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Functional Status of Neonatal and Pediatric Patients after Extracorporeal Membrane Oxygenation

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Abstract

Objective—To describe functional status at hospital discharge for neonatal and pediatric patients treated with extracorporeal membrane oxygenation (ECMO), and identify factors associated with functional status and mortality.

Design—Secondary analysis of observational data collected by the Collaborative Pediatric Critical Care Research Network (CPCCRN) between December 2012 and September 2014.

Setting—Eight hospitals affiliated with the CPCCRN.

Patients—Patients were <19 years of age and treated with ECMO.

Interventions—Functional status was evaluated among survivors using the Functional Status Scale (FSS). Total FSS scores range from 6–30 and are categorized as 6–7 (good), 8–9 (mildly abnormal), 10–15 (moderately abnormal), 16–21 (severely abnormal) and >21 (very severely abnormal).

Measurements and Main Results—Of 514 patients, 267 (52%) were neonates (<30 days old). Indication for ECMO was respiratory for 237 (46%), cardiac for 207 (40%) and extracorporeal cardiopulmonary resuscitation (eCPR) for 70 (14%). Among 282 survivors, 89 (32%) had good, 112 (40%) mildly abnormal, 67 (24%) moderately abnormal, and 14 (5%) severely or very severely abnormal function at hospital discharge. Among neonates, development of renal failure and longer hospitalization were independently associated with worse FSS. Chronic conditions, prematurity, venoarterial ECMO, increased red cell transfusion in the first 24 hours of ECMO, and longer ECMO duration were independently associated with mortality. Among pediatric patients, chronic neurologic conditions, tracheostomy or home ventilator, eCPR, hepatic dysfunction and longer intensive care unit stay were independently associated with worse FSS. Chronic cardiac conditions, hepatic dysfunction, and neurologic or thrombotic complications were independently associated with mortality. Achieving blood lactate concentration <2 mmol/L during ECMO was independently associated with survival in both neonatal and pediatric patients.

Conclusions—In this study, about half of ECMO patients survived with good, mildly abnormal or moderately abnormal function at hospital discharge. Patient and ECMO related factors are associated with functional status and mortality.

Keywords

Extracorporeal Membrane Oxygenation; Functional Status Scale; Extracorporeal Life Support Organization; child; infant; neonate

INTRODUCTION

Extracorporeal membrane oxygenation (ECMO) is a widely used form of mechanical circulatory support for neonatal and pediatric patients with refractory respiratory and cardiac failure. The use of ECMO continues to grow with an increasing number of ECMO centers and additional applications for use (1). ECMO remains a highly invasive therapy with substantial cost and complications. The morbidity and mortality associated with ECMO is due to both the underlying disease processes that lead to ECMO as well as the use of ECMO itself.

Neonatal and pediatric ECMO patients are at risk of neurologic injury due to both pre-ECMO factors (e.g., hypoxia, acidosis, low cardiac output, organ failure) and ECMO factors (arterial cannulation, thrombosis, hemorrhage, seizures, and disrupted cerebral circulation) (2–5). Most reports of neurologic outcome following ECMO focus on acute neurologic complications and rely on data from the Extracorporeal Life Support Organization (ELSO) registry (6, 7). The ELSO registry contains data from almost 300 centers regarding indications for ECMO, complications and outcomes. A recent ELSO registry report suggests acute neurologic complications including seizures occur in 20–25% of neonatal and pediatric ECMO patients (1). While informative, the ELSO registry does not include details of many clinical factors that potentially contribute to neurologic morbidity.

Neurologic morbidity has lasting effects on the functional status of survivors of critical illness. Until recently, morbidity outcomes in large pediatric studies have been limited due to a lack of rapid and reliable assessment tools applicable to the wide age range of pediatric patients. The Pediatric Overall Performance Category (POPC) and Pediatric Cerebral Performance Category (PCPC) scales are subjective scales used to assess overall functional morbidity and cognitive impairment, respectively (8). POPC and PCPC are scored on a six-point scale of increasing disability ranging from normal (score=1) to death (score=6). Although commonly used, the POPC and PCPC are limited in the amount of information they provide. The Functional Status Scale (FSS) is a recently developed tool that evaluates six functional domains using more objective definitions for all domain categories than the POPC and PCPC (9). In a recent study, the FSS correlated well with the POPC and PCPC scales (10); however, the FSS is more granular thereby providing more precise estimates of functional status. The objective of this study is to describe the overall functional status at hospital discharge of a large cohort of neonatal and pediatric ECMO patients using the FSS, and identify factors associated with functional status and mortality.

