Survival and Developmental Outcomes of Neonates Treated with Extracorporeal Membrane Oxygenation: A 10-Year Single-Center Experience

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Objective To evaluate the associations between the primary indication for extracorporeal membrane oxygenation (ECMO) in neonates and neurodevelopmental outcomes at 12 and 24 months of age.

Study design This is a retrospective cohort study of neonates treated with ECMO between January 2006 and January 2016 in the Children's Hospital of Philadelphia newborn/infant intensive care unit. Primary indication for ECMO was classified as medical (eg, meconium aspiration syndrome) or surgical (eg, congenital diaphragmatic hernia). Primary study endpoints were assessed with the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III). Groups were compared with standard bivariate testing and multivariable regression.

Results A total of 191 neonates met the study's inclusion criteria, including 96 with a medical indication and 95 with a surgical indication. Survival to discharge was 71%, with significantly higher survival in the medical group (82% vs 60%; P = .001). Survivors had high rates of developmental therapies and neurosensory abnormalities. Developmental outcomes were available for 66% at 12 months and 70% at 24 months. Average performance on the Bayley-III was significantly below expected population normative values. Surgical patients had modestly lower the Bayley-III scores over time; most notably, 15% of medical infants and 49% of surgical infants had motor delay at 24 months (P = .03).

Conclusions In this single-center cohort, surgical patients had lower survival rates and higher incidence of motor delays. Strategies to reduce barriers to follow-up and improve rates of postdischarge developmental surveillance and intervention in this high-risk population are needed. *(J Pediatr 2021;229:134-40)*.

Extracorporeal membrane oxygenation (ECMO) is a widely accepted treatment for neonates with cardiorespiratory failure refractory to maximal ventilatory and pharmacologic support. According to the Extracorporeal Life Support Organization (ELSO) registry, 36 964 neonates had been treated with ECMO as of 2016, and neonates composed the majority of the patient population supported by ECMO.[1] Neonates with meconium aspiration syndrome (MAS) or congenital diaphragmatic hernia (CDH) represented the largest group of patients requiring ECMO, with survival rates of 93% and 50%, respectively.[1]

Neonates receiving ECMO are prone to neurologic injury, including intracranial hemorrhage (ICH), stroke, and seizure.[2-8] Studies have reported major disabilities, including developmental delay, cerebral palsy, and visual or hearing loss, among survivors.[9,10] Most studies do not stratify outcomes based on the primary indication for ECMO, and thus the distribution of these risks is unknown. The primary objective of the present study was to evaluate the developmental outcomes at age 12 and 24 months of infants treated with ECMO in a quaternary care neonatal/infant intensive care unit (N/IICU) over a 10-year period based on the indication for ECMO. We hypothesized that neonates who had a surgical indication as the primary cause of cardiorespiratory failure would have lower survival rates, more comorbidities, and a higher rate of neurodevelopmental impairment compared with neonates who had a medical indication warranting ECMO.

Bayley-III	Bayley Scales of Infant and Toddler Development, Third Edition
CDH	Congenital diaphragmatic hernia
CHOP	Children's Hospital of Philadelphia
ECMO	Extracorporeal membrane oxygenation
ELSO	Extracorporeal Life Support Organization
ICH	Intracranial hemorrhage
N/IICU	Newborn/infant intensive care unit
SDU	Special delivery unit

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Methods

This was a retrospective single-center cohort study of neonates born at ≥34 weeks gestation and a birth weight of ≥2000 g treated with ECMO within the first 28 days after birth between January 2006 and January 2016 in the N/IICU at Children's Hospital of Philadelphia (CHOP). Infants with uncorrectable congenital heart disease and preexisting ICH were excluded. At CHOP, perioperative cardiac patients are not cared for in the N/IICU and were not eligible for this study. The indication for ECMO was categorized as medical (eg, macrophage activation syndrome, sepsis) or surgical if the patient's respiratory failure was directly related to an anomaly that required a surgical intervention (eg, CDH). Maternal and neonatal demographic data as well as hospital outcomes were collected from review of electronic medical records. Sepsis was defined as any episode of blood culture–confirmed growth of a bacterial pathogen in the setting of a clinical change occurring at any point during hospitalization. ECMO complications were obtained from CHOP's ELSO registry.[1] Acute neurologic lesions reported to ELSO include seizures, ICH, and infarction.[4]

Among survivors followed by CHOP's Neonatal Follow-up Program, developmental testing results including the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), physical and neurologic examination findings, diagnoses, and hearing or vision problems at age 12 and 24 months were collected.[11] In our Neonatal Follow-up Program, psychologists and clinicians who administer the Bayley-III undergo yearly recertification to ensure valid and reliable assessment.[12] For children not seen in follow-up, data from other specialty or primary care visits through the CHOP network were used to estimate other neurosensory outcomes, such as neurologic exam findings, receipt of outpatient therapies, developmental and behavioral assessments, and hearing and vision impairment.

The groups were compared with standard bivariate tests including the χ^2, Fisher exact, Student t, and Kruskal-Wallis tests, as appropriate. Multivariable regression models were used to compare outcomes in the 2 groups. Baseline characteristics that were significantly different between the groups in bivariate comparisons were included in all models (**Table I**); in addition, perinatal morbidities that were significantly different between groups in bivariate comparisons were included in models of developmental outcomes. Model fit is reported with R^2 statistics and Hosmer–Lemeshow goodness-of-fit tests. Bayley-III data were studied as continuous outcomes and compared with mean standard composite scores of 100 ± 15 and scaled scores of 10 ± 3. Bayley-III composite scores were categorized as average (≥85), mildly delayed (70-84), or severely delayed (<70). Study data were collected and managed using REDCap electronic data capture tools hosted at CHOP, and statistical analyses were performed with Stata/SE 13.1 (StataCorp, College Station, Texas).[13,14] For all statistical tests, a significance level of 0.05 was used.

Table I. Characteristics of neonates on ECMO between 2006 and 2016

Characteristics	Medical (N = 96)	Surgical (N = 95)	*P* value
Gestational age, n (%)			
Preterm (≤36 weeks gestation)	14 (15)	25 (26)	.001
Early term (37-38 wk gestation)	29 (30)	43 (45)	
Full term (≥39 weeks gestation)	53 (55)	27 (28)	
Birth weight, g, mean ± SD	3184 ± 615	3053 ± 464	.10
Female sex, n (%)	43 (45)	43 (45)	.95
Maternal race, n (%)			
African American/black	31 (36)	13 (15)	.005
Caucasian/white	49 (57)	67 (80)	
Other*	6 (7)	4 (5)	
Antenatal steroids, n (%)†	2 (2)	14 (15)	.003
Multiple gestation, n (%)	2 (2)	4 (4)	.44
Cesarean delivery, n (%)	46 (48)	50 (53)	.52
1-minute Apgar score, mean ± SD‡	5.3 ± 2.7	4.4 ± 2.4	.02
5-minute Apgar score, mean ± SD‡	7.0 ± 2.0	6.8 ± 1.9	.60
Inborn, n (%)	4 (4)	80 (84)	<.0001
Age at admission to CHOP among those not inborn, d, mean ± SD	2.4 ± 4.2	0.2 ± 0.4	.04
Major congenital anomaly (other than an anomaly that is an indication for ECMO) or significant genetic difference, n (%)	16 (17)	15 (16)	.87
Age at ECMO cannulation, d, mean ± SD	3.3 ± 4.7	2.3 ± 3.1	.07
Age at ECMO decannulation, d, mean ± SD	11.7 ± 5.8	19.6 ± 8.9	<.0001
Duration of ECMO run, d, mean ± SD	8.4 ± 4.9	17.4 ± 8.4	<.0001

*Unknown in 21 patients; other includes Asian (n = 8), Native American (n = 1), and multiple races (n = 1).
†Unknown in 1 patient.
‡Unknown for in 10 patients at 1 minute and 11 patients at 5 minutes.

This retrospective study was approved by the Institutional Review Board at CHOP. Parental consent was not required.

Results

A total of 196 neonates were treated with ECMO in the CHOP N/IICU between January 2006 and January 2016. Five neonates were excluded from this analysis, including 1 with significant congenital heart disease and 4 who had undergone cannulation after 28 days of life. The remaining 191 infants were included in this study, including 96 with a primary medical indication and 95 with a primary surgical indication. Medical diagnoses included MAS in 45 neonates; persistent pulmonary hypertension of the newborn in 32; sepsis in 8, including group B *Streptococcus* sepsis in 4 and *Escherichia coli* sepsis, rhinovirus, adenovirus, and pertussis in 1 each; and respiratory distress syndrome in 9. The remaining 2 patients had respiratory failure, subsequently found to be secondary to congenital lymphangiectasia and alveolar capillary dysplasia. Surgical diagnoses included CDH in 82 patients,

congenital pulmonary airway malformation of the lung in 9 patients, and bronchopulmonary sequestration with effusion, congenital bronchial atresia, tracheal stenosis, and pulmonary hypoplasia secondary to posterior urethral valves in 1 patient each. Compared with the children with medical indications, those with surgical indications were younger, more likely to have been exposed to antenatal steroids, more likely to be white, and had lower 1-minute Apgar scores (Table I).

