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"Awake" Cannulation of Patients for Venovenous Extracorporeal Membrane Oxygen: An Analysis of the Extracorporeal Life Support Organization Registry

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IMPORTANCE: "Awake" cannulation for venovenous extracorporeal membrane oxygenation (ECMO), where patients remain spontaneously breathing without invasive mechanical ventilation during the cannulation procedure, may reduce lung injury from positive pressure ventilation and promote patient mobility.

OBJECTIVES: To examine the association between "awake" cannulation for venovenous ECMO and patient outcomes.

DESIGN, SETTING, AND PARTICIPANTS: Analysis of the prospectively collected by the multicenter Extracorporeal Life Support Organization registry. Patients 18 years old or older who were cannulated for venovenous ECMO between 2016 and 2022 were included.

MAIN OUTCOMES AND MEASURES: Propensity score matching techniques were used to examine the association between the primary exposure of "awake" cannulation and the primary outcome of hospital mortality.

RESULTS: This study analyzed data from 28,627 patients who received venovenous ECMO, including 797 (2.8%) who underwent awake cannulation. Patients undergoing awake cannulation were older (52.2 vs. 47.8 yr), had greater prevalence of chronic lung diseases (50.6% vs. 48.9%), and ischemic heart disease (4.3% vs. 2.7%) compared with those cannulated while receiving mechanical ventilation. Hospital survival to discharge was did not differ significantly between awake and nonawake cannulation groups after propensity score matching (2.4% increased rate of survival for patients cannulated awake; 95% CI, −1.7% to 6.4%; $p = 0.26$).

CONCLUSIONS AND RELEVANCE: In this large, multicenter study, awake cannulation for venovenous ECMO was uncommon but increasingly used over time. Survival to hospital discharge was similar to patients cannulated while on mechanical ventilation. Future research should focus on identification of patient cohorts most likely to benefit from ""awake" cannulation.

KEYWORDS: awake cannulation; Extracorporeal Life Support Organization; extracorporeal membrane oxygenation; respiratory failure

Extracorporeal membrane oxygenation (ECMO) (1) is a potentially lifesaving intervention, predominantly used as a rescue therapy in cases of cardiogenic shock (venoarterial cannulation) and severe respiratory failure (venovenous cannulation). Given the discomfort associated with the procedure, the mechanical complexity of cannulation, and the severe hypoxia and/or shock often present in patients requiring ECMO support, most ECMO cannulations are performed in patients who are sedated and receiving mechanical ventilation. Intubation, mechanical ventilation, and sedation, however,

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KEY POINTS

Question: Does avoiding mechanical ventilation at the time of venovenous extracorporeal membrane oxygenation (ECMO) cannulation improve outcomes.

Findings: Cannulation for venovenous ECMO on nonmechanically ventilated patients remains rare although it has recently increased. It does not seem to improve survival but does decrease the length of stay and ECMO duration in a small subset of patients.

Meaning: Awake cannulation may benefit a select group of patients who are being considered for lung transplantation.

may result in lung injury, prolonged immobilization, and delirium (2).

"Awake" cannulation for ECMO, the cannulation of patients who are nonintubated and spontaneously breathing, has emerged as a potential strategy to avoid lung injury from mechanical ventilation and to promote awareness and mobilization in critically ill patients. However, the feasibility, safety, and advantages of awake cannulation in ECMO remain poorly understood, and existing evidence is limited. While a retrospective review focusing on awake peripheral cannulation in venoarterial ECMO demonstrated promising outcomes such as decreased ICU length of stay, data on awake venovenous ECMO cannulation are scarce (3, 4). Most of the data on awake ECMO cannulation is specific for the lung transplant population with some evidence of decreased mortality and improved 3-year survival (5). Evidence from studies on awake cannulation for other interventions, such as awake extracorporeal CO_2 removal, is mixed and therefore, further investigation is warranted (3, 6).

Given the importance of promoting patient mobility, facilitating early rehabilitation, minimizing sedatives and associated delirium, and avoiding mechanical lung injury in patients with acute respiratory failure receiving ECMO, exploring the impact of awake cannulation in venovenous ECMO is crucial (7). In the present study, we assess the prevalence and outcomes of venovenous ECMO awake cannulation using the large, multicenter Extracorporeal Life Support Organization (ELSO) registry. By addressing this critical gap in the literature, we aim to provide valuable insights that will inform and optimize patient care in the challenging setting of venovenous ECMO cannulation.

