oxygenation (ECMO) cannulation details and post-ECMO characteristics of 51 patients who underwent veno-venous ECMO for severe COVID–19-associated acute respiratory distress syndrome

	Discharge alive (n = 32)	In- hospital death (n = 19)	*P* value*
During-ECMO characteristics			
Initial access cannulation site			.42
Internal jugular, right	18 (56.3)	13 (68.4)	
Superior vena cava	0 (0)	1 (5.3)	
Common femoral vein, right	9 (28.1)	3 (15.8)	
Common femoral vein, left	3 (9.4)	2 (10.5)	
Initial return cannulation site			.84
Internal jugular, right	19 (59.4)	12 (63.2)	
Superior vena cava	1 (3.1)	0 (0)	
Common femoral vein, right	8 (25)	6 (31.6)	
Common femoral vein, left	3 (6.3)	2 (10.5)	
Access cannulation site conversion			.32
Internal jugular, right	0 (0)	1 (5.3)	
Common femoral vein, left	1 (3.1)	0 (0)	
Return cannulation site conversion			.39
Internal jugular, right	1 (3.1)	1 (5.3)	
Common femoral vein, right	0 (0)	1 (5.3)	
Prone positioning	9 (28.1)	6 (31.6)	.89
Anticoagulation			.24
Heparin	29 (90.6)	15 (78.9)	
Bivalirudin	3 (9.4)	4 (21.1)	
Laboratory values 24 h after cannulation			
pH	7.39 ± 0.06	7.39 ± 0.06	.76
$Paco_2$	47.5 ± 7.5	48.7 ± 48.7	.68
Pao_2	92.7 ± 36.4	92.9 ± 42.9	.98
Bicarbonate	28.8 ± 5.6	28.6 ± 4.9	.90
Sao_2	94.5 ± 3.0	95.7 ± 2.1	.14
Svo_2	67.6 ± 12.6	67.3 ± 7.4	.97
Fio_2	55.6 ± 23.1	56.5 ± 16.9	.90
Creatinine	1.63 ± 1.5	1.62 ± 1.5	.98
Bilirubin, total	1.59 ± 1.7	1.7 ± 2.2	.84
Sodium, serum	142.1 ± 4.7	138.8 ± 23.7	.58
Platelets	225 ± 83.7	182.6 ± 77.4	.09
White blood cell count	10.7 ± 4.3	13.7 ± 6.8	.10
Hemoglobin	9.86 ± 1.5	9.76 ± 1.3	.63
ProBNP	592.8 ± 934.2	3338.4 ± 5412	.11
ProBNP, maximum during ECMO	1185 ± 1825	16,411 ± 25,059	**.039**
Troponin, maximum	0.09 ± 0.21	0.29 ± 0.53	.14
During-ECMO markers of inflammation			
C-Reactive protein, 24 h postcannulation	154.4 ± 123.6	170.7 ± 120.7	.68
C-Reactive protein, maximum	196.5 ± 120.6	290.8 ± 135.0	**.023**
Procalcitonin, 24 h postcannulation	3.03 ± 8.6	4.08 ± 5.7	.84
Procalcitonin, maximum	3.14 ± 8.3	6.76 ± 11.5	.47
D-Dimer, 24 h postcannulation	**5349.7 ± 7604.7**	**15,724 ± 2147**	**.05**
D-Dimer, maximum	26,831 ± 27,599	43,929 ± 31,272	.07
Ferritin, 24 h postcannulation	1207 ± 1016.7	1493 ± 824	.40
Ferritin, maximum	1561 ± 1529	12,224 ± 31,747	.12
ECMO settings			
Flow at 4 h	4.15 ± 1.03	4.24 ± 1.98	.84
Flow at 24 h	4.35 ± 0.98	4.25 ± 1.07	.74
Sweep at 4 h	**3.28 ± 1.55**	**4.7 ± 2.60**	**.02**
Sweep at 24 h	4.04 ± 2.12	5.44 ± 3.12	.06

(Continued)

