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Prevalence and Survival of Prolonged Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome: An Analysis of the Extracorporeal Life Support Organization Registry*

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OBJECTIVES: To examine trends in utilization and outcomes among patients with the acute respiratory distress syndrome (ARDS) requiring prolonged venovenous extracorporeal membrane oxygenation (VV ECMO) support.

DESIGN: Retrospective observational cohort study.

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

PATIENTS: Thirteen thousand six hundred eighty-one patients that required ECMO for the support of ARDS between January 2012 and December 2022.

INTERVENTIONS: None.

MEASUREMENTS AND MAIN RESULTS: Mortality while supported with VV ECMO and survival to hospital discharge based on ECMO duration were examined utilizing multivariable logistic regression. Among the 13,681 patients supported with VV ECMO, 4,040 (29.5%) were supported for greater than or equal to 21 days and 975 (7.1%) for greater than or equal to 50 days. Patients supported with prolonged VV ECMO were less likely to be discharged alive from the hospital compared with those with short duration of support (46.5% vs. 59.7%; $p < 0.001$). However, among patients supported with VV ECMO greater than or equal to 21 days, duration of extracorporeal life support was not significantly associated with mortality (odds ratio [OR], 0.99; 95% CI, 0.98–1.01; $p = 0.87$ and adjusted OR, 0.99; 95% CI, 0.97–1.02; $p = 0.48$). Even in those supported with VV ECMO for at least 120 days ($n = 113$), 52 (46.0%) of these patients were ultimately discharged alive from the hospital.

CONCLUSIONS: Prolonged VV ECMO support of ARDS has increased and accounts for a substantial portion of cases. Among patients that survive for greater than or equal to 21 days while receiving VV ECMO support, duration is not predictive of survival to hospital discharge and clinical recovery may occur even after very prolonged VV ECMO support.

KEYWORDS: acute respiratory distress syndrome; extracorporeal membrane oxygenation; respiratory distress; respiratory insufficiency

Referrals for the initiation of venovenous extracorporeal membrane oxygenation (VV ECMO) dramatically increased during the COVID-19 pandemic (1). Extracorporeal life support (ECLS), including VV ECMO, places a significant demand on medical resources. Better understanding of which patients are likely to benefit from this intensive life-supporting measure is critical to improve resource allocation and outcomes (2).

***See also p. 974.**

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KEY POINTS

Question: How does the duration of venovenous extracorporeal membrane oxygenation (VV ECMO) for the support of acute respiratory distress syndrome (ARDS) relate to patient outcomes?

Findings: In this retrospective observational study of patients enrolled in the Extracorporeal Life Support Organization registry, we found that prolonged VV ECMO support of ARDS has increased. Among patients that survive for greater than or equal to 21 days while receiving VV ECMO support, duration is not predictive of survival to hospital discharge and clinical recovery may occur even after very prolonged VV ECMO support.

Meaning: Patients that survive the initial inflammatory cascade of ARDS may benefit from prolonged VV ECMO support to allow for respiratory recovery.

In the management of acute respiratory distress syndrome (ARDS), including ARDS secondary to COVID-19, extended duration of VV ECMO support may allow for respiratory recovery (3). Prolonged VV ECMO in adults has previously been defined in studies as support lasting for greater than 14 or 21 days (4, 5). Compared with shorter duration, prolonged ECMO support has been associated with decreased survival; however, it remains unclear how ECMO duration can be used to guide withdrawal of ECLS (4–6).

Recently, very prolonged duration of VV ECMO support, including for greater than 100 days, has been reported (7–9). In this evolving landscape of ARDS management, we sought to reassess trends in implementation and outcome among patients supported with prolonged VV ECMO.

MATERIALS AND METHODS

We analyzed patients in the Extracorporeal Life Support Organization (ELSO) registry supported with ECMO between January 2012 and December 2022. The Cooper University Healthcare Institutional Review Board deemed this study exempt from review, as it did not fall under the board's guidelines as human subjects research. Adult patients supported with VV ECMO (as an initial ECLS mode) for the management of ARDS were included in the analysis. The analysis followed the Strengthening the Reporting of Observational Studies in Epidemiology guidelines (**eTable 1**, http://links.lww.com/CCM/H494).

