Extracorporeal Membrane Oxygenation for COVID-19: Comparison of Outcomes to Non-COVID-19–Related Viral Acute Respiratory Distress Syndrome From the Extracorporeal Life Support Organization Registry

OBJECTIVES: To compare complications and mortality between patients that required extracorporeal membrane oxygenation (ECMO) support for acute respiratory distress syndrome (ARDS) due to COVID-19 and non-COVID-19 viral pathogens.

DESIGN: Retrospective observational cohort study.

SETTING: Adult patients in the Extracorporeal Life Support Organization registry.

PATIENTS: Nine-thousand two-hundred ninety-one patients that required ECMO for viral mediated ARDS between January 2017 and December 2021.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: The primary outcomes of interest were mortality during ECMO support and prior to hospital discharge. Time-to-event analysis and logistic regression were used to compare outcomes between the groups. Among 9,291 included patients, 1,155 required ECMO for non-COVID-19 viral ARDS and 8,136 required ECMO for ARDS due to COVID-19. Patients with COVID-19 had longer duration of ECMO (19.6 d [interquartile range (IQR), 10.1–34.0 d] vs 10.7 d [IQR, 6.3–19.7 d]; $p < 0.001$), higher mortality during ECMO support (44.4% vs 27.5%; $p < 0.001$), and higher in-hospital mortality (50.2% vs 34.5%; $p < 0.001$). Further, patients with COVID-19 were more likely to experience mechanical and clinical complications (membrane lung failure, pneumothorax, intracranial hemorrhage, and superimposed infection). After adjusting for pre-ECMO disease severity, patients with COVID-19 were more than two times as likely to die in the hospital compared with patients with non-COVID-19 viral ARDS.

CONCLUSIONS: Patients with COVID-19 that require ECMO have longer duration of ECMO, more complications, and higher in-hospital mortality compared with patients with non-COVID-19–related viral ARDS. Further study in patients with COVID-19 is critical to identify the patient phenotype most likely to benefit from ECMO and to better define the role of ECMO in the management of this disease process.

KEY WORDS: COVID-19; extracorporeal membrane oxygenation; respiratory distress syndrome; respiratory insufficiency; viral pneumonia

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Since December 2019, over 6 million deaths related to COVID-19 have been reported worldwide and COVID-19 has emerged as a distinct etiology of the acute respiratory distress syndrome (ARDS) (1, 2). Patients who fail conventional ARDS management strategies may be considered for extracorporeal membrane oxygenation (ECMO) (3). Estimates

KEY POINTS

Question: Do outcomes differ between patients supported with extracorporeal membrane oxygenation (ECMO) for acute respiratory distress syndrome (ARDS) due to COVID-19 compared with patients supported with ECMO for ARDS related to non-COVID-19 viral pathogens?

Findings: In this retrospective observational study of patients enrolled in the Extracorporeal Life Support Organization registry, we found patients with COVID-19 that require ECMO have a statistically higher rate of death while supported with ECMO and statistically higher overall in-hospital mortality compared with patients with non-COVID-19 viral pathogens.

Meaning: Prognosis for patients with COVID-19 supported with ECMO differs substantially compared with patients with ARDS related to other viral pathogens.

of survival for patients with COVID-19 that require ECMO have varied and the reported rate of survival has fluctuated over the course of the pandemic (4–6). Few studies have directly compared mortality and complication rates for patients supported with ECMO for the management of COVID-19–related ARDS versus non-COVID-19–related viral ARDS. Studies with such direct comparisons have used small sample sizes and reached varying conclusions (7–12).

We examined the Extracorporeal Life Support Organization (ELSO) patient registry to compare outcomes between patients receiving ECMO support for ARDS due to COVID-19 to patients with ARDS due to non-COVID-19 viral pathogens.

MATERIALS AND METHODS

We analyzed patients in the ELSO registry enrolled between January 2017 and December 2021. ELSO is a global organization which maintains a comprehensive registry of patients undergoing Extracorporeal Life Support (ECLS) from many centers across the world. Data reported to the registry are approved member institutions by their local Institutional Review Board (IRB). The registry's data user agreement allows member centers to obtain de-identified data for the purpose of research without the need for additional IRB approval. As such, the Cooper University Healthcare IRB deemed this study exempt from review as it did not fall under the board's guidelines as human subjects research. Adult patients supported with venovenous ECMO for the management of non-COVID-19–related viral ARDS or ARDS related to COVID-19 were included. A complete description of the inclusion, exclusion criteria, ELSO registry search strategy, and additional detail regarding the statistical analysis (including the handling of missing data) is included within the **Supplementary Material** (http://links.lww.com/CCX/B139). The analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (**eTable 1**, http://links.lww.com/CCX/B139).

Outcomes

The primary outcomes were in-hospital mortality and mortality during ECMO support. Duration of ECMO and observed complications while receiving ECMO were also examined. Additionally, we evaluated whether the overall in-hospital mortality rate for patients with COVID-19–related ARDS managed with ECMO changed over the course of the years 2020 to 2021. Finally, we examined if in-hospital mortality in patients with COVID-19 was associated with the ECMO experience level of the supporting center. Patients were considered deceased while receiving ECMO if support was discontinued for patient demise or an anticipated poor prognosis.

Statistical Analysis

Characteristics of the groups for continuous data are presented as the mean and sd for normally distributed variables and the median and interquartile range (IQR) for skewed variables. Comparisons were made by two-sample *t* tests and the Wilcoxon rank-sum test, respectively. Categorical data are presented as counts and compared using chi-square tests. To compare in-hospital mortality between patients with non-COVID-19–related viral ARDS and those with COVID-19–related ARDS logistic regression was used. Patients whose outcome was unknown, including those who were discharged or transferred while supported with ECMO were excluded from this analysis. For the outcome of

survival while receiving ECMO, Fine and Gray competing-risk regression was performed estimating the subdistribution hazard ratio (sHR) of death while receiving ECMO considering discontinuation of ECMO as a competing risk. Discontinuation for 1) recovery or organ transplantation or 2) resource limitation or ECLS complication were considered separate composite competing risks. The assumption of proportional subhazards in these survival models were evaluated through the inclusion of time varying covariates and found to be valid. Both models were adjusted for the Respiratory ECMO Survival Prediction (RESP) score which has previously been constructed and validated to estimate survival in patients supported with ECMO (13). As evidence suggests this score may perform poorly in patients with COVID-19, we constructed an additional multivariable logistic regression model to predict in-hospital mortality (14). Possible predictors associated with mortality were included in the model if α less than 0.2 in univariate analysis and removed by means of stepwise backward elimination with α greater than 0.1.

As a sensitivity analysis, outcomes were compared between non-COVID-19–related ARDS and COVID-19–related ARDS when only patients where a culprit virus (e.g., influenza) was identified were included. In general, patients with COVID-19 were managed more contemporaneously than patients with non-COVID-19–related ARDS. Therefore, the final survival outcome of patients with COVID-19 was more frequently unknown at the time of data analysis. To evaluate if this difference may have introduced bias, a comparison of in-hospital death between the two groups was performed under the hypothetical extreme assumption that all patients with COVID-19–related ARDS whose final disposition was unknown survived, while those with non-COVID-19–related ARDS died.

Finally, for patients with ARDS related to COVID-19, we examined center ECLS volume for the management of ARDS (including all patients in the ELSO database classified by data managers as being related to ARDS) at each support center in the 3 years prior to the COVID-19 pandemic (2017–2019). Total ECMO cases during this period were summed and outcomes in patients with COVID-19 supported with ECMO were compared. Comparisons were made based on summed cases on a continuous scale and when case volume was categorized based on the 25th and 75th percentiles in centers that supported patients with COVID-19.

RESULTS

During the study period, we identified 9,291 patients managed with venovenous ECMO for viral related ARDS in the ELSO registry (**Fig. 1**). Eight-thousand one-hundred thirty-six patients were supported for a diagnosis of COVID-19–related ARDS, while 1,155 patients were placed on ECMO for viral ARDS not related to COVID-19. The characteristics of included patients based on diagnosis are included in **Table 1**. The median age of all patients was 47.8 years (IQR, 38.3–56.0 yr), 2,965 (31.9%) were female, and 6,083 (65.5%) were classified as obese (body mass index $\geq 30 \mathrm{kg/m^2}$). Of the patients with non-COVID-19–related viral ARDS, a specific microbial agent was identified in 431 instances. Of these, n = 323 (74.9%) were caused by influenza. A breakdown of the specific microbial causes of non-COVID-19–related viral ARDS in the cohort is included in Figure 1 and the case volume by year and by diagnostic category is provided in **eFigure 1** (http://links.lww.com/CCX/B139).

Compared with patients with non-COVID-19–related viral ARDS, patients with COVID-19–related ARDS had significantly lower rates of preexisting CNS dysfunction (12.0% vs 14.6%), immunocompromising conditions (3.8% vs 10.6%), and co-existing non-pulmonary-related infection (5.9% vs 9.8%). Duration of mechanical ventilation prior to ECMO support was significantly longer in patients with COVID-19 (76 vs 38 hr), although peak inspiratory pressure prior to ECLS support was similar between the two groups (34 vs 34 cm H_2O). Patients with COVID-19 were more likely to have received systemic steroids (44.4% vs 22.6%), more likely to undergo prone positioning (58.0% vs 22.9%) and were less likely to have received renal replacement therapy (4.8% vs 11.1%) prior to ECMO support.

Unadjusted clinical outcomes are included in **Table 2**. Overall, median duration of ECMO support was significantly longer in patients with COVID-19 compared with patients with non-COVID-19–related viral ARDS (19.6 d [IQR, 10.1–34.0 d] vs 10.7 d [IQR, 6.3–19.7 d]; $p < 0.001$). Three-hundred fourteen patients (27.5%) with non-COVID-19–related viral ARDS versus 3,554 patients (44.4%) with COVID-19 died during ECMO support ($p < 0.001$). Outcome data was incomplete (i.e., the patient was transferred to another facility on ECLS) in 10 patients (0.87%) with non-COVID-19–related viral ARDS and 201 instances (2.5%) of patients with COVID-19–related ARDS. In
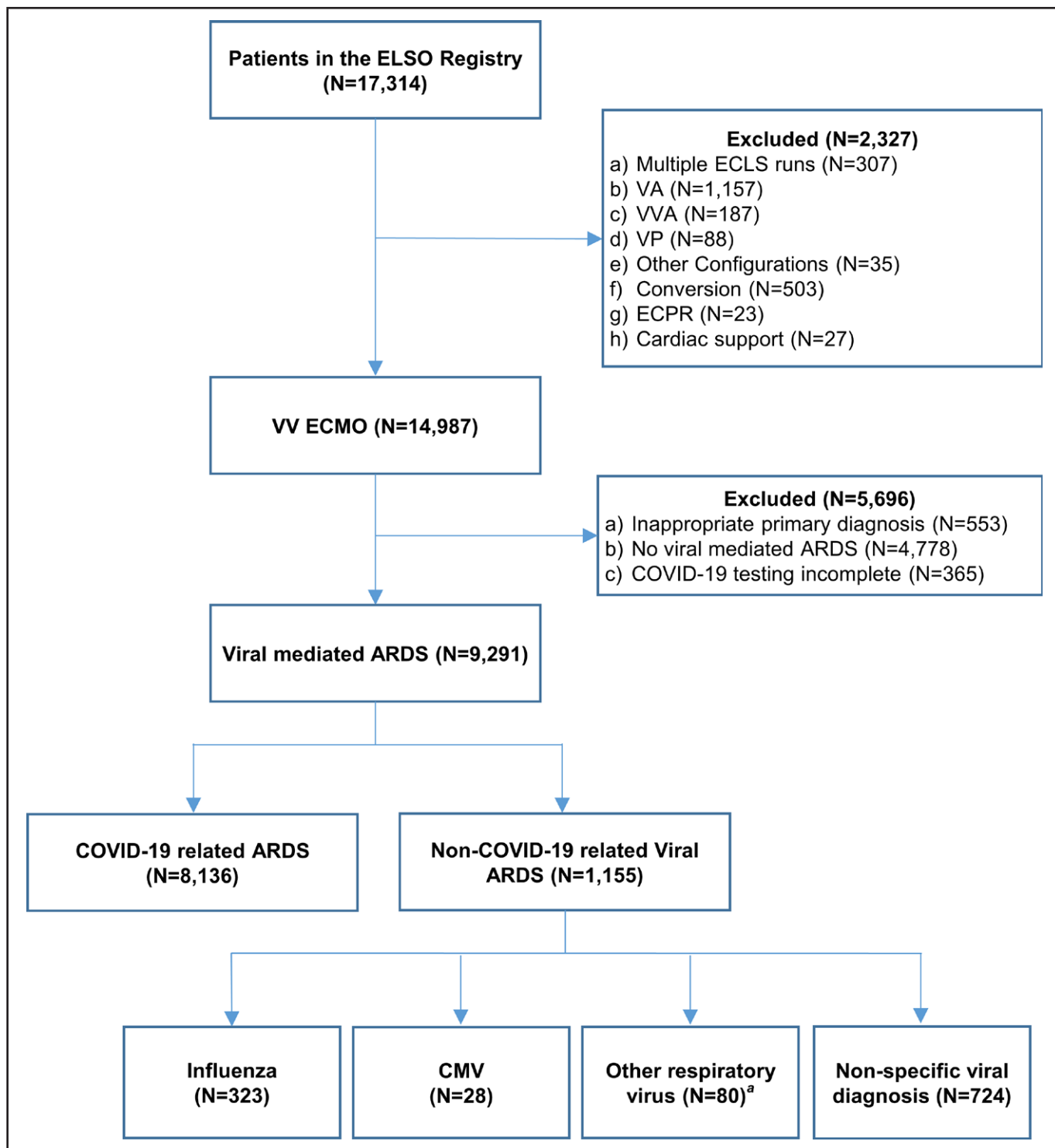
Figure 1. Flowchart of the patients with viral acute respiratory distress syndrome (ARDS) related to COVID-19 or another viral cause identified for inclusion. ªIncludes patients with adenovirus, coronavirus, enterovirus, human metapneumovirus, parainfluenza, rhinovirus, and the respiratory syncytial virus. CMV = Cytomegalovirus, ECLS = Extracorporeal Life Support, ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation, ELSO = Extracorporeal Life Support Organization, VA = venoarterial, VP = venopulmonary, VV = venovenous, VVA = venoveno-arterial.

TABLE 1.

Baseline Characteristics of Patients Based on viral Acute Respiratory Distress Syndrome Related to COVID-19 or to Another Cause

Characteristics	Non-COVID-19 ($n = 1,155$)	COVID-19 ($n = 8,136$)	p
Demographic and baseline characteristics			
Age, yr	48.4 (37.3–58.1)	47.7 (38.4–55.7)	0.082
Age category			< 0.001
18–49	625 (54.1)	4,693 (57.7)	
50–59	299 (25.9)	2,392 (29.4)	
> 60	231 (20.0)	1,052 (12.9)	
Gender, female	461 (40.2)	2,504 (30.8)	< 0.001
Race			< 0.001
Asian	187 (16.7)	674 (8.6)	
Black	125 (11.2)	924 (11.8)	
Hispanic	106 (9.5)	1,731 (22.1)	
White	619 (55.4)	3,490 (44.6)	
Other	81 (7.3)	1,007 (12.9)	
Body mass index (kg/m^2)	31.1 (25.9–38.2)	32.7 (28.2–38.0)	< 0.001
CNS dysfunction[a]	169 (14.6)	973 (12.0)	0.009
Immunocompromised[a]	122 (10.6)	308 (3.8)	< 0.001
Nonpulmonary infection[a]	113 (9.8)	478 (5.9)	< 0.001
Pre-ECMO disease severity			
Mean arterial pressure (mm Hg)	75 (66–86)	80 (72–90)	< 0.001
pH	7.26 (7.16–7.34)	7.30 (7.21–7.37)	< 0.001
P_{CO_2}	58 (47–72)	61 (50–75)	< 0.001
Pa_{O_2}/F_{IO_2}	68 (54–87)	70 (57–89)	0.067
Peak inspiratory pressure (cm H$_2$O)	34 ± 7.3	34 ± 6.8	0.367
Positive end-expiratory pressure (cm H$_2$O)	15 (12–18)	14 (10–16)	< 0.001
Cardiac arrest prior to ECMO	67 (5.9)	225 (2.8)	< 0.001
Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score	3 (0–5)	3 (1–5)	0.002
Pre-ECMO support			
Intubation to ECMO initiation (hr)	38 (13–109)	76 (24–144)	< 0.001
Systemic steroids	271 (22.6)	3,625 (44.4)	< 0.001
Vasopressors	748 (62.4)	4,431 (54.3)	< 0.001
Bicarbonate infusion	147 (12.3)	514 (6.3)	< 0.001
Prone positioning	274 (22.9)	4,736 (58.0)	< 0.001
Pulmonary vasodilator	290 (24.2)	2,739 (33.6)	< 0.001
Neuromuscular blockade	789 (65.9)	6,071 (74.4)	< 0.001
Renal replacement therapy	133 (11.1)	388 (4.8)	< 0.001

ECMO = extracorporeal membrane oxygenation.

[a]CNS dysfunction (neurotrauma, stroke encephalopathy, cerebral embolism, seizure, or epileptic syndrome), immunocompromise (hematologic malignancy, solid tumor, solid organ transplantation, HIV, or cirrhosis), and nonpulmonary infection were included as defined in the Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score and based on *International Classification of Diseases*, 10th Revision codes previously described by Joshi et al (13,14).

Data are presented as median (25th percentile–75th percentile) or *n* (%) unless otherwise indicated.

TABLE 2.
Overall Outcomes of Patients Based on Viral Acute Respiratory Distress Syndrome Related to COVID-19 or to Another Cause

Outcome	Non-COVID-19	COVID-19	p
Duration of ECMO support (d)	10.7 (6.3–19.7)	19.6 (10.1–34.0)	< 0.001
Mortality during ECMO[a]	314 (27.5)	3,554 (44.4)	< 0.001
In-hospital mortality[b]	395 (34.5)	3,984 (50.2)	< 0.001

ECMO = extracorporeal membrane oxygenation.
[a]Death defined by Extracorporeal Life Support discontinuation for patient demise or anticipated poor prognosis.
[b]Excludes patients where hospital discharge data was not available, or patients were transferred while supported with ECMO.
Data are presented as median (25th percentile–75th percentile) or n (%). Table includes complete cases where relevant outcomes are known.

TABLE 3.
COVID-19 Associated Mortality While Receiving Extracorporeal Membrane Oxygenation and In-Hospital Mortality With Adjustment for Confounders (Non-COVID-19 Viral Acute Respiratory Distress Syndrome As Baseline)

Outcome	Unadjusted sHR (95% CI)	p	Adjusted sHR (95% CI)[a]	p	Adjusted sHR (95% CI)[b]	p
Mortality while receiving extracorporeal membrane oxygenation	1.72 (1.52–1.94)	< 0.001	1.80 (1.59–2.03)	< 0.001	1.86 (1.63–2.11)	< 0.001
	Unadjusted OR (95% CI)	p	Adjusted OR (95% CI)[a]	p	Adjusted OR (95% CI)[b]	p
In-hospital mortality	1.91 (1.68–2.17)	< 0.001	2.09 (1.83–2.39)	< 0.001	2.17 (1.87–2.51)	< 0.001

OR = odds ratio, sHR = subdistribution hazard ratio.
[a]Adjusted for Respiratory Extracorporeal Membrane Oxygenation Survival Prediction score.
[b]Adjusted for multivariable model in eTable 4 (http://links.lww.com/CCX/B139).

patients where survival status at time of discharge was known, 395 patients (34.5%) with non-COVID-19–related viral ARDS died compared with 3,984 patients (50.2%) with COVID-19–related ARDS.

Mechanical and infectious complications experienced by the two groups are included in **eTables 2 and 3** (http://links.lww.com/CCX/B139). Patients with COVID-19 experienced higher rates of pneumothorax and intracranial hemorrhage compared with non-COVID-19–related ARDS. Furthermore, patients with COVID-19 were more likely to have bacterial organisms cultured from respiratory, blood, and urinary sites during ECMO. In addition, patients with COVID-19 were more likely to have mechanical complications including circuit thrombosis and membrane lung failure.

eTable 4 (http://links.lww.com/CCX/B139) demonstrates the relationship between demographic and pre-ECLS support factors and in-hospital mortality in all patients with viral mediated ARDS. When applied to all patients with viral mediated ARDS, the discrimination of the RESP score to predict in-hospital mortality was moderate (area under the curve [AUC], 0.64; 95% CI, 0.63–0.65). Whereas the multivariable model presented in eTable 4 (http://links.lww.com/CCX/B139) resulted in improved discrimination of in-hospital mortality (AUC, 0.69; 95% CI, 0.68–0.70).