TABLE 3. Continued

	Discharge alive (n = 32)	In- hospital death (n = 19)	P value*
Ventilator settings 24 h after cannulation			
Respiratory rate	15.1 (4.5)	15.2 (5.7)	.94
Tidal volume	273.9 (98.7)	293.6 (128.7)	.64
Peak pressure	27.5 (3.9)	30.9 (8.9)	.13
Mean airway pressure	17.0 (3.8)	16.8 (2.3)	.86
Positive end expiratory pressure	12.6 (3.2)	11.4 (2.5)	.21
Plateau pressure	27.6 (4.6)	26 (4.6)	.65
Pao_2/Fio_2	174.3 (103.9)	133.4 (59.6)	.056
Procedures performed during ECMO			
Chest tube	3 (9.4)	2 (10.5)	.89
Reintubation	1 (3.1)	1 (3.1)	.70
Therapeutic bronchoscopy	6 (18.8)	6 (31.6)	.30
Blood product use during ECMO			
Red blood cell units	7.95 (8.7)	8.93 (10.1)	.75
Platelet	1.93 (2.8)	1.3 (1.5)	.49
Fresh frozen plasma	1.88 (3.6)	1.25 (1.8)	.58

Values are presented as n (row %) or mean $\pm$ SD. Bold values indicate P-value <0.05. $Paco_2$, partial pressure of carbon dioxide; Pao_2, partial pressure of oxygen; Sao_2, oxygen saturation; Svo_2, mixed venous oxygen saturation; Fio_2, inspired oxygen fraction; $proBNP$, B-type natriuretic peptide. *P values are either χ^2 or Fisher exact for categorical variables and t test for continuous variables.

associated with a higher risk for in-hospital mortality. Hemodynamic instability needing inotropic support is indicative of escalating heart failure and ultimately cardiogenic shock. Consistent with our data, the ELSO VV-ECMO study demonstrated that patients in severe cardiogenic shock requiring veno-arterial ECMO support had a significant association with in-hospital mortality.[8] Our study found pro-BNP elevation to be associated with mortality. As a marker for heart failure, elevated pro-BNP is congruent with our findings, indicating adverse outcomes in VV-ECMO patients with cardiac dysfunction. This association between elevated pro-BNP and mortality has also been supported by previous COVID-19 reports.[14,15]

The use of steroids for ARDS has been focus of numerous clinical trials. Recent data from the Dexamethasone Treatment for the Acute Respiratory Distress Syndrome trial (DEXA-ARDS) demonstrated a lower 60-day all-cause mortality (21% vs 36%; P = .005) and increased ventilator-free days (12 vs 7; P <.001).[16] Accordingly, corticosteroids emerged as an early treatment option for patients with COVID-19, with early observational data from China demonstrating a mortality benefit.[17] The UK-based Dexamethasone in Hospitalized Patients with Covid-19 trial (RECOVERY) recruited 6425 patients with COVID-19 and showed a significant reduction in mortality (29.3% vs 41.4%) in patients receiving mechanical ventilation who received dexamethasone treatment.[18] However, this mortality benefit did not extend to patients not receiving ventilation. The Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community- Acquired Pneumonia (REMAP-CAP) trial randomized 403 patients with severe COVID-19 into fixed low-dose hydrocortisone, a

shock-dependent hydrocortisone dose, and no steroids groups. The results from this trial's Bayesian analysis found that steroid treatment was likely superior to nontreatment. However, the trial lacked the sample size and granularity to determine the optimal steroid treatment regimen. The Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19 (CoDEX) trial took place in Brazil and randomized 299 patients with severe ARDS with COVID-19 to high-dose dexamethasone versus usual care alone and found an increase in ventilator-free days with steroid use. The use of steroids in the patients in our study, due to their deteriorating clinical condition, may have a temporal association with their cannulation and indicates severe inflammatory response.