Overall survival to hospital discharge was 71%, with higher survival in the medical group compared with the surgical group (82% vs 60%; $P = .001$). In the medical group, 93% of infants with MAS, 81% of those with persistent pulmonary hypertension of the newborn, 78% of those with respiratory distress syndrome, and 38% of those with sepsis survived to discharge. In the surgical group, 57% of infants with CDH and 67% of those with congenital pulmonary airway malformation survived to discharge. In a logistic regression model, the date of birth was not associated with the odds of mortality in either the entire cohort or in the medical or surgical group. After CHOP opened its special delivery unit (SDU) in 2008, the majority of infants with prenatally diagnosed congenital anomalies were inborn. There was increased survival in the surgical cohort after the SDU was opened (38% before vs 66% after; $P = .02$).

Surgical patients had longer and more complicated hospitalizations than medical patients (Table II). Although the number of neonates who died on ECMO or the day of decannulation was similar in the 2 groups, more neonates in the surgical group died after decannulation ($P = .001$), received a tracheostomy, and were discharged with tube feedings. In multivariable logistic regression analyses adjusted for baseline characteristics that differed between the groups (gestational age, antenatal steroid exposure, 1-minute Apgar score, race, and inborn status), the OR for mortality in the surgical group compared with the medical group was 3.9 (95% CI, 1.3-12.2). Inclusion of duration of ECMO as an indicator of severity of illness reduced, but did not eliminate, this difference. Fully adjusted models with ORs for all included covariates are provided in Table III.

There was a significant difference in mode of ECMO cannulation between the 2 groups. Nearly all infants in the surgical group (98%; n = 93) were cannulated to venoarterial ECMO, compared with 42% (n = 40) of the medical group ($P < .0001$). Four infants in the medical group and 1 infant in the surgical group were started on venovenous ECMO and then transitioned to venoarterial ECMO. Further data on precannulation treatments, mechanical complications, and patient complications are provided in Table IV (available at www.jpeds.com). Surgical infants were on ECMO for approximately twice as long as infants in the medical group, but did not have higher rates of ECMO complications (Tables I and IV).

Outcome data were available for 89 (66%) surviving children at age 12 months and for 94 (70%) surviving children at age 24 months. One infant in the surgical group died after discharge and before follow-up. Of the remaining children, 54 12-month-olds (40% of survivors) and 61 24-month-olds (45% of survivors) attended follow-up at our institution and were assessed with the Bayley-III (Table V). Attendance rates improved over the 10-year study period ($P = .001$) and were higher in the surgical group. Survivors seen in follow-up were more likely to be inborn, to have a surgical diagnosis, and to have had sepsis. They were less likely to have been transferred to another facility before discharge, and had longer length of mechanical ventilation and hospitalization (Table VI [available at www.jpeds.com] and Table VII [available at www.jpeds.com]).

The average age at the 2 follow-ups was 12.9 ± 1.4 months and 24.1 ± 2.7 months. For the entire cohort, Bayley-III scores in all domains were significantly below population-

Table II. Major inpatient outcomes and major discharge characteristics of survivors

Parameter	Medical	Surgical	
Inpatient outcomes	**(N = 96)**	**(N = 95)**	***P* value**
Any intracranial hemorrhage or periventricular leukomalacia, n (%)	25 (26)	29 (31)	.49
Seizures on electroencephalography, n (%)*	17 (18)	20 (21)	.56
Culture-proven sepsis, n (%)	14 (15)	25 (26)	.04
Tracheostomy, n (%)	0 (0)	8 (8)	.003
Transfer to another acute care hospital before discharge, n (%)	22 (23)	2 (2)	<.0001
Died before discharge, n (%)	17 (18)	38 (40)	.001
Age at death d, (IQR)	16 (6-23)	28 (17-41)	.01
Timing of death relative to decannulation, n (%)			.19
Died while on ECMO or on day of decannulation	9 (53)	13 (34)	
Died after day of decannulation	8 (47)	25 (66)	
Among infants who died after day of decannulation, age when death occurred, d, median (IQR)	7 (4-12)	4 (2-29)	.82
Characteristics of infants who survived to discharge†	**(N = 57)**	**(N = 55)**	
Length of hospitalization, d, median (IQR)	37 (31-64)	91 (70-132)	.0001
Duration of mechanical ventilation after decannulation, until extubation or tracheostomy, d, median (IQR)	6 (3-9)	23 (13-35)	.0001
Feeding route at discharge, n (%)			<.0001
Gastrostomy tube (with or without oral feeding)	4 (7)	13 (24)	
Nasogastric tube (with or without oral feeding)	23 (40)	33 (60)	
Oral	30 (53)	9 (16)	
Respiratory support at discharge, n (%)			.003
Tracheostomy	0 (0)	4 (7)	
Continuous positive airway pressure	0 (0)	1 (2)	
Nasal cannula	2 (4)	11 (20)	
None	55 (96)	39 (71)	
Normal findings on neurologic exam at discharge from the NICU by attending provider, n (%)	52 (91)	44 (80)	.09
Abnormal hearing screen before discharge necessitating referral, n (%)‡	9 (16)	18 (33)	.04
Discharge to home with biological parents, n (%)	55 (96)	55 (100)	.37