Table 3 includes the results of the primary outcomes of in-hospital mortality and mortality while receiving ECMO adjusted for pre-ECMO clinical factors and disease severity via the RESP score and for the multivariable model included in eTable 4 (http://links.lww.com/CCX/B139). Both in-hospital mortality and mortality while receiving ECMO were significantly higher for patients with COVID-19–related ARDS (odds ratio

[OR], 1.91; 95% CI, 1.68–2.17; $p < 0.001$ and sHR, 1.72; 95% CI, 1.52–1.94; $p < 0.001$, respectively) and this relationship persisted after adjustment for the RESP score and the multivariable model. When this analysis was repeated including only patients with a specific microbial diagnosis as the cause of non-COVID-19–related ARDS, the results were similar (**eTables 5 and 6,** http://links.lww.com/CCX/B139). The cumulative incidence of mortality while receiving ECMO between the two groups is visually displayed in **Figure 2** and likewise, for the subgroup analysis in **eFigure 2** (http://links.lww.com/CCX/B139). Finally, under the hypothetical extreme assumption that all patients where outcome data were unavailable survived in the group with COVID-19 and all those in the non-COVID-19 group died, COVID-19 remained associated with a significantly higher risk of in-hospital mortality (OR, 1.78; 95% CI, 1.56–2.02; $p < 0.001$), a finding which persisted after adjustment for the multivariable model (OR, 2.02; 95% CI, 1.74–2.34; $p < 0.001$) (**eTable 7,** http://links.lww.com/CCX/B139).

In 2020, 3,608 patients with COVID-19–related ARDS were identified that were supported with ECMO. Of these 1,817 (50.4%) died. Likewise, in 2021, 4,327 patients were supported and 2,167 (50.1%) of these patients died. Year of ECMO initiation (2020 vs 2021) was not associated with in-hospital mortality (OR, 0.98; 95% CI, 0.90–1.07; $p = 0.624$) or with mortality while receiving ECMO (sHR, 1.01; 95% CI, 0.94–1.08; $p = 0.853$). This relationship persisted when both models were adjusted for RESP score and for the multivariable model included in eTable 4 (http://links.lww.com/CCX/B139) (data not shown).

A total of 376 ELSO registry sites provided ECMO support for ARDS between the years of 2020 and 2021. Of these, the median number of patients managed with ECMO for the treatment of all causes of ARDS in the 3 years preceding the COVID-19 pandemic was 13 (IQR, 3–33), with the highest number of ECMO runs being 165. When ECMO case volume was analyzed as a continuous variable, case volume was significantly associated with both in-hospital mortality (per 10 ECMO events) (OR, 0.97; 95% CI, 0.95–0.98; $p < 0.001$) (for every 10 additional total cases, in-hospital mortality decreases by 3%) and with mortality while receiving ECMO (sHR, 0.97; 95% CI, 0.96–0.99; $p < 0.001$). Mortality while receiving ECMO support by volume category is included in **eFigure 3** (http://links.lww.com/CCX/B139).

DISCUSSION

This study from the international ELSO Registry analyzed 9,291 patients with viral ARDS requiring venovenous ECMO. Patients with COVID-19 had a significantly higher in-hospital mortality when compared with other viral pathogens (50.2% vs 34.5%; $p < 0.001$). After adjusting for demographic factors and pre-ECMO disease severity, patients with COVID-19 ARDS were more than two times as likely to die in the hospital compared with patients with non-COVID-19 viral ARDS.

