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RESEARCH REPORT

Neurological Complications During Venoarterial Extracorporeal Membrane Oxygenation and Their Implications for 6-Month Patient-Centered Outcomes

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OBJECTIVES: Venoarterial extracorporeal membrane oxygenation (ECMO) is associated with neurologic complications but their impact on long-term outcomes are poorly understood. Our objective was to assess the association of neurologic complications with death and new disability at 6 months.

DESIGN: Prospective, multicenter, observational study.

SETTING: Thirty ECMO centers in Australia and New Zealand between February 2019 and December 2022.

SUBJECTS: seven hundred four adult patients admitted to the ICU on venoarterial ECMO other than for extracorporeal cardiopulmonary resuscitation.

INTERVENTIONS: None.

MEASUREMENT AND MAIN RESULTS: Patients were divided according to whether they experienced neurologic complications. Neurologic complications include diffuse cerebral ischemia, stroke, cerebral hemorrhage, and brain death. The primary outcome was a composite of death or new disability at 6 months. Secondary outcomes included disability measured by the World Health Organization Disability Assessment Schedule and quality of life measured with EuroQoL 5D five levels. The median age of patients was 54.5 years (42–64 yr) and 259 (36.8%) were female. The primary outcome was available for 613 of 706 patients (86.2%). Of these, 425 patients (69.3%) had either died or had new disability at 6 months. Neurologic events occurred in 85 patients (12%). Patients who experienced neurologic complications were at increased risk of death or new disability (risk difference [RD], 17.28% [6.44–25.92%]). This was primarily due to an increased risk of mortality RD, 23.75 (12.06–34.75) rather than new disability (RD, −11.90% [−30.58% to 13.56%]). These findings were consistent across types of complications and after adjustment for confounders. Patients with neurologic complications more commonly had ECMO discontinued due to a perceived poor prognosis (odds ratio, 2.7; 95% CI, 1.35–24.7).

CONCLUSIONS: Neurologic complications during ECMO increased the risk of death and disability at 6 months, primarily driven by increased death at 6 months. Prevention of these complications and development of better prognostic tools for functional outcomes should be prioritized.

KEYWORDS: bleeding; complications; extracorporeal membrane oxygenation

Cardiogenic shock (CS) is a medical emergency characterized by reduced cardiac output with organ hypoperfusion. It has a 40–90% mortality rate depending on the underlying etiology, patient characteristics, and response to treatment (1). The use of venoarterial extracorporeal membrane

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KEY POINTS

Question: Are neurologic complications during venoarterial extracorporeal membrane oxygenation (ECMO) associated with an increase in 6-month mortality and disability.

Findings: This prospective observational study of 704 venoarterial ECMO patients at 30 Hospitals in Australia and New Zealand demonstrated that neurologic complications occurred in over 10% of patients and increased the risk of death and new disability at 6 months, primarily due to an increased risk of death. Nonsurvivors commonly had support stopped due to a predicted poor prognosis.

Meaning: There is a need to reduce neurologic complications during ECMO to improve patient outcomes and for better prognostic tools in this group.

oxygenation (ECMO) for refractory CS has increased substantially in the last 10 years (2). Despite increased experience and improved circuit and pump technology, neurologic complications remain common (3, 4).

Recently, a venoarterial ECMO core outcome set, developed by consumers and clinicians, identified neurologic complications as one of the most important complications in this support modality (5). While there are many existing reports on types and rates of venoarterial ECMO complications, data on their effect on longer-term functional outcomes post-hospital discharge are limited (2, 6). Therefore, we conducted an analysis of our binational ECMO registry to assess the impact of neurologic complications on longer-term survival, disability, and quality of life in patients who have received venoarterial ECMO support for CS.

MATERIALS AND METHODS

Study Design and Setting

This was a prospective, multicenter, registry-embedded cohort study of patients receiving venoarterial ECMO in Australian and New Zealand ICUs. The study was performed in accordance with the Strengthening Reporting of Observational Studies in Epidemiology statement (7).

Participants

All adult patients (≥ 18 yr old) receiving venoarterial ECMO at participating sites between February 18, 2019, and June 30, 2022, were eligible for inclusion. Patients receiving venoarterial ECMO-assisted extracorporeal cardiopulmonary resuscitation (ECPR), defined as active chest compressions during cannulation, were excluded due to the difference in the nature of the neurologic insult. For those with multiple venoarterial ECMO runs, only the first run was included. Those patients who had a change in ECMO configuration during their run were included if their first run was on venoarterial ECMO.

Data Source

The EXCEL Registry (a Comprehensive Binational Registry on the Treatment and Outcomes of Patients Requiring ECMO) is a binational registry, across 30 sites in Australia and New Zealand, that prospectively collects baseline, clinical, and outcome data on all ECMO patients from participating institutions (ClinicalTrials.gov NCT03793257).

Ethical Approval

Ethical approval was obtained under the national mutual agreement from the Alfred Human Research Ethics Committee on November 28, 2018 (Project Title: The EXCEL registry ID: HREC 534/18), including a waiver of consent for hospital data and opt-out consent for 6-month follow-up (The Alfred HREC Project title 534/18). All sites completed governance approval before commencement to ensure study were performed according to relevant state and institutional requirements. All study procedures are in line with the declaration of Helsinki.

Data Collection

Data collection processes have been outlined in detail previously (8). In brief, data were collected by trained research coordinators at participating sites and data monitoring was also conducted to ensure data quality. Baseline pre-ECMO data included demographics, cardiac arrest, diabetes status, frailty, and physiologic parameters on the day of admission to ICU. Data were also collected for severity of illness and risk prediction scores, physiologic and laboratory parameters, and

pharmacological interventions including sedation and vasoactive drugs. ECMO cannulation details, ECMO and mechanical ventilation settings, adjunctive therapies in ICU, and adverse events were also collected. Death was confirmed in-hospital from the medical records by research coordinators or by telephone contact with next-of-kin at 6 months after ECMO initiation. Patients surviving the hospital admission were contacted by mail and phone. Patient-reported disability and health status were assessed using the 12-level World Health Organization Disability Assessment Schedule 2.0 (WHODAS) questionnaire and the EuroQoL 5D five levels (EQ-5D-5L) score at 6 months by telephone using trained central assessors. Data were collected from hospital admission until 6 months after ECMO initiation or death, whichever occurred first.