METHODS

Data Source

This was a retrospective analysis of the prospectively collected ELSO registry. The ELSO registry is an international database established in 1989 where cases of both adult and pediatric patients who underwent ECMO treatment are documented prospectively by participating sites. The registry currently contains over 200,000 ECMO cases from 430 participating medical centers. The variables within the registry have been detailed in prior publications. The data received was deidentified and the study was conducted under a waiver of informed consent (Informed consent was waived by Einstein Institutional Review Board [IRB] on May 22, 2023 under the title: Cannulation of Awake Patients for ECMO and the Effect on Outcomes, IRB approval number 2023-14974). Procedures were followed in accordance with the ethical standards of the Einstein IRB on human experimentation and with the Helsinki Declaration of 1975.).

Patient Cohort

We identified patients in the registry who received ECMO support between the years 2016 and 2022. Patients who were over 18 years old and cannulated for venovenous ECMO were included. Patients were excluded if they received nonvenovenous ECMO extracorporeal support (e.g., venoarterial ECMO), if they were missing data regarding mechanical ventilation at time of ECMO cannulation, and if the time from admission to cannulation was less than 0 hours (suspected transfers from other hospitals). Only the initial ECMO cannulation was considered for all patients. The years 2016–2022 were selected as the *International Classification of Diseases* codes used to identify the primary diagnoses were changed in 2015. A separate subgroup of patients who were cannulated with the planned destination of lung transplants was created and a comparison was made between awake and nonawake patients in that subgroup because of previous evidence

of increased survival in awake patients bridged to lung transplant (5). See **Figure 1** for patient flow chart.

Definitions of Exposures and Outcomes

The primary exposure for the study was awake venovenous ECMO cannulation. Awake cannulation patients were defined by a selection of the "No Ventilator" variable in the ELSO registry at time of ECMO cannulation. The term awake was used to describe spontaneously breathing, nonmechanically ventilated patients in previous studies (8). The primary outcome was survival to hospital discharge, whereas secondary outcomes were intubation within 24 hours of cannulation, post-cannulation hospital length of stay in hospital survivors, discharge destination in hospital survivors, duration on ECMO in hospital survivors, and highest degree of mobilization (dichotomized as an ICU Mobility Scale score of ≥ 3 [sitting at edge of bed] or < 3). We also reported ECMO complications as collected by the ELSO registry including bleeding complications, neurologic complications, and mechanical complications. For the cohort of patients who were cannulated with a planned destination of lung transplant, we additionally assessed the rate of lung transplantation.

Statistical Analysis Plan

Categorical variables are described with counts and frequencies and continuous variables are described with means and SDs or medians and interquartile ranges (IQRs) depending on the distribution of the data.

Rates of survival to hospital discharge were compared between patients cannulated awake for venovenous ECMO and those cannulated while receiving mechanical ventilation. The primary analysis was performed using propensity score matching with a nearest-neighbor approach and with replacement. Four patients cannulated while on mechanical ventilation were matched to each patient cannulated awake. A caliper of 0.10 SDs of the logit of the estimated propensity scores. Variables included in the propensity score match included age, year of cannulation, biologic sex, body mass index (BMI), COVID-19 status, receipt of renal replacement therapy before cannulation, Pao_2/Fio_2 ratio at time of cannulation, pH at tine of cannulation, Pco_2 at time of cannulation, vasopressor use before cannulation, the acute respiratory distress syndrome as reason for cannulation, bridge to transplant as reason for cannulation, admit time until cannulation,

