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Early Neurodevelopmental Outcomes in Children Supported with ECMO for Cardiac Indications

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Abstract

Extracorporeal membrane oxygenation (ECMO) is life saving for many critically ill children with congenital heart disease (CHD). However, limited information is available about their ensuing neurodevelopmental (ND) outcomes. We describe early ND outcomes in a cohort of children supported with ECMO for cardiac indications. Twenty-eight patients supported with ECMO at age < 36 months underwent later ND testing at 12-42 months of age using the Bayley Scales of Infant

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and Toddler Development, Third Edition (Bayley-III). ND scores were compared with normative means and with ND outcomes of a matched cohort of 79 children with CHD undergoing cardiac surgery but not requiring ECMO support. Risk factors for worse ND outcomes were identified using multivariable linear regression models. Cardiac ECMO patients had ND scores at least one standard deviation below the normative mean in the gross motor (61%), language (43%), and cognitive (29%) domains of the Bayley-III. Cardiac ECMO patients had lower scores on the motor, language, and cognitive domains as compared to the matched non-ECMO group and clinically important (1/2 SD) differences in the motor domain persisted after controlling for primary caregiver education and number of cardiac catheterizations. Risk factors of worse ND outcomes among cardiac ECMO patients in more than one developmental domain, included older age at first cannulation and more cardiac catheterization and cardiac surgical procedures prior to ND assessment. Overall, children supported on ECMO for cardiac indications have significant developmental delays and warrant close ND follow-up.

Keywords

ECMO; neurodevelopment; cardiac; toddlers; assessment; developmental delay

Introduction

Extracorporeal membrane oxygenation (ECMO) has been successfully used to support refractory cardio-respiratory failure in children with heart disease, ranging from congenital heart disease (CHD), often after open heart surgery, to acquired lesions such as myocarditis [1–5]. It is estimated that 2–5% of all children undergoing cardiac surgery are supported with ECMO in the post-operative period [6,7], with survival to discharge ranging between 40–49% [8]. Although ECMO is lifesaving, significant long-term adverse medical outcomes, including sensorineural hearing loss [9], chronic kidney disease [10], and neurologic complications are common and reduce quality of life in ECMO survivors [11]. Neurologic complications acquired during ECMO, including seizures, intracranial hemorrhage, and stroke [11,12], are observed in 19% of cardiac ECMO survivors and associated with significant long-term functional impairment [13].

Compared to the many recent studies documenting short-term survival after ECMO support for children with cardiac disease [11,14,15], far fewer studies report long-term functional and neurodevelopmental (ND) outcomes for these children [15–17]. Currently, available studies describing ND outcomes in cardiac ECMO survivors [18–22] report a wide range of rates of developmental disability (20–50%). Studies reporting in-person ND testing [19,21] have shown worse ND outcomes than studies utilizing telephone questionnaires [18,20] with in-person testing noting cognitive domains to be more commonly impacted than motor domains [19,21]. In addition, worse ND outcomes were shown to be associated with factors such as genetic abnormalities, time to resolution of lactic acidosis after ECMO deployment, inotrope score, and aortic cross clamp time in children undergoing cardiac surgery prior to ECMO [21].

In our single-center study, we describe early ND outcomes in a cohort of young cardiac ECMO survivors using a standardized battery of in-person clinician-administered and parent-reported measures. We compare ND outcomes of children with CHD supported with ECMO after cardiac surgery with normative data and as well as with ND outcomes of a matched cohort of children with CHD who underwent cardiac surgery but did not require ECMO support to assess the extent to which ECMO contributes to additional ND risk. We also sought to identify factors associated with worse ND outcomes in cardiac ECMO survivors.

Materials and Methods

Study Population

This retrospective study included children with heart disease who underwent ND testing at the Cardiac Neurodevelopmental Program (CNP) at Boston Children's Hospital (BCH) from September 2009 through March 2016. Inclusion criteria for the ECMO cohort included: 1) ECMO support for cardiac indications < 36 months of age and survived to ND follow-up; 2) follow-up ND assessment performed at BCH after ECMO, when the patient was between 12–42 months of age; 3) parents or legal guardian signed informed consent for the addition of their ND and medical history data to the CNP registry prior to analyses. Children with a known pre-admission genetic syndrome or a known brain or spinal cord congenital or acquired anomaly known to significantly impact ND functioning were excluded from the study.

To evaluate the impact of ECMO on ND outcomes in children with CHD undergoing cardiac surgery, we identified a matched cohort of children with CHD undergoing cardiac surgery at BCH who did *not* receive ECMO support (i.e. matched non-ECMO group) and returned to CNP for ND testing during the same time frame using similar inclusion criteria as the ECMO cohort (criteria 2 and 3). All eligible non-ECMO subjects were first matched with ECMO subjects having the same cardiac diagnosis. Children with myocarditis from the ECMO cohort were not included in these matching comparisons. In addition, one ECMO subject with ASD with mitral stenosis did not have a valid match and is also not included, resulting in 25 ECMO patients who had matches (i.e. matched ECMO group).