Exposure and Outcomes Definitions

The primary outcome was a composite of death or new disability at 6 months post-ECMO commencement. New disability was defined as an increase greater than or equal to 10% in the WHODAS at 6 months compared with baseline. Baseline disability was assessed at the 6 months follow-up interview asking patients or carers to report the participants function before hospital admission. Other secondary outcomes included survival at hospital discharge and 6 months, hospital length of stay, and disability at 6 months defined as a WHODAS of greater than or equal to 25%. Additional 6-month functional outcomes were quality of life measured by EuroQoL Visual Analogue Scale (EuroQoL VAS) and EQ-5D-5L and the Katz instrumental activities of daily living (IADL) with a score of 6 classified as fully independent and 0 as fully dependent. In addition, the EQ-5D-5L utility score was calculated using U.K. population EQ-5D-5L health status norms, as at the time of analysis, these were not available for Australia.

A neurologic complication included intracranial hemorrhage, ischemic stroke, hypoxic-ischemic encephalopathy, and brain death. All forms of cerebral hemorrhage were combined into a category of cerebral hemorrhage. With the exception of brain death all complications required imaging confirmation but the performance of neuroimaging was at the discretion of the treating clinician, it is not known whether brain death was confirmed clinically or by radiological testing. Detailed definitions are available in the electronic supplementary material (**Exposure Definitions**, https://links.lww.com/CCM/H832). All complication data were censored at ICU discharge or 7 days following ECMO discontinuation or death, whichever occurred first. Patients who experienced multiple neurologic complications during ECMO were only counted once.

Statistical Analysis

Continuous variables are reported as median and interquartile range (IQR), and categorical variables are reported as number and percentage. To compare categorical variables, we used the Fisher exact tests; to compare continuous variables, we used the Wilcoxon rank-sum tests (for two groups) or the Kruskal-Wallis test (for three or more groups). To estimate the effect of neurologic complications on the primary outcome and other categorical outcomes, we fit generalized linear models with an identity link for univariate analyses and performed a linear mixed-effect regression for adjusted analyses. Data on 180-day mortality, time to first complication, and the time from first complication to death were compared between groups using a log-rank test and are presented as Kaplan-Meier curves. All time intervals were taken from the point of ECMO initiation. When estimating the association of neurologic complications on death patients with brain death were excluded. For continuous outcomes, we performed univariable and multivariable median regression using an interior point algorithm. For all adjusted models age, Acute Physiology and Chronic Health Evaluation (APACHE) IV score, episode of cardiac arrest pre-ECMO, Charlson comorbidity score, use of renal replacement therapy before ECMO, lactate before ECMO, and diagnosis were chosen a priori based on available evidence and clinical rationale. For the mixed-effects regression model site was included as a random effect. No imputation was performed for missing data. As cardiac arrest was expected to be strongly associated with neurologic complications and mortality, we performed a sensitivity analysis excluding patients with cardiac arrest pre-ECMO. We also performed a further sensitivity analysis in which seizures were classified as neurologic complications.

RESULTS

Baseline Patient Characteristics

Within the study period, 706 patients required veno-arterial ECMO support and had full complication data (**Fig. 1**); 259 of 704 (36.8%) were female; and median

