Functional Status of Neonatal and Pediatric Patients After Extracorporeal Membrane Oxygenation*

Katherine Cashen, DO[1]; Ron Reeder, PhD[2]; Heidi J. Dalton, MD[3]; Robert A. Berg, MD[4]; Thomas P. Shanley, MD[5]; Christopher J. L. Newth, MD[6]; Murray M. Pollack, MD[7]; David Wessel, MD[7]; Joseph Carcillo, MD[8]; Rick Harrison, MD[9]; J. Michael Dean, MD[2]; Tammara Jenkins, MSN, RN[10]; Kathleen L. Meert, MD[1]; for the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN)

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[1]Division of Critical Care, Department of Pediatrics, Children's Hospital of Michigan/Wayne State University, Detroit, MI.

[2]Department of Pediatrics, University of Utah, Salt Lake City, UT.

[3]Department of Child Health, Phoenix Children's Hospital, Phoenix, AZ.

[4]Department of Anesthesiology and Critical Care, Children's Hospital of Philadelphia, Philadelphia, PA.

[5]Department of Pediatrics and Communicable Diseases, University of Michigan, Ann Arbor, MI.

[6]Department of Anesthesiology and Critical Care Medicine, Children's Hospital Los Angeles, Los Angeles, CA.

[7]Department of Pediatrics, Children's National Medical Center, Washington, DC.

[8]Department of Critical Care Medicine, Children's Hospital of Pittsburgh, Pittsburgh, PA.

[9]Department of Pediatrics, Mattel Children's Hospital UCLA, Los Angeles, CA.

[10]Pediatric Trauma and Critical Illness Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD.

Additional members of the *Eunice Kennedy Shriver* National Institute of Child Health and Human Development Collaborative Pediatric Critical Care Research Network (CPCCRN) are as follows: Allan Doctor (Professor of Pediatrics at St. Louis Children's Hospital, Washington University, St. Louis, MO) and Robert F. Tamburro (Pediatric Trauma and Critical Illness Branch, *Eunice Kennedy Shriver* National Institute of Child Health and Human Development, National Institutes of Health, Bethesda, MD).

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For information regarding this article, E-mail: kmeert@med.wayne.edu

Objectives: To describe functional status at hospital discharge for neonatal and pediatric patients treated with extracorporeal membrane oxygenation, and identify factors associated with functional status and mortality.

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

Setting: Eight hospitals affiliated with the Collaborative Pediatric Critical Care Research Network.

Patients: Patients were less than 19 years old and treated with extracorporeal membrane oxygenation.

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

Measurements and Main Results: Of 514 patients, 267 (52%) were neonates (≤ 30 d old). Indication for extracorporeal membrane oxygenation was respiratory for 237 (46%), cardiac for 207 (40%), and extracorporeal cardiopulmonary resuscitation

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 Functional Status Scale. Chronic conditions, prematurity, venoarterial extracorporeal membrane oxygenation, increased red cell transfusion in the first 24 hours of extracorporeal membrane oxygenation, and longer extracorporeal membrane oxygenation duration were independently associated with mortality. Among pediatric patients, chronic neurologic conditions, tracheostomy or home ventilator, extracorporeal cardiopulmonary resuscitation, hepatic dysfunction, and longer ICU stay were independently associated with worse Functional Status Scale. Chronic cardiac conditions, hepatic dysfunction, and neurologic or thrombotic complications were independently associated with mortality. Achieving blood lactate concentration less than or equal to 2 mmol/L during extracorporeal membrane oxygenation was independently associated with survival in both neonatal and pediatric patients.

Conclusions: In this study, about half of extracorporeal membrane oxygenation patients survived with good, mildly abnormal, or moderately abnormal function at hospital discharge. Patient and extracorporeal membrane oxygenation-related factors are associated with functional status and mortality. (*Pediatr Crit Care Med* 2017; 18:561–570)

Key Words: extracorporeal membrane oxygenation; functional status

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). Although 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 frequency of bleeding and thrombosis in neonatal and pediatric ECMO patients. In the BATE study, observational data were 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 (CPCCRN) 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 old treated with ECMO in a neonatal, pediatric or cardiac ICU were included (n = 514). Only the initial ECMO course was included for patients who required multiple courses of ECMO.

Data Collection

All data were 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

less than or equal to 2 mmol/L; estimated volume of packed RBCs (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 less than or equal to 30 days of age were categorized as neonatal and those greater than 30 days as pediatric. Prematurity was less than 37 weeks of 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 (BMI)-for-age percentiles for patients greater than or equal to 2 years old, and weight-for-length percentiles for patients less than 2 years old. 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 was greater than or equal to 95th percentile, and underweight if less than fifth percentile.

Indications for ECMO were categorized as respiratory, cardiac, or extracorporeal cardiopulmonary resuscitation (eCPR). Mode of ECMO was categorized as venoarterial or venovenous. Venovenous ECMO that was converted to venoarterial was categorized as venoarterial 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) × 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 1 ECMO day. Neurologic events included seizures (clinical or electrographic), intracranial hemorrhage or infarction, and brain death. Renal failure was defined as creatinine greater than 2 mg/dL (> 176.8 µmol/L) or use of renal replacement therapy. Hepatic dysfunction was defined as international normalized ratio greater than or equal to two. Thrombotic events included intracranial infarction, limb ischemia, pulmonary embolus, intracardiac thrombus, aortopulmonary 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 six 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 to 30 and are categorized as 6–7 (good), 8–9 (mildly abnormal), 10–15 (moderately abnormal), 16–21 (severely abnormal), and greater than 21 (very severely abnormal).

TABLE 1. Description of Neonatal and Pediatric Extracorporeal Membrane Oxygenation (ECMO) Cohort Demographics, ECMO Characteristics, and Outcomes

Characteristic	Overall (*n* = 514)
Neonate[a], *n* (%)	267 (52)
Male, *n* (%)	302 (59)
Race, *n* (%)	
Black or African-American	91 (18)
White	254 (49)
Other	26 (5)
Unknown or not reported	143 (28)
Hispanic or Latino, *n* (%)	86 (17)
Premature[b], *n* (%)	50 (10)
Weight for neonates only (g), median (Q1, Q3)	3,100 (2,780, 3,450)
Chronic diagnosis, *n* (%)	335 (65)
Primary ECMO indication, *n* (%)	
Respiratory	237 (46)
Cardiac	207 (40)
Extracorporeal cardiopulmonary resuscitation	70 (14)
Venoarterial ECMO, *n* (%)	431 (84)
Duration of ECMO (d), median (Q1, Q3)	5 (3, 9)
Length of hospital stay (d), median (Q1, Q3)	36 (16, 68)
Length of ICU stay (d), median (Q1, Q3)	28 (14, 51)
Functional Status Scale at hospital discharge, *n* (%)	
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)

ECMO = extracorporeal membrane oxygenation.

[a]Neonate is ≤ 30 d of age.

[b]Premature is < 37 wk of gestational age at birth and was collected for neonates only.

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

TABLE 2. Univariate Analyses for Neonatal Extracorporeal Membrane Oxygenation (ECMO) Cohort Describing Relationships Between Patient and ECMO Characteristics and Outcomes

	Outcome			
	Death		Functional Status Score (Among Survivors)	
Characteristic	Relative Risk[a] (95% CI)	*p*	Effect[b] (95% CI)	*p*
Indication for ECMO		0.03		0.29
Respiratory	Reference		Reference	
Cardiac	1.49 (1.11–1.99)		−0.54 (−1.46 to 0.39)	
Extracorporeal cardiopulmonary resuscitation	1.42 (0.90–2.25)		−1.04 (−2.60 to 0.52)	
Primary diagnosis category		0.20		0.15
Respiratory	Reference		Reference	
Cardiovascular/shock	1.29 (0.98–1.71)		−0.73 (−1.57 to 0.11)	
Other	1.34 (0.33–5.43)		−2.86 (−7.97 to 2.25)	
Chronic diagnosis	1.55 (1.14–2.10)	< 0.01	1.09 (0.27–1.90)	< 0.01
Congenital anomaly or chromosomal defect	1.30 (0.96–1.76)	0.11	1.53 (0.47–2.59)	< 0.01
Cardiovascular disease	1.27 (0.96–1.67)	0.10	0.58 (−0.29 to 1.44)	0.19
Other	0.94 (0.44–2.04)	0.88	1.51 (−0.62 to 3.63)	0.17
Mode of ECMO		< 0.01		0.11
Venoarterial	Reference		Reference	
Venovenous	0.42 (0.21–0.84)		−0.85 (−1.90 to 0.20)	
Neurologic event	1.57 (1.19–2.07)	< 0.01	0.98 (0.10–1.86)	0.03
Renal organ failure	1.52 (1.16–2.00)	< 0.01	1.29 (0.40–2.18)	< 0.01
Hepatic organ dysfunction	1.61 (1.23–2.11)	< 0.01	−0.14 (−1.10 to 0.82)	0.78
Thrombotic event	1.17 (0.88–1.55)	0.28	0.75 (−0.11 to 1.61)	0.09
Bleeding event	1.65 (1.15–2.35)	< 0.01	0.60 (−0.24 to 1.44)	0.16
Baseline Vasoactive Inotropic Score[c]		0.35		0.52
None	Reference		Reference	
Low	0.76 (0.52–1.10)		0.41 (−0.73 to 1.55)	
High	0.86 (0.62–1.19)		0.64 (−0.46 to 1.74)	
Premature[d]	1.87 (1.44–2.42)	< 0.01	−0.62 (−1.97 to 0.74)	0.37
Duration of ECMO (d)		0.02		< 0.01
< 2	1.64 (1.10–2.44)		−1.23 (−2.51 to 0.06)	
2 to < 4	1.00 (0.62–1.62)		0.95 (−0.10 to 2.00)	
4 to < 9	Reference		Reference	
≥ 9	1.54 (1.07–2.21)		0.82 (−0.19 to 1.84)	
ICU LOS (wk)	0.87 (0.80–0.95)	< 0.01	0.11 (0.05 to 0.18)	< 0.01
Hospital LOS (wk)	0.86 (0.79–0.93)	< 0.01	0.11 (0.05 to 0.16)	< 0.01

(*Continued*)

TABLE 2. (*Continued*). Univariate Analyses for Neonatal Extracorporeal Membrane Oxygenation (ECMO) Cohort Describing Relationships Between Patient and ECMO Characteristics and Outcomes

	Outcome			
	Death		Functional Status Score (Among Survivors)	
Characteristic	Relative Risk[a] (95% CI)	*p*	Effect[b] (95% CI)	*p*
Body habitus		0.34		0.98
Underweight	1.14 (0.80–1.64)		0.10 (−1.02 to 1.23)	
Normal	Reference		Reference	
Obese	0.64 (0.27–1.52)		−0.03 (−1.62 to 1.55)	
Baseline lactate (mmol/L)	1.02 (0.99–1.04)	0.19	0.04 (−0.06 to 0.14)	0.47
Highest lactate in 24 hr post ECMO initiation (mmol/L)	1.06 (1.04–1.08)	< 0.01	−0.00 (−0.11 to 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 to 0.29)	0.82
Lactate ≤ 2 mmol/L achieved	0.51 (0.39–0.65)	< 0.01	0.81 (−0.47 to 2.10)	0.22
Lowest pH within 24 hr post ECMO initiation	0.54 (0.18–1.63)	0.28	1.26 (−2.08 to 4.61)	0.46
Estimated packed RBC in first 24 hr post ECMO initiation (dL/kg)	1.10 (1.05–1.15)	0.01	0.08 (−0.33 to 0.49)	0.71

ECMO = extracorporeal membrane oxygenation, LOS = length of stay.
[a]Mortality was modeled using Poisson regression with robust error estimates.
[b]Functional Status Score among survivors was modeled using standard linear regression.
[c]None is Vasoactive Inotropic Score (VIS) = 0, low is VIS > 0 and < 20, and high is VIS ≥ 20.
[d]Premature is < 37 weeks of gestational age at birth.

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* value of less than 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 thirty-seven (46%) received ECMO for a respiratory indication and 431 (84%) received venoarterial ECMO. The median duration of ECMO was 5 days (3–9 d). Two hundred 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** (http://links.lww.com/PCC/A411), **Supplemental Digital Content 2** (http://links.lww.com/PCC/A413), and **Supplemental Digital Content 3** (http://links.lww.com/PCC/A414).

Neonates (≤ 30 D 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 less than 2 days was associated with better FSS. Univariable analysis also showed presence of a chronic condition, prematurity, initiation of ECMO for cardiac indication, venoarterial 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 less than or equal to 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 less than 2 days was independently associated with better FSS at hospital discharge. Multivariable analysis

TABLE 3. Multivariable Model for Neonatal Extracorporeal Membrane Oxygenation (ECMO) Cohort Describing Patient and ECMO Characteristics Independently Associated With Outcomes

	Outcome			
	Death		Functional Status Scale (Among Survivors)	
Characteristic	Adjusted Relative Risk[a] (95% CI)	*p*	Adjusted Effect[b] (95% CI)	*p*
Renal organ failure	–	–	1.24 (0.33–2.14)	< 0.01
Hospital length of stay (wk)	0.87 (0.80–0.96)	< 0.01	0.09 (0.04–0.15)	< 0.01
ECMO duration (d)		< 0.01		0.05
< 2	0.72 (0.49–1.05)		−0.88 (−2.12 to 0.36)	
2 to < 4	0.88 (0.58–1.34)		0.96 (−0.06 to 1.98)	
4 to < 9	Reference		Reference	
≥ 9	1.64 (1.23–2.18)		0.06 (−0.96 to 1.09)	
Chronic diagnosis	1.46 (1.14–1.86)	< 0.01	–	–
Mode of ECMO		< 0.01	–	–
Venoarterial	Reference		–	–
Venovenous	0.47 (0.26–0.84)		–	–
Premature[c]	1.36 (1.05–1.76)	0.02	–	–
Lactate ≤ 2 mmol/L achieved	0.60 (0.44–0.82)	< 0.01	–	–
Estimated packed RBC in 24 hr post ECMO initiation (dL/kg)	1.07 (1.01–1.12)	< 0.01	–	–

ECMO = extracorporeal membrane oxygenation.

[a]Mortality was modeled using Poisson regression with robust error estimates.

[b]FSS among survivors was modeled using standard linear regression.

[c]Premature is < 37 wk of gestational age.

Dashes indicate the variable was not included in the multivariable analysis for one of the outcomes.

also showed presence of a chronic condition, prematurity, venoarterial ECMO, increased estimated volume of PRBC transfused during the first 24 hours of ECMO, and ECMO duration greater than 9 days were independently associated with increased relative risk of death. Achieving a lactate less than or equal to 2 mmol/L and longer duration of hospital stay were independently associated with decreased relative risk of death.

Pediatric Patients (30 D < 19 Yr Old)

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 less than or equal to 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 less than or equal to 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

TABLE 4. Univariate Analyses for Pediatric Extracorporeal Membrane Oxygenation (ECMO) Cohort Describing Relationships Between Patient and ECMO Characteristics and Outcomes

	Outcome			
	Death		Functional Status Score (Among Survivors)	
Characteristic	Relative Risk[a] (95% CI)	*p*	Effect[b] (95% CI)	*p*
Indication for ECMO		< 0.01		< 0.01
Respiratory	Reference		Reference	
Cardiac	1.42 (1.01–2.00)		−1.09 (−2.29 to 0.11)	
Extracorporeal cardiopulmonary resuscitation	1.99 (1.41–2.82)		2.39 (0.48–4.31)	
Primary diagnosis category		< 0.01		0.91
Respiratory	Reference		Reference	
Cardiovascular/shock	1.76 (1.24–2.48)		−0.14 (−1.39 to 1.10)	
Other	1.38 (0.78–2.47)		−0.46 (−2.69 to 1.76)	
Chronic diagnosis	1.18 (0.85–1.64)	0.30	0.85 (−0.49 to 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 to 0.21)	0.11
Neurologic disease	0.89 (0.55–1.45)	0.63	3.01 (1.12–4.91)	< 0.01
Respiratory disease	1.00 (0.67–1.50)	0.99	1.23 (−0.60 to 3.07)	0.19
Other	1.14 (0.87–1.51)	0.36	1.25 (−0.15 to 2.66)	0.08
Mode of ECMO		0.13		0.85
Venoarterial	Reference		Reference	
Venovenous	0.76 (0.51–1.12)		0.14 (−1.28 to 1.56)	
Neurologic event	2.37 (1.82–3.07)	< 0.01	0.99 (−0.52 to 2.50)	0.20
Renal organ failure	1.50 (1.17–1.93)	< 0.01	1.24 (−0.10 to 2.58)	0.07
Hepatic organ dysfunction	1.83 (1.43–2.35)	< 0.01	2.55 (1.19–3.90)	< 0.01
Thrombotic event	1.40 (1.09–1.80)	0.01	0.00 (−1.30 to 1.30)	1.00
Bleeding event	1.28 (0.92–1.78)	0.12	0.01 (−1.28 to 1.31)	0.98
Baseline Vasoactive Inotropic Score[c]		0.19		0.88
None	Reference		Reference	
Low	0.87 (0.61–1.22)		0.13 (−1.26 to 1.53)	
High	1.18 (0.88–1.57)		−0.26 (−1.75 to 1.22)	
Baseline technology dependence				
Feeding tube	0.99 (0.72–1.38)	0.97	2.73 (1.30–4.15)	< 0.01
Ventilator or tracheostomy	1.50 (0.92–2.45)	0.22	13.26 (9.05–17.47)	< 0.01
Oxygen	1.00 (0.68–1.48)	0.98	2.42 (0.67–4.17)	< 0.01
Duration of ECMO (d)		0.71		0.63
< 2	1.23 (0.86–1.77)		0.16 (−1.62 to 1.94)	
2 to < 4	1.13 (0.80–1.59)		0.68 (−0.85 to 2.20)	
4 to < 9	Reference		Reference	
≥ 9	1.07 (0.74–1.55)		0.96 (−0.63 to 2.55)	