Possible non-ECMO subject matches were then ranked by the sum of the absolute differences in age at 1st operation (but within 60 days) plus one-third of the absolute differences in age at ND testing (but within 180 days). Up to five non-ECMO subjects were matched to each matched ECMO subject, with the lowest sums selected as the matches. Any potential duplication in best-matched subjects (i.e. the same non-ECMO subject was among the highest ranked matches for two or more matched ECMO subjects) was resolved by selecting matches to minimize the sums for all pairings of the best-matched subjects. These analyses resulted in 79 patients in the matched non-ECMO group.

Demographic and Medical Details

Parents completed an intake form that included patient demographic characteristics and developmental history, such as developmental status at assessment, receipt of early

intervention services, and maternal education. Medical details were abstracted by the study team's cardiac research nurse from the participant's medical record, and ECMO data were obtained by reviewing the medical records and from BCH's ECMO database.

Clinically-obtained neurologic data was reviewed for the ECMO cohort. A pediatric neurologist (C.K.R.) reviewed clinically available electroencephalogram (EEG) reports and neuroimaging performed during and after ECMO at our institution. EEG findings were classified as presence/absence of seizures. At BCH, head ultrasounds are performed every 48 hours for newborns and young infants during ECMO support. Other radiological imaging of the brain, including computed tomography (CT) or brain magnetic resonance imaging (MRI), are performed for clinical indications. Brain imaging findings were dichotomized based on presence/absence of parenchymal brain injury, with injury further specified as diffuse or focal. Diffuse injury was defined as injury to both hemispheres or to cortical and subcortical tissue of at least three lobes in a single hemisphere. Focal injury included small intraventricular hemorrhage, focal ischemic infarction, focal parenchymal hemorrhage, or non-specific T2 hyperintensities. Given the diverse methods of neuroimaging used across the study cohort, accurate assessment of parenchymal volume loss was not possible and hence not analyzed. Ventriculomegaly and developmental brain malformations were not classified as injuries and are not reported.

Neurodevelopmental Assessment

The Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III) [23] was administered by a licensed clinical psychologist. The Bayley-III is a standardized measure evaluating development of infants and children up to 42 months of age. Standard composite scores (normative mean $\pm$ standard deviation [SD]: 100 ± 15) and subscale scores (10 ± 3) are reported for the cognitive, language, and motor domains. Parents were also interviewed using the Receptive-Expressive Emergent Language Test, Third Edition (REEL-3) [24] to obtain descriptions of typical communicative abilities they observed at home. Standard scores (100 ± 15) for the receptive language, expressive language, and overall language ability domains were obtained.

In addition, parents completed the Bayley Social-Emotional and Adaptive Behavior Questionnaire [23], a standardized questionnaire assessing the social-emotional and adaptive functioning of children observed at home. Standard composite scores for overall socio-emotional functioning, adaptive functioning, conceptual, social, and practical domains (100 ± 15) as well as related subscales (10 ± 3) are reported. To assess behavior and socio-emotional functioning of children < 2 years of age, parents completed the Infant-Toddler Social and Emotional Assessment (ITSEA) [25], while parents of children ≥ 2 years of age completed the Behavior Assessment System for Children, Second Edition (BASC-2) [26]. T scores of the Externalizing Problems and Internalizing Problems Composites (50 ± 10) for the ITSEA and BASC-2 were obtained. For participants seen at multiple visits, we analyzed data from the most recent visit in which all three domains of the Bayley-III were completed.

Statistical Analyses

Descriptive statistics, including means, medians, standard deviations, and ranges, were calculated for continuous variables and frequency counts and percentages for categorical variables. We compared demographic and medical details of our ECMO cohort, i.e. children supported with ECMO for cardiac indications at BCH during the study period and who returned for ND follow-up, with similar children who did not return for ND follow-up using Fisher's exact tests for categorical measures and Kruskal-Wallis tests for continuous measures to assess for selection bias. For our ECMO cohort, we compared standard scores to normative mean scores using 1-sample *t*-tests. Effect sizes are represented by Cohen's *d*, i.e. the difference of the sample mean from the normative mean divided by the sample SD. Percentage of participants who had standard scores <85 and <70 were also calculated. Standard scores <85 are indicative of moderate-severe ND delay [27].

We also compared demographic, medical history, and ND outcomes of the matched ECMO patients with ND outcomes of the matched non-ECMO patients. Group comparisons were obtained by repeated measures regression models with compound symmetry within-group covariance matrix for continuous measures or conditional logistic regression for binary measures; follow-up analyses of the ND outcomes adjusted for primary caregiver education and number of cardiac catheterizations.

Spearman correlations were used to examine the relationships of ND outcomes with ECMO measures. Linear regression models were used to examine the relationships between specific ND outcomes (i.e. Bayley-III composite and subscale scores; the General Adaptive Composite [GAC], Conceptual Composite, Social Composite, and Practical Composite scores from the Bayley Social-Emotional and Adaptive Behavior Questionnaire) and potential risk factors for the ECMO subjects. Given that our regression analyses were exploratory in nature, a range of medical- and ECMO- specific risk factors known to be associated with worse ND outcomes in children with CHD were considered [28–30]. Risk factors included *demographic details*: sex and Hispanic ethnicity; *medical history details*: gestational age; cardiac anatomy; numbers of cardiac operations and catheterizations; occurrence of cardiac arrest, reoperation, and seizure; and presence of non-cardiac congenital anomalies; *ECMO details*: age at first cannulation; ECMO duration; hospital length of stay (LOS); extracorporeal cardiopulmonary support following cardiac arrest (ECPR); and chest cannulation; *peri-ECMO details*: any anatomic brain injury; and *post-ECMO details*: time from first cannulation to ND assessment. Linear regression was used to identify significant predictors ($p < 0.05$) of lower ND scores after adjustment for primary caregiver education. Predictors associated with ND outcomes at a level of $p < 0.15$ were considered for inclusion in multivariable linear regression models. Stepwise backward elimination was conducted with criterion for risk factor retention set at $p < 0.05$.

Data for purposes of this study were collected and managed using REDCap electronic capture tools [31]. Statistical analyses were performed using SAS (version 9.4, SAS Institute, Cary, NC).

Results

ECMO Population

Between April 2007 and May 2014, 184 children with CHD < 36 months of age underwent 222 runs of ECMO for cardiac indications at BCH and 82 (45%) survived to hospital discharge. Among the 82 survivors, six children died before 24 months of age, and five patients were excluded due to diagnosis of genetic syndrome ($n = 4$) or brain malformation ($n = 1$). Of the remaining 71 patients, 25 (35%) returned to BCH for ND follow-up between 12–42 months of age. Patients not returning for follow-up included children who lived outside of the New England (CT, MA, RI, NH, VT, ME) and NY area ($n = 15/46$; 33%) and those living outside the US ($n = 7/46$; 15%) (Figure 1). Demographic, medical, and ECMO characteristics for patients seen for ND follow-up were comparable to those who were not seen (i.e. sex, cardiac anatomy, number of ECMO runs, age at first cannulation, ECMO LOS, duration of ECMO, duration of CPR, and chest cannulation) with the exception of ECPR. Patients who were not seen for ND follow-up were less likely to undergo ECPR than those who were seen for ND follow-up (54% vs 80%, $p = 0.04$). We included three additional children who underwent ND evaluation and otherwise met the study inclusion criteria except that they received cardiac ECMO support at another medical facility, resulting in the study cohort of 28 children with ECMO (i.e. cardiac ECMO group).

Demographic and Medical Characteristics

Demographic and medical characteristics for the cardiac ECMO cohort, matched ECMO cohort, and matched non-ECMO cohort are presented in Table 1. Of the 28 cardiac ECMO patients, 3 (11%) were born preterm (gestational age < 37 weeks) and 21% had non-cardiac congenital anomalies. Cardiac diagnoses included 29% with single ventricle CHD and 7% with acquired heart disease (i.e. myocarditis). The matched ECMO group was comparable to the matched non-ECMO group on most demographic and medical characteristics with the exception of events prior to ND assessment: the matched ECMO group had higher number of cardiac operations and cardiac catheterizations and was more likely to have reoperations and seizures than the matched non-ECMO group (Table 1).

ECMO support information for the cardiac ECMO group is presented in Table 2. Median age at ECMO was 5.4 weeks and for 20 patients (71%) ECMO was initiated during cardiac arrest. Median total ECMO duration was 96 hours. Peri-ECMO brain imaging was available for 25 patients (89%) including brain MRI for 9 patients, head CT for two patients, and head ultrasound for 14 patients. Results of the imaging showed parenchymal brain injury in 11 patients (44%), with diffuse injury in 7 (28%), and focal injury in 4 (16%) patients. Detailed neurological findings on imaging for each ECMO recipient are outline in Table 5. Only 10 patients (36%) had EEG testing, and of those 4 had EEG seizures.

ND Assessment

Cardiac ECMO patients underwent ND assessment at median age of 25 months (IQR: 18–33 months) and at a median of 19 months (IQR: 13–28 months) after their first ECMO cannulation. At the time of ND assessment, 8 (29%) were fed with gastrostomy tube, 3 (11%) had a tracheostomy tube, and 1 (4%) had hearing loss. Additionally, 20 of 26 children

(77%) were receiving early intervention services for a median duration of 2 hours per week (IQR: 1.3–3 hours per week).

Results of ND assessment are presented in Table 3. Comparing the cardiac ECMO patients to the normative means on the Bayley-III, we found that participants showed the poorest performance in the motor domain. The Motor Composite score (mean = 80.4) was significantly lower than the normative mean ($p < 0.001$) with a large effect size of -1.07 ; additionally, 17 participants (61%) scored ≥ 1 SD below the normative mean. Scores on the Gross Motor subscale were the lowest (mean = 5.7, $p < 0.001$). The Language Composite score (mean = 87.6) was significantly lower than the normative mean ($p = 0.003$) with a moderate effect size of -0.61 . The Cognitive Composite score (mean = 93.4) was not significantly different from the normative mean and had an effect size of -0.32 . On the REEL-3, the mean Receptive Language, Expressive Language, and Language Ability scores were each approximately $2/3$ SD lower than their respective normative means ($p = 0.01$, $p = 0.003$, and $p = 0.006$, respectively).