Patients with severe COVID-19 infection can manifest an inflammatory cytokine storm that results in the elevation of several acute phase reactants.[19] Our study found pre-ECMO elevation of the inflammatory marker ferritin to be associated with mortality. Similarly, a few prior studies have corroborated this finding. A recent meta-analysis of 18 COVID-19 trials found that ferritin levels were significantly higher in patients who eventually required intubation and in those who did not survive hospitalization.[20]

Early in the course of the COVID-19 pandemic, it was noted that patients with severe disease manifest signs of disseminated intravascular coagulation,[21] with micro- and macrovascular thromboses being the predominating phenotype. Regardless of etiology, a defining feature of ARDS is airspace fibrin deposition resulting in fibrin-platelet conglomeration and ultimately microthrombi in the pulmonary vasculature.[22] With increased pulmonary vascular

TABLE 4. Patient outcomes and cause of death of 51 patients who underwent veno-venous extracorporeal membrane oxygenation (VV-ECMO) for COVID–19-associated acute respiratory distress syndrome

ECMO outcome	Discharge alive (n = 32)	In-hospital death (n = 19)	P value
ECMO cannulation time	11 (8-18)	17 (12-25)	
Pre-ECMO ventilator days	6 (3-8.6)	4.5 (1-6)	
Pre-ECMO hospital days	7 (1-9)	5 (0-7)	
Postdecannulation length of stay (days)	17.5 (12.4-25)	0 (0-6)	
Total intensive care unit length of stay (days)	26 (19-38)	22 (16-37)	
Total hospitalization days	37 (28-47)	23 (16-37)	
Cause of death			
End stage respiratory failure		14	
Multisystem organ failure		4	
Intracranial hemorrhage		1	
Hospital discharge location			
Long-term acute care	8		
Home	14		
Acute rehab unit	9		
Other	1		
Complications during ECMO			
Conversion to veno-arterio-venous ECMO	0 (0)	1 (5.3)	.35
Upper extremity deep vein thrombosis	11 (34.4)	2 (10.5)	.16
Lower extremity deep vein thrombosis	4 (12.5)	1 (5.3)	.62
Acute kidney injury	10 (31.3)	7 (36.8)	.69
Renal failure requiring dialysis	6 (18.8)	12 (63.2)	**.0013**
Pneumothorax	4 (12.5)	4 (21.05)	.42
Hemothorax	0 (0)	1 (5.3)	.19
Secondary bacterial pneumonia	10 (31.3)	7 (36.8)	.68
Positive blood culture	11 (34.4)	6 (31.6)	.86
Positive urine culture	5 (15.6)	2 (10.5)	.78
Positive body cavity fluid culture	2 (6.3)	6 (31.6)	**.014**
Right heart failure	0 (0)	3 (15.8)	**.02**
New inotrope requirement	1 (3.1)	3 (15.8)	.11
New vasodilator/antihypertensive agent requirement	6 (18.8)	2 (10.5)	.44
New vasopressor requirement	4 (12.5)	4 (21.1)	.42
Atrial fibrillation	1 (3.1)	1 (5.3)	.70
Ventricular tachycardia	2 (6.3)	0 (0)	.27
Cardiopulmonary resuscitation during ECMO	1 (3.1)	2 (10.5)	.28
Hemorrhagic stroke	1 (3.1)	7 (36.8)	**.0014**
Seizures	1 (3.1)	0 (0)	.44
Oxygenator failure	0 (0)	3 (15.8)	**.02**
Cannulation site bleeding	3 (9.4)	6 (31.6)	**.044**
Gastrointestinal bleeding	8 (25)	3 (15.8)	.44
Retroperitoneal bleed	1 (3.1)	0 (0)	.44
Hematuria	2 (6.3)	0 (0)	.27

Values are presented as median (interquartile range), n, or n (%). Bold values indicate *P*-value <.05.

resistance, patients with ARDS can often exhibit significant right heart failure. Our results support this finding of COVID-19 induced hypercoagulability with elevated D-dimer, a by-product of clot dissolution, and right heart strain on echocardiography associated with in-hospital mortality.

Another key finding is the similarity in mortality rates between our study and ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial. The EOLIA trial found improved 60-day mortality (41% vs 57%) with the institution of VV-ECMO support in patients with severe ARDS.[5] The average PaO_2 to fraction of inspired oxygen ratio was 74 mm Hg in our study, and the mean PaO_2 to fraction of inspired oxygen ratio in the EOLIA trial was 73 mm Hg. Although our study did not strictly measure 60-day survival, our 38.3% mortality is in line with the expected mortality in

patients receiving VV-ECMO for ARDS who were not infected with COVID-19.

Previous studies[1,3,8,23] have noted findings that are discordant with our study. These include the association of elevated body mass index with mortality and the finding that early ECMO support being associated with improved survival. Additionally, these studies have noted a correlation between respiratory ECMO survival prediction score and successful VV-ECMO implementation in patients with COVID-19, but our report did not demonstrate a linear correlation between increasing respiratory ECMO survival prediction score and mortality.

Our study has significant limitations. First, it describes the outcomes of selected 4 academic centers located in the Midwest and Rocky Mountain West with established ECMO programs and a significant cumulative experience. These centers have the resources to efficiently place patients on this therapy and collect and submit patient data during a pandemic. Second, our study does not incorporate long-term outcomes for patients after index hospitalization needing VV-ECMO support. Indeed, many of the ARDS studies[5,8,10] have longer follow-up times, between 60 days and 6 months, which limits our ability to directly compare mortality rates. Given the recently described coagulopathies arising in patients with COVID-19,[24,25] it is possible that our study underreports the prevalence of many long-term complications arising after COVID-19 infection. Finally, the observational nature of this study and lack of randomization limits our ability to draw definitive conclusions about the comparative efficacy of VV-ECMO as a therapy in patients with COVID-19.

Veno-Venous Extracorporeal Membrane Oxygenation in COVID-19 Patients with Severe ARDS
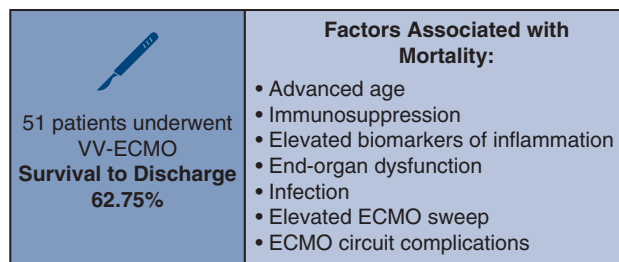
FIGURE 1. The outcomes of patients with COVID-19 undergoing venovenous extracorporeal membrane oxygenation (*VV-ECMO*) are favorable, and survival is comparable to patients without COVID-19 with acute respiratory distress syndrome (*ARDS*). Clinical markers associated with mortality may help guide patient selection for VV-ECMO cannulation and prognostication. *COVID-19*, Coronavirus disease 2019.

CONCLUSIONS

The results of our multicenter registry confirm the potential utility of VV-ECMO in the treatment of critically ill patients with COVID-19 with severe ARDS (Figure 1 and Video Abstract). Advanced age, immunosuppression, severe inflammatory response with increasing biomarkers, end-organ dysfunction, stroke, heart failure, renal failure, superimposed infection while on ECMO support, and ECMO-related complications are associated with higher mortality. The overall survival of patients with COVID-19 undergoing VV-ECMO is comparable to patients without COVID-19 with ARDS undergoing VV-ECMO. Further prospective studies are needed to investigate a mortality benefit in COVID-19 patients undergoing VV-ECMO cannulation.

Conflict of Interest Statement
The 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.