(*Continued*)

TABLE 4. (*Continued*). Univariate Analyses for Pediatric Extracorporeal Membrane Oxygenation (ECMO) Cohort Describing Relationships Between Patient and ECMO Characteristics and Outcomes

	Outcome			
	Death		Functional Status Score (Among Survivors)	
Characteristic	Relative Risk[a] (95% CI)	*p*	Effect[b] (95% CI)	*p*
ICU LOS (wk)	0.98 (0.95–1.00)	0.02	0.09 (0.03–0.15)	< 0.01
Hospital LOS (wk)	0.97 (0.94–0.99)	< 0.01	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 to 1.44)	
Normal	Reference		Reference	
Obese	1.09 (0.71–1.66)		0.92 (−1.20 to 3.03)	
Baseline lactate (mmol/L)	1.05 (1.03–1.06)	< 0.01	0.10 (−0.12 to 0.31)	0.37
Highest lactate in 24 hr post ECMO initiation (mmol/L)	1.04 (1.03–1.06)	< 0.01	0.11 (−0.00 to 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)	< 0.01
Lactate ≤ 2 mmol/L achieved	0.40 (0.33–0.49)	< 0.01	−0.57 (−4.50 to 3.36)	0.78
Lowest pH within 24 hr post ECMO initiation	0.30 (0.14–0.63)	< 0.01	−1.25 (−5.87 to 3.38)	0.60
Estimated packed RBC in first 24 hr post ECMO initiation (dL/kg)	1.06 (0.94–1.20)	0.38	0.12 (−0.49 to 0.73)	0.70

ECMO is extracorporeal membrane oxygenation, LOS = length of stay.

[a]Mortality was modeled using Poisson regression with robust error estimates.

[b]Functional Status Score among survivors was modeled using standard linear regression.

[c]None is Vasoactive Inotropic Score (VIS) = 0, low is VIS > 0 and < 20, high is VIS ≥ 20.

less than or equal to 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 venoarterial 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 postcannulation 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 venovenous 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

TABLE 5. Multivariable Model for Pediatric Extracorporeal Membrane Oxygenation (ECMO) Cohort Describing Patient and ECMO Characteristics Independently Associated With Outcomes

	Outcome			
	Mortality		Functional Status Score (Among Survivors)	
Characteristic	Adjusted Relative Risk[a] (95% CI)	*p*	Adjusted Effect[b] (95% CI)	*p*
Indication for extracorporeal membrane oxygenation				< 0.01
Respiratory	–	–	Reference	
Cardiac	–	–	−0.89 (−1.85 to 0.07)	
Extracorporeal cardiopulmonary resuscitation	–	–	1.41 (−0.09 to 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)	< 0.01	2.03 (0.96–3.10)	< 0.01
Baseline ventilator or tracheostomy	–	–	11.67 (8.01–15.33)	< 0.01
ICU length of stay (wk)	–	–	0.08 (0.03–0.13)	< 0.01
Neurologic event	1.82 (1.39–2.37)	< 0.01	–	–
Thrombotic event	1.43 (1.13–1.80)	< 0.01	–	–
Achieved lactate < 2 mmol/L	0.54 (0.43–0.68)	< 0.01	–	–

[a]Mortality was modeled using Poisson regression with robust error estimates.
[b]Functional Status Score among survivors was modeled using standard linear regression.
Dashes indicate the variable was not included in the multivariable analysis for one of the outcomes.

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 noncardiac 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, immunodysfunction, 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 at 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 venoarterial ECMO. The underlying reason clinicians chose a particular mode of ECMO was not elicited in this study. Despite potential benefits of venovenous ECMO in many situations, our findings reflect actual clinical practice at CPCCRN sites. Venoarterial ECMO seems 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 preillness 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 seems worse than reported for other intensive care populations where hospital discharge FSS has been evaluated. In a large general PICU 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 less than 18 years old

admitted to an ICU with acute traumatic brain injury and either a Glasgow Coma Scale (GCS) (26) score less than or equal to 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 score less than or equal to 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.

CONCLUSIONS

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.

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