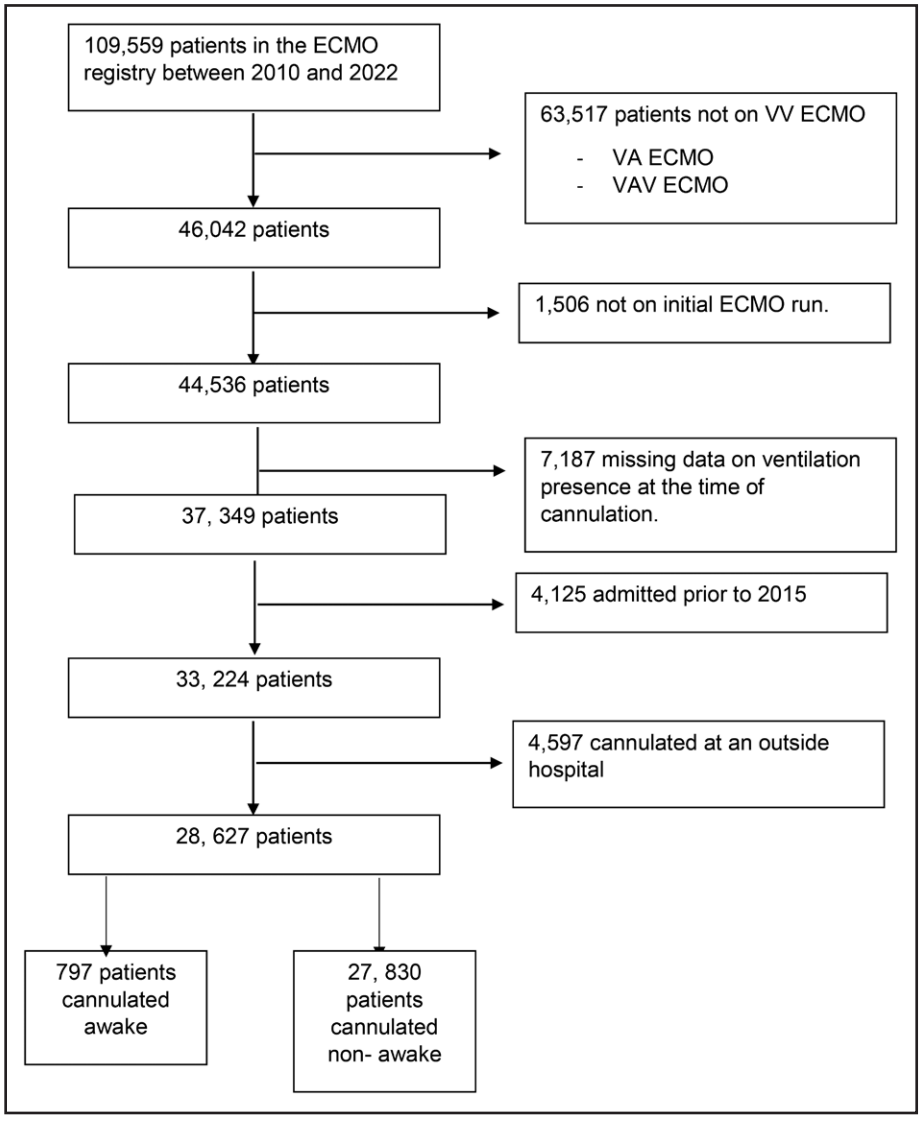

Figure 1. Patient flowchart and inclusion criteria. ECMO = extracorporeal membrane oxygenation, VA = venoarterial, VAV = veno-arterial-venous, VV = venovenous.

pre-cannulation cardiac arrest, and various comorbidities. Patients admitted before 2020 were coded as not have COVID-19. Matching success was determined based on examination of pre- and post-match standardized differences as well as examination of propensity score overlap in the matched and unmatched groups. Results are reported as the average treatment effect for the treated. As a sensitivity analysis, we performed logistic regression using generalized estimating equations (GEEs) with an exchangeable correlation structure and robust SEs to account for clustering by hospital site. The GEE model was also used to compare key secondary outcomes and to identify predictors of intubation within 24 hours. Duration outcomes were log-transformed before analysis given the distribution of the data.

Because of existing data showing potential benefit of awake cannulation in lung transplant candidates, a subgroup analysis of patients who were cannulated for ECMO with intention to undergo lung transplant was analyzed in a similar fashion to the above. Given the smaller number of patients in the subgroup, one-to-one matching was performed for the primary analysis. Duration of ECMO and hospital length of stay was analyzed only in patients who survived to hospital discharge.

An additional post hoc sensitivity analysis was performed in which patients from the years 2020–2022 were excluded. This analysis was performed to examine the association between awake cannulation and outcomes in patients before the COVID-19 pandemic. For this analysis, because of the smaller sample size, 1:1 matching was performed.

To explore hospital-to-hospital variation in use of awake cannulation, we created a caterpillar plot of percent of patients undergoing awake cannulation by hospital site. For this analysis, only sites at which at least 50 patients underwent venovenous cannulation during the study period were included (or at least five cannulations for site for an analysis restricted to patients cannulated to undergo lung transplant). We additionally explored trends in the use of awake cannulation comparing the year 2022 to the year 2016 (year with the lowest proportion of awake cannulation).