A systematic review of all studies published between 2011 and 2019 that included at least 100 patients found an overall survival of 60% among patients supported with venovenous ECMO (15). Mortality specifically observed in non-COVID-19–related viral ARDS has
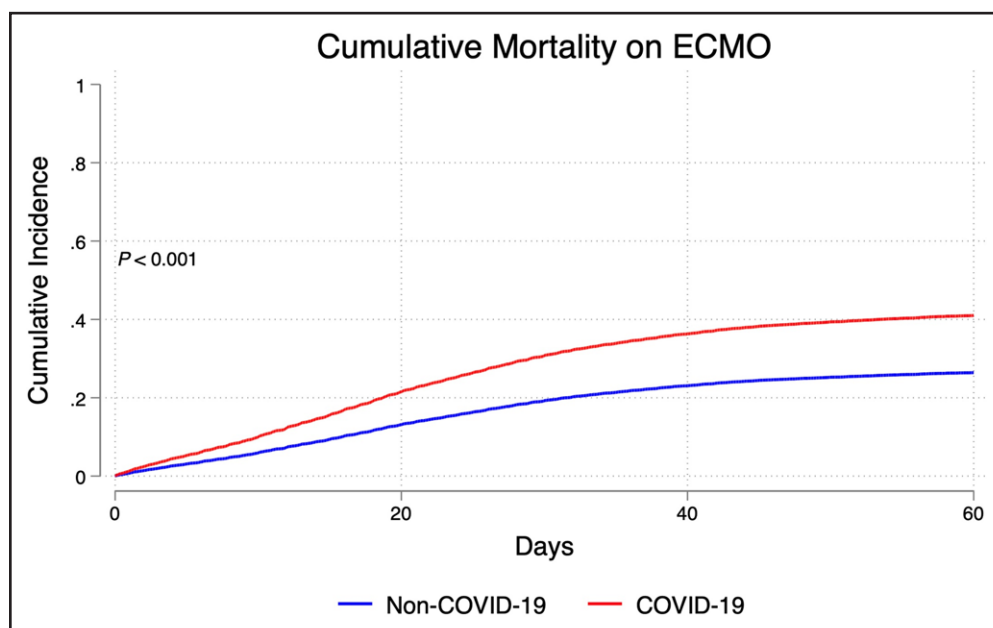

Figure 2. Comparison of the rate of mortality while receiving extracorporeal membrane oxygenation (ECMO) between patients with viral acute respiratory distress syndrome related to COVID-19 or to another cause in complete cases.

been reported to be lower than that of all patients with ARDS. A meta-analysis of patients with H1N1 influenza demonstrated an overall in-hospital mortality of 28% (16). Mortality of patients with COVID-19–induced ARDS requiring ECLS is reported to be worse, ranging between 36.9% and 58.9% (4, 6, 16–20). The range in mortality has varied during different stages of the pandemic examined with worse outcomes noted in the later surges (6, 21).

Direct comparison of the two groups have been done in cohorts of limited size with variable results. A cohort of 53 patients with COVID-19 had significantly higher survival than the non-COVID-19 viral group (84.9% vs 66.0%; $p = 0.04$) (8). Although the discrepancy in the reported survival of the COVID-19 group in this small cohort compared with other larger published studies make these results hard to generalize. Two other small studies ($n = 138$ and $n = 62$) showed statistically similar survival between the two groups (9, 10). The large number of patients in our study along with the geographic and temporal diversity likely has resulted in the most robust and generalizable estimates of outcomes related to the management of COVID-19–related ARDS with venovenous ECMO to date.

Venovenous ECMO for the support of ARDS is a tool to decrease the physiologic insult of mechanical ventilation and allow the damaged lung time to recover (22). The difference in mortality between COVID-19–related ARDS and ARDS related to other viral processes is likely multifactorial but may be driven by the pathogen itself and the related protracted lung recovery. Despite similar pre-ECMO, respiratory parameters (peak inspiratory pressure and Pao_2/Fio_2 ratio), the median duration of ECMO support in patients with COVID-19 compared with non-COVID viral ARDS was more than a week longer (19.6 vs 10.7 d), implying a dramatically different disease course. This prolonged time where ECMO support was required may explain the observed increase in ECMO related mechanical and clinical complications including infection, bleeding, and right ventricular failure (23, 24).

The non-COVID-19 group had a higher incidence of pre-ECMO CNS dysfunction, immunocompromised state, and co-existing nonpulmonary infection but significantly lower overall mortality. These pre-ECMO clinical parameters are components of the RESP score, an in-hospital mortality prediction score validated for use in patients with respiratory failure not related to

COVID-19 (13). Although the RESP score was significantly worse in the group with COVID-19, the magnitude of this difference was small and the accuracy of the score in predicting mortality in COVID-19–related ARDS has been questioned (14). When applied to the current data, our results support the findings of Joshi et al (14) who documented weak predictive ability of the RESP score for in-hospital mortality in COVID-19–related ARDS (AUC, 0.62; 95% CI, 0.60–0.64) (17). Interestingly, discrimination of the RESP score for in-hospital mortality prediction in non-COVID viral ARDS in the current data showed only weak predictive ability (AUC, 0.67; 95% CI, 0.64–0.70) (eFig. 4, http://links.lww.com/CCX/B139). The especially poor performance of the RESP score when applied to patients with COVID-19 serves to highlight the need for further research into prognostic factors to allow for appropriate patient selection to optimize outcomes when ECMO is applied to patients with this unique clinical condition.