On the Bayley Social-Emotional and Adaptive Behavior Questionnaire, the mean GAC score, indicative of overall adaptive functioning, for the cardiac ECMO group was significantly lower than the normative mean ($p = 0.007$) with a moderate effect size of -0.64 and 8 of 22 patients (36%) scoring ≥ 1 SD below the normative mean. Specifically, the cardiac ECMO group scored significantly lower than the normative mean in the health and safety, self-care, and motor domains. Social-Emotional Composite scores were comparable to the normative mean. Mean scores for the Externalizing Problems and Internalizing Problems subscales of the ITSEA and the BASC-2 also did not differ significantly from their normative mean scores. Notably, these sample sizes were small.

In comparing ND scores of the matched ECMO group to the matched non-ECMO group, we found that matched ECMO subjects had lower composite scores on average and larger standard deviations for the cognitive, language, and motor domains of the Bayley-III as compared to the matched non-ECMO subjects (Table 3). After adjusting for primary caregiver education and number of cardiac catheterizations, the Bayley-III motor composite mean of the matched ECMO group was approximately $1/2$ SD lower than the non-matched ECMO group, although this difference did not reach statistical significance (estimated difference [95% confidence interval] -8.2 [-16.5 , 0.1], $p = 0.05$). Interestingly, no differences were found between the two groups on parental measures of language, adaptive, and behavioral functioning.

Factors Associated with Reduced ND Performance for Cardiac ECMO Survivors

Among relationships of Bayley-III composite and subscale scores and Bayley Social-Emotional and Adaptive Behavior Questionnaire composite scores with ECMO variables for the cardiac ECMO group, older age at first cannulation was significantly associated with lower Bayley-III Expressive Communication subscales scores ($r_s = -0.39$; $p = 0.04$) and lower GAC scores ($r_s = -0.43$; $p = 0.045$).

Results of linear regression modeling to identify risk factors associated with lower ND scores in the cardiac ECMO group are presented in Table 4. After adjusting for primary

caregiver education, factors associated with poor ND performance in more than one assessment domain included older age at first cannulation for lower GAC scores, including specifically lower Conceptual Composite and Social Composite scores; higher number of cardiac catheterization procedures for lower Bayley-III Cognitive Composite and Motor Composite scores, including specifically lower Expressive Communication and Fine Motor subscale scores; higher number of surgical procedures for lower Bayley-III Language Composite scores, including specifically lower Receptive Communication subscale scores; and male sex for lower GAC scores, including specifically lower Conceptual Composite scores.

Discussion

In this single-center study examining early ND outcomes in children supported with ECMO at <36 months of age for cardiac indications, we found significant delays in multiple areas of development: language, motor, and adaptive functioning. Gross motor skills were most impaired. Approximately 29% of the patients had cognitive delays. Children with CHD requiring ECMO support after cardiac surgery had lower performance on the motor domain of the Bayley-III compared to matched children with CHD who did not require ECMO support. Worse ND outcomes were associated with multiple medical and demographic factors including older age at first cannulation, more cardiac catheterization procedures, and more cardiac operations. Additionally, 44% of our study cohort of ECMO survivors had central nervous system (CNS) injury documented by radiological imaging of the brain. Our findings underscore the high incidence of ND and neuroimaging abnormalities in children supported with ECMO for cardiac indications and thus the need for early ND assessment to improve long-term outcomes of cardiac ECMO survivors.

ND Outcomes

Prior studies of ND outcomes in cardiac ECMO survivors found higher incidence of cognitive delays (approximately 50% in some studies) [19,21], whereas our findings highlighted a larger impact on language and motor domains than cognition. The inclusion of children with genetic syndromes in prior studies may explain the higher incidence of cognitive delays. The higher incidence of motor delays in our cohort could be potentially attributed to immobility as a result of the use of sedation and neuromuscular blocking agents during ECMO, long hospitalization, and exercise restriction during hospitalization and after discharge as well as the increased percentage (71%) of patients in our study who received ECPR which is known to be associated with worse neurologic outcomes [15]. Alternatively, motor dysfunction may possibly be related to the high rate (44%) of neuroimaging abnormalities seen on brain imaging. Other studies describe a progressive decline in motor function over time in the ECMO population [32] and a study of quality of life in cardiac ECMO survivors [33] showed reduced physical functioning compared with a normative population during long-term follow-up. These issues highlight the need for, and early initiation of, physical and occupational therapy to maintain motor function and continuous evaluation for motor disability in ECMO survivors, especially in those with CNS abnormalities on brain imaging studies.

Language delays seen in our study may have resulted from unrecognized sensorineural hearing loss [9], or may be due to poor oral motor coordination. Hearing loss is seen in 25% of ECMO survivors and may be present at the time of discharge, or may develop or worsen over time [9]. Thus, systematic hearing evaluations are essential in ECMO survivors, especially for those presenting with language delays, and children should be evaluated for speech and language challenges in order to provide speech services if necessary.