METHODS

Design and Setting

The study was a secondary analysis of data collected for the Bleeding and Thrombosis during ECMO (BATE) study (unpublished data) which aimed to describe the incidence of bleeding and thrombosis in neonatal and pediatric ECMO patients. In the BATE study, observational data was collected prospectively at eight hospitals affiliated with the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network between December 2012 and September 2014. The study was approved with waiver of informed consent by the Institutional Review Boards for each hospital and the Data Coordinating Center at the University of Utah.

Study Population

All patients less than 19 years of age treated with ECMO in a neonatal, pediatric or cardiac intensive care unit (ICU) were included (n=514). Only the initial ECMO course was included for patients who required multiple courses of ECMO.

Data Collection

All data was collected daily by trained research coordinators via direct observation, discussion with bedside clinicians, and review of medical records. Data included demographics; primary diagnosis; chronic diagnoses; history of prematurity; baseline technology dependence; body habitus; indications for ECMO; mode of ECMO; Vasoactive Inotrope Score (VIS) (11,12) at time of ECMO initiation; blood lactate concentration closest and prior to ECMO initiation; highest blood lactate and lowest pH during the first 24 hours of ECMO; days from ECMO initiation until blood lactate concentration was ≤ 2 mmol/L; estimated volume of packed red blood cells (PRBC) transfused during the first 24 hours of ECMO; complications during ECMO; duration of ECMO, and ICU and hospital stay; survival to hospital discharge; and functional status at hospital discharge among survivors.

Demographics included age at ECMO initiation, gender, race and ethnicity. Patients ≤ 30 days of age were categorized as neonatal and those >30 days as pediatric. Prematurity was <37 weeks gestational age at birth and was collected for neonates only. Technology dependence included dependence on a gastrostomy or other feeding tube, supplemental oxygen, or tracheostomy or mechanical ventilator used at home prior to the hospitalization in which ECMO was initiated. Body habitus was assessed using body mass index-for-age (BMI-for-age) percentiles for patients ≥ 2 years of age, and weight-for-length percentiles for patients <2 years of age. BMI-for-age and weight-for-length percentiles were determined using the patient's age, gender, weight and length and resources from the U.S. Centers for Disease Control and Prevention (13). Patients were categorized as obese if their BMI-for-age or weight-for-length were $\geq 95^{\text{th}}$ percentile, and underweight if $<5^{\text{th}}$ percentile.

Indications for ECMO were categorized as respiratory, cardiac or extracorporeal cardiopulmonary resuscitation (eCPR). Mode of ECMO was categorized as venoarterial (VA) or venovenous (VV). VV ECMO that was converted to VA was categorized as VA ECMO. VIS (11, 12) was calculated from the hourly dose of dopamine, dobutamine, epinephrine, milrinone, vasopressin and norepinephrine administered at time of ECMO initiation. Estimated volume of PRBC transfused during the first 24 hours of ECMO was determined as the actual volume of PRBC + $(40/70) \times$ volume of whole blood transfused. The conversion factor for whole blood was based on whole blood and PRBCs having estimated hematocrits of 40% and 70%, respectively.

Complications during ECMO were categorized as neurologic events, renal failure, hepatic dysfunction, thrombotic events and bleeding events occurring on at least one ECMO day. Neurologic events included seizures (clinical or electrographic), intracranial hemorrhage or infarction, and brain death. Renal failure was defined as creatinine >2 mg/dL (>176.8 $\mu\text{mol/L}$) or use of renal replacement therapy. Hepatic dysfunction was defined as International Normalized Ratio (INR) >2 . Thrombotic events included intracranial infarction, limb ischemia, pulmonary embolus, intracardiac thrombus, aorto-pulmonary shunt thrombus, other sites of thrombosis, and circuit thrombosis requiring replacement of a circuit component. Bleeding events were defined as blood loss requiring a transfusion, and intracranial hemorrhage.

