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Neurodevelopmental outcomes of pediatric cardiac ECMO survivors with central cannulation

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Abstract:	Extracorporeal life support, such as pediatric cardiac extracorporeal membrane oxygenation(ECMO), is associated with significant mortality and morbidity risk. This study evaluated cardiac ECMO survivors with central cannulation and found that 51.1% were discharged from the hospital. The study also revealed high rates of developmental delay (82.7%), motor dysfunction(58.8%), and cognitive dysfunction (70.6%) among survivors. No significant correlation was found between the duration of ECMO, age at ECMO, pre-ECMO maximum lactate levels, and cognitive scores. Participants with motor dysfunction were significantly younger(p=0.04). PRISM scores of those with an abnormal developmental status were significantly higher(p=0.03). Logistic regression analysis did not show a significantly increased risk. Factors such as age, disease severity, and ECMO itself were identified as potential contributors to neurodevelopmental delay.

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Abstract

Extracorporeal life support, such as pediatric cardiac extracorporeal membrane oxygenation(ECMO), is associated with significant mortality and morbidity risk. This study evaluated cardiac ECMO survivors with central cannulation and found that 51.1% were discharged from the hospital. The study also revealed high rates of developmental delay (82.7%), motor dysfunction(58.8%), and cognitive dysfunction (70.6%) among survivors. No significant correlation was found between the duration of ECMO, age at ECMO, pre-ECMO maximum lactate levels, and cognitive scores. Participants with motor dysfunction were significantly younger(p=0.04). PRISM scores of those with an abnormal developmental status were significantly higher(p=0.03). Logistic regression analysis did not show a significantly increased risk. Factors such as age, disease severity, and ECMO itself were identified as potential contributors to neurodevelopmental delay.

Keywords: ECMO, developmental, cognitive dysfunction, critical care, neuromonitoring.

Objective

Since extracorporeal membrane oxygenation (ECMO) was introduced in the late 1970s, outcomes for children receiving ECMO have improved significantly. Pediatric ECMO's overall successful weaning rate is reported to be 51.7%, and the survival to discharge rate is 37.1-56.4% (Fernando et al., 2020; Kim et al., 2017). In the surgical pediatric population, the successful weaning rate from venoarterial (VA) ECMO is as high as 70.6%. However, the in-hospital mortality rate remains at 52.9% (Jin et al., 2021). Survival to hospital discharge for children with heart disease is approximately 40% but varies widely based on age, indication for support, and underlying cardiac disease (Brown et al., 2013). Although cardiac ECMO is a life-saving intervention, it is associated with a significant risk of mortality and neurological morbidity. Moderate or severe neurological and psychosocial impairment was reported in 72.7% of children treated with ECMO (Wagner et al., 2007). Over half (56%) of long-term survivors of cardiac ECMO were reported to have neurologic morbidity (Lequier et al., 2008)[6]. Data on quality of life and neurodevelopmental outcomes for children requiring ECMO have become another focus in parallel with survival. The neurological outcomes based on the cannulation site of ECMO in children had been investigated separately. The previous studies on children's and adults' literature have explored the technical utilities, bleeding, and infectious complