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Outcomes of Extracorporeal Membrane Oxygenation in Patients With Severe Acute Respiratory Distress Syndrome Caused by COVID-19 Versus Influenza

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ABSTRACT

BACKGROUND Extracorporeal membrane oxygenation (ECMO) can be effective for refractory acute respiratory distress syndrome (ARDS) in patients with influenza, but its utility in patients with coronavirus disease 2019 (COVID-19) is uncertain. We compared outcomes of patients with refractory ARDS from COVID-19 and influenza placed on ECMO.

METHODS We conducted a retrospective analysis of 120 patients with refractory ARDS due to COVID-19 or influenza placed on ECMO at 2 referral centers from January 2013 to October 2020. Patient characteristics and clinical outcomes were compared. The primary endpoint was survival to discharge.

RESULTS Baseline characteristics and comorbidities were similar. During the study period, 53 patients with COVID-19 and 67 patients with influenza were supported. Venovenous ECMO was the predominant initial cannulation strategy in both groups (COVID 92.5% vs influenza 95.5%; $P = .5$). Survival to hospital discharge was 62.3% (33 of 53 patients) in the COVID-19 group and 64.2% (43 of 67 patients) in the influenza group ($P = .8$). In patients successfully decannulated, median length of time on ECMO was longer in COVID-19 patients (14 [interquartile range (IQR), 9-30] days vs influenza 10.5 [IQR, 6.8-14.3] days; $P = .004$). Among patients discharged alive, COVID-19 patients had longer overall length of stay (COVID-19 37 [IQR, 27-62] days vs influenza 13.5 [IQR, 9.3-24] days; $P = .007$).

CONCLUSIONS In patients with refractory ARDS from COVID-19 or influenza placed on ECMO, there was no significant difference in survival to hospital discharge. In patients surviving to decannulation, the duration of ECMO support and total length of stay were longer in COVID-19 patients.

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The novel 2019 coronavirus (severe acute respiratory syndrome coronavirus 2, the causative agent of coronavirus disease 2019 [COVID-19]) was declared a global pandemic by the World Health Organization nearly 1 year ago. The spectrum of clinical manifestations ranges from asymptomatic spread of the virus to severe acute respiratory distress syndrome (ARDS) and multisystem organ failure.[1] Venovenous extracorporeal membrane oxygenation (VV ECMO) has been implemented for treatment of severe ARDS for the last several decades.[2] Most notably, ECMO was successfully used for severe ARDS in patients during the influenza (H1N1) pandemic in 2009,[3] and referral to an ECMO center for consideration of initiation of extracorporeal life support was shown to benefit patients with severe ARDS in the CESAR (Conventional Ventilatory

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Support Versus Extracorporeal Membrane Oxygenation for Severe Adult Respiratory Failure) trial.[4] However, there is scarce information available regarding the clinical course of patients with COVID-19 and severe ARDS placed on ECMO support,[5-8] limited to case series without comparison groups. In order to better understand the success rate of ECMO therapy in patients with refractory COVID-19, we compared outcomes of these patients against those with ARDS from influenza A or B who were initiated on ECMO over the last 7 years within our healthcare system.

PATIENTS AND METHODS

STUDY DESIGN. We conducted a retrospective analysis of 53 patients with laboratory-confirmed COVID-19 and 67 patients with laboratory-confirmed influenza A or B, all of whom had refractory ARDS and were placed on ECMO at 2 referral centers from February 2013 to October 2020 within an integrated healthcare system. The study was approved by the Institutional Review Board, and the requirement for informed consent was waived due to the retrospective nature of the study. All authors were responsible for designing the study and for compiling and analyzing the data. The manuscript was prepared by the first author (E.S.) and completed with input from all authors.

PATIENT MANAGEMENT. Daily ECMO and general critical care management were at the discretion of the treatment team at each center. Patients were managed by multidisciplinary teams including medical and surgical intensivists, cardiothoracic surgeons, ECMO specialists, infectious disease specialists, nephrologists, and other consultants at indicated. The details of ECMO management and healthcare system protocols for COVID-19 patients have been described in detail previously.[8,9]

OUTCOMES MEASURES. The primary endpoint was survival to hospital discharge from the ECMO facility. Secondary outcomes of interest included death after withdrawal of care on ECMO, successful ECMO decannulation, duration of continuous ventilation, duration of ECMO support, intensive care unit (ICU) and hospital length of stay (LOS), need for concurrent interventions, rates of complications potentially related to ECMO therapy, and postdischarge survival.

Total continuous ventilator days, ICU LOS, and total LOS were determined only from patients who survived to discharge. Total continuous ventilator days were calculated from the date of intubation, whether or not this occurred at the ECMO facility, until date of extubation at the ECMO hospital. Total hospital LOS and ICU LOS were calculated by the total number of days that the patients were admitted to the ICU and the hospital at the ECMO centers, respectively (not including days at another facility). Days on ECMO was determined from the patients who were successfully decannulated. Successful decannulation from ECMO was defined as freedom from ECMO without subsequent recannulation during the hospitalization. ARDS was defined according to the Berlin criteria.[10] Bleeding was defined as new intracranial, pulmonary, gastrointestinal, cannulation site, or retroperitoneal hemorrhage requiring transfusion while on ECMO. Postdischarge vital status was determined by review of hospital medical records and systematic obituary searches using a previously validated protocol.[11]

STATISTICAL ANALYSIS. Continuous variables were presented as the mean ± SD or median with interquartile range (IQR) as appropriate, and categorical variables as proportions, unless otherwise specified. Depending on the type of data, Student's *t* test, unequal variance *t* test, Mann-Whitney *U* test, Fisher's exact test, or chi-square test were used. Kaplan-Meier analysis was used with the log-rank test to determine differences in survival rate between 2 groups. A *P* value of less than .05 was considered statistically significant, and no adjustments were made for multiple comparisons. All statistical analyses were performed using R version 3.5.0 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

PATIENTS. The baseline characteristics of all patients on admission to the hospital are summarized in Table 1. Median age was similar between the 2 groups (COVID-19 50 [IQR, 41-56] years vs influenza 46 [IQR, 35.5-56] years; $P = .1$), and most patients were male (COVID-19 67.9% vs influenza 56.7%; $P = .2$). The largest ethnic group in the COVID-19 group was Hispanic (43.4%) compared with Caucasian (50.7%) in the influenza group. In both groups, the median body mass index suggested that patients tended to be obese (COVID-19 33.6 [IQR, 30.6-37.9] kg/m^2 vs influenza 32.5 [IQR, 28.1-43.9] kg/m^2; $P = .4$). The most common comorbidities were similar in each group: hypertension (COVID-19 52.8% vs influenza 38.8%; $P = .1$) and diabetes (COVID-19 39.6% vs influenza 25.4%; $P = .1$). Of note, there was a higher reported incidence of active smoking in the influenza group (COVID-19 5.7% vs influenza 16.4%; $P = .05$). The proportion of patients with immunodeficiency was similar between the 2 groups (COVID-19 7.5% vs influenza 7.5%; $P = 1$). In the COVID-19 group, there were 4 immunosuppressed patients: 2 patients with history of solid organ transplants, 1 patient on chemotherapy for lymphoma, and 1 patient with a history of HIV. In the influenza group, there were 5 immunosuppressed patients: 2 patients with a history of rheumatoid arthritis, 1 patient with sarcoidosis, 1 patient with lymphoma, and 1 patient with a history of AIDS.

The number of patients who were directly admitted to one of the ECMO centers was higher in the COVID-19

group (COVID-19 43.4% vs influenza 20.9%; $P = .008$). The remaining patients in each group were transferred to one of the study centers for ECMO evaluation and management; pretransfer ECMO cannulation was more common in the influenza group than in the COVID-19 group (COVID-19 7.5% vs influenza 47.8%; $P < .001$).

Influenza patients had a shorter median length of time from admission to any hospital facility to intubation (COVID-19 3.5 [IQR, 1-6.8] days vs influenza 1 [IQR, 0-2.5] day; $P = .002$) as well as to initiation of ECMO (COVID-19 10 [IQR, 5-13] days vs influenza 3 [IQR, 1-8.3] days; $P = .36$). Before ECMO cannulation, patients in both groups were critically ill: approximately half of patients in both groups were on vasopressor support at the time of cannulation (COVID-19 45.3% vs influenza 53.7%; $P = .4$). There were similar number of patients who had undergone cardiopulmonary resuscitation with return of spontaneous circulation (COVID-19 5.7% vs influenza 3%; $P = .5$) and continuous renal replacement therapy (COVID-19 11.3% vs influenza 11.9%; $P = .9$). However, there was a significantly higher percentage of patients in the COVID-19 group who were paralyzed (COVID-19 83% vs influenza 31.3%; $P < .002$) and proned (COVID-19 66% vs influenza 22.4%; $P < .002$) before initiation of ECMO.

ECMO MANAGEMENT. The majority of patients in both groups were initiated on VV ECMO (COVID-19 92.5% vs influenza 95.5%; $P = .5$). There was a higher tendency to use the bifemoral approach as the initial cannulation strategy in the COVID-19 patients (COVID-19 79.2% vs influenza 35.8%; $P < .002$). The next most common site was internal jugular dual lumen bicaval in both groups (COVID-19 20.8% vs influenza 14.9%; $P = .4$) with transesophageal echocardiography imaging guidance. Some patients in the influenza group underwent femoral internal jugular (14.9%) and femoral subclavian cannulation (28.4%) strategies, which were not utilized in the COVID-19 group. In the 2 groups, there were similar rates of continuous renal replacement therapy while on ECMO (COVID-19 43.4% vs influenza 52.2%; $P = .3$), but patients in the COVID-19 group had a higher rate of chest tube insertion (COVID-19 30.2% vs influenza 7.5%; $P = .0005$).

CLINICAL OUTCOMES. The primary endpoint of survival to discharge from the ECMO hospital was similar between the 2 groups (COVID-19 62.3% vs influenza 64.2%; $P = .8$). Withdrawal of ECMO support due to futility of care also occurred at similar rates (COVID-19 35.8% vs influenza 28.4%; $P = .4$). The remainder of the patients were weaned to decannulation (COVID-19 64.2% vs influenza 71.6%; $P = 1$). No patients with COVID-19 who were successfully decannulated expired before discharge, but 5 (7.5%) patients in the influenza group expired after decannulation. Of these, 3 had worsening respiratory status after decannulation, and ECMO was not reinstituted due to futility of care. One patient developed acute peritonitis with shock and multiorgan system failure and was unable to recover. The last patient developed a large retroperitoneal bleed and there was no return of spontaneous circulation.

A tracheostomy was required in the majority of patients in both groups (COVID-19 60.4% vs influenza

TABLE 1 Characteristics of the Participants Included in This Study

Variable	COVID-19 (n = 53)	Influenza (n = 67)	*P* Value
Age, y	50 (41-56)	46 (35.5-56)	.1262
Male	36/53 (67.9)	38/67 (56.7)	.2098
Ethnicity			
Hispanic	23/53 (43.4)	21/67 (31.3)	.1736
African American	12/53 (22.6)	9/67 (13.4)	.1874
White	16/53 (30.2)	34/67 (50.7)	.0233
Asian	2/53 (3.8)	3/67 (4.4)	.8480
Body mass index, kg/m^2	33.6 (30.6-37.9)	32.5 (28.1-43.9)	.4020
Comorbidities			
HTN	28/53 (52.8)	26/67 (38.8)	.1252
Diabetes	21/53 (39.6)	17/67 (25.4)	.0956
COPD	4/53 (7.5)	4/67 (6)	.7309
Active smoker	3/53 (5.7)	11/67 (16.4)	.0544
ESRD on HD	1/53 (1.9)	1/67 (1.5)	.8670
Immunodeficiency	4/53 (7.5)	5/67 (7.5)	.9861
Admission setting			
Direct admission to ECMO center	23/53 (43.4)	14/67 (20.9)	.0080
Transfer to ECMO center	30/53 (56.6)	53/67 (79.1)	.0080
Pre-ECMO hospital course			
Days from admit to intubation	3.5 (1-6.8)	1 (0-2.5)	.0022
Days from admit to ECMO	10 (5-13)	3 (1-8.25)	.3579
Other interventions before ECLS			
Paralyzed	44/53 (83)	21/67 (31.3)	<.002
Proned	35/53 (66)	15/67 (22.4)	<.002
CPR	3/53 (5.7)	2/67 (3)	.4664
CRRT	6/53 (11.3)	8/67 (11.9)	.9164
Intubated	53/53 (100)	67/67 (100)	1.0000
Vasopressors	24/53 (45.3)	36/67 (53.7)	.3580
Initial cannulation site			
Internal jugular	11/53 (20.8)	10/67 (14.9)	.4040
Bilateral femoral	42/53 (79.2)	24/67 (35.8)	<.002
Femoral and internal jugular	0/53 (0)	10/67 (14.9)	.0033
Femoral and subclavian	0/53 (0)	19/67 (28.4)	<.002
Cannulation location			
Bedside	49/53 (92.5)	27/67 (40.3)	<.002
Operating room	0/53 (0)	8/67 (11.9)	.0092
Outside facility	4/53 (7.5)	32/67 (47.8)	<.002
Cannulation strategy			
VV	49/53 (92.5)	64/67 (95.5)	.4762
VA	4/53 (7.5)	3/67 (4.5)	.4762
Cannula site revision	30/53 (56.6)	11/67 (16.4)	.0404

Values are median (interquartile range) or n/n (%). COPD, chronic obstructive pulmonary disease; COVID-19, coronavirus disease 2019; CPR, cardiopulmonary resuscitation; CRRT, continuous renal replacement therapy; ECLS, extracorporeal life support; ECMO, extracorporeal membrane oxygenation; ESRD, end-stage renal disease; HD, hemodialysis; HTN, hypertension; VA, venoarterial; VV, venovenous.

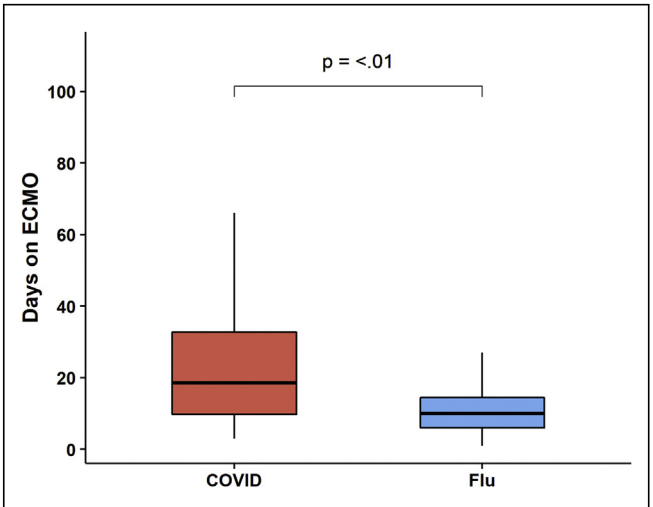

FIGURE 1 Comparison of length of time on extracorporeal membrane oxygenation (ECMO) between COVID-19 (coronavirus disease 2019) and flu patients among patients who were successfully decannulated. COVID-19 patients had a statistically significant longer length of time than influenza patients. Data are presented as median (thick horizontal line), interquartile range (colored box), and 95% confidence intervals (vertical lines).

53.7%; $P = .47$), and the median length of time from admission to tracheostomy was similar between the 2 groups (COVID-19 15.5 [IQR, 6.8-22] days vs influenza 15 [IQR, 7.8-24] days; $P = .9$). Among the patients who were decannulated from ECMO, patients in the COVID-19 group required a longer median length of time on ECMO (COVID-19 14 [IQR, 9-30] days vs influenza 10.5 [IQR, 6.8-14.3] days; $P = .004$) (Figure 1). Of patients who survived to discharge, the duration of continuous ventilator support was similar between the 2 groups (COVID-19 28 [IQR, 16.5-42.5] days vs influenza 25.5 [IQR, 13.3-29.5] days; $P = .2$); however, patients with COVID-19 had longer ICU LOS (COVID-19 27 [IQR, 23-58] days vs influenza 25 [IQR, 17-33.8] days; $P = .007$) and total hospital LOS in the ECMO centers (COVID-19 37 [IQR, 27-62] days vs influenza 28.5 [IQR, 19.3-41.8] days; $P = .007$) than influenza patients. These outcomes are summarized in Table 2.

Among patients surviving to discharge from the ECMO centers, postdischarge survival was similar between the 2 groups (Figure 2). Survival at 30 days was 100% (18 of 18 patients) in COVID-19 patients and 97.3% (36 of 37 patients) in influenza patients ($P = .5$). Survival at 60 days was 100% (14 of 14 patients) in COVID-19 patients and 97.1% (34 of 35 patients) in influenza patients ($P = .5$).