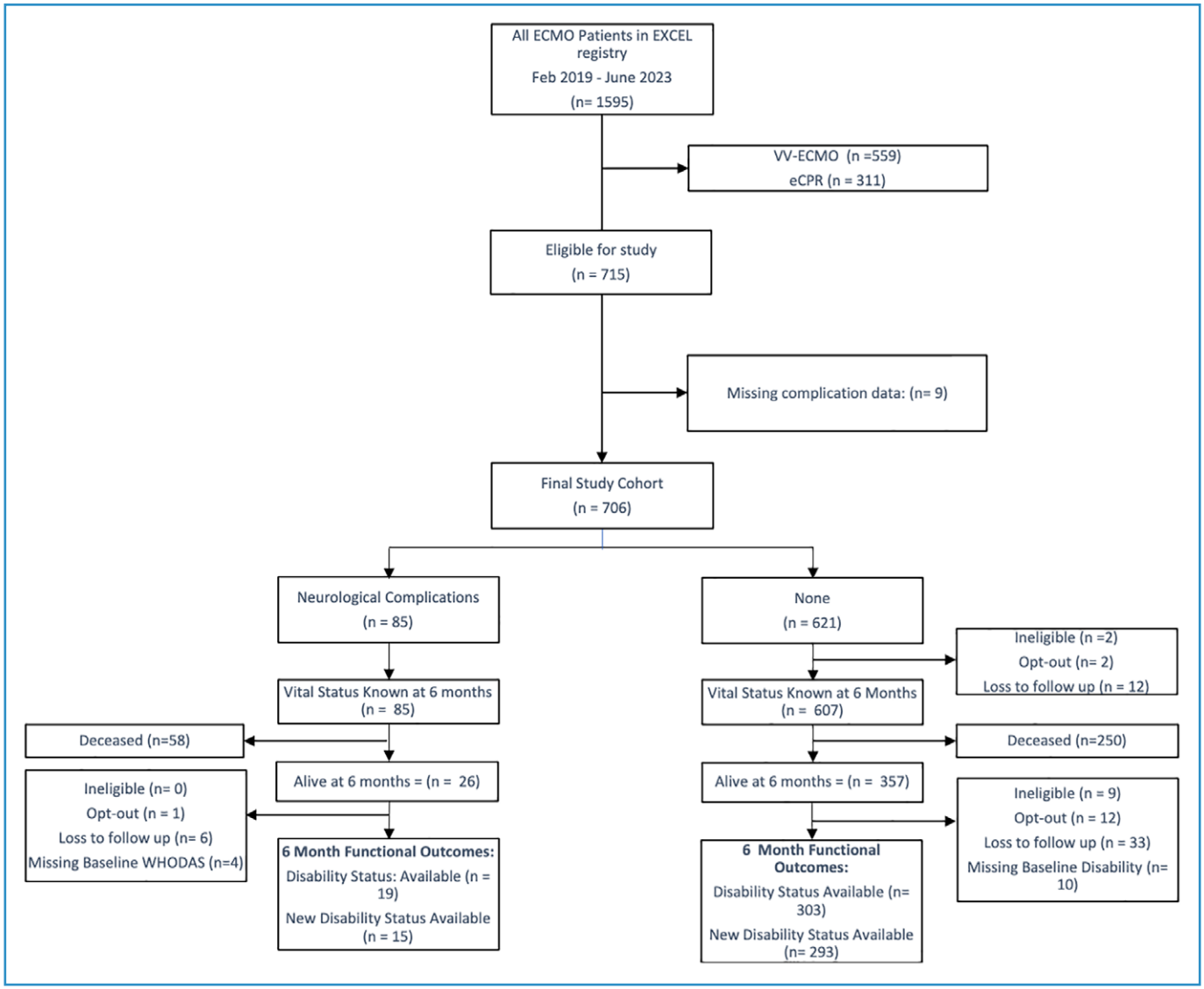

Figure 1. Flow of patients through study. ECMO = extracorporeal membrane oxygenation, ECPR = extracorporeal cardiopulmonary resuscitation, EXCEL = a Comprehensive Binational Registry on the Treatment and Outcomes of Patients Requiring ECMO, VV = venovenous, WHODAS = World Health Organization Disability Assessment Schedule.

age 54.5 years (IQR, 42–64 yr) and body mass index 27.2 (IQR, 23.8–31.5). The median Survival After Venoarterial ECMO and APACHE IV scores were –4.0 (IQR, –8 to –1) and 79 (IQR, 59–104), respectively, and the median duration of venoarterial ECMO support was 4.9 days (IQR, 2.9–7.9 d). The most common indications for venoarterial ECMO support were post-cardiotomy 186 (27%) and acute myocardial infarction 155 (22.6%). Twenty-three patients (3.3%) required venoarterial ECMO support for COVID-19-related myocardial dysfunction. The median lactate before venoarterial ECMO initiation was 5.2 (IQR, 2.5–9.1) and was highest in patients with neurologic complication 7.2 (IQR, 3.1–10.1). One hundred ninety patients had a cardiac arrest before ECMO (27.1%). Additional baseline characteristics can be found in **eTable 1** (https://links.lww.com/CCM/H832). Details of missing data are available in **eTable 2** (https://links.lww.com/CCM/H832). Details of the ECMO support patients received on the first day of ECMO therapy are available in **eTable 3** (https://links.lww.com/CCM/H832).

Neurologic Events

Eighty-five of 706 patients receiving venoarterial ECMO (12%) developed neurologic complications, of whom 52 (61.2%) had an ischemic stroke, 21 (24.7%) had diffuse ischemia, 9 (10.6%) had cerebral

hemorrhage, and 3 (3.5%) brain death. Patients with neurologic complications more often suffered a pre-ECMO cardiac arrest 32 of 85 (38.6%) compared with 158 of 621 patients (25.6%) without neurologic complications (p = 0.017). There were no differences in the proportion of patients with supplementary cardiac supports (**Table 1**). There appeared to be differences in the timing of neurologic complications with hypoxic brain injury occurring earlier than bleeding and stroke, although these were not statistically significant (**Fig. 2*B***). Ischemic stroke complications continued to occur at a continuous rate up to day 40.

Primary Outcome: Death or New Disability at 6 Months

Primary outcome data was available for 613 of 706 patients (86.8%). Of these, 425 of 613 patients (69.3%) had either died or had new disability at 6 months (including 308 patients [72.4%] who died and 117 [27.5%] patients who experienced new disability). Patients who experienced neurologic complications were at significantly increased risk of the primary outcome at 6 months risk difference (RD), 17.28% (6.44–25.92%). This association persisted after adjusting for illness severity and treating center (**Table 2** and **Fig 3**). This effect, however, was not consistent across both components of the primary outcome. While patients with neurologic complications did have an increased risk of mortality adjusted RD, 23.75 (12.06–34.57), there was no increase in the risk of new disability adjusted RD, –11.90% (–30.58% to 13.56%). When considering the subgroups of neurologic complication, each of these was significantly associated with an increased risk of the primary outcome after adjustment for illness severity. The effect was strongest for hypoxic-ischemic encephalopathy and least strong for ischemic stroke. In the sensitivity analysis excluding patients with pre-ECMO cardiac arrest and including patients with seizures, the pattern of the results was unchanged; however, the results were no longer significant for the individual components due to wide CIs (**eFigs. 1** and **2**, https://links.lww.com/CCM/H832).

Mortality at 6 Months and Complications

The majority of deaths occurred during the index hospital admission with only 15 of 308 deaths (4.0%) occurring between hospital discharge and 6-month follow-up. At 6 months, 58 patients (69.0%) with a neurologic event had died compared with 250 (41.5%) of those without these complications. There was a significantly increased risk of 6-month mortality for those experiencing a neurologic complication compared with those with no complication (**Fig. 2*A***). There were significant differences in the risk of death across the three subgroups of neurologic complication and patients who experienced hypoxic ischemic injury appeared to die sooner after their complication than those with stroke and cerebral hemorrhage (**Fig. 2*C***). There were also differences in the proximate cause of death between groups. Among 37 of 58 (63.8%) of those with neurologic complications who died, the proximate cause of death was due to neurologic causes, whereas CS accounted for the majority of the deaths in the those without neurologic complications (**eTable 4**, https://links.lww.com/CCM/H832). Furthermore, patients with neurologic complications were also more likely to have ECMO discontinued due to poor prognosis (odds ratio, 2.7; 95% CI, 1.35–24.7; **eTable 5**, https://links.lww.com/CCM/H832). When excluding patients with pre-ECMO cardiac arrest, the association of the complication with 6-month mortality was consistent with the primary analysis.