There is evidence that ECMO was applied differently during the COVID-19 pandemic. The longer period of mechanical ventilation prior to ECMO initiation raises concern that ventilator induced lung injury could be a contributing factor (25). Relatedly, prolonged use of noninvasive ventilation prior to endotracheal intubation has also been observed during the COVID-19 pandemic and has been associated with worse ECMO outcomes (26, 27). We hypothesize that alteration in standard practices, especially the delay in time from hospital admission to ECMO initiation may have significantly contributed to the higher rate of mortality observed in this cohort, possibly due to increased lung damage prior to ECMO support and increased time required for lung recovery. Unfortunately, data regarding time receiving noninvasive ventilation is not recorded in the ELSO registry and could not be separately examined in this cohort. In addition, the increased use of neuromuscular blockade, pulmonary vasodilators and prone positioning may further imply a delay in ECMO initiation. This delay may be related to resource limitations, concern for ineffectiveness of ECMO, and potentially a misunderstanding of how to apply ECMO appropriately (22). A return to pre-pandemic care and further research regarding the effects of prolonged noninvasive ventilation on ECMO outcomes may help minimize the difference in outcomes between patients with COVID-19–related ARDS and those with other viral pathogens.

The large increase in patients with ARDS during the COVID-19 pandemic led to a greater need for ECMO. This manifested by both a large increase in the number of centers utilizing ECMO as well as a dramatic increase in the total number of patients receiving ECMO (28). Like previously published data, centers with lower pre-pandemic annual ECMO volume have higher mortality (29). This finding emphasizes the point that rapid ECMO expansion by inexperienced centers during a period of crisis could be contributing to our findings.

It should be noted that our search strategy to identify patients with non-COVID-19–related viral ARDS was broad. More than half the included patients were identified based on *International Classification of Diseases* coding that did not correspond to a specific viral pathogen, such as "viral pneumonia, unspecified," and others were included based on nonspecific diagnostic codes that may overlap with other causes of ARDS. Given this, misclassification bias (bias introduced by incorrectly assigning a patient to a specific category), has the potential to have incorrectly altered the observed association of COVID-19 with elevated overall mortality. However, when the analysis was repeated and confined to only patients diagnosed with ARDS attributed to a specific viral organism, rate of survival while receiving ECMO and the risk of in-hospital mortality were essentially identical to those observed in the primary analysis (eTables 5 and 6, http://links.lww.com/CCX/B139).

Our study has limitations that should be highlighted. First, outcome data for all included patients with COVID-19–related ARDS in the ELSO registry was not known since a small percentage (2.5%) of patients remained on ECMO at the time of data collection. As the final disposition of these patients was not known, some bias is introduced into the estimation of in-hospital mortality. While we evaluated this bias by repeating the analysis under extreme assumptions, this consideration may slightly diminish the precision of our provided in-hospital mortality estimate. Although patients transferred while supported with ECMO were excluded from the primary analysis of in-hospital mortality, when performing this sensitivity analysis patients transferred on ECMO from one ELSO center to another may have been double counted given the used data was de-identified and registry data may have been provided by both the transferring and receiving centers. This situation was likely extremely rare and more common among patients with ARDS related to COVID-19 rather than other viral illnesses. Relatedly, this consideration would be expected to bias the results of the sensitivity analysis toward the finding of no difference in mortality between patients with COVID-19 and those with non-COVID-19 ARDS. Despite these data limitation, COVID-19 remained associated with significantly higher in-hospital mortality compared with non-COVID-19 ARDS under the extreme assumptions examined in this sensitivity analysis. Additionally, estimates of center specific case volume between 2017 and 2019 were based on the number of ECMO cases performed for the support of ARDS during this period. Overall ECMO experience of centers providing care for patients with COVID-19 was not analyzed and this additional data may provide further insights related to the observed difference in outcomes in viral ARDS processes.

CONCLUSIONS

When comparing viral induced ARDS, patients with COVID-19 that require ECMO have longer duration of ECMO, more complications, and higher in-hospital mortality than patients with ARDS related to other viral pathogens. Reporting on these findings is not to discourage the use of ECMO for COVID-19–related ARDS, but rather to acknowledge the need for further investigation regarding appropriate patient selection, implementation, and associated outcomes.

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