Functional status at hospital discharge was evaluated among survivors using the FSS (9). The FSS assesses function in 6 domains including mental, sensory, communication, motor, feeding and respiratory. Domain scores range from 1 (normal) to 5 (very severe dysfunction). Total scores range from 6–30 and are categorized as 6–7 (good), 8–9 (mildly abnormal), 10–15 (moderately abnormal), 16–21 (severely abnormal) and >21 (very severely abnormal).

Statistical Analysis

Patient and ECMO characteristics were summarized using frequencies and percentages for categorical variables and medians and quartiles for quantitative variables. Standard linear regression was used to evaluate predictors of functional status at hospital discharge among survivors. Poisson regression models with robust error estimates based on generalized estimating equations were used to evaluate predictors of mortality. Multivariable models were developed for functional status among survivors and mortality. Independent models were developed for neonatal and pediatric patients. Variables were considered potential predictors if they were associated with the outcome in univariable analysis ($p < 0.10$) and available for at least 90% of the cohort. Final models were selected using backward stepwise selection on the potential predictors with a significance criterion of $p < 0.05$ to stay in the model. No variables were forced into the model. All analyses were performed using SAS 9.4 (SAS Institute, Cary, NC).

RESULTS

Of 514 patients enrolled in the study, 267 (52%) were neonates, 302 (59%) were male, 254 (49%) were White, and 335 (65%) had a chronic condition (Table 1). Two hundred and thirty-seven (46%) received ECMO for a respiratory indication and 431 (84%) received VA ECMO. The median duration of ECMO was 5 days (3, 9 days). Two hundred and thirty-two (45%) patients died. Among survivors, 89 (32%) had good, 112 (40%) mildly abnormal, 67 (24%) moderately abnormal, 13 (5%) severely abnormal and one very severely abnormal functional outcome at hospital discharge. Further details of the neonatal and pediatric cohorts are shown in Supplemental Digital Content 1–3.

Neonates (30 days of age)

For neonatal patients, univariable analyses showed presence of a chronic condition, development of a neurologic event or renal failure, and longer durations of ICU and hospital stay were associated with worse FSS at hospital discharge among survivors (Table 2). ECMO duration < 2 days was associated with better FSS. Univariable analysis also showed presence of a chronic condition, prematurity, initiation of ECMO for cardiac indication, VA ECMO, development of a neurologic event, renal failure, hepatic dysfunction or bleeding event, and higher blood lactate concentration within the first 24 hours of ECMO were associated with increased relative risk of death. Achieving a lactate ≤ 2 mmol/L during the ECMO course, and longer durations of ICU and hospital stay were associated with decreased relative risk of death.

Multivariable analysis showed development of renal failure and longer duration of hospital stay were independently associated with worse FSS at hospital discharge among neonatal ECMO survivors (Table 3). ECMO duration <2 days was independently associated with better FSS at hospital discharge. Multivariable analysis also showed presence of a chronic condition, prematurity, VA ECMO, increased estimated volume of PRBC transfused during the first 24 hours of ECMO, and ECMO duration >9 days were independently associated with increased relative risk of death. Achieving a lactate ≤ 2 mmol/L and longer duration of hospital stay were independently associated with decreased relative risk of death.

Pediatric patients (30 days to <19 years of age)

For pediatric patients, univariable analyses showed presence of congenital anomalies or chromosomal defects, chronic neurologic conditions, baseline technology dependence (i.e., gastrostomy or feeding tube, supplemental oxygen, tracheostomy or ventilator), initiation of ECMO during eCPR, and development of hepatic dysfunction were associated with worse FSS at hospital discharge among survivors (Table 4). Number of days from ECMO initiation until lactate was ≤ 2 mmol/L, and longer ICU and hospital stay were associated with worse FSS at hospital discharge. Univariable analyses also showed primary diagnosis of cardiovascular disease or shock, chronic cardiac disease, initiation of ECMO during eCPR or for cardiac indication, development of a neurologic event, renal failure, hepatic dysfunction or thrombotic event were associated with increased relative risk of death. Higher baseline blood lactate concentration and higher blood lactate during the first 24 hours of ECMO were associated with increased relative risk of death. Higher lowest pH in the first 24 hours of ECMO and achieving a lactate ≤ 2 mmol/L during ECMO decreased the relative risk of death. Longer durations of ICU and hospital stay were associated with decreased relative risk of death.

Multivariable analysis showed presence of a chronic neurologic condition or other chronic condition (i.e., excluding congenital anomaly or chromosomal defect, cardiovascular, and respiratory conditions), baseline technology dependence (i.e., tracheostomy or ventilator), initiation of ECMO during eCPR, development of hepatic dysfunction, and longer ICU stay were independently associated with worse FSS at hospital discharge among pediatric ECMO survivors (Table 5). Multivariable analysis also showed presence of a chronic cardiovascular condition, development of hepatic dysfunction, neurologic event or thrombotic event were independently associated with increased relative risk of death. Achieving a blood lactate concentration ≤ 2 mmol/L during ECMO was independently associated with decreased relative risk of death.

DISCUSSION

In this study, about half of neonatal and pediatric patients treated with ECMO survived with good, mildly abnormal or moderately abnormal functional status at hospital discharge. Patient and ECMO characteristics reflecting increased chronicity and severity of illness were associated with worse functional status and increased mortality among both neonatal and pediatric patients. In the neonatal cohort, renal failure was independently associated with worse FSS at hospital discharge. Consistent with other studies, we also found that neonates

with prematurity, chronic conditions, and need for VA ECMO had increased mortality (14). In the pediatric cohort, the presence of a chronic neurologic condition, baseline tracheostomy or home ventilator, eCPR, and hepatic dysfunction were independently associated with worse FSS at hospital discharge. Chronic cardiovascular conditions, hepatic dysfunction, and neurologic and thrombotic events during ECMO were independently associated with increased mortality. The observation that chronic conditions lead to worse outcomes following ECMO is not surprising as prior pediatric studies have shown that patients with chronic illnesses, in general, have longer hospitalizations, and increased use of critical care services and mortality (15–17).

In addition to patient and ECMO characteristics, laboratory values such as higher blood lactate concentration prior to ECMO and during the first 24 hours of ECMO were associated with increased mortality on univariable analyses; whereas achieving a normal blood lactate level during the ECMO course was independently associated with decreased mortality in both neonatal and pediatric patients. Elevated lactate levels are often a marker of inadequate tissue oxygenation and inability to clear lactate while receiving ECMO may indicate ongoing oxygen debt. Among neonatal and pediatric patients undergoing cardiac ECMO, prior studies have shown elevated lactate more than 24–72 hours post-cannulation is associated with increased mortality (18, 19) and that the time required for lactate to normalize (<2 mmol/L) on ECMO is associated with worse cognitive outcome in survivors (20). A recent study in adults receiving VV ECMO for acute respiratory distress syndrome found increased mortality among those who failed to clear lactate within the first 72 hours of ECMO (21). These findings and ours suggest that clearance of lactate may be an important therapeutic target during ECMO.

We found that neonates with increased volume of PRBC transfusion during the first 24 hours of ECMO had increased risk of mortality. Two previous retrospective single center studies found that increasing volume of red cell transfusion over the entire ECMO course was associated with increased mortality in neonatal and pediatric patients undergoing ECMO for non-cardiac indications (22, 23). The mechanism is unclear but could reflect increased bleeding complications and the need for red cell replacement, or a secondary adverse effect of red cell transfusion such as fluid overload, immune dysfunction or acute lung injury. A randomized prospective evaluation of restrictive red cell transfusion strategies in neonatal and pediatric patients receiving ECMO for various indications may be indicated to identify best practice.

Longer duration of ICU stay was independently associated with worse FSS at hospital discharge in pediatric patients, and longer duration of ECMO and hospital stay were independently associated with worse FSS in neonatal patients. Longer ICU and hospital stay could be due to increased severity of illness on admission potentially contributing to worse functional status at discharge. Longer ECMO runs have been shown to be associated with increased complications (18, 24) which could also contribute to worse functional status. Longer durations of ICU and hospital stay were also associated with decreased mortality in our study suggesting that death occurs early in the treatment course.

Although almost half of our study patients were placed on ECMO for a respiratory indication, we found that 84% of our cohort was placed on VA ECMO. The underlying reason clinicians chose a particular mode of ECMO was not elicited in this study. Despite potential benefits of VV ECMO in many situations, our findings reflect actual clinical practice at CPCCRN sites. VA ECMO appears to be the preferred mode even for respiratory cases.