Neurological Injury

The high incidence of abnormalities on brain imaging highlights the vulnerability of this population to neurological injury. While it is possible that known neurological injury is associated with return for follow-up, possibly biasing our results to a high estimate, only a subset of our study cohort underwent detailed neuroimaging with brain MRI and/or head CT. Sedation and paralysis often limit clinical neurological assessment and diagnosis of seizures. Given the known risk of seizures in this population [11], children on ECMO benefit from routine EEG monitoring. Indeed, the American Clinical Neurophysiology Society identifies neonates requiring ECMO as a high risk scenario in which long-term EEG monitoring should be considered [34]. Early control of seizures may also lower the neurologic morbidity [12]. The risk of brain injury during ECMO may be affected by a multitude of variables, including indication for ECMO, timing of ECMO deployment, optimization of ECMO support, anticoagulation, and use of optimal neuro-monitoring and protective therapies during ECMO. Further research into how these factors contribute to brain injury could better inform ECMO care pathways to improve ND outcomes in survivors. Finally, a substantial proportion of ECMO survivors have radiological evidence of neurologic injury. Although advanced radiological imaging is often not feasible during ECMO support, careful consideration should be given to incorporating advanced brain imaging in ECMO patients prior to hospital discharge.

Factors Associated with Reduced ND Performance

Consistent with other studies examining the development of children with CHD [28–30], we found that factors associated with poorer ND outcomes included demographic factors such as older age at first cannulation and male sex, cardiac diagnosis (more specifically, complex cardiac disease as indicated by the need for more frequent surgical and cardiac catheterization procedures), and longer length of hospitalization.

Our data offer preliminary evidence of additional risk for worse ND outcomes in children who require ECMO support coincident with their course of cardiac clinical care. Overall, children with CHD requiring ECMO support generally had lower scores for most domains of the Bayley-III compared to a matched group of children with CHD who did not require ECMO support. Though these findings were tempered after adjusting for primary caregiver education and number of catheterizations, the sizeable difference persisting for the motor domain (1/2 SD) between these groups despite the small study sample size encourages further examination of the additional risk posed by ECMO in larger studies.

In examining ECMO-specific factors associated with worse outcomes, we found that while age at ECMO initiation was associated with worse ND outcomes, duration of ECMO was

not. This may be due to the short duration of ECMO support that cardiac patients receive compared to duration of ECMO for other indications. Further research is needed to identify other ECMO factors that contribute to adverse ND outcomes as modification of these factors may help enhance the quality of life of the cardiac ECMO survivor.

Need for Structured ND Follow-up

Given the level of developmental delay seen in our ECMO patients our study not only highlights the need for longitudinal follow-up [35] but also illustrates some important challenges to ND follow-up in ECMO survivors managed at tertiary centers. Only about a third of ECMO survivors from our center returned for follow-up. Low follow-up rates may be related in part to absence of a structured ND follow-up program for ECMO survivors, distance from or availability of local services, or lack of knowledge regarding ND morbidities in ECMO survivors. We hypothesize that parent education on the importance of ND follow-up and a structured referral pattern to ND specialists may help promote ND follow-up in these patients. A structured ND follow-up program should include standardized assessment tools, predetermined time points for follow-up, and seamless referral to early intervention services to help optimize ND outcomes for ECMO survivors [36,37]. Finally, tertiary care ECMO programs should be able to refer ECMO survivors to ND follow-up centers locally when ECMO care is provided at tertiary care centers far away from their area of residence. These services should begin soon after discharge and continue into adolescence and adulthood as studies have shown that early neurocognitive deficits of ECMO survivors persist into school age and young adulthood, impacting their well-being, adaptation, and quality of life. [32,33,38,39]

Limitations

Our study is limited by the small number of ECMO patients who returned for follow-up and hence our results may have reduced generalizability. The study was conducted in a single center with substantial experience with cardiac ECMO, also potentially limiting generalizability. We used length of hospitalization and number of cardiac surgical and catheterization procedures as surrogates for severity of illness rather than the physiologic postoperative factors such as low cardiac output. We compared ND outcomes of ECMO survivors with CHD against children with CHD who underwent cardiac surgery but did not receive ECMO by matching, but our analyses should be viewed as exploratory and interpreted with caution given the small sample size. Though we matched patients on cardiac diagnosis, the ECMO survivors had worse medical courses requiring more cardiac operations and catheterizations and were medically more challenged than patients who did not receive ECMO, suggesting an equitable matched group may not exist. In addition, given that our regression analyses to identify risk factors for worse ND outcomes were exploratory in nature, additional confirmation of findings is needed in future studies. Although we reviewed existing clinical neuroimaging data, due to the retrospective nature of the study, not all patients underwent neuroimaging, and the modality and timeframe of imaging varied. This heterogeneity limits interpretation of the imaging data and precluded exploration of associations between neurodevelopment and structural brain abnormalities. In addition, we collected information on whether the parents reported the patients had documented hearing

loss, but did not collect systematic information on the frequency and results of hearing evaluations for purposes of this study. Finally, ND testing at a young age has limited predictive validity for later development [40]; thus longitudinal follow-up is essential to better understand the trajectory of ND function after ECMO.