Disability and Complications at 6 Months

The proportion of new disability was numerically lower among patients with neurologic complications than those without these complications (26.7 vs. 38.6%), although these differences were not statistically significant (**Table 3**). After adjustment for illness severity, there remained no significant association between neurologic complications and new disability RD, 4.02 (–18.75 to 26.36). The median WHODAS score and the proportion of participants with disability (WHODAS ≥ 25%) were similar among those with and without neurologic complications, although the overall proportion of survivors with disability was high (34.2%; Table 3). The neurologic complications groups seemed to have more new disability in cognitive and emotional domains (**eFig. 3**, https://links.lww.com/CCM/H832).

Additional Functional Outcomes at 6 Months

There was no difference in health-related quality of life as measured by EQ-5D-5L scores, EuroQol VAS score or in the proportion of patients who were independent according to the KATZ IADL score between those with

TABLE 1.
Baseline Characteristics

Variable	Overall (*n* = 706)	None[a] (*n* = 621)	Neurologic (*n* = 85)	*p*
Age, yr	54.5 (42.0–64.0)	54.0 (42.0–64.0)	55.0 (42.5–62.5)	0.629
Female gender, *n* (%)	259 (36.8)	227 (36.6)	32 (38.1)	0.810
Transferred on ECMO, *n* (%)	146 (20.8)	116 (18.7)	30 (35.7)	0.001
Acute Physiology and Chronic Health Evaluation IV	79.0 (59.0–104.0)	78.0 (59.0–103.0)	84.5 (66.0–111.0)	0.199
Survival After Venoarterial ECMO score	−4.0 (−8.0 to −1.0)	−4.0 (−8.0 to −1.0)	−4.0 (−9.0 to −1.0)	0.990
COVID-19, *n* (%)	23 (3.3)	20 (3.2)	3 (3.6)	0.748
Cardiac arrest pre-ECMO, *n* (%)	190 (27.1)	158 (25.6)	32 (38.6)	0.017
Charlson comorbidity score	2.0 (1.0–4.0)	2.0 (1.0–4.0)	2.0 (1.0–3.0)	0.575
Respiratory diagnosis, *n* (%)				0.234
Acute respiratory distress syndrome	7 (33.3)	7 (38.9)	0 (0.0)	
Post-lung transplant	8 (38.1)	6 (33.3)	2 (66.7)	
Focal lung disease	1 (4.8)	0 (0.0)	1 (33.3)	
Drug/toxin pulmonary disease	2 (9.5)	2 (11.1)	0 (0.0)	
Asthma	1 (4.8)	1 (5.6)	0 (0.0)	
Chronic end stage lung disease	2 (9.5)	2 (11.1)	0 (0.0)	
Cardiac diagnosis, *n* (%)				0.179
Acute myocardial infarction	155 (22.6)	132 (21.9)	23 (28.0)	
Myocarditis	44 (6.4)	38 (6.3)	6 (7.3)	
Toxic	11 (1.6)	10 (1.7)	1 (1.2)	
Septic shock with myocardial depression	20 (2.9)	20 (3.3)	0 (0.0)	
Pulmonary embolism	55 (8.0)	49 (8.1)	6 (7.2)	
Advanced pulmonary hypertension	15 (2.2)	15 (2.5)	0 (0.0)	
Congenital heart disease	4 (0.6)	4 (0.7)	0 (0.0)	
Primary arrhythmia (“channelopathy”)	12 (1.7)	11 (1.8)	1 (1.2)	
Chronic graft (heart) dysfunction	6 (0.9)	6 (1.0)	0 (0.0)	
Chronic cardiomyopathy, not covered above	40 (5.8)	35 (5.8)	5 (6.0)	
Acute decompensated heart failure, not covered above	141 (20.5)	129 (21.3)	12 (14.5)	
Post-cardiotomy	186 (27.0)	157 (25.9)	29 (34.9)	
Invasive ventilation	608 (86.6)	528 (85.4)	80 (95.2)	0.010
Renal replacement therapy	102 (14.6)	91 (14.7)	11 (13.3)	0.868
ECMO configuration				
Additional mechanical support, *n* (%)	146 (20.7)	129 (20.8)	17 (20.0)	1.000
Central cannulation, *n* (%)	97 (14.5)	89 (15.1)	8 (10.0)	0.308
pH	7.3 (7.2–7.4)	7.3 (7.2–7.4)	7.3 (7.1–7.3)	0.133
$Paco_2$, mm Hg	40.0 (33.0–48.0)	40.1 (33.0–48.0)	39.5 (34.0–47.4)	0.888
Lactate, mmol/L	5.2 (2.5–9.1)	4.9 (2.4–8.8)	7.2 (3.1–10.1)	0.019

ECMO = extracorporeal membrane oxygenation.
[a]No neurologic complication.
Data are median (25th–75th interquartile range) and *n* (%).