Objectives

We evaluated the impact of ECMO duration on subsequent VV ECMO decannulation and survival to hospital discharge. We also compared outcomes among patients supported with prolonged ECMO to those that received shorter durations of support and assessed how outcomes have evolved over time.

For the primary analysis, prolonged VV ECMO was defined as support for greater than or equal to 21 days. Given contemporary trends in duration of VV ECMO, a secondary analysis was performed for patients supported for greater than or equal to 50 days. Additionally, we examined how ELSO center case volume relates to the use of prolonged VV ECMO and how center volume impacts survival while receiving VV ECMO. Finally, given the potential that COVID-19 may have impacted VV ECMO utilization and outcomes during the recent pandemic, we performed a sensitivity analysis to reevaluate outcomes after excluding patients with COVID-19.

Statistical Analysis

To facilitate examination over time, patients were divided into three groups based on year of support. The outcomes of discontinuation of VV ECMO for death or an expected poor prognosis (referred to as mortality on VV ECMO) and additionally, discharge alive from hospital (referred to as survival to hospital discharge) between these groups were compared by multivariable logistic regression. The multivariable models were adjusted for potential confounding variables, identified a priori, through the inclusion of the unweighted component parameters of the Respiratory ECMO Survival Prediction (RESP) score (10).

VV ECMO case volume (total number of cases) at participating centers was assessed in the period from 2012 to 2017. This case volume, as a continuous variable, was then evaluated as a predictor of prolonged VV ECMO support and mortality in the period from 2018 to 2022. Finally, reason for discontinuation of VV ECMO (death or expected poor prognosis, recovery, complication, or resource limitation) based on year