Conclusions

Our study shows that children supported with ECMO for cardiac indications are at high risk for developmental delays. We found that motor and language domains are more commonly affected than cognition. Consistent with the general literature on cardiac neurodevelopment, worse ND outcomes in ECMO survivors are associated with a greater number of cardiac surgical and catheterization procedures, as well as with longer LOS. Finally, older age at cardiac ECMO was associated with worse ND outcomes. Our findings add to the ECMO literature in highlighting the need for a standardized and long-term ND follow-up program to support developmental functioning and quality of life in this vulnerable population.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Figure:
Flow Chart of Cardiac ECMO Recipients in Study

TABLE 1.**Demographic and Medical History Characteristics of Study Participants**

Variable	ECMO (N = 28)	Matched ECMO ^a (N = 25)	Matched Non-ECMO ^a (N = 79)	Estimated Difference or Odds Ratio (95% CI) ^b	<i>p</i> ^b
<i>n/N (%) or Median (IQR)</i>					
Demographic characteristics					
Male sex	17/28 (61)	15/25 (60)	45/79 (57)	1.2 (0.5, 3.1)	0.68
Caucasian race	22/28 (79)	21/25 (84)	66/77 (86)	1.0 (0.3, 3.6)	0.94
Hispanic ethnicity	6/28 (21)	5/25 (20)	5/76 (7)	3.5 (0.7, 18.2)	0.14
Primary caregiver education: Bachelor's or graduate degree	14/28 (50)	12/25 (48)	46/78 (59)	0.6 (0.2, 1.6)	0.28
Age at neurodevelopmental assessment (mo)	24.5 (17.5–33)	24 (17–33)	23 (17–33)	−0.4 (−1.5, 0.6)	0.41
Medical history characteristics					
Birth weight (kg)	3.1 (2.6–3.5)	3.2 (2.5–3.6)	3.3 (2.8–3.6)	−0.09 (−0.41, 0.23)	0.55
Gestational age (wk)	39 (37.5–40)	39 (37–40)	39 (38–39)	0.3 (−0.8, 15)	0.56
Non-specific genetic diagnosis	3/28 (11)	2/25 (8)	9/79 (11)	0.5 (0.1, 2.7)	0.46
Cardiac anatomy				–	–
Single ventricle	8/28 (29)	8/25 (32)	17/78 (22)		
Biventricle	18/28 (64)	17/25 (68)	61/78 (78)		
Myocarditis	2/28 (7)	0	0		
Non-cardiac congenital anomaly	6/28 (21)	5/25 (20)	11/79 (14)	1.9 (0.5, 7.1)	0.32
Age at first operation (d)	5.5 (3–20)	5 (3–13)	6 (3–14)	−5.9 (−13.3, 16)	0.12
Events prior to neurodevelopmental assessment					
Number of cardiac operations	2 (1–3)	2 (1–3)	1 (1–2)	1.0 (0.5, 1.6)	<0.001
Number of cardiac catheterizations	3 (1–6.5)	3 (1–7)	1 (0–2)	3.5 (2.4, 4.7)	<0.001
Any cardiac arrest	21/28 (75)	19/25 (76)	2/79 (3)	–	–
Any reoperation	11/28 (39)	10/25 (40)	6/79 (8)	4.8 (1.3, 18.1)	0.02
Any respiratory arrest	1/28 (4)	0	0	–	–
Any seizure	8/28 (29)	7/25 (28)	2/79 (3)	12.6 (2.5, 62.8)	0.002

ECMO, extracorporeal membrane oxygenation; CI, confidence interval; IQR, interquartile range.

^aSubjects were matched on cardiac diagnosis, age at first operation, and age at ND assessment. Subjects with myocarditis were not included in the comparisons. One ECMO subject with atrial septal defect with mitral stenosis did not have a qualifying match and is also not included.

^bComparisons of the matched ECMO and matched non-ECMO group were obtained by repeated measures regression models with compound symmetry within-group covariance matrix for continuous measures or conditional logistic regression for binary measures. Only the estimates, confidence intervals, and *p* values for the group differences are shown.

TABLE 2.ECMO Characteristics of Cardiac ECMO Recipients ($N = 28$)

Variable	<i>n/N (%) or Median (IQR)</i>
<i>ECMO characteristics</i>	
Number of runs	
One	26/28 (93)
Two	2/28 (7)
Age at first cannulation (wk)	5.4 (0.7–19.4)
1 wk	10/28 (36)
> 1 to 11 wks	10/28 (36)
> 11 wks	8/28 (29)
Total duration (hr)	96 (67–155)
120 hrs	18/28 (64)
> 120 hrs	10/28 (36)
Total duration of related hospital stay (wk)	5.9 (4.9–13.4)
9 wks	17/25 (68)
> 9 wks	8/25 (32)
ECPR, any run	20/28 (71)
Duration of ECPR (min)	27 (17–42)
Chest cannulation, any run, n/N (%)	18/27 (67)
<i>Peri- and post-ECMO characteristics</i>	
Parenchymal brain injury, n/N (%)	
Diffuse	7/25 (28)
Focal	4/25 (16)
None	14/25 (56)
Time from first cannulation to neurodevelopmental assessment (mo)	19 (13–27.5)

ECMO, extracorporeal membrane oxygenation; *IQR*, interquartile range; *ECPR*, extracorporeal cardiopulmonary support following cardiac arrest.

TABLE 3.

Neurodevelopmental Outcomes of Study Participants

Outcomes	ECMO (n = 28)	<i>p</i> ^a	Matched ECMO (n = 25)	Matched Non-ECMO (n = 79)	Estimated Difference (95% CI) ^b	<i>p</i> ^b	Estimated Difference (95% CI) ^c	<i>p</i> ^c
<i>n (%) or Mean ± SD</i>								
Bayley-III								
Composite	(n = 28)		(n = 25)	(n = 79)				
Cognitive	93.4 ± 20.6	0.10	92.2 ± 20.9	101.5 ± 13.7	−9.3 (−16.8, −1.9)	0.02	−3.8 (−12.3, 4.7)	0.37
85	8 (29)		8 (32)	7 (9)				
70	4 (14)		4 (16)	4 (5)				
Language	87.6 ± 20.4	0.003	87.6 ± 21.1	97.5 ± 17.2	−9.8 (−18.3, −1.4)	0.02	−2.4 (−12.0, 7.1)	0.60
85	12 (43)		10 (40)	16 (20)				
70	4 (14)		4 (16)	6 (8)				
Motor	80.4 ± 18.3	<0.001	78.9 ± 18.8	94.5 ± 14.2	−15.5 (−22.8, −8.3)	<0.001	−8.2 (−16.5, 0.1)	0.05
85	17 (61)		17 (68)	19 (24)				
70	7 (25)		7 (28)	6 (8)				
Subscale								
Receptive Communication	8.0 ± 3.6	0.006	7.8 ± 3.7	9.9 ± 2.9	−2.1 (−3.5, −0.6)	0.007	−0.8 (−2.4, 0.8)	0.32
Expressive Communication	7.8 ± 3.7	0.003	7.9 ± 3.8	9.2 ± 3.3	−1.3 (−2.9, 0.3)	0.11	−0.1 (−1.9, 1.8)	0.94
Fine Motor	7.8 ± 3.3	0.001	7.5 ± 3.4	9.9 ± 2.8	−2.4 (−3.9, −1.0)	0.002	−1.4 (−3.0, 0.3)	0.09
Gross Motor	5.7 ± 3.0	<0.001	5.5 ± 3.1	8.2 ± 2.6	−2.7 (−4.0, −1.4)	<0.001	−1.3 (−2.7, 0.2)	0.08
REEL-3	(n = 23)		(n = 20)	(n = 63)				
Language Ability	87.3 ± 20.1	0.006	87.4 ± 20.7	93.2 ± 18.1	−5.8 (−15.8, 4.3)	0.24	−0.5 (−11.7, 10.8)	0.93
Receptive Language	90.5 ± 17.2	0.01	90.7 ± 17.9	96.5 ± 16.2	−5.7 (−14.6, 3.1)	0.19	−1.8 (−11.7, 8.1)	0.70
Expressive Language	88.2 ± 17.0	0.003	88.1 ± 17.3	92.2 ± 15.8	−3.9 (−12.5, 4.7)	0.35	1.2 (−8.5, 10.9)	0.80
Bayley Social-Emotional and Adaptive Behavior Questionnaire	(n = 22)		(n = 19)	(n = 68)				
Composite								
General Adaptive	86.6 ± 21.0	0.007	88.1 ± 21.9	91.6 ± 18.0	−4.0 (−14.6, 6.6)	0.43	−0.7 (−12.3, 10.9)	0.90
85	8 (36)		6 (32)	18 (27)				
70	7 (32)		6 (32)	11 (17)				
Conceptual	91.5 ± 21.3	0.07	93.9 ± 21.7	95.5 ± 17.9	−1.6 (−12.1, 8.8)	0.74	−0.2 (−11.9, 11.5)	0.97
85	8 (36)		6 (32)	15 (22)				
70	4 (18)		3 (16)	8 (12)				