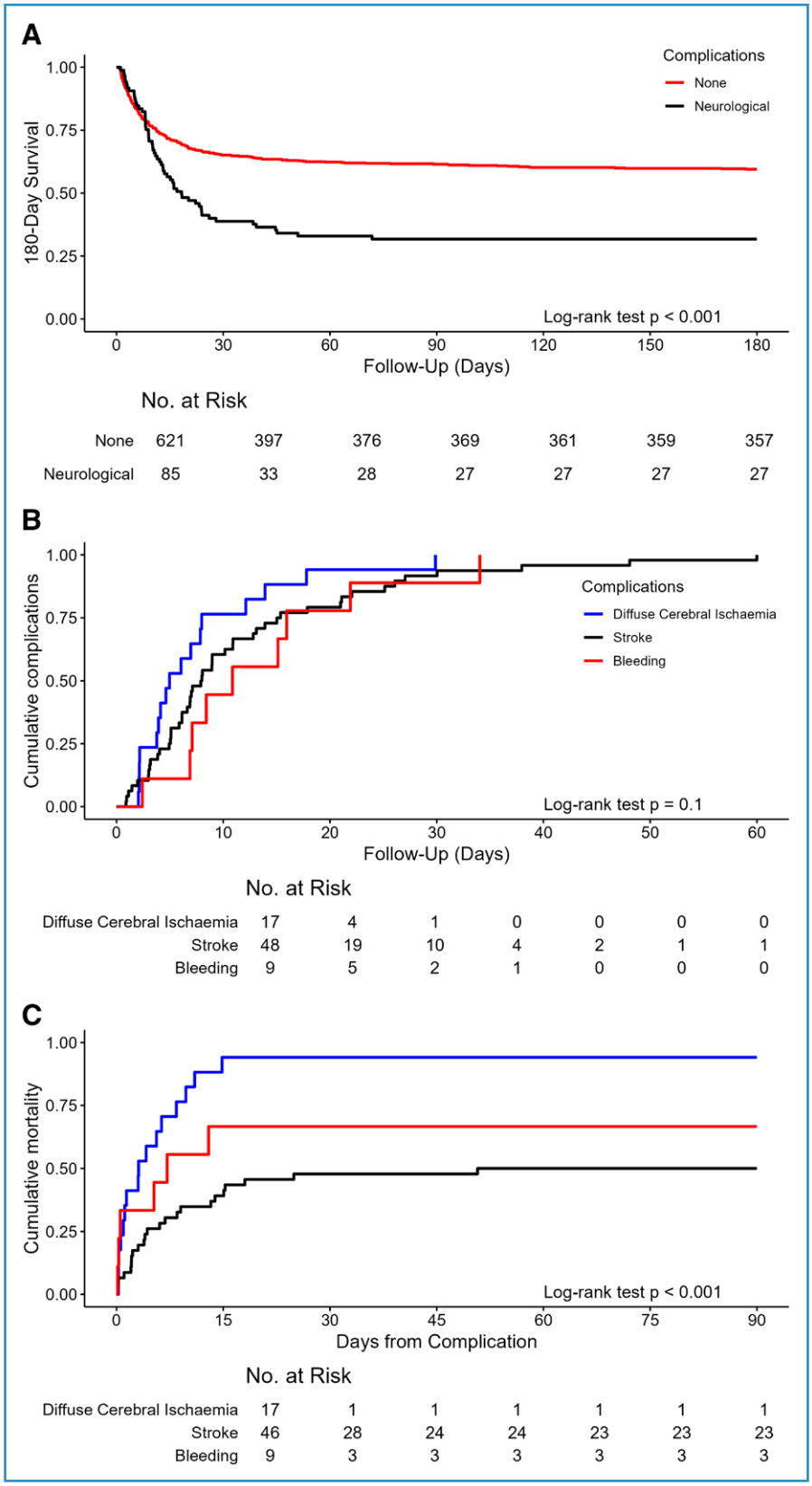

Figure 2. Time to event analyses. **A**, Kaplan-Meier graphs of survival to day 180 for entire study cohort. **B**, Cumulative event graph for time to first complication among those experiencing complications. **C**, Cumulative events graph for time to death after occurrence of a complication. Follow-up = days from extracorporeal membrane oxygenation initiation.

and without complications (Table 3). On multivariate analysis, neurologic events were not associated with a difference in quality of life in survivors of ECMO (Table 2).

Other Hospital Outcomes

The median length of stay in ICU for patients overall was 13.0 days (IQR, 6.8–22.9 d). Surviving patients with neurologic complications had a length of stay that was nearly twice that of the other groups (Table 3).

In the unadjusted analyses, neurologic complications were also associated with an increased use of renal replacement therapy, and a 2.35 days (1.09–1.91 d) increase in the duration of ECMO this persisted after adjustment for confounders. The length of ICU and hospital stay were also longer for those with neurologic complications, although this was only statistically significant for survivors (Table 2).

DISCUSSION

Summary of Findings

In this binational cohort of veno-arterial ECMO patients, we found that neurologic complications were not uncommon (12%). Hypoxic-ischemic encephalopathy was the most common neurologic complication, followed by ischemic stroke and intracranial hemorrhage was the least common complication. Neurologic complications were associated with increased ECMO duration, use of other organ supports, and ICU and hospital stay. At 6 months, neurologic complications were associated with an increased risk of death or new disability—predominantly driven by a higher mortality rate in those with neurologic complications and not by an