COMPLICATIONS. During ECMO support, 5 (9.4%) patients in the COVID-19 group and 5 (7.5%) patients in the influenza group developed new brain injury. Patients in both groups had similar rates of hemorrhagic (COVID-19 9.4% vs influenza 4.5%; $P = .3$) and ischemic intracranial insults (COVID-19 0% vs influenza 3%; $P = .2$). Development of secondary bacterial pneumonia was higher in COVID-19 patients but was not statistically different (COVID-19 20% vs influenza 11.9; $P = .3$).

COVID-19 patients had a higher rate of ECMO-related bleeding (COVID-19 39.6% vs influenza 14.9%; $P = .002$) but similar rates of complications related to cannula migration (COVID-19 1.9% vs influenza 3%; $P = .7$) and ECMO circuit malfunction (COVID-19 3.8% vs 4.5%; $P = .9$).

COMMENT

Historically, ECMO has been used as a means of respiratory and cardiac support and is regarded as a rescue therapy for severe ARDS. The application of ECMO therapy has been shown be useful for influenza patients,[3,12] and over the last year, several reports have suggested that ECMO can be a useful therapy in certain patients with COVID-19 infection.[5,7,8,13] The primary findings of our study were that patients with severe ARDS from COVID-19 and influenza requiring ECMO support have a similar survival to discharge. Although overall survival to discharge was similar between the COVID-19 and influenza cohorts, several notable differences including time to cannulation, duration of ECMO and ventilator support, death after decannulation, bleeding complications, and chest tube placement were observed in the study.

The survival to discharge in both the influenza and COVID-19 groups was just over 60% at our ECMO facilities. Early studies from Wuhan, China, reported a relatively high mortality of 83% patients with COVID-19 on ECMO therapy.[14] Our reported in-hospital mortality of 36% in patients with COVID-19 is comparable to the in-hospital mortality of 37.4% reported from the international Extracorporeal Life Support Organization database of patients with COVID-19 placed on ECMO.[6] Survival of patients placed on ECMO for ARDS due to influenza was also consistent with other reports. For example, the Australia and New Zealand ECMO influenza Investigators reported a 21% mortality rate in patients suffering from ARDS during the 2009 influenza A pandemic who were treated with ECMO.[12] Moreover, 6-month mortality after assignment to the ECMO arm in the CESAR trial was 37%.[4] In the EOLIA (Extracorporeal Membrane Oxygenation for Severe Acute Respiratory Distress Syndrome) trial, a mortality of 35% in the ECMO arm was reported.[15] Thus, our findings in both study cohorts reflect those of key landmark studies that have encouraged broader adoption of ECMO salvage therapy in patients with viral ARDS.

In our study, patients with COVID-19 had a longer median time from admission to intubation as well as to initiation of ECMO. However, a higher percentage of

COVID-19 patients were paralyzed and proned before being initiated on ECMO. This difference can be accounted for by more aggressive efforts to manage COVID-19 patients with noninvasive ventilator strategies and proning only, motivated by early reports of poor outcomes associated with liberal intubation.[16] Patients with COVID-19 also had a longer duration of ECMO therapy, ICU LOS, and hospital LOS than did those with influenza, suggesting that the inflammatory process may be more severe in COVID-19 infection. The median duration of time on ECMO support was 10 to 14 days in the study cohorts, but the duration of continuous ventilation was nearly 1 month in both groups. After decannulation patients most patients required ventilatory weaning in the hospital and long-term assisted care facilities. Despite differences in support duration, among patients who survived to discharge, nearly all patients in both groups were alive at 30 and 60 days.

Although the in-hospital mortality was similar, death after decannulation was higher in the influenza group (7.5% vs 0%). Of the 5 patients with influenza that expired after decannulation, 3 died from respiratory failure, suggesting that decannulation was performed prematurely in some or all of these cases. We suspect that increased provider experience and improvement in ECMO management protocols over time may have allowed better timing of ECMO decannulation in the COVID-19 group. Otherwise, very limited data are currently available regarding death after decannulation in patients with COVID-19 placed on ECMO. Kon and colleagues[17] have reported 100% survival after decannulation of 13 patients with COVID-19. The Extracorporeal Life Support Organization registry report documented that 47 (5%) of 968 patients with a final disposition died after decannulation from ECMO despite expected recovery at the time of decannulation.[6] Therefore, the observed difference in our study may only reflect the limited sample size available for analysis.