Outcomes	ECMO (n = 28)	<i>p</i> ^a	Matched ECMO (n = 25)	Matched Non-ECMO (n = 79)	Estimated Difference (95% CI) ^b	<i>p</i> ^b	Estimated Difference (95% CI) ^c	<i>p</i> ^c
Social	90.7 ± 21.3	0.05	93.3 ± 21.7	95.0 ± 18.6	-2.8 (-13.6, 8.1)	0.60	-1.4 (-13.2, 10.5)	0.81
85	9 (41)		6 (32)	19 (28)				
70	5 (23)		4 (21)	8 (12)				
Practical	84.0 ± 17.6	<0.001	84.1 ± 18.3	89.0 ± 16.4	-5.3 (-14.7, 4.1)	0.25	-2.4 (-12.7, 7.9)	0.63
85	10 (45)		9 (47)	29 (43)				
70	5 (23)		4 (21)	11 (16)				
Social-Emotional	98.9 ± 23.2	0.82	101.3 ± 24.0	101.9 ± 23.2	-1.0 (-14.0, 12.1)	0.88	13 (12.6, 15.1)	0.85
85	7 (32)		5 (26)	21 (32)				
70	2 (9)		2 (11)	6 (9)				
Subscale								
Communication	8.7 ± 3.7	0.12	8.9 ± 3.8	9.3 ± 3.6	-0.2 (-2.2, 1.8)	0.80	-0.1 (-2.3, 2.2)	0.94
Self-direction	9.2 ± 4.2	0.37	9.7 ± 4.3	9.7 ± 3.4	-0.0 (-2.0, 2.0)	>0.99	0.1 (-2.1, 2.4)	0.91
Social	9.1 ± 4.1	0.34	9.5 ± 4.4	9.1 ± 3.4	0.4 (-1.6, 2.4)	0.70	0.4 (-1.8, 2.7)	0.68
Health and Safety	8.0 ± 3.2	0.007	7.9 ± 3.3	9.0 ± 3.2	-1.2 (3.0, 0.6)	0.17	-0.6 (2.6, 1.3)	0.50
Self-care	5.6 ± 2.7	<0.001	5.7 ± 2.9	6.2 ± 3.0	-0.6 (-2.2, 1.1)	0.49	0.2 (-1.7, 2.0)	0.84
Motor	8.0 ± 4.3	0.04	7.9 ± 4.6	8.8 ± 3.4	-0.9 (-2.9, 1.1)	0.37	0.4 (-1.8, 2.6)	0.73
ITSEA	(n = 8)		(n = 8)	(n = 27)				
Externalizing Problems	49.0 ± 7.3	0.71	49.0 ± 7.3	47.9 ± 9.7	1.0 (-8.0, 10.0)	0.79	1.8 (-7.8, 11.4)	0.66
Internalizing Problems	48.9 ± 8.0	0.70	48.9 ± 8.0	47.2 ± 10.9	1.6 (-8.6, 11.8)	0.72	1.7 (-11.2, 14.5)	0.76
BASC-2	(n = 7)		(n = 6)	(n = 28)				
Externalizing Problems	43.0 ± 8.0	0.06	44.2 ± 8.1	48.8 ± 10.9	-4.6 (-17.8, 8.7)	0.39	-3.7 (-18.2, 10.8)	0.52
Internalizing Problems	50.6 ± 13.5	0.91	53.0 ± 13.0	50.1 ± 12.9	2.7 (-12.0, 17.5)	0.63	-5.3 (-22.1, 11.6)	0.43

ECMO, extracorporeal membrane oxygenation; CI, confidence interval; SD, standard deviation; Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition; REEL-3, Receptive-Expressive Emergent Language Test, Third Edition; ITSEA, Infant-Toddler Social and Emotional Assessment; BASC, Behavior Assessment System for Children, Second Edition.

^aDetermined by one-sample *t*-test comparisons with expected population means of 100 or 10, as appropriate.

^bComparisons of the matched ECMO and matched non-ECMO groups were obtained by repeated measures regression models with compound symmetry within-group covariance matrix. Only the estimates, confidence intervals, and P values for the group differences are shown.

^cComparisons of the matched ECMO and matched non-ECMO groups were obtained by repeated measures regression models with compound symmetry within-group covariance matrix and adjusting for primary caregiver education and number of cardiac catheterizations. Only the estimates, confidence intervals, and P values for the group differences are shown.

TABLE 4.**Linear Regression Models to Predict Neurodevelopmental Outcomes of Cardiac ECMO Recipients**

Outcomes	Covariates
Bayley-III	(n = 28)
Composite	
Cognitive	Total catheterizations (per catheterization): -2.0 ± 0.8 (0.02)
Language	Total operations (per operation): -5.3 ± 1.7 (0.005)
Motor	Total catheterizations (per catheterization): -1.7 ± 0.7 (0.03)
Subscale	
Receptive Communication	Total operations (per operation): -1.0 ± 0.3 (0.002)
Expressive Communication	Total catheterizations (per catheterization): -0.4 ± 0.1 (0.01)
Fine Motor	Total catheterizations (per catheterization): -0.3 ± 0.1 (0.03)
Gross Motor	Total duration of related hospital stays, > 9 wks (vs. 9 wks): -2.9 ± 1.1 (0.01)
Bayley Social-Emotional and Adaptive Behavior Questionnaire	(n = 22)
Composite	
General Adaptive	Male (vs. female): -18.3 ± 7.8 (0.03)
	Age at first cannulation (per wk): -0.3 ± 0.1 (0.03)
Conceptual	Male (vs. female): -21.3 ± 7.9 (0.01)
	Age at first cannulation (per wk): -0.3 ± 0.1 (0.03)
Social	Age at first cannulation, > 1 to 11 wks (vs. 1 wk): -6.3 ± 8.1 (0.45)
	Age at first cannulation, > 11 wks (vs. 1 wk): -29.2 ± 8.8 (0.004)
	Any seizure: -17.0 ± 7.8 (0.04)
Practical	—

Bayley-III, Bayley Scales of Infant and Toddler Development, Third Edition.

Coefficients for intercepts and primary caregiver education are not reported.

Values are β -estimate $\pm$ standard error (p).