Strengths of this study include the multicenter design and daily prospective collection of data from all ECMO patients during the study period. Strengths also include the use of the FSS to evaluate functional status among survivors.

Limitations include the lack of pre-illness FSS assessment obviating change in FSS as a potential outcome variable. Many patients placed on ECMO have chronic underlying conditions that affect their baseline functional status. Therefore, some of the functional deficits identified at hospital discharge among ECMO survivors were not new but were present prior to their ECMO course. Nevertheless, FSS at hospital discharge among ECMO survivors appears worse than reported for other intensive care populations where hospital discharge FSS has been evaluated. In a large general pediatric ICU population, 92% of patients survived to hospital discharge with good, mildly abnormal, or moderately abnormal functional status as assessed by the FSS (25). In a recently reported cohort of patients <18 years of age admitted to an ICU with acute traumatic brain injury and either a Glasgow Coma Scale (GCS) (26) score ≥ 12 or a neurosurgical procedure in the first 24 hours, 78% survived to hospital discharge with good, mildly abnormal, or moderately abnormal hospital discharge FSS (27). Among the subgroup with GCS ≤ 8 , 68% survived to hospital discharge with good, mildly abnormal, or moderately abnormal hospital discharge FSS. Other limitations of our study include the collection of laboratory values (e.g., lactate) only when needed for clinical care rather than as indicated by a study protocol. Although a large number of associations were evaluated, not all factors potentially related to ECMO outcomes were considered.

CONCLUSION

In this study, about half of neonatal and pediatric ECMO patients survived with good, mildly abnormal or moderately abnormal functional status at hospital discharge. Patient characteristics reflecting increased chronicity and severity of illness are associated with reduced functional status and mortality. Potentially modifiable factors associated with mortality include lactate clearance and volume of red cell transfusion during ECMO.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Description of Cohort

Characteristic	Overall (N = 514)
Neonate^a	267 (52%)
Male	302 (59%)
Race	
Black or African American	91 (18%)
White	254 (49%)
Other	26 (5%)
Unknown or Not Reported	143 (28%)
Hispanic or Latino	86 (17%)
Premature^b	50 (10%)
Weight for neonates only (g): Median [Q1, Q3]	3100 [2780, 3450]
Chronic diagnosis	335 (65%)
Primary ECMO indication^c	
Respiratory	237 (46%)
Cardiac	207 (40%)
ECPR ^d	70 (14%)
VA ECMO^e	431 (84%)
Duration of ECMO (days): Median [Q1, Q3]	5 [3, 9]
Length of hospital stay (days): Median [Q1, Q3]	36 [16, 68]
Length of ICU stay (days): Median [Q1, Q3]	28 [14, 51]
FSS at hospital discharge^f	
Good	89 (17%)
Mildly abnormal	112 (22%)
Moderately abnormal	67 (13%)
Severely abnormal	13 (3%)
Very severely abnormal	1 (0%)
Not applicable (dead)	232 (45%)

^aNeonate is <30 days of age;

^bPremature is <37 weeks gestational age at birth and was collected for neonates only;

^cECMO is extracorporeal membrane oxygenation;

^dECPR is extracorporeal cardiopulmonary resuscitation;

^eVA is venoarterial;