The COVID-19 cohort had more bleeding events than the influenza cohort (40% vs 15%). These rates are comparable to previous reports. A retrospective study of 492 patients with COVID-19-related ARDS placed on ECMO has reported a major bleeding rate of 42%,[18] whereas a separate study of influenza patients reported that only 10% suffered hemorrhagic complications.[19] Bleeding complications were higher in the COVID-19 cohort because our institutional anticoagulation protocols differed between the cohorts. Heparin was titrated to a partial thromboplastin time of 40 to 60 seconds in patients with influenza, whereas in COVID-19 patients, this target was increased to partial thromboplastin time of 55 to 65 seconds due to the higher reported thrombosis rates in these patients as the pandemic has progressed.[20] Thus, the more aggressive therapeutic goal in the COVID-19 patients, which predisposed patients to an increased risk of bleeding, was accepted in order to reduce the occurrence of thrombotic events in these patients.

Of note, patients with COVID-19 also had higher rates of chest tube insertion, which we hypothesize was due to the inflammatory and fibrotic pathophysiology of the disease causing stiffening of the lungs. A multicenter retrospective study reported a 1% incidence of all COVID-19 patients who developed pneumothorax or pneumomediastinum. Of the patients who developed pneumothorax, 44% were ventilated and 20% were placed on ECMO support. Surgical pathology from 1 patient showed localized parenchymal collapse and fibrosis, vascular congestion, and cystic spaces consistent with pneumatocele formation.[21] Further study to determine the underlying cause(s) that seem to predispose patients with COVID-19 to pneumothorax is warranted.

TABLE 2 Outcomes

Variable	COVID-19 (n = 53)	Influenza (n = 67)	*P* Value
In-hospital mortality	17/53 (34)	24/67 (35.8)	.8823
Death from withdrawal of care on ECMO	17/53 (34)	19/67 (28.4)	.6590
Decannulated from ECMO	33/53 (62.3)	48/67 (71.6)	.2761
Survival to discharge or transfer	33/53 (62.3)	43/67 (64.2)	.8289
Deceased after decannulation	0/53 (0)	5/67 (7.5)	.0422
Time from admission to tracheostomy, d	15.5 (6.8-22)	15 (7.8-24)	.8496
Tracheostomy	32/53 (60.4)	36/67 (53.7)	.4656
Duration of continuous ventilation, d	28 (16.5-42.5)	25.5 (13.3-29.5)	.2195
Duration of ECMO, d	14 (9-30)	10.5 (6.8-14.3)	.0038
ICU LOS, d	27 (23-58)	25 (17-33.8)	.0065
Hospital LOS, d	37 (27-62)	28.5 (19.3-41.8)	.0065
Time from decannulation to discharge, d	19 (13.5-30.3)	13.5 (9.3-24)	.4397
30-d survival	18/18 (100)	36/37 (97.3)	.4815
60-d survival	14/14 (100)	34/35 (97.1)	.5228
New brain injury			
CVA	0/53 (0)	2/67 (3)	.2046
Hemorrhagic	5/53 (9.4)	3/67 (4.5)	.2798
Secondary bacterial pneumonia infection	7/35 (20)	8/67 (11.9)	.2752
Concurrent ECMO therapies			
CRRT	23/53 (43.4)	35/67 (52.2)	.3358
Chest tubes	15/53 (28.3)	5/67 (7.5)	.0024
ECMO complications			
Bleeding	20/53 (37.7)	10/67 (14.9)	.0042
Cannula site revision	1/53 (1.9)	2/67 (3)	.7020
ECMO circuit	2/53 (3.8)	3/67 (4.5)	.8480

Values are n/n (%) or median (interquartile range). COVID-19, coronavirus disease 2019; CRRT, continuous renal replacement therapy; CVA, cerebrovascular accident; ECMO, extracorporeal membrane oxygenation; ICU, intensive care unit; LOS, length of stay.