For all hypothesis tests, a p value of less than 0.05 was considered statistically significant. There was no missing data for the primary outcome or exposure variable. A table of data missingness for other model variables included can be found in **Table E3** (http://links.lww.com/CCX/B433). For missing variables in the model, multiple imputation with chained equations was performed. Stata, Version 15.1 (StataCorp, College Station, TX) was used for all analyses. The teffects psmatch command was used for propensity matching and the xtgee command was used for the sensitivity analysis.

RESULTS

We identified 109, 559 patients from a total of 568 centers, of whom 46,042 received venovenous ECMO and were ultimately included in the cohort (Fig. 1 for cohort selection processes). Seven hundred ninety-seven patients (2.8%) were categorized as undergoing awake cannulation.

Baseline Characteristics

As compared with patients who were receiving mechanical ventilation at time of cannulation, patients who underwent awake cannulation were older (mean age, 52.2 vs. 47.8 yr), with a lower mean BMI (29.1 vs. 31.5), a higher prevalence of chronic lung diseases (50.6% vs. 48.9%), and had more ischemic heart disease at baseline (4.3% vs. 2.7%). Patients cannulated awake had better pre-extracorporeal life support clinical parameters including lower rates of vasopressor support (21.5% vs. 55.0%), renal replacement therapy (2.1% vs. 8.1%), and were more likely to have been cannulated as a bridge to transplant (35.1% vs. 4.7%). See a summary of patients' and baseline characteristics in **Table 1** and **Table E1** (http://links.lww.com/CCX/B433).

Patient Outcomes

Among 797 patients cannulated while awake, 520 (65.2%) survived to hospital discharge compared with 15,787 (56.7%) of those cannulated while receiving mechanical ventilation ($p < 0.001$). After propensity score matching, there was no association between awake cannulation and hospital survival (2.4% increased rate of survival for patients cannulated awake, 95% CI, –1.7% to 6.4%; $p = 0.26$; see **Table E2** and **Fig. F1** [http://links.lww.com/CCX/B433] for details of matching success). Results from the sensitivity analysis were similar (adjusted odds ratio [aOR], 1.1; 95% CI, 0.94–1.36; $p = 0.18$). Of those patients who were discharged alive, 263 patients (33.0%) who were cannulated awake were

TABLE 1.
Patient Demographics and Characteristics

Variable	Awake Cannulation (797)	Nonawake Cannulation (27,830)	Total (28,627)
Age, mean (SD)	52.2 (14.4)	47.8 (14.4)	47.9 (14.4)
Body mass index, mean (SD)	29.1 (9.9)	31.5 (10.6)	31.4 (10.6)
Sex, *n* (%)			
Female	280 (35.1)	9,742 (35.0)	10,022 (35.0)
Unknown	1 (0.1)	61 (0.22)	62 (0.22)
Race, *n* (%)			
Asian	66 (8.28)	2,883 (10.4)	2,949 (10.3)
Black	84 (10.5)	3,394 (12.2)	3,478 (12.2)
Hispanic	81 (10.2)	3,131 (11.3)	3,212 (11.2)
Middle Eastern or North African	8 (1.0)	801 (2.9)	809 (2.8
Multiple	68 (8.5	1,613 (5.8)	1,681 (5.9)
Native American	4 (0.5)	179 (0.6)	183 (0.6)
Native Pacific Islander	2 (0.3)	54 (0.2)	56 (0.2)
Other	10 (1.3)	611 (2.2)	621 (2.2)
Unknown	36 (4.5)	1,064 (3.8)	1,100 (3.8)
White	438 (55.0)	14,100 (52.7)	14,538 (53.8)
COVID-19 positive	148 (18.6)	9,846 (35.3)	7,994 (34.9)
Pre-extracorporeal life support hemodynamics			
Mean arterial pressure (mm Hg), mean (SD)	85.8 (18.0)	77.1 (17.0)	77.3 (17.0)
pH, mean (SD)	7.35 (0.14)	7.25 (0.14)	7.26 (0.14)
Pa_{O_2}, mean (SD)	113.8 (104.1)	82.6 (65.7)	83.2 (66.9)
P_{CO_2}, mean (SD)	52.5 (21.0)	63.4 (22.8)	63.2 (22.9)
Oxygen requirement (Pa_{O_2}/F_{IO_2}), median (interquartile range)	91 (62.7–173.3)	70.5 (56.3–95.6)	71 (56.7–96.7)
Vasopressor support, *n* (%)	171 (21.5)	15,312 (55.0)	15,483 (54.1)
Renal replacement therapy, *n* (%)	17 (2.1)	2,267 (8.1)	2,284 (8.0)
Bridge to transplant, *n* (%)	280 (35.1)	1,316 (4.7)	1,596 (5.6)

discharged to home as compared with 5716 patients (20.5%) cannulated while on mechanical ventilation.