^fFSS is Functional Status Scale

Table 2

Univariate Analyses for Neonatal Cohort

Characteristic	Outcome			
	Death		FSS ^a (among survivors)	
	Relative risk ^b (95% CI)	P-value	Effect ^c (95% CI)	P-value
Indication for ECMO^d		0.03		0.29
Respiratory	Reference		Reference	
Cardiac	1.49 (1.11, 1.99)		−0.54 (−1.46, 0.39)	
ECPR ^e	1.42 (0.90, 2.25)		−1.04 (−2.60, 0.52)	
Primary diagnosis category		0.20		0.15
Respiratory	Reference		Reference	
Cardiovascular/Shock	1.29 (0.98, 1.71)		−0.73 (−1.57, 0.11)	
Other	1.34 (0.33, 5.43)		−2.86 (−7.97, 2.25)	
Chronic diagnosis	1.55 (1.14, 2.10)	<.01	1.09 (0.27, 1.90)	<.01
Congenital anomaly or chromosomal defect	1.30 (0.96, 1.76)	0.11	1.53 (0.47, 2.59)	<.01
Cardiovascular disease	1.27 (0.96, 1.67)	0.10	0.58 (−0.29, 1.44)	0.19
Other	0.94 (0.44, 2.04)	0.88	1.51 (−0.62, 3.63)	0.17
Mode of ECMO		<.01		0.11
VA ^f	Reference		Reference	
VV ^g	0.42 (0.21, 0.84)		−0.85 (−1.90, 0.20)	
Neurologic event	1.57 (1.19, 2.07)	<.01	0.98 (0.10, 1.86)	0.03
Renal organ failure	1.52 (1.16, 2.00)	<.01	1.29 (0.40, 2.18)	<.01
Hepatic organ dysfunction	1.61 (1.23, 2.11)	<.01	−0.14 (−1.10, 0.82)	0.78
Thrombotic event	1.17 (0.88, 1.55)	0.28	0.75 (−0.11, 1.61)	0.09
Bleeding event	1.65 (1.15, 2.35)	<.01	0.60 (−0.24, 1.44)	0.16
Baseline VIS^h		0.35		0.52
None	Reference		Reference	
Low	0.76 (0.52, 1.10)		0.41 (−0.73, 1.55)	
High	0.86 (0.62, 1.19)		0.64 (−0.46, 1.74)	
Prematureⁱ	1.87 (1.44, 2.42)	<.01	−0.62 (−1.97, 0.74)	0.37
Duration of ECMO (days)		0.02		<.01
< 2	1.64 (1.10, 2.44)		−1.23 (−2.51, 0.06)	
2– < 4	1.00 (0.62, 1.62)		0.95 (−0.10, 2.00)	
4– < 9	Reference		Reference	
9	1.54 (1.07, 2.21)		0.82 (−0.19, 1.84)	
ICU LOS (weeks)^j	0.87 (0.80, 0.95)	<.01	0.11 (0.05, 0.18)	<.01
Hospital LOS (weeks)	0.86 (0.79, 0.93)	<.01	0.11 (0.05, 0.16)	<.01
Body habitus		0.34		0.98
Underweight	1.14 (0.80, 1.64)		0.10 (−1.02, 1.23)	
Normal	Reference		Reference	

Characteristic	Outcome			
	Death		FSS ^a (among survivors)	
	Relative risk ^b (95% CI)	P-value	Effect ^c (95% CI)	P-value
Obese	0.64 (0.27, 1.52)		−0.03 (−1.62, 1.55)	
Baseline lactate (mmol/L)	1.02 (0.99, 1.04)	0.19	0.04 (−0.06, 0.14)	0.47
Highest lactate in 24 hours post ECMO initiation (mmol/L)	1.06 (1.04, 1.08)	<.01	−0.00 (−0.11, 0.10)	0.95
Days from ECMO initiation to lactate > 2 mmol/L	1.08 (0.99, 1.17)	0.07	0.03 (−0.23, 0.29)	0.82
Lactate > 2 mmol/L achieved	0.51 (0.39, 0.65)	<.01	0.81 (−0.47, 2.10)	0.22
Lowest pH within 24 hours post ECMO initiation	0.54 (0.18, 1.63)	0.28	1.26 (−2.08, 4.61)	0.46
Estimated PRBC in first 24 hours post ECMO initiation (dL/kg)^k	1.10 (1.05, 1.15)	0.01	0.08 (−0.33, 0.49)	0.71

^aFSS is Functional Status Score;

^bMortality was modeled using Poisson regression with robust error estimates;

^cFSS among survivors was modeled using standard linear regression;

^dECMO is extracorporeal membrane oxygenation;

^eECPR is extracorporeal cardiopulmonary resuscitation;

^fVA is venoarterial;

^gVV is venovenous;

^hVIS is Vasoactive inotropic score, None is VIS=0, Low is VIS >0 and <20, High is VIS ≥ 20;

ⁱPremature is <37 weeks gestational age at birth;

^jLOS is length of stay;

^kPRBC is packed red blood cells

Table 3

Multivariable Model for Neonatal Cohort

Characteristic	Outcome			
	Death		FSS ^a (among survivors)	
	Adjusted Relative Risk ^b (95% CI)	P-value	Adjusted Effect ^c (95% CI)	P-value
Renal organ failure	---	---	1.24 (0.33, 2.14)	<.01
Hospital LOS (weeks)^d	0.87 (0.80, 0.96)	<.01	0.09 (0.04, 0.15)	<.01
ECMO duration (days)^e		<.01		0.05
< 2	0.72 (0.49, 1.05)		-0.88 (-2.12, 0.36)	
2 – < 4	0.88 (0.58, 1.34)		0.96 (-0.06, 1.98)	
4 – < 9	Reference		Reference	
9	1.64 (1.23, 2.18)		0.06 (-0.96, 1.09)	
Chronic diagnosis	1.46 (1.14, 1.86)	<.01	---	---
Mode of ECMO		<.01	---	---
VA ^f	Reference		---	---
VV ^g	0.47 (0.26, 0.84)		---	---
Premature^h	1.36 (1.05, 1.76)	0.02	---	---
Lactate 2 mmol/L achieved	0.60 (0.44, 0.82)	<.01	---	---
Estimated PRBC in 24 hours post ECMO initiation (dL/kg)ⁱ	1.07 (1.01, 1.12)	<.01	---	---

^aFSS is Functional Status Scale;^bMortality was modeled using Poisson regression with robust error estimates;^cFSS among survivors was modeled using standard linear regression;^dLOS is length of stay;^eECMO is extracorporeal membrane oxygenation;^fVA is Venoarterial;^gVV is Venovenous;^hPremature is <37 weeks gestational age;ⁱPRBC is packed red blood cells

Table 4

Univariate Analyses for Pediatric Cohort

Characteristic	Outcome			
	Death		FSS ^a (among survivors)	
	Relative risk ^b (95% CI)	P-value	Effect ^c (95% CI)	P-value
Indication for ECMO^d		<.01		<.01
Respiratory	Reference		Reference	
Cardiac	1.42 (1.01, 2.00)		-1.09 (-2.29, 0.11)	
ECPR ^e	1.99 (1.41, 2.82)		2.39 (0.48, 4.31)	
Primary diagnosis category		<.01		0.91
Respiratory	Reference		Reference	
Cardiovascular/Shock	1.76 (1.24, 2.48)		-0.14 (-1.39, 1.10)	
Other	1.38 (0.78, 2.47)		-0.46 (-2.69, 1.76)	
Chronic diagnosis	1.18 (0.85, 1.64)	0.30	0.85 (-0.49, 2.18)	0.22
Congenital anomaly or chromosomal defect	1.22 (0.89, 1.69)	0.25	2.06 (0.25, 3.88)	0.03
Cardiovascular disease	1.30 (1.00, 1.70)	0.05	-0.97 (-2.15, 0.21)	0.11
Neurologic disease	0.89 (0.55, 1.45)	0.63	3.01 (1.12, 4.91)	<.01
Respiratory disease	1.00 (0.67, 1.50)	0.99	1.23 (-0.60, 3.07)	0.19
Other	1.14 (0.87, 1.51)	0.36	1.25 (-0.15, 2.66)	0.08
Mode of ECMO		0.13		0.85
VA ^f	Reference		Reference	
VV ^g	0.76 (0.51, 1.12)		0.14 (-1.28, 1.56)	
Neurologic event	2.37 (1.82, 3.07)	<.01	0.99 (-0.52, 2.50)	0.20
Renal organ failure	1.50 (1.17, 1.93)	<.01	1.24 (-0.10, 2.58)	0.07
Hepatic organ dysfunction	1.83 (1.43, 2.35)	<.01	2.55 (1.19, 3.90)	<.01
Thrombotic event	1.40 (1.09, 1.80)	0.01	0.00 (-1.30, 1.30)	1.00
Bleeding event	1.28 (0.92, 1.78)	0.12	0.01 (-1.28, 1.31)	0.98
Baseline VIS^h		0.19		0.88
None	Reference		Reference	
Low	0.87 (0.61, 1.22)		0.13 (-1.26, 1.53)	
High	1.18 (0.88, 1.57)		-0.26 (-1.75, 1.22)	
Baseline technology dependence				
Feeding tube	0.99 (0.72, 1.38)	0.97	2.73 (1.30, 4.15)	<.01
Ventilator or tracheostomy	1.50 (0.92, 2.45)	0.22	13.26 (9.05, 17.47)	<.01
Oxygen	1.00 (0.68, 1.48)	0.98	2.42 (0.67, 4.17)	<.01
Duration of ECMO (days)		0.71		0.63
< 2	1.23 (0.86, 1.77)		0.16 (-1.62, 1.94)	
2- < 4	1.13 (0.80, 1.59)		0.68 (-0.85, 2.20)	
4- < 9	Reference		Reference	
9	1.07 (0.74, 1.55)		0.96 (-0.63, 2.55)	
ICU LOS (weeks)ⁱ	0.98 (0.95, 1.00)	0.02	0.09 (0.03, 0.15)	<.01