TABLE 2.
Analyses for Outcomes

Outcome	None[a] (*n* = 620)		Neurologic (*n* = 84)	
	Unadjusted Effect Estimate (95% CI)	*p*	Adjusted Effect Estimate (95% CI)	*p*
Primary outcome and components				
Death or new disability at 6 mo	1 (reference)	RD 17.28 (6.44–25.92)	0.001	RD 22.31 (10.21–34.11)	< 0.001
Mortality at 6 mo	1 (reference)	RD 23.75 (12.06–34.57)	< 0.001	RD 25.71 (14.37–36.90)	< 0.001
New disability	1 (reference)	RD −11.90 (−30.58 to 13.56)	0.312	RD 4.02 (−18.75 to 26.36)	0.734
Additional hospital outcomes				
Change in ECMO mode	1 (reference)	RD −3.00 (−6.19 to 2.43)	0.141	RD −2.26 (−7.51 to 3.03)	0.412
Renal replacement therapy	1 (reference)	RD 14.35 (3.62–23.38)	0.005	RD 6.94 (−3.87 to 18.16)	0.216
Duration of ECMO, d	1 (reference)	MD 2.22 (1.02–1.80)	< 0.001	MD 2.53 (1.31–3.75)	< 0.001
ICU length of stay[b], d	1 (reference)	MD 1.84 (−1.39 to 4.88)	0.264	MD 2.58 (0.58–4.58)	0.012
Survivors	1 (reference)	MD 9.82 (−0.92 to 16.21)	0.074	MD 7.06 (−4.23 to 18.35)	0.221
Nonsurvivors	1 (reference)	MD 4.70 (1.66–4.59)	0.003	MD 4.40 (2.22–6.59)	0.000
Hospital length of stay, d	1 (reference)	MD −5.39 (−11.48 to 9.20)	0.084	MD −1.62 (−7.56 to 4.32)	0.592
Survivors	1 (reference)	MD 12.23 (−14.04 to 39.68)	0.362	MD 10.40 (−12.66 to 33.46)	0.377
Nonsurvivors	1 (reference)	MD 5.25 (2.08–4.78)	0.001	MD 4.26 (1.98–6.53)	< 0.001
ICU mortality	1 (reference)	RD 23.03 (11.25–34.22)	< 0.001	RD 24.24 (12.98–35.26)	< 0.001
Hospital mortality	1 (reference)	RD 25.63 (13.93–36.53)	< 0.001	RD 26.07 (14.79–37.18)	< 0.001
6-mo outcomes				
World Health Organization Disability Assessment Schedule score, %	1 (reference)	MD −0.00 (−19.40 to 29.30)	1.000	MD −5.47 (−18.97 to 8.04)	0.428
Disability	1 (reference)	RD 8.44 (−12.49 to 31.23)	0.469	RD 4.03 (−18.75 to 26.36)	0.733
EuroQol Visual Analogue Scale score	1 (reference)	MD −5.00 (−16.36 to 17.15)	0.389	MD −6.18 (−14.85 to 2.50)	0.164
EuroQol 5D five levels utility score	1 (reference)	MD 0.01 (−0.06 to 0.11)	0.782	MD 0.04 (−0.01 to 0.09)	0.094
Instrumental activities of daily living		MD −1.00 (−3.08 to 3.13)	0.346	MD 0.00 (−0.94 to 0.94)	1.00
Fully dependent	1 (reference)	RD, 10.63 (−1.43 to 30.99)	0.148	RD, 7.17 (−3.86 to 18.05)	0.212
Fully independent	1 (reference)	RD −4.18 (−26.06 to 18.33)	0.724	RD −1.12 (−24.96 to 22.81)	0.929

ECMO = extracorporeal membrane oxygenation, MD = median difference, RD = risk difference.

[a]No neurologic complication.

[b]In survivors.

Models adjusted for: age, sex, Acute Physiology and Chronic Health Evaluation IV, cardiac arrest pre-ECMO, Charlson comorbidity score, renal replacement therapy, before ECMO, lactate before ECMO, and diagnosis.

increased rate of new disability. Patients with neurologic complications more often had ECMO discontinued due to poor prognosis and commonly had the neurologic condition listed as the proximate cause of death.

Comparison With Previous Literature

Effect of Complications on 6-Month Mortality. The frequency of neurologic events while on venoarterial ECMO are well described and occur in 2–10% of

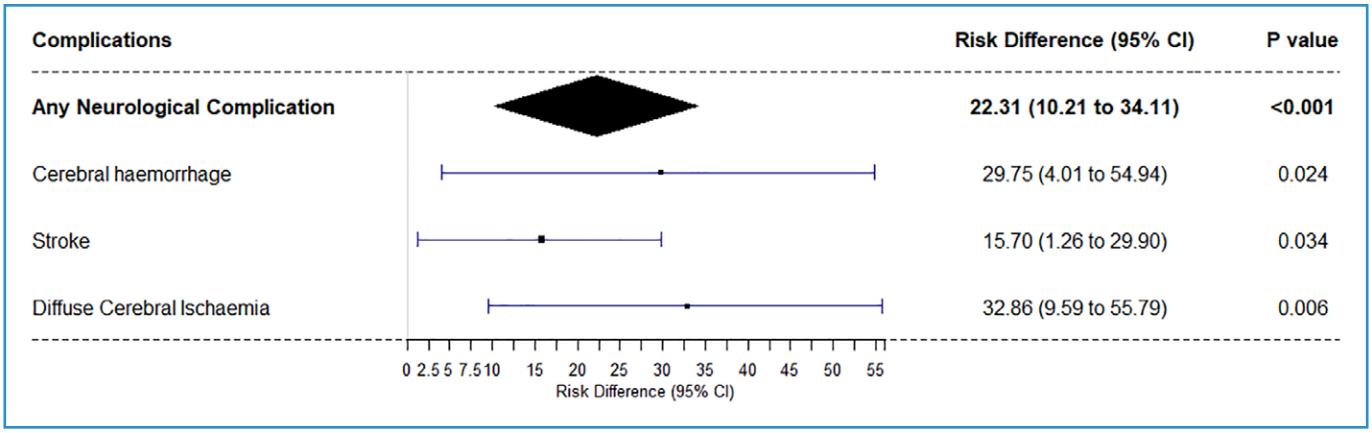

Figure 3. Adjusted effects of neurologic complications on risk of death and new disability at 6 mo. Results are risk differences from linear mixed-effects model adjusted for age, Acute Physiology and Chronic Health Evaluation IV score, renal replacement therapy pre-extracorporeal membrane oxygenation (ECMO), cardiac arrest pre-ECMO, final diagnosis, and lactate as fixed effect with center as a random effect.

patients (9, 10). Our data demonstrated neurologic events in 12%, which is slightly higher than previous studies (4, 11–13). This increased rate could be due to either an increase events or the capture of asymptomatic neurologic events identified on imaging. While neurologic events are reported to negatively affect survival to hospital discharge (4, 14–16), there exists limited long-term survival data for venoarterial ECMO patients (6) and extremely limited functional assessments post-discharge (17). Our study confirmed a strong association of neurologic events on hospital and 6-month mortality. Importantly, little additional mortality was seen post-hospital discharge and, therefore, the survival decrement reported was driven by death during hospitalization and predominantly in the ICU. This suggests that hospital or 28-day mortality may be a reasonable surrogate for longer-term mortality in venoarterial ECMO patients. Among those with neurologic complications, ECMO was often stopped due to a perceived poor prognosis, death occurred soon after the complication, and the proximate cause of death was commonly recorded as neurologic. Although we do not have direct data on this, it is therefore probable that a high proportion of patients with neurologic injury underwent withdrawal of life-sustaining therapy. This complicates the interpretation of the association of these complications with mortality as has been previously observed and may explain the low level of new disability in survivors (18).