Four hundred six patients (50.9%) in the awake cannulated group were placed on mechanical ventilation within 24 hours of cannulation. Awake patients cannulated with the goal of lung transplantation and those not receiving vasopressors at time of cannulation were less likely to be placed on mechanical ventilation within 24 hours (aOR, 0.2; 95% CI, 0.14–0.33; $p < 0.01$ for potential transplant recipients and aOR, 1.9; 95% CI, 1.23–2.83; $p = 0.003$ for those receiving vasopressors). Hospital survivors who were cannulated awake had shorter post-cannulation durations of hospital stay (median, 24.0 d [12.7–44.0 d] vs. 24.4 d [12.4–43.7 d]; adjusted geometric mean difference, 0.86 d; 95% CI, 0.79–0.95; $p < 0.002$). Patients cannulated awake who survived to hospital discharge also had fewer number of hours on ECMO (median, 159 hr [63–356 hr] vs. 230 hr [123–449 hr]; adjusted geometric mean difference, 0.72 hr; 95% CI, 0.61–0.84; $p < 0.01$) (**Table 2**).

TABLE 2.
Outcomes

Outcomes	Awake Cannulation	Nonawake Cannulation	Total
Primary outcome, *n* (%)			
In-hospital survival	520 (65.2)	15,787 (56.7)	16,307 (57.0)
Intubated at 24 hr	406 (50.9)	27,830 (100)	28,221 (98.6)
Secondary outcomes, median (interquartile range)			
Extracorporeal membrane oxygenation duration in survivors (d)	159 (63–356)	230 (123–449)	227 (121–447)
Hospital length of stay in survivors (d)	37 (21–63)	36 (22–58)	36 (22–59)
Post-cannulation hospital length of stay (d)	24.0 (12.7–44.0)	24.4 (12.4–43.7)	24.4 (12.4–43.7)
Lung transplanted, *n* (%)	94 (11.8)	485 (1.7)	579 (2.0)
Discharge location of survivors, *n* (%)			
Home	263 (33.0)	5,716 (20.5)	5,979 (21.0)
Other, unknown	33 (4.1)	2,361 (8.5)	2,394 (8.4)
Transfer to LTAC	22 (2.8)	1,233 (4.4)	1,255 (4.4)
Transfer to LTAC or rehabilitation	66 (8.3)	1,958 (7.0)	2,024 (7.1)
Transfer to rehabilitation	70 (8.8)	2,014 (7.2)	2,084 (7.3)
Transfer to hospice	6 (0.8)	126 (0.5)	132 (0.5)
Transfer to another hospital	50 (6.3)	2,868 (10.3)	2,918 (10.2)

LTAC = long-term acute care.

A maximum level of mobilization of greater than or equal to 3 was more common in the population of patients cannulated while awake as compared with those cannulated while receiving mechanical ventilation (225 [28.2%] patients vs. 2579 [9.3%] patients). The incidence of complications while on ECMO including neurologic, pulmonary, and limb complications were all numerically lower in the patients cannulated while awake. See **Table 3** for more details on mobilization and complications.

Lung Transplant Subgroup

A total of 1596 patients (5.6%) of the overall cohort were cannulated with intent of pursuing lung transplant. Within the subgroup cannulated as a bridge to lung transplant, 280 patients (35.1%) were cannulated while awake and 1316 patients (4.7%) were cannulated while on mechanical ventilation. There was no difference in survival to discharge after propensity matching (5% lower rate of survival for patients cannulated awake; 95% CI, –0.15 to 0.05; $p = 0.32$). Of those who survived to discharge, patients cannulated awake and patients cannulated on mechanical ventilation had a similar duration of post-cannulation length of stay (median, 29.4 d [IQR, 15.0–56.3 d] if cannulated awake vs. median 34.1 d [IQR, 15.2–34.1 d] if cannulated while on mechanical ventilation; adjusted geometric mean difference, 1.0 d; 95% CI, 0.84–1.20 d; $p = 0.9$). Patients cannulated awake who survived to hospital discharge had more hours on ECMO that was not significant after adjusting for disease severity (273 hr [IQR, 138.0–524.5 hr] as compared with 268 hr [IQR, 116.0–597.0 hr]; adjusted geometric mean difference, 1.12 hr; 95% CI, 0.82–1.52 hr; $p = 0.48$). Patients cannulated awake were more likely to achieve a maximum level of mobilization of greater than or equal to 3 (136 [48.6%] vs. 321 [24.4%]). Of those cannulated awake 94 (11.8%) underwent lung transplant as compared with 485 (1.7%) (**Table 4**).