Characteristic	Outcome			
	Death		FSS ^a (among survivors)	
	Relative risk ^b (95% CI)	P-value	Effect ^c (95% CI)	P-value
Hospital LOS (weeks)	0.97 (0.94, 0.99)	<.01	0.07 (0.01, 0.13)	0.02
Body habitus		0.86		0.62
Underweight	1.09 (0.76, 1.55)		-0.30 (-2.03, 1.44)	
Normal	Reference		Reference	
Obese	1.09 (0.71, 1.66)		0.92 (-1.20, 3.03)	
Baseline lactate (mmol/L)	1.05 (1.03, 1.06)	<.01	0.10 (-0.12, 0.31)	0.37
Highest lactate in 24 hours post ECMO initiation (mmol/L)	1.04 (1.03, 1.06)	<.01	0.11 (-0.00, 0.22)	0.06
Days from ECMO initiation to lactate 2 mmol/L	1.02 (0.92, 1.14)	0.67	0.65 (0.26, 1.04)	<.01
Lactate 2 mmol/L achieved	0.40 (0.33, 0.49)	<.01	-0.57 (-4.50, 3.36)	0.78
Lowest pH within 24 hours post ECMO initiation	0.30 (0.14, 0.63)	<.01	-1.25 (-5.87, 3.38)	0.60
Estimated PRBC in first 24 hours post ECMO initiation (dL/kg)^j	1.06 (0.94, 1.20)	0.38	0.12 (-0.49, 0.73)	0.70

^aFSS is Functional Status Score;

^bMortality was modeled using Poisson regression with robust error estimates;

^cFSS among survivors was modeled using standard linear regression;

^dECMO is extracorporeal membrane oxygenation;

^eECPR is extracorporeal cardiopulmonary resuscitation;

^fVA is venoarterial;

^gVV is venovenous;

^hVIS is Vasoactive inotropic score, None is VIS=0, Low is VIS >0 and <20, High is VIS ≥20;

ⁱLOS is length of stay;

^jPRBC is packed red blood cells

Table 5

Multivariable Model for Pediatric Cohort

Characteristic	Outcome			
	Mortality		FSS ^a (among survivors)	
	Adjusted Relative Risk ^b (95% CI)	P-value	Adjusted Effect ^c (95% CI)	P-value
Indication for ECMO^d				<.01
Respiratory	---	---	Reference	
Cardiac	---	---	-0.89 (-1.85, 0.07)	
ECPR ^e	---	---	1.41 (-0.09, 2.91)	
Neurologic chronic diagnosis			1.82 (0.31, 3.33)	0.02
Chronic cardiovascular diagnosis	1.33 (1.06, 1.67)	0.01	---	
Other chronic diagnosis	---	---	1.11 (0.04, 2.18)	0.04
Hepatic organ dysfunction	1.39 (1.09, 1.76)	<.01	2.03 (0.96, 3.10)	<.01
Baseline ventilator or tracheostomy	---	---	11.67 (8.01, 15.33)	<.01
ICU LOS (weeks) ^f	---	---	0.08 (0.03, 0.13)	<.01
Neurologic event	1.82 (1.39, 2.37)	<.01	---	---
Thrombotic event	1.43 (1.13, 1.80)	<.01	---	---
Achieved lactate < 2 mmol/L	0.54 (0.43, 0.68)	<.01	---	---

^aFSS is Functional Status Score;^bMortality was modeled using Poisson regression with robust error estimates;^cFSS among survivors was modeled using standard linear regression;^dECMO is extracorporeal membrane oxygenation;^eECPR is extracorporeal cardiopulmonary resuscitation;^fLOS is length of stay