Complications and 6-Month Functional Outcomes. Data on longer-term functional outcomes in ECMO patients is lacking. We have previously reported new disability at 6 months in over a third of ECMO survivors, a finding consistent with the current data (8). There was no statistically significant difference in median WHODAS score or the proportion of survivors with new disability between those with and without complications. Paradoxically, the point estimates for the association of neurologic complications with new disability suggested a lower prevalence of new disability in these patients. The reason for this is uncertain; however, it may relate to higher rate of loss to follow-up among survivors with neurologic events causing an ascertainment bias, or a higher rate of withdrawal of life support in those with neurologic injury resulting in a survivor bias. It is also possible that among survivor's cognitive issues may have affected the accuracy of their responses to follow-up questions. However, patients with neurologic complications show a nonstatistically significant trend to be more likely to be fully dependent at 6 months (Table 3). Consistent with our previous findings, despite a high proportion of patients describing disability at 6 months, the perceived quality of life of patients as demonstrated by EQ-5D-5L and EuroQol VAS scores did not differ between groups and were not dissimilar to population norms (19).

Implications. Our findings suggest that neurologic complications are strongly associated with mortality and significant increases in resource utilization in ECMO patients and therefore prevention of these, if possible, should be a research priority. It is unclear whether hypoxic brain injury should be considered a complication of ECMO or a complication of the disease state; however, our sensitivity analysis that excluded

TABLE 3.
Outcomes

Outcome	Overall (*n* = 706)	None (*n* = 621)	Neurologic (*n* = 85)	*p*
Primary outcome				
Death or new disability[a] at 6 mo, *n* (%)	425/613 (69.3)	363/541 (67.1)	62/72 (86.1)	0.001
Mortality at 6 mo, *n* (%)	308/692 (44.5)	250/607 (41.2)	58/85 (68.2)	< 0.001
New disability[a], *n* (%)	117/308 (38.0)	113/293 (38.6)	4/15 (26.7)	0.264
Additional hospital outcomes				
Change in ECMO mode[b], *n* (%)	39/706 (5.5)	35/621 (5.6)	4/85 (4.7)	1.000
Renal replacement therapy, *n* (%)	463/694 (66.7)	400/612 (65.4)	63/82 (76.8)	0.045
Duration of ECMO[c], d	4.9 (2.9–7.9)	4.8 (2.8–7.6)	6.8 (4.0–11.7)	< 0.001
ICU length of stay, d	13.0 (6.8–22.9)	13.0 (6.2–22.8)	14.1 (7.7–25.1)	0.219
Survivors	16.6 (10.8–27.9)	16.1 (10.4–27.6)	25.9 (15.3–47.9)	0.002
Nonsurvivors	6.2 (2.1–13.7)	5.4 (1.7–12.8)	9.8 (6.0–15.8)	0.002
Hospital length of stay, d	21.4 (8.1–40.8)	22.6 (8.3–40.9)	15.7 (7.7–35.6)	0.248
Survivors	32.9 (21.1–52.1)	32.4 (21.0–49.6)	43.4 (26.8–80.2)	0.039
Nonsurvivors	6.9 (2.3–15.1)	5.7 (1.9–14.1)	10.0 (6.6–17.0)	0.002
ICU mortality, *n* (%)	282/706 (39.9)	228/621 (36.7)	54/85 (63.5)	< 0.001
Hospital mortality, *n* (%)	293/706 (41.5)	236/621 (38.0)	57/85 (67.1)	< 0.001
Additional 6-mo outcomes				
World Health Organization Disability Assessment Schedule score, %	14.6 (6.2–31.2)	14.6 (6.2–31.2)	14.6 (4.2–39.6)	0.828
Disability, *n* (%)	110/322 (34.2)	102/303 (33.7)	8/19 (42.1)	0.462
EuroQol Visual Analogue Scale score[d]	75.0 (60.0–85.0)	75.0 (60.0–85.0)	70.0 (60.0–82.5)	0.693
EuroQol 5D five levels utility score[e]	0.8 (0.7–0.9)	0.8 (0.7–0.9)	0.8 (0.7–0.8)	0.916
Instrumental activities of daily living[f]	8.0 (6.0–8.0)	8.0 (6.0–8.0)	7.5 (4.2–8.0)	0.436
Fully dependent, *n* (%)	18/310 (5.8)	15/291 (5.2)	3/19 (15.8)	0.089
Fully independent, *n* (%)	159/310 (51.3)	150/291 (51.5)	9/19 (47.4)	0.815

ECMO = extracorporeal membrane oxygenation.
[a]Defined as an increase of 10% or more in World Health Organization Disability Assessment Schedule score from baseline.
[b]Change in ECMO mode available for 692 patients.
[c]ECMO duration available for 685 patients.
[d]EuroQol available for 322 patients.
[e]EuroQol 5D five levels available for 322 patients.
[f]Katz instrumental activities of daily living available for 310 patients.
Data are median (25th–75th interquartile range) and *n* (%).

patients with pre-ECMO arrest still demonstrated the same association. The mechanisms of increased mortality following neurologic events may be due in part to withdrawal of treatment, which complicates the interpretation of observational data in this setting. This emphasizes the need for objective tools to aid clinicians when prognosticating outcomes in this group. Finally, clinicians can be reassured that among the selected group of ECMO survivors who have experienced neurologic injury the long-term functional outcomes are similar to other ECMO survivors.