*EEG results unavailable for 2 patients.
†Excludes children transferred to another acute care facility before discharge.
‡Unknown in 2 patients in the medical group and 1 patient in the surgical group.

Table III. Multivariable models for death and Bayley-III composite scores at 12 and 24 months

Model covariates	Death, OR (95% CI)	12-mo cognitive coefficient (95% CI)	12-mo language coefficient (95% CI)	12-mo motor coefficient (95% CI)	24-mo cognitive coefficient (95% CI)	24-mo language coefficient (95% CI)	24-mo motor coefficient (95% CI)
Surgical diagnosis	3.9 (1.3-12.2)	8.0 (−6.9 to 23.0)	24.0 (6.0-41.9)	−1.1 (−22.0 to 19.8)	6.7 (−14.9 to 28.4)	36.9 (8.1-65.7)	5.4 (−23.0 to 33.9)
Gestational age (each week)	0.9 (0.7-1.1)	1.4 (−0.7 to 3.4)	0.4 (−2.0 to 2.8)	1.2 (−1.6 to 3.9)	1.6 (−0.8 to 4.1)	2.0 (−1.5 to 5.5)	2.9 (−0.3 to 6.1)
Race*							
White	2.6 (0.9-7.8)	4.0 (−3.8 to 11.8)	0.5 (−9.2 to 10.2)	2.4 (−8.2 to 13.0)	6.9 (−4.3 to 18)	10.4 (−5.1 to 26.0)	2.0 (−11.4 to 15.4)
Other	4.4 (0.7-26.2)	9.4 (−4.1 to 22.9)	4.5 (−12.0 to 21.0)	8.3 (−10.1 to 26.6)	15.9 (−5.2 to 37.0)	25.2 (−3.3 to 53.7)	32.1 (−7.5 to 71.7)
Unknown	5.1 (1.3-20.2)	−0.3 (−18.7 to 18.2)	5.7 (−16.6 to 28.0)	−0.19 (−25.3 to 24.9)	−12.8 (−32.4 to 6.8)	−15.6 (−47.6 to 16.5)	−51.0 (−82.6 to −19.5)
Antenatal steroid exposure	1.5 (0.4-5.7)	4.5 (−8.8 to 17.8)	2.0 (−13.9 to 17.9)	−4.5 (−24.2 to 15.2)	5.7 (−9.6 to 21.0)	1.7 (−19.3 to 22.7)	11.2 (−10.1 to 32.5)
1-minute Apgar score	0.8 (0.7-0.9)	0.3 (−1.0 to 1.7)	−0.2 (−1.9 to 1.4)	0.2 (−1.7 to 2.1)	−0.3 (−1.8 to 1.2)	−0.2 (−2.3 to 1.8)	−0.6 (−2.5 to 1.2)
Inborn	0.8 (0.2-2.3)	−13.1 (−25.8 to −0.3)	−15.8 (−31.2 to −0.5)	−12.2 (−30.7 to 6.3)	−7.7 (−28.3 to 12.9)	−39.7 (−67.5 to −11.8)	−10.2 (−36.7 to 16.4)
ECMO duration, d	N/A	−0.3 (−0.8 to 0.2)	−0.3 (−0.9 to 0.3)	−0.7 (−1.4 to −0.01)	−0.3 (−0.9 to 0.3)	−0.3 (−1.1 to 0.6)	−0.3 (−1.1 to 0.4)
ECMO mode	N/A	−4.8 (−15.6 to 6.0)	−7.1 (−20.0 to 5.9)	5.3 (−9.4 to 19.9)	−3.1 (−14.4 to 8.1)	−5.3 (−20.2 to 9.7)	1.6 (−10.9 to 14.1)
Culture-proven sepsis	N/A	−1.8 (−9.6 to 6.0)	2.7 (−6.7 to 12.2)	−2.0 (−13.0 to 9.1)	2.9 (−7.3 to 13.2)	19.5 (5.4-33.6)	5.2 (−7.9 to 18.2)
Respiratory support at discharge	N/A	−1.2 (−5.3 to 2.9)	1.5 (−3.4 to 6.4)	2.8 (−3.1 to 8.7)	1.7 (−1.9 to 5.4)	2.1 (−2.7 to 7.0)	−1.1 (−5.3 to 3.1)
Model R^2 statistic	N/A†	0.5	0.3	0.4	0.4	0.4	0.6

N/A, not available.
*Black is reference category for race.
†Goodness of fit for the logistic model of mortality was assessed with C-statistic (area under the receiver operating characteristic curve = 0.73) and Hosmer-Lemeshow goodness of fit test ($P = .075$).

Table V. Bayley-III scores in survivors at 12 months and 24 months*

Outcomes	Medical	Surgical	Unadjusted *P* value
Outcomes at 12 mo†	N = 20	N = 34	
Age at follow-up visit, mo	12.2 ± 1.7	12.5 ± 1.4	.36
Cognitive composite score	96 ± 9	86 ± 12	.004
Receptive language scaled score	7.1 ± 2.1	7.4 ± 2.6	.71
Expressive language scaled score	7.8 ± 2.6	8.5 ± 2.4	.27
Language composite score	85 ± 11	88 ± 13	.42
Fine motor scaled score	9.0 ± 1.7	7.8 ± 2.5	.06
Gross motor scaled score	8.9 ± 2.6	5.6 ± 3.2	.0004
Motor composite scaled score	94 ± 11	80 ± 17	.002
Outcomes at 24 mo‡	**N = 23**	**N = 38**	
Age at follow-up visit, mo	23.7 ± 3.2	24.8 ± 2.5	.06
Cognitive composite score	94 ± 13	86 ± 15	.06
Receptive language scaled score	9.5 ± 2.7	8.0 ± 4.2	.17
Expressive language scaled score	9.3 ± 3.1	7.7 ± 4.0	.13
Language composite score	96 ± 14	87 ± 22	.11
Fine motor scaled score	9.2 ± 2.6	8.6 ± 3.2	.45
Gross motor scaled score	8.2 ± 3.0	6.2 ± 2.9	.03
Motor composite scaled score	91 ± 14	84 ± 17	.13

All results presented as mean ± SD.
*Population expected mean composite scores 100 ± 15; scaled scores 10 ± 3.
†Two patients had incomplete data, and 2 could not be scored.
‡Fifteen patients had incomplete data, and 4 could not be scored.

expected norms at both time points ($P \leq .01$ for all comparisons). At 12 months, surgical patients had lower unadjusted cognitive, motor composite, and gross motor scaled scores than medical patients (**Table V**). At 24 months, unadjusted differences between the groups were modestly smaller in most domains.

Among the 23 patients in the surgical group and 15 patients in the medical group who were tested at both time points, the mean cognitive and motor composite scores and gross motor scaled scores were not significantly different at the 2 time points, but the mean language composite score increased significantly (from 86 ± 12 to 93 ± 20; $P = .02$). This was attributed to both a significant increase in receptive language scaled score (from 7.3 ± 2.4 to 8.9 ± 4.0; $P = .01$) and a modest increase in expressive language scaled score (from 8.2 ± 2.3 to 9.0 ± 3.5; $P = .10$). In addition, the mean fine motor skills scaled score improved over time (from 8.0 ± 2.4 to 9.3 ± 2.7; $P = .006$).

Functional developmental outcomes are compared between the 2 groups in **Table VIII** (available at www.jpeds.com). The medical group had consistently higher motor performance than the surgical group. More importantly, the majority of patients had average or mildly delayed performance in all domains at both time points.

Using linear regression models adjusted for the same covariates included in the mortality model (ie, gestational age, antenatal steroid exposure, 1-minute Apgar score, race, and inborn status), indication for ECMO was only associated with language composite and expressive language scaled scores at 12 months. This model was further adjusted for in-hospital factors that might be associated with developmental outcomes and differed between the groups (ie,

duration of ECMO, mode of ECMO, discharge on respiratory support and culture-positive sepsis). Full models with regression coefficients for all covariates are provided in **Table III**. In the fully adjusted model, surgical patients had significantly higher language composite scores at both 12 and 24 months.

Resource utilization at 12 months and neurosensory outcomes at 24 months are provided in **Table IX** (available at www.jpeds.com). More surgical infants were receiving physical, occupational, speech, and feeding therapy, and more medical infants were receiving therapy from a special instructor at 12 months. Although the rate of abnormal hearing screen at discharge was higher in the surgical group, the rate of suspected or confirmed hearing impairment did not differ between the 2 groups at 24 months. Although rates of cerebral palsy were low in both groups, surgical infants were more likely to have abnormal tone at 24 months.

Discussion

In our large retrospective cohort of 191 neonates treated with ECMO, overall survival was similar to what has been reported by ELSO,[15] but neonates with surgical conditions had lower survival, more comorbidities, and delayed development at the end of the first year of life compared with infants with medical indications for ECMO. Sharma et al recently reported a one-third reduction in neonatal ECMO for respiratory indications, but an increase in its use for patients with complex diagnoses such as CDH along with prolonged ECMO runs and significantly decreased survival.[16] Previous single-center and review studies have reported similar survival rates in infants with CDH, and even called into question the use of ECMO for this indication.[6,17] Multiple studies have attempted to assess the impact of management changes over time that may influence survival, such as the timing and method of ECMO initiation, timing of surgical repair, and use of various clinical protocols, with conflicting results and little change in survival over time.[18,19] Previous studies have shown that early referral (<24 hours) of patients with CDH to an ECMO center is correlated with increased survival.[20-23] Survival among surgical patients in our cohort improved after opening of the SDU within our hospital, suggesting that immediate access to the surgical and ECMO teams and ancillary services may improve survival in these high-risk patients.

ECMO-related complication rates were similar in the present study and a 2017 ELSO report.[24] In our cohort, 19% had confirmed seizures and 28% had evidence of any grade of ICH or periventricular leukomalacia. Not all of our patients underwent brain magnetic resonance imaging, which might have identified more subtle injuries missed on cranial ultrasound.[25-28] Furthermore, the more severely ill infants may have been more likely to undergo magnetic resonance imaging.

Twenty-five years ago, Bernbaum et al conducted a retrospective review assessing the relationship between primary diagnosis and outcomes at 6 and 12 months among ECMO survivors.[29] The CDH cohort had a higher incidences of chronic lung disease and gastroesophageal reflux and lower motor and cognitive scores at age 1 year using the Bayley Scales of Infant and Toddler Development, Second Edition.[29] In our larger contemporary cohort, surgical infants more often required feeding tubes and respiratory support at discharge and were receiving more treatments than the medical group at 1 year. Unadjusted developmental scores were modestly lower in the surgical group compared with the medical group at 1 and 2 years; however, the surgical group also had younger gestational age and greater illness severity, including longer duration of ECMO, ventilation, and hospitalization, and greater need for tracheostomy, all of which are known to confer higher risk for developmental delays. In the fully adjusted model, language development scores were significantly higher in the surgical group than in the medical group. This suggests that continued efforts to minimize the duration of ECMO and in-hospital complications, such as sepsis, may lead to improved developmental outcomes in this high-risk population.

In our cohort, infants in the surgical group were more likely to be delivered at an earlier gestational age than medical infants. The CDH Group Registry recently reported worse outcomes at younger gestational ages.[30,31] None of the infants in our surgical cohort underwent fetal intervention that could explain their younger gestational age. Furthermore, despite differences in gestational age between the groups, gestational age was not an important factor in our multivariable analyses of mortality or developmental outcomes after ECMO.

Only a few studies have reported long-term follow-up after ECMO.[32] In our cohort, most children had developmental skills in the average range, although more children had mild or severe delays than would be expected in the general population. Although the majority of the children were receiving outpatient therapy, the surgical cohort had persistent delays in gross motor development. Longitudinal follow-up of the United Kingdom ECMO Trial also found that patients with CDH treated with ECMO had poorer motor function performance at 6 and 12 months, highlighting the need to analyze subgroups individually and provide follow-up beyond the first year of life.[33,34]

A key finding of the present study is our relatively low rate of neurodevelopmental follow-up, particularly among patients with medical indications for ECMO. Similar problems with attrition have been reported previously. In a single-center 1-year ECMO follow-up clinic in the United Kingdom, follow-up rates were similar to those in the present study.[35] Among the 50% assessed at 1 year, neurodevelopmental morbidity was identified in one-third of patients.[35] Many of those lost to follow-up had significant neurologic complications during their course of hospitalization. In our institution, families are counseled about the need for neurodevelopmental follow-up before delivery and throughout their N/IICU stay. However, for outborn infants, traveling

long distances for follow-up can be logistically difficult and stressful for families of high-risk patients.[36] More broadly, established follow-up clinics are not widely available, and guidelines on the timing and frequency of follow-up are lacking. Although ELSO previously recommended that centers offer follow-up until age 5 years in infants treated with ECMO, very few centers can provide this level of follow-up.[37] In The Netherlands, follow-up is a standard of care to all neonates treated with ECMO with a follow-up rate of 75% at age 8 years; however, this is not an accepted standard of care and remains a challenge in most settings.[38] In addition, there are often funding limitations when certain insurance plans or state policies do not cover the cost of additional services, including therapies and developmental assessments. Novel strategies to identify and address such barriers are needed to provide optimal postdischarge developmental care of this population.

Strengths of our study include the 10-year study period at a large academic institution and consistent care practices, particularly for management of neonates with CDH. Our data provide detailed information about inpatient complications and standardized developmental assessment up to 2 years in a large contemporary population of neonates treated with ECMO, with key comparisons between infants treated for medical and surgical indications. Compared with most previous reports, our study includes a larger population and follows developmental outcomes up to an older age.[39,40] Our updated description of neurodevelopmental outcomes of neonates treated with ECMO highlights the need for standardized, rigorous developmental surveillance in this high-risk population.

Limitations of the study include its retrospective nature and low follow-up rate. Owing to missing data, we did not adjust for socioeconomic factors, such as maternal education status, that are known determinants of neurodevelopmental outcomes. Lack of outcome information in survivors lost to follow-up may bias results, particularly when there is differential loss to follow-up between the 2 groups being compared. Once infants are decannulated, our institution generally transfers them back to their birth hospitals, which maintains continuity of care in their own region and alleviates strain on parents' ability to visit but may lead to loss of longer-term developmental follow-up in the quaternary center. Similarly, outcome information extracted from other visits outside of our Neonatal Follow-up Program may have missed the presence or absence of abnormal findings that otherwise would have been picked up on a standardized test, such as the Bayley-III, or by a trained psychologist and/or follow-up provider. Previous research has suggested that lower-risk children are most likely to be lost to follow-up.[41] Consistent with previous findings, the children lost to follow-up in our cohort were less ill and thus at lower risk for poor outcomes. In contrast, other studies have reported higher rates of neurodevelopmental disabilities in children who are difficult to follow.[42] Variation of ECMO practices between institutions and over time may have had an unmeasured impact on outcomes in our cohort. However, because our study had broad inclusion criteria and most of our short-term outcomes were similar to those reported by ELSO, our longer-term outcomes should be generalizable to other large populations of infants placed on ECMO. Finally, this study was designed to answer the question of whether infants cannulated to ECMO for medical indications vs surgical indications have different outcomes, and was not intended to specifically identify other predictors of developmental outcomes.

In conclusion, infants with a surgical condition leading to ECMO had lower survival rates with more medical comorbidities before discharge compared with those with medical indications. Among those tested with the Bayley-III, most children scored within the expected range for their age, although surgical patients were more likely than medical patients to have early delayed motor development. These results highlight the need for early intervention and close developmental surveillance for children treated with ECMO. Counseling regarding early psychological assessment and follow-up should begin in the prenatal period, and larger referral and regional centers should partner together to identify barriers to participation in follow-up. It is imperative to standardize and improve rates of neurodevelopmental follow-up over the first several years of life, and next steps should include following survivors through school-age to evaluate and support each child's ongoing developmental needs. ■

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Table IV. ECMO course details and therapies before cannulation and mechanical and patient-related complications during ECMO course

Parameters	Medical (N = 96)	Surgical (N = 95)	*P* value
Other therapies used before ECMO			
Inotrope	91 (95)	89 (94)	.74
Surfactant	60 (63)	10 (11)	<.0001
Inhaled nitric oxide	90 (94)	86 (91)	.41
Steroids	45 (47)	49 (52)	.52
Muscle relaxant	62 (65)	54 (57)	.27
Prostaglandin	6 (6)	17 (18)	.013
Mechanical complications			
Oxygenator failure	2 (2)	8 (8)	.06
Tubing rupture	2 (2)	0 (0)	.50
Pump malfunction	2 (2)	2 (2)	.99
Cannula problems	15 (16)	9 (9)	.28
Clots	24 (25)	30 (32)	.31
Air in circuit	0 (0)	1 (1)	.50
Patient-related complications			
Intracranial hemorrhage or stroke	11 (11)	12 (13)	.80
Cannula site bleeding	9 (9)	6 (6)	.59
Surgical site bleeding	0 (0)	9 (9)	.002
Cardiac tamponade	2 (2)	1 (1)	.99
Systemic hypertension requiring medication	18 (19)	18 (19)	.97
Arrythmia	1 (1)	4 (4)	.21

All results presented as n (%).