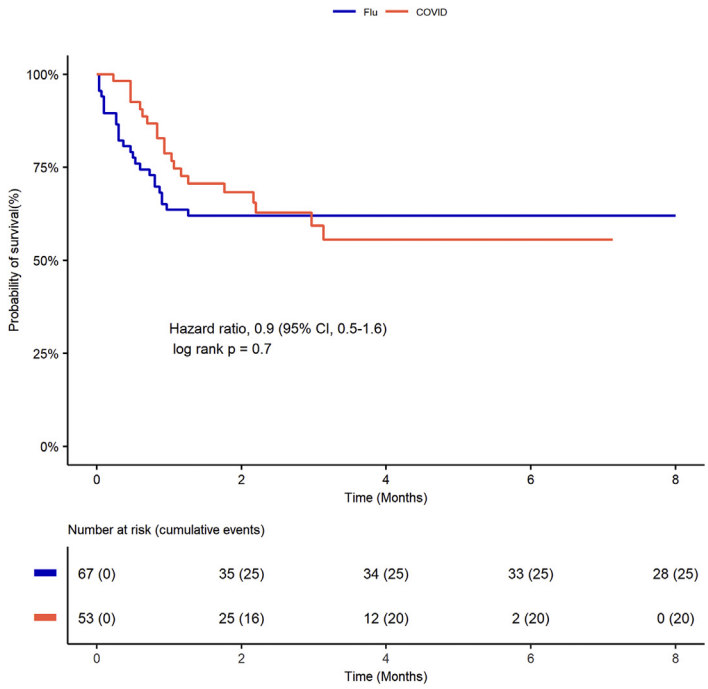

FIGURE 2 Kaplan-Meier curve depicting survival between coronavirus disease 2019 (COVID-19) and influenza patients. There was no significant difference between 2 groups. (CI, confidence interval.)

Ultimately, all of these direct comparisons of outcomes of patients with COVID-19 or influenza supported on ECMO are limited by the noncontemporaneous nature of the study cohorts. Provider experience increased over the years of ECMO utilization for influenza patients before the beginning of the COVID-19 pandemic, and ECMO management protocols also evolved based on this experience. This gained knowledge provided the greatest benefit to patients with COVID-19. Thus, differences in outcomes were influenced by a combination of factors and should not be solely attributed to different viral etiologies. Nevertheless, these comparisons are important because they provide data by which utilization of ECMO in patients with COVID-19 can be benchmarked against a widely accepted standard—specifically, utilization of ECMO in refractory ARDS from influenza. ECMO is a resource-intensive therapy, and prima facie outcomes of this therapy presented without any context may not appear to justify its use in patients with COVID-19. However, our data suggest that, even taking into account improved provider experience and evolution of ECMO protocols, similar outcomes can be achieved in both groups of patients. Thus, we believe that centers with ECMO capability should continue to offer this intervention to carefully selected patients with COVID-19 and severe ARDS, just as ECMO has been made available for carefully selected patients with influenza and ARDS. Outcomes across both cohorts also make clear that further investigation is necessary to improve patient selection and outcomes in all patients.

Our study is subject to several other limitations, including those inherent to any retrospective observational study. Interpretation of our results is limited by the size of study cohorts, which increases the risk for type II errors among comparisons. As previously mentioned, there were key differences in ECMO protocols among the study cohorts, which may have led to differences in outcomes that could not be detected in a study with the current sample size. For example, although we did not detect a statistically significant difference in the use of VV vs venoarterial ECMO between the study cohorts, studies with a larger sample size are necessary to confirm this finding. We have also reported only relatively short-term follow-up, especially in the COVID-19 arm. Although 60-day follow-up has been frequently used as a key outcome in previous landmark trials evaluating the efficacy of ECMO in ARDS of other etiologies, there is paucity of literature regarding any posthospital survival in patients with COVID-19 managed with ECMO therapy.[4,15] Finally, while this study was focused on reporting outcomes in the 2 study cohorts, we have provided details of our ECMO protocols specific to patients with COVID-19 separately.[8]

This report compares the ECMO outcomes between COVID-19 and influenza from a large healthcare system with multiple ECMO referral centers. The comparison of the clinical course of COVID-19 and influenza patients requiring EMCO support has demonstrated utility in contributing to the growing understanding of the COVID-19 disease process. The success of ECMO in treating influenza ARDS invites optimism for the potential of ECMO therapy to treat refractory ARDS in COVID-19 patients who do not recover with conventional ventilation as medical management evolves. Our findings show that although COVID-19 patients have a longer duration of hospital treatment, the 2 groups have similar survival to discharge from the ECMO center and for at least 2 months after discharge. Further studies are necessary to identify which patients most likely to benefit from ECMO salvage and to understand long-term outcomes of patients with severe ARDS secondary to respiratory viral infections.

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