Strength and Limitations

This study has several strengths. First, data were drawn from a prospectively collected, nationally representative database, with experienced data collectors and routine monitoring to ensure data quality. All complications were prospectively defined and standardized

across sites and according to a core outcome set where available (5). We included long-term functional outcomes, which is rare, with assessments performed by trained assessors centrally using tools that have been validated in survivors of critical illness (8). Despite these strengths, our study has several limitations. First, as an observational study, there remains the possibility of residual confounding. Second, as the sample size was determined by the number of participants in the registry, it is possible that our study was underpowered to detect clinically significant effects of disability. Third, the rate of follow-up was lower among survivors with neurologic events. Combined with the effect of treatment withdrawal, this may have introduced a selection bias resulting in an underestimation of the effect of neurologic events on disability. There is also a risk of recall bias as baseline function was also collected at the 6 months follow-up call. Fourth, the diagnosis of a neurologic complication was based on radiological findings, and the decision to perform imaging was at clinical discretion. It is, therefore, possible that this introduced an ascertainment bias whereby some asymptomatic lesions were discovered incidentally, while other asymptomatic lesions were not discovered. In the future, standardized neuroimaging protocols would reduce this issue. Fifth, our sample size limited the ability to examine the relationships between type and severity of CNS injury and disability, which would be a valuable area of future research. Sixth, as this is observational data and neurologic events are recorded up to 7 days after ECMO discontinuation, we cannot be certain of the cause of the neurologic events. We acknowledge that the inclusion of hypoxic-ischemic encephalopathy as a complication of ECMO is contentious; however, it was prospectively collected in our registry as such, and a sensitivity analysis, in which patients with cardiac arrest were excluded was consistent with our primary analysis. Finally, we did not include ECPR, as the frequency and nature of neurologic injury may be very different to other venoarterial ECMO patients.

CONCLUSIONS

Neurologic complications during ECMO increased the risk of death and disability at 6 months, which was primarily driven by increased death in the hospital. Prevention of these complications and better tools to prognosticate ECMO patients with hypoxic brain injury should be a research priority to improve clinical outcomes.

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The EXCEL (a Comprehensive Binational Registry on the Treatment and Outcomes of Patients Requiring ECMO) Study Investigators and the International ECMO Network are listed in the ***Online Supplement*** *(https://links.lww.com/CCM/H832).*

REFERENCES

1. Fux T, Holm M, Corbascio M, et al: VA-ECMO support in nonsurgical patients with refractory cardiogenic shock: Pre-implant outcome predictors. *Artif Organs* 2019; 43:132–141
2. Thiagarajan RR, Barbaro RP, Rycus PT, et al; ELSO member centers: Extracorporeal life support organization registry international report 2016. *ASAIO J* 2017; 63:60–67
3. Burrell AJC, Bennett V, Serra AL, et al; International ECMO Network (ECMONet): Venoarterial extracorporeal membrane oxygenation: A systematic review of selection criteria, outcome

measures and definitions of complications. *J Crit Care* 2019; 53:32–37

4. Aubron C, DePuydt J, Belon F, et al: Predictive factors of bleeding events in adults undergoing extracorporeal membrane oxygenation. *Ann Intensive Care* 2016; 6:97
5. Hodgson CL, Burrell AJC, Engeler DM, et al; International ECMO Network: Core outcome measures for research in critically ill patients receiving extracorporeal membrane oxygenation for acute respiratory or cardiac failure: An international, multidisciplinary, modified Delphi consensus study*. *Crit Care Med* 2019; 47:1557–1563
6. Berger R, Nemeth A, Boburg RS, et al: Long-term follow-up of survivors of extracorporeal life support therapy for cardiogenic shock: Are they really survivors? *Medicina* 2022; 58:427
7. STROBE: Strengthening the Reporting of Observational Studies in Epidemiology. Available at: https://www.strobe-statement.org/. Accessed December 11, 2023
8. Hodgson CL, Higgins AM, Bailey MJ, et al; EXCEL Study Investigators on behalf of the International ECMO Network and the Australian and New Zealand Intensive Care Society Clinical Trials Group: Incidence of death or disability at 6 months after extracorporeal membrane oxygenation in Australia: A prospective, multicentre, registry-embedded cohort study. *Lancet Respir Med* 2022; 10:1038–1048
9. Guennec LL, Cholet C, Huang F, et al: Ischemic and hemorrhagic brain injury during venoarterial-extracorporeal membrane oxygenation. *Ann Intensive Care* 2018; 8:129
10. Omar HR, Mirsaeidi M, Shumac J, et al: Incidence and predictors of ischemic cerebrovascular stroke among patients on extracorporeal membrane oxygenation support. *J Crit Care*; 32:48–51
11. Cheng R, Hachamovitch R, Kittleson M, et al: Complications of extracorporeal membrane oxygenation for treatment of cardiogenic shock and cardiac arrest: A meta-analysis of 1,866 adult patients. *Ann Thorac Surg* 2014; 97:610–616
12. Sy E, Sklar MC, Lequier L, et al: Anticoagulation practices and the prevalence of major bleeding, thromboembolic events, and mortality in venoarterial extracorporeal membrane oxygenation: A systematic review and meta-analysis. *J Crit Care* 2017; 39:87–96
13. Rajsic S, Treml B, Jadzic D, et al: Extracorporeal membrane oxygenation for cardiogenic shock: A meta-analysis of mortality and complications. *Ann Intensive Care* 2022; 12:93
14. Lorusso R, Barili F, Mauro MD, et al: In-hospital neurologic complications in adult patients undergoing venoarterial extracorporeal membrane oxygenation. *Crit Care Med* 2016; 44:e964–e972
15. Hou D, Wang H, Yang F, et al: Neurologic complications in adult post-cardiotomy cardiogenic shock patients receiving venoarterial extracorporeal membrane oxygenation: A cohort study. *Front Med* 2021; 8:721774
16. Cho S-M, Canner J, Chiarini G, et al: Modifiable risk factors and mortality from ischemic and hemorrhagic strokes in patients receiving venoarterial extracorporeal membrane oxygenation: Results from the extracorporeal life support organization registry. *Crit Care Med* 2020; 48:e897–e905
17. Luo Y, Gu Q, Wen X, et al: Neurological complications of veno-arterial extracorporeal membrane oxygenation: A retrospective case-control study. *Front Med* 2021; 8:698242
18. Sutter R, Tisljar K, Marsch S: Acute neurologic complications during extracorporeal membrane oxygenation. *Crit Care Med* 2018; 46:1506–1513
19. McCaffrey N, Kaambwa B, Currow DC, et al: Health-related quality of life measured using the EQ-5D–5L: South Australian population norms. *Health Qual Life Out* 2016; 14:133