Epidemiology of Awake Cannulation Use

The proportion of patients cannulated awake varied substantially by site, ranging from 0% to 9.4% of

TABLE 3.
Complications

Complication	Awake Cannulation	Non Awake Cannulation	Total
Hemorrhagic complications, *n* (%)	113 (14.2)	4619 (16.6)	4732 (16.5)
Pulmonary complications, *n* (%)	61 (7.7)	3080 (11.1)	3141 (11.0)
Neurologic complications, *n* (%)	30 (3.8)	2037 (7.3)	2067 (7.2)
Cardiac complications, *n* (%)	97 (12.2)	4555 (16.4)	4652 (16.3)
Renal complications, *n* (%)	155 (19.4)	8865 (31.9)	9020 (31.5)
Limb complications, *n* (%)	8 (1.0)	337 (1.2)	345 (1.2)
Mechanical complications, *n* (%)	170 (21.3)	6870 (24.7)	7040 (24.6)
Mobilized on extracorporeal membrane oxygenation (ICU mobility level > 2), *n* (%)	225 (28.2)	2579 (9.3)	2804 (9.8)

TABLE 4.
Lung Transplant Subgroup

Outcomes	Awake Cannulation, 280 (35.1%)	Nonawake Cannulation, 1316 (4.7%)	Total, 1596 (5.58%)
Primary outcome			
In-hospital survival, *n* (%)	158 (56.4)	711 (54.0)	869 (54.5)
Mobilized on ECMO (ICU mobility level > 2), *n* (%)	136 (48.6)	321 (24.4)	465 (29.1)
Post-cannulation hospital LOS (d), median (IQR)	29.4 (15.0–56.3)	34.1 (15.2–34.1)	33.0 (15–63.6)
ECMO duration in transplant recipients (hr), median (IQR)	273 (138–524.5)	268 (116–597)	270 (118–579)
Hospital LOS (d), median (IQR)	44 (24.5–77.5)	48 (24–82)	46 (24–81)

ECMO = extracorporeal membrane oxygenation, IQR = interquartile range, LOS = length of stay.

cases and from 0% to 8.9% of the cases when the cohort was limited to patients who were cannulated with intent to pursue lung transplant. This information is presented visually in **Figure F2** (http://links.lww.com/CCX/B433; for all comers) and **Figure F3** (http://links.lww.com/CCX/B433; when the cohort is restricted to potential lung transplant recipients). Use of awake cannulation has increased over time from the years 2016–2022 (15/1725 cannulations [0.9%] in 2016 to 158/3168 cannulations [5.0%] and in 2022 [aOR, 6.9; 95% CI, 1.3–37.7; $p < 0.025$). This trend also held among a cohort of patients cannulated for lung transplant (1/98 cannulations [1.0%] in 2016 to 52/254 cannulations [20.5%] and in 2022 [aOR, 6.9; 95% CI, 1.3–37.7; $p = 0.03$) (**Figs. F4** and **F5**, http://links.lww.com/CCX/B433).

In the sensitivity analysis excluding patients from the years 2020–2022 (n = 16,862 patients excluded), results were similar to the primary analysis. After propensity score matching, there was no association between awake cannulation and hospital survival (4.0% increased rate of survival for patients cannulated awake; 95% CI, –3.0% to 13.0%; $p = 0.30$). Results from the GEE sensitivity analysis were similar (aOR, 1.1; 95% CI, 0.85–1.50; $p = 0.41$).