Table VI. Perinatal characteristics of neonates in survivors seen at 12 and/or 24 months vs survivors not seen at follow-up

Characteristics	Survivors seen at 12 and/or 24 m (N = 75)	Survivors not seen (N = 61)	*P* value
Gestational age, wk, mean ± SD	38.0 ± 1.8	38.2 ± 1.7	.59
Birth weight, g, mean ± SD	3149 ± 505	3146 ± 553	.97
Female sex, n (%)	38 (51)	23 (38)	.13
Maternal race and ethnicity, n (%)			.19
African American/black	17 (24)	21 (39)	
Caucasian or white	50 (70)	30 (56)	
Other*	4 (6)	3 (6)	
Antenatal steroids, n (%)	8 (11)	3 (5)	.34
Multiple gestation, n (%)	0 (0)	1 (2)	.45
Cesarean section, n (%)	42 (56)	26 (43)	.12
1-minute Apgar, n (%)	4.6 ± 2.5	5.8 ± 2.6	.01
5-minute Apgar, n (%)	6.9 ± 2.0	7.2 ± 1.9	.35
Inborn, n (%)	41 (55)	11 (18)	<.0001
Age at admission to CHOP if not inborn, d, mean ± SD	1.6 ± 2.7	1.6 ± 1.2	.95
Medical indication for ECMO, n (%)	28 (37)	51 (84)	<.0001

*Unknown in 10 patients.

Table VII. Major inpatient outcomes of survivors seen at 12 and/or 24 months compared with survivors lost to follow-up

Inpatient outcomes	Survivors seen at 12 and/or 24 mo (N = 75)	Survivors not seen (N = 61)	*P* value
Any documented intracranial hemorrhage or periventricular leukomalacia on postnatal ultrasound or magnetic resonance imaging during hospitalization, n (%)	21 (28)	23 (38)	.23
Seizures confirmed on electroencephalography, n (%)	11 (15)	9 (15)	.99
Culture-proven sepsis, n (%)	21 (28)	8 (13)	.04
Tracheostomy, n (%)	4 (5)	2 (3)	.56
Transferred to another acute care facility before discharge, n (%)	3 (4)	21 (34)	<.0001
Length of hospitalization among those discharged alive and not transferred to another acute care facility, d, median (IQR)	76 (51-112)	45 (31-87)	.006
Duration of mechanical ventilation after decannulation until extubation or tracheostomy among those discharged alive and not transferred to another acute care facility, d, median (IQR)	16 (7-31)	7 (4-17)	.007

Table VIII. Bayley-III composite scores, comparison by categories of function

	Medical, n (%)			Surgical, n (%)			
Categories	Average	Mildly delayed	Severely delayed	Average	Mildly delayed	Severely delayed	*P* value
12 mo*		N = 20			N = 33		
Cognitive	18 (90)	2 (10)	0 (0)	21 (64)	11 (33)	1 (3)	.10
Language	9 (45)	10 (50)	1 (5)	21 (64)	9 (27)	3 (9)	.24
Motor	17 (85)	3 (15)	0 (0)	16 (48)	10 (30)	7 (21)	.02
24 mo†		N = 23			N = 38		
Cognitive	17 (74)	4 (17)	2 (9)	24 (65)	8 (22)	5 (14)	.75
Language	16 (73)	4 (18)	2 (9)	21 (58)	8 (22)	7 (19)	.47
Motor	18 (86)	1 (5)	2 (10)	18 (51)	8 (23)	9 (26)	.03

*One patient was not tested during the follow-up visit at 12 months.
†One patient could not be categorized in the cognitive domain, 3 patients could not be categorized in the language domain, and 5 patients could not be categorized in the motor domain.

Table IX. Additional therapies and neurosensory outcomes in survivors followed up

Parameters	Medical	Surgical	*P* value
Therapies received and equipment used at 12 mo	N = 42	N = 47	
Any type of therapy	22 (52)	36 (77)	.02
Physical therapy	15 (36)	33 (70)	.001
Occupational therapy	9 (21)	24 (51)	.004
Special instructor	5 (12)	0 (0)	.02
Speech, communication, or feeding therapy	9 (21)	22 (47)	.01
Feeding equipment	7 (17)	27 (57)	<.001
Neurosensory outcomes at 24 months	N = 45	N = 49	
Hearing impairment (sensorineural and/or conductive), suspected or confirmed*	8 (18)	6 (13)	.57
Visual impairment, suspected or confirmed	7 (16)	2 (4)	.08
Cerebral palsy†	4 (9)	3 (7)	.71
Abnormal tone on neurologic examination‡	10 (23)	26 (58)	.001

All results presented as n (%).
*Unknown in 2 patients.
†Unknown in 7 patients.
‡Unknown in 6 patients; abnormal tone includes either high or low tone on neurologic examination.