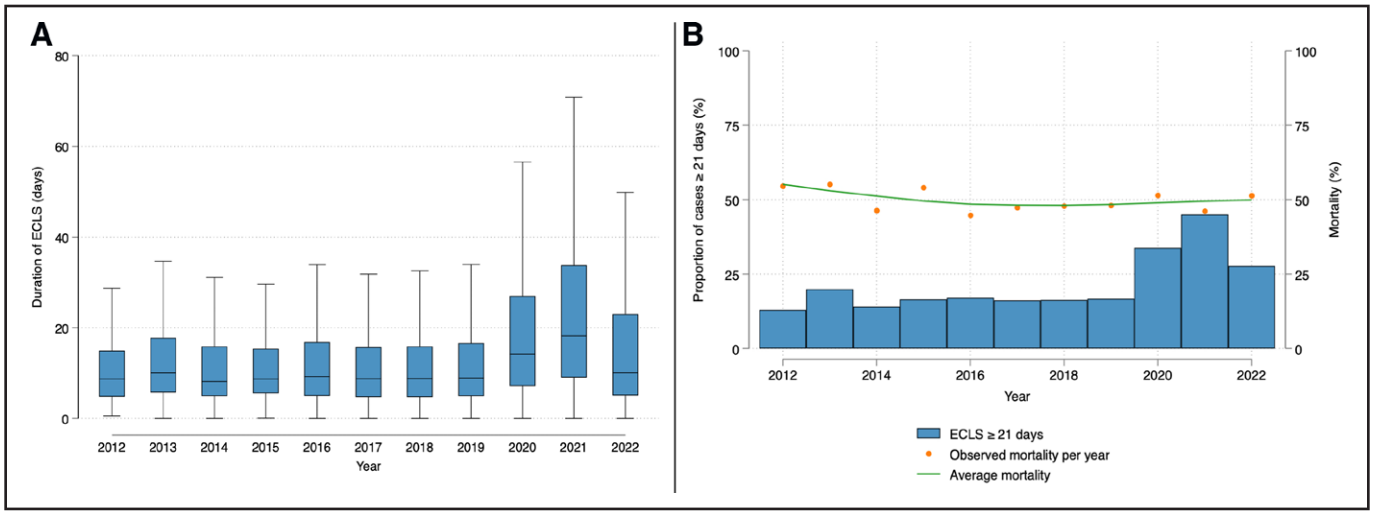

Figure 1. Venovenous extracorporeal membrane oxygenation (VV ECMO) duration and mortality. **A**, *Box plot* of VV ECMO duration based on year. **B**, Observed rateof discontinuation of VV ECMO for death or anticipated poor prognosis (*circles*), averaged rate (*line*), and proportion of prolonged VV ECMO (*bar graph*). ECLS = extracorporeal life support.

of support was compared visually with stacked probability plots to examine if the frequency of these outcomes or the time to these events have changed over the included time periods. Additional description of the ELSO registry, multivariable model, handling of missing data, and other statistical considerations are presented in detail within the **eMethods** (http://links.lww.com/CCM/H494). All statistical analyses were performed with STATA/SE 17.0 (StataCorp, College Station, TX) and R, Version 4.1.2 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

We identified 14,003 patients supported with VV ECMO for the diagnosis of ARDS during the study period. Three hundred twenty-two patients were removed for missing data related to ECMO duration or reason for ECLS discontinuation. As a result, data related to 13,681 adult patients supported with VV ECMO for ARDS was available for analysis. Of these patients, the median age was 47 years (25th percentile [Q1]–75th percentile [Q3]: 36–57 yr), 34.8% were female, 47.6% were White, and the median duration of support was 12 days (Q1–Q3: 6–24 d). Four thousand forty patients (29.5%) were supported for greater than or equal to 21 days and 975 patients (7.1%) were supported for greater than or equal to 50 days. Duration of VV ECMO support has remained steady since 2012; although an increase in the median duration of support was observed during 2020 and 2021 ($p < 0.001$). This increase in observed duration trended back toward baseline in 2022 (**Fig. 1*A***).

Characteristics of all patients categorized by duration of support is displayed in **eTable 2** (http://links.lww.com/CCM/H494). Longer duration of mechanical ventilation before VV ECMO (81 vs. 49 hr; $p < 0.001$) and more frequent acute associated nonpulmonary infection at the time of VV ECMO initiation (43.9% vs. 19.8%; $p < 0.001$) were noted in the group supported with longer ECMO duration compared with short ECMO duration. Cardiac arrest before VV ECMO was less common in the prolonged support group (3.2% vs. 8.2%; $p < 0.001$) compared with the short support group. Patients that received prolonged support were less likely to be discharged alive from the hospital compared with those with VV ECMO duration less than 21 days (46.5% vs. 59.7%; $p < 0.001$) (**Table 1**).

A plot reflecting the observed probability of being discharged alive based on duration of VV ECMO support is provided in **Figure 2**. Notably, a qualitative decrease in the probability of discharge alive is observed through day 21. When considering patients supported with VV ECMO for less than 21 days, duration of VV ECMO (per additional day) was significantly associated with reduced survival to hospital discharge (odds ratio [OR], 0.96; 95% CI, 0.95–0.97; $p < 0.001$ and adjusted OR, 0.97; 95% CI, 0.95–0.98; $p < 0.001$). However, when the analysis was restricted to patients supported with VV ECMO for greater than or equal to 21 days, duration was not significantly associated with mortality (OR, 1.00; 95% CI,

TABLE 1.
Outcomes of All Patients Supported With Venovenous Extracorporeal Membrane Oxygenation for Acute Respiratory Distress Syndrome Between 2012 and 2022 by Duration of Support

All Patients	All Patients, *n* = 13,681	< 21 d, *n* = 9,641	≥ 21 d, *n* = 4,040	*p*
ECLS discontinuation reason				
Deceased or poor prognosis	5,181 (37.9)	3,224 (33.4)	1,957 (48.4)	< 0.001
ECLS complication or resource limitation	179 (1.3)	140 (1.5)	39 (1.0)	0.02
Hospitalization outcome[a]				
Discharged alive	7,584/13,589 (55.8)	5,723/9,590 (59.7)	1,861/3,999 (46.5)	< 0.001

ECLS = extracorporeal life support.
[a]Patients that remained supported with extracorporeal membrane oxygenation at the time of hospital discharge were excluded.
Data are presented as *n* (%).

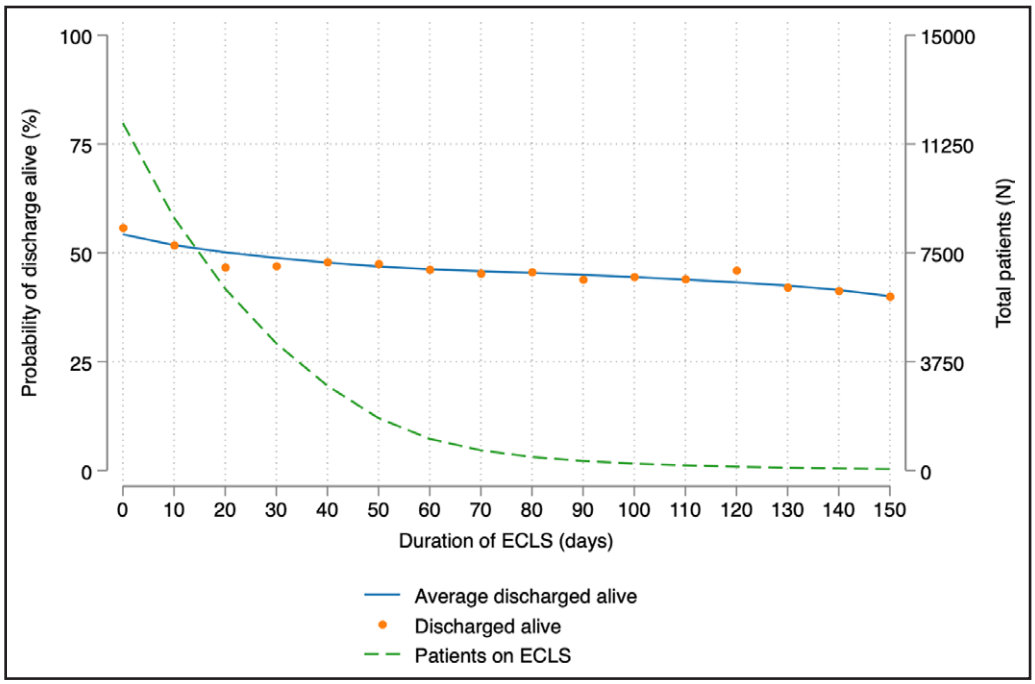

Figure 2. Observed probabilities of discharge alive (*circles*) for a patient based on duration of extracorporeal life support (ECLS), average probabilities (*solid line*), and total number of patients that remain on ECLS at specific time points (*dashed line*).

0.99–1.00; $p = 0.44$ and adjusted OR, 1.00; 95% CI, 0.99–1.00; $p = 0.22$). Even among those supported for the most prolonged durations, survival remained only slightly lower than the entire cohort. For example, among patients supported with VV ECMO for at least 21 days ($n = 3999$), 1861 (46.5%) of these patients were ultimately discharged alive from the hospital. Likewise, among those supported for at least 50 days ($n = 948$), and even among those supported for at least 120 days ($n = 113$), a substantial number ($n = 450$ [47.5%] and $n = 52$ [46.0%], respectively) were discharged alive from the hospital. Discharge location for patients supported with prolonged VV ECMO since 2021 are included in **eTable 3** (http://links.lww.com/CCM/H494), with 271 (27.5%) of surviving patients discharged home. Of note, lung transplantation was added as a recorded variable to the ELSO registry in 2016. In the years from 2016 to 2022, lung transplantation following VV ECMO was recorded in 295 of 13,027 (2.3%) of all cases, in 174 of 3,935 (4.4%) of patients supported with VV ECMO for at least 21 days, and in 104 of 955 (10.9%) of patients supported for at least 50 days. Notably, since 2018, 1277 of 1589 patients (80.4%) supported with VV ECMO for at least 21 days underwent tracheostomy.

Patients were then grouped into three categories based on the year of VV ECMO initiation (2012–2016, 2017–2019, and 2020–2022). Characteristics of all patients supported during these time periods and

those patients supported with prolonged VV ECMO by period are displayed in **eTable 4** (http://links.lww.com/CCM/H494); and **Table 2**, respectively. No difference in the percent of patients discharged alive was noted based on period ($p = 0.96$) (**Table 3**). This finding was confirmed when patients with COVID-19 ($n = 2661$) were removed from the analysis ($p = 0.24$; **eTable 5**, http://links.lww.com/CCM/H494). Similarly, survival to hospital discharge has not changed significantly among patients supported with VV ECMO for greater than or equal to 50 days (**eTables 6–8**, http://links.lww.com/CCM/H494). Despite the proportion of cases of prolonged support rising considerably in the final 3 years of analysis, the mortality rate among patients supported with prolonged VV ECMO has remained generally stable since 2012 (**Fig. 1*B***). Likewise, although time to discontinuation (reflective of longer VV ECMO support) has increased during the most recent time group, the proportion of patients discontinued from VV ECMO for death or expected poor prognosis, recovery, complication, or resource limitation reason has remained consistent over time (**Fig. 3**).

Finally, ELSO center case volume was considered as a predictor of prolonged VV ECMO and mortality while receiving VV ECMO. Two hundred twenty-one centers provided data to ELSO between 2012 and 2017. Number of cases per center range from 1 to a maximum of 156 (median, 5; Q1–Q3: 2–14). Case

TABLE 2.
Demographics of Patients Supported With Prolonged Venovenous Extracorporeal Membrane Oxygenation (≥ 21 d) by Year

Total No. of Cases	2012–2016, *n* = 221 (5.5)	2017–2019, *n* = 677 (16.8)	2020–2022, *n* = 3142 (77.8)
Demographics			
Age (yr)	47 (32–58)	48 (36–58)	47 (37–56)
Gender (female)	81/210 (38.6)	253/671 (37.8)	964/3142 (30.7)
Race			
Asian	29 (13.1)	109 (16.1)	258 (8.2)
Black	20 (9.0)	63 (9.3)	318 (10.1)
Hispanic	28 (12.7)	58 (8.6)	671 (21.4)
White	89 (40.3)	317 (46.8)	1336 (42.5)
Body mass index (kg/m^2)	28.2 (24.1–33.8)	28.3 (24.7–34.2)	31.4 (27.3–36.7)
Respiratory ECMO Survival Prediction score parameters (pre-ECMO)			
Immunocompromised	21 (9.5)	52 (7.7)	225 (7.2)
Mechanical ventilation duration (hr)	80 (23–170)	79 (21–177)	81 (27–156)
CNS dysfunction	18 (8.1)	79 (11.7)	464 (14.8)
Acute associated nonpulmonary infection	100 (45.2)	190 (28.1)	1484 (47.2)
Neuromuscular blockade	95 (43.0)	415 (61.3)	2313 (73.6)
Inhaled nitric oxide	27 (12.2)	81 (12.0)	510 (16.2)
Bicarbonate	14 (6.3)	59 (8.7)	203 (6.5)
Cardiac arrest	4 (1.8)	35 (5.2)	91 (2.9)
$Paco_2$ (mm Hg)	61 (48–78)	62 (50–76)	62 (51–76)
Peak inspiratory pressure (cm H_2O)	34 (30–40)	35 (30–39)	34 (30–38)

ECMO = extracorporeal membrane oxygenation.
Data are presented as median (25th–75th percentiles) or *n* (%).

TABLE 3.
Outcomes of Patients Supported With Prolonged Venovenous Extracorporeal Membrane Oxygenation (≥ 21 d) by Year

All Patients	2012–2016, *n* = 221	2017–2019, *n* = 677	2020–2022, *n* = 3142	*p*
Extracorporeal life support discontinuation reason				
Deceased or poor prognosis	107 (48.4)	324 (47.9)	1526 (48.6)	0.95
Extracorporeal membrane oxygenation complication or resource limitation	2 (0.9)	10 (1.5)	27 (0.9)	0.28
Hospitalization outcome[a]				
Discharged alive	104/220 (47.3)	312/676 (46.2)	1445/3103 (46.6)	0.96

[a]Patients that remained supported with extracorporeal membrane oxygenation at the time of hospital discharge were excluded. Data are presented as *n* (%).

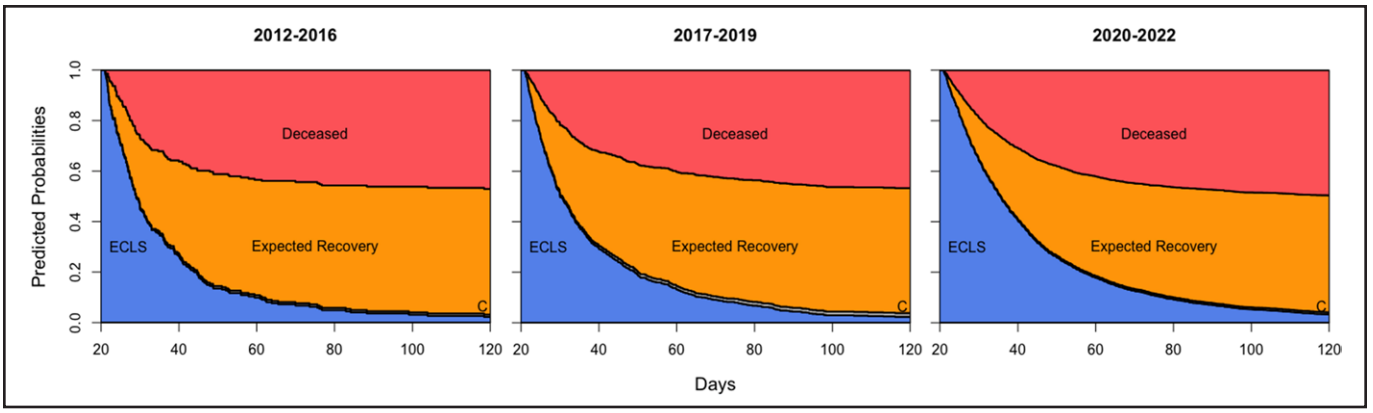

Figure 3. *Stacked probability plots* based on time period reflecting time from initiation of venovenous extracorporeal membrane oxygenation (VV ECMO) to discontinuation for death or expected poor prognosis, expected recovery, or VV ECMO complication or resource limitation. The proportion of patients discontinued from VV ECMO for complication or resource limitation is delineated in the *rightmost column* of the figure. ECLS = extracorporeal life support.

volume between 2012 and 2017 was inversely related to prolonged support (≥ 21 d). Per ten cases, the rate of prolonged support decreased by approximately 4% (OR, 0.94; 95% CI, 0.94–0.98; $p < 0.001$). This relationship persisted when the model was adjusted for RESP score parameters (adjusted OR, 0.94; 95% CI, 0.91–0.98; $p = 0.001$). In patients supported with prolonged VV ECMO after 2017, case volume between 2012 and 2017 was associated with significantly lower mortality on VV ECMO in unadjusted analysis (OR, 0.96; 95% CI, 0.93–0.99; $p = 0.041$). However, this finding did not persist in the adjusted model (adjusted OR, 0.99; 95% CI, 0.94–1.05; $p = 0.77$). A sensitivity analysis of this and the previously reported multivariable models was performed to evaluate the impact of missing data. Findings utilizing imputation for missing data were consistent to those presented above (**eTable 9**, http://links.lww.com/CCM/H494).

DISCUSSION

In this analysis of 13,681 patients supported with VV ECMO for ARDS between 2012 and 2022, we found the use of prolonged support (≥ 21 d) to be common. Of the 4040 patients (29.5%) that received prolonged VV ECMO, duration of support was not a significant factor associated with mortality. Strikingly, the rate of survival to hospital discharge among patients supported with even the most prolonged duration of VV ECMO remained comparable to that observed among patients supported for much shorter periods of time. These results indicate that time supported with ECLS should not be used as a sole factor in the decision-making regarding withdrawal of VV ECMO support.

Previous estimates of expected mortality in those requiring long periods of VV ECMO support have

been mixed and may no longer reflect current care. One large study examining 974 patients enrolled in the ELSO registry between 1989 and 2013 demonstrated worse outcomes in those supported with VV ECMO for more than 14 days when compared with those supported for 14 days or less (5). Although this previous study demonstrated worse overall outcomes in patients supported with prolonged ECLS, the data presented were crucial in better defining the survivability of prolonged VV ECMO and identified an estimated survival greater than 45% in patients supported for longer than 14 days. Another study of 127 patients, including 19 patients that required VV ECMO support for more than 21 days, found the survival rate of patients supported with VV ECMO for more than 21 days was approximately 52% (4). Reflective of evolving trends in practice, a recent case series of 12 patients that received VV ECMO support for greater than 50 days demonstrated feasibility of this strategy (11). Finally, several reports exist of patients surviving after over 100 days of VV ECMO support (7–9). We used the longer cutoff of 21 days and a subanalysis of 50 days to better reflect current practice where VV ECMO duration goes far beyond prior historical standards.

Despite increased experience with VV ECMO and changes in practice patterns over the past decade, the mortality rate we observed in patients supported with prolonged support was similar to that seen in earlier studies (5, 11). Likewise, our analysis of outcomes based on era provides additional evidence that outcomes in patients supported by prolonged VV ECMO has changed little over the past decade. Several factors may be responsible for these observed finding. First, discontinuation of ECLS for a VV ECMO complication has remained rare over this period. Despite the significantly longer ECMO duration observed during the most recent period, the rate of discontinuation of prolonged support related to an VV ECMO complication or resource limitation remains less than 1%. Additionally, strategies to mitigate lung injury in ARDS have remained limited to reducing ventilator-induced lung injury and allowing time for lung recovery. As such, VV ECMO represents one specific tool to decrease the physiologic insult of mechanical ventilation. Finally, increased experience supporting patients with VV ECMO may have resulted in less selective criteria for candidacy over the past decade. Expanded access to prolonged support for patients with more baseline comorbidities or higher illness severity may therefore have resulted in a higher observed mortality among patients managed more contemporarily (12).

When considering patients supported for less than 21 days, each additional day of VV ECMO was associated with a 4% decrease in survival to discharge. However, this association did not remain when evaluating the prolonged support group alone. In this group, the mortality rate of patients supported the longest was similar to the mortality rate observed among patients with shorter, albeit still prolonged ECMO duration. We postulate that among patients that survive for at least 21 days following initiation of VV ECMO for ARDS, prognosis may be less related to pre-ECMO prognostic factors, severity of initial ARDS insult, or complications related to ECMO support and become increasingly dependent on gradual recovery of the damaged lungs. The survival rate among patients supported with VV ECMO for very prolonged durations (with a significant rate of survival described even among the minority of patients with ARDS supported for 4 mo) reported in this analysis serves to highlight the capacity of the lung to recover, even after a very prolonged period. Unsurprisingly, tracheostomy was common and lung transplantation was more frequently used as duration of support increased.

We identified some important patient-specific factors that differentiated the prolonged VV ECMO support group from those supported less than 21 days. A notable difference was the duration of mechanical ventilation before initiation of VV ECMO (81 vs. 49 hr). This finding may be reflective of ventilator-induced lung injury resulting in prolonged time to ARDS recovery and is consistent with prior evidence reflecting worse outcomes in patients with prolonged duration of mechanical ventilation before VV ECMO support (13). Those patients with associated nonpulmonary infections at the time of VV ECMO initiation were also more likely to require prolonged support, and this may reflect an increase in the duration of time to resolution of complex acute critical illness. Finally, administration of bicarbonate and cardiac arrest before VV ECMO initiation were both associated with shorter ECMO duration, presumably due to higher immediate risk of mortality (10).

Interestingly, we observed an inverse relationship between the number of cases performed at a particular center and the rate of prolonged VV ECMO. Per ten cases, the rate of prolonged support decreased by

4%. This relationship persisted when adjustments were made for baseline severity of illness. This finding is likely multifactorial in etiology as high-volume centers with large number of patient referrals may select more optimal candidates, adhere to institutional protocols, and have safety mechanisms in place to best avoid VV ECMO-related complications. Supporting the assertion that patient selection is likely a key driver of outcome, we found that though center case volume was associated with improved outcomes among patients supported with prolonged VV ECMO in unadjusted analysis, this was not the case after adjusting for RESP score parameters.

The COVID-19 pandemic resulted in increased referrals for VV ECMO (1). A prior analysis of the ELSO registry suggested that patients with ARDS related to COVID-19 had worse VV ECMO-related outcomes compared with patients with ARDS related to other conditions (14). However, it is not clear if these observed differences in outcome remain when considering only patients supported with prolonged VV ECMO. To better understand the impact of the COVID-19 pandemic, we examined three discrete timeframes: 2012–2016, 2017–2019, and 2020–2022. From 2020 to 2022 (reflective of the COVID-19 pandemic), the percent of patients receiving VV ECMO more than 21 days significantly increased; however, the rate of discontinuation, survival at discharge, and VV ECMO-related complications were unchanged. These results suggest that though patients with COVID-19 supported with VV ECMO may have a worse overall prognosis than patients that required support of ARDS related to other viral illnesses, patients in both groups that survived for at least 21 days may experience a similar rate of recovery. Likely, this reflects a similar protracted course of lung recovery following ARDS regardless of the underlying inciting cause (15, 16).

Several limitations associated with examination of the ELSO registry are important to note. First, parameters collected in the registry during the period analyzed include limited data reflective of important aspects of clinical care, such as level of physical mobilization or other interventions that occurs while receiving VV ECMO support. This limits efforts to identify factors associated with survival in patients that received prolonged support. As we described, prognosis in patients supported with prolonged VV ECMO has changed minimally over the past decade and future research to better define factors associated with survival may help to change this trajectory. Relatedly, decannulation practices and criteria for liberation from VV ECMO may vary substantially among included institutions and analysis of these practices is likewise limited by the data available within the ELSO registry. Missing data related to RESP score parameters was common and additionally, it was frequently not possible to determine the primary indication for VV ECMO support among individual patients. As a result, the RESP score parameter of diagnostic group was not included in our multivariable model. As our analysis was restricted to only those patients supported with VV ECMO for ARDS (excluding most patients supported with ECMO for chronic lung disease) and our results were robust to supplemental mechanisms of analyzing missing data, we suspect bias introduced due to these limitations to be minimal. Finally, although our data reflects the survivability of prolonged VV ECMO for ARDS, registry limitations prevent analysis of patient disability following discharge from these hospitalizations. Long-term outcomes such as quality of life and functional status following prolonged ECLS remain important considerations not addressed in this current work.

CONCLUSIONS

The understanding of prolonged VV ECMO in the setting of ARDS is evolving and durations of support once considered extreme are now commonplace. Given the observed survivability of VV ECMO for ARDS in even the most prolonged cases, the practice of subjectively withdrawing care for presumed futility based on duration of VV ECMO support should be reconsidered. Patients that survive the initial inflammatory cascade of ARDS without clear contraindications to continued support may benefit from prolonged support to allow for respiratory recovery.

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