DISCUSSION

Our study aimed to investigate the outcomes of veno-venous ECMO patients based on ventilation status at time of cannulation, comparing those cannulated while "awake" vs. those cannulated while receiving mechanical ventilation. We found similar rates of hospital survival but shorter post-cannulation hospital length of stay and ECMO duration in the awake cannulation subgroup. Substantial site-to-site variability

exists for use of awake cannulation, although the incidence of awake cannulation has been generally increasing over time. Approximately half of patients cannulated awake are receiving mechanical ventilation at 24 hours. In the subgroup of patients cannulated with plans for lung transplantation, the incidence of awake cannulation was higher than for patients on venovenous ECMO as bridge to recovery, and awake cannulation was associated with an increased rate of lung transplantation.

"Awake" venovenous ECMO cannulation has been suggested as an approach to care that preserves the benefits of spontaneous breathing, limits trauma and complications related to endotracheal intubation, and may reduce the need for high doses of sedative medications (8). In a cohort of patients with cardiogenic shock, awake venoarterial cannulation was associated with improved mortality, potentially related to lower rates of pneumonia (3). Previous studies of awake cannulation in venovenous ECMO support have generally been small, single-center, and focused solely on the bridge-to-transplant population. These studies found an association between awake cannulation and improved survival. One study of patients who underwent lung transplant found that the small proportion who received ECMO support without invasive mechanical ventilation (0.5% of the cohort) had better outcomes than those who received either ECMO with invasive mechanical support or those who received invasive mechanical support alone (5). During the pandemic, a small study of 18 patients with severe acute respiratory syndrome-related coronavirus who were cannulated awake did not show any survival benefit when compared with patients cannulated while on mechanical ventilation (9). Conversely, in the present study, point-estimates favored awake cannulation although there was no significant difference in mortality after multivariable adjustment. While patients cannulated awake did spend less time on ECMO support after cannulation and were more likely to be mobilized, our null findings with respect to mortality may reflect the more diverse, multicenter population included in the present cohort as compared with the single-center studies previously reported.

Awake cannulation in the studied cohort was uncommon overall but increasing in incidence over time, with substantial site-to-site variation in use. This finding held for both the population as a whole and for the subgroup of patients cannulated as a bridge to lung transplant. The high variation in use of awake cannulation, coupled with the finding that half of awake cannulation patients are receiving mechanical ventilation at 24 hours, highlights a key knowledge gap in the optimal approach to patient selection for awake cannulation. In our study, receipt of vasopressors at the time of cannulation was associated with a higher risk of receiving mechanical ventilation at 24 hours and awake cannulation as bridge-to-transplant was associated with a lower risk of mechanical ventilation. Future work should expand on our results to better understand reasons for site-to-site variation in awake cannulation and to identify predictors of awake cannulation success.

Our findings provide supportive evidence for the theory that awake cannulation improves the ability to mobilize patients. Twenty-eight percent of patients cannulated awake in our study achieved an ICU mobilization score of greater than or equal to 3 as compared with 9% of those not cannulated awake. While this finding is hypothesis generating only, it warrants further investigation as a potential mechanism of the shorter ECMO duration and higher rates of lung transplantation seen in awake cannulated patients in this cohort.

This study has a number of strengths—most importantly, it is the largest study to date examining awake cannulation for venovenous ECMO and includes patients from a number of different hospitals contributing to the ELSO registry. The study also has several weaknesses. First, the relatively small sample size of awake patients may have led to a statistical type 2 error wherein a small, but significant association between awake cannulation and mortality was incorrectly rejected. Another limitation is the potential misclassification of patients. We defined our "awake" cohort as patients who were documented as having "No Ventilator" at the time of cannulation and who had no intubation procedure documented; however, it is possible that misclassification occurred due to errors in data entry, which could have affected the categorization of patients in our analysis. Future research with larger sample sizes and prospective study designs is warranted to further elucidate the impact of awake cannulation on patient outcomes in venovenous ECMO. Finally, we were limited by the data available

in the registry and were therefore unable to further compare specific causes of respiratory failure.

In summary, in this large, multicenter cohort, cannulation for venovenous ECMO while awake was uncommon but has been increasing in incidence over time. Patients cannulated awake have unique clinical features, are often placed on mechanical ventilation within 24 hours and are equally likely to survive until hospital discharge as patients cannulated while on mechanical ventilation. Awake cannulation is associated with a shorter duration of post-cannulation length of stay and increased rates of mobility. These important findings highlight knowledge gaps for potential future studies.

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Dr. Mohamed conceived the presented idea. Drs. Mohamed and Moskowitz processed the data, performed the analysis, drafted the article, and designed the figures. All authors provided critical feedback and helped shape the research analysis and article.

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