References
1. Grasselli G, Zangrillo A, Zanella A, Antonelli M, Cabrini L, Castelli A, et al. Baseline characteristics and outcomes of 1591 patients infected with SARS-CoV-2 admitted to ICUs of the Lombardy Region, Italy. *JAMA*. 2020;323: 1574-81.
2. Yang X, Yu Y, Xu J, Shu H, Xia J, Liu H, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020; 8:475-81.
3. Richardson S, Hirsch JS, Narasimhan M, Crawford JM, McGinn T, Davidson KW, et al. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323:2052-9.
4. 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.
5. Combes A, Hajage D, Capellier G, Demoule A, Lavoue S, Guervilly C, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome. *N Engl J Med*. 2018;378:1965-75.
6. Goligher EC, Tomlinson G, Hajage D, Wijeysundera DN, Fan E, Juni P, et al. Extracorporeal membrane oxygenation for severe acute respiratory distress syndrome and posterior probability of mortality benefit in a post hoc bayesian analysis of a randomized clinical trial. *JAMA*. 2018;320:2251-9.
7. Li X, Guo Z, Li B, Zhang X, Tian R, Wu W, et al. Extracorporeal membrane oxygenation for coronavirus disease 2019 in Shanghai, China. *ASAIO J*. 2020; 66:475-81.
8. Barbaro RP, MacLaren G, Boonstra PS, Iwashyna TJ, Slutsky AS, Fan E, et al. Extracorporeal membrane oxygenation support in COVID-19: an international cohort study of the Extracorporeal Life Support Organization Registry. *Lancet*. 2020;396:1071-8.
9. Namendys-Silva SA. ECMO for ARDS due to COVID-19. *Heart Lung*. 2020;49: 348-9.
10. Peek GJ, Mugford M, Tiruvoipati R, Wilson A, Allen E, Thalanany MM, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CE-SAR): a multicentre randomised controlled trial. *Lancet*. 2009;374:1351-63.
11. Kulkarni S, Jenner BL, Wilkinson I. COVID-19 and hypertension. *J Renin Angiotensin Aldosterone Syst*. 2020;21:1470320320927851.

12. Guan WJ, Ni ZY, Hu Y, Liang WH, Ou CQ, He JX, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020;382:1708-20.

13. Li B, Yang J, Zhao F, Zhi L, Wang X, Liu L, et al. Prevalence and impact of cardiovascular metabolic diseases on COVID-19 in China. *Clin Res Cardiol*. 2020; 109:531-8.

14. Gao L, Jiang D, Wen XS, Cheng XC, Sun M, He B, et al. Prognostic value of NT-proBNP in patients with severe COVID-19. *Respir Res*. 2020;21:83.

15. Pranata R, Huang I, Lukito AA, Raharjo SB. Elevated N-terminal pro-brain natriuretic peptide is associated with increased mortality in patients with COVID-19: systematic review and meta-analysis. *Postgrad Med J*. 2020;96:387-91.

16. Villar J, Ferrando C, Martinez D, Ambros A, Munoz T, Soler JA, et al. Dexamethasone treatment for the acute respiratory distress syndrome: a multicentre, randomised controlled trial. *Lancet Respir Med*. 2020;8:267-76.

17. Wu C, Chen X, Cai Y, Xia J, Zhou X, Xu S, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180: 934-43.

18. Group RC, Horby P, Lim WS, Emberson JR, Mafham M, Bell JL, et al. Dexamethasone in hospitalized patients with Covid-19. *N Engl J Med*. 2021;384: 693-704.

19. Zhou F, Yu T, Du R, Fan G, Liu Y, Liu Z, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395:1054-62.

20. Cheng L, Li H, Li L, Liu C, Yan S, Chen H, et al. Ferritin in the coronavirus disease 2019 (COVID-19): a systematic review and meta-analysis. *J Clin Lab Anal*. 2020;34:e23618.

21. Lillicrap D. Disseminated intravascular coagulation in patients with 2019-nCoV pneumonia. *J Thromb Haemost*. 2020;18:786-7.

22. Ware LB, Matthay MA. The acute respiratory distress syndrome. *N Engl J Med*. 2000;342:1334-49.

23. Yang BY, Barnard LM, Emert JM, Drucker C, Schwarcz L, Counts CR, et al. Clinical characteristics of patients with coronavirus disease 2019 (COVID-19) receiving emergency medical services in King County, Washington. *JAMA Netw Open*. 2020;3:e2014549.

24. Wang J, Hajizadeh N, Moore EE, McIntyre RC, Moore PK, Veress LA, et al. Tissue plasminogen activator (tPA) treatment for COVID-19 associated acute respiratory distress syndrome (ARDS): a case series. *J Thromb Haemost*. 2020;18:1752-5.

25. Moore HB, Barrett CD, Moore EE, McIntyre RC, Moore PK, Talmor DS, et al. Is there a role for tissue plasminogen activator as a novel treatment for refractory COVID-19 associated acute respiratory distress syndrome? *J Trauma Acute Care Surg*. 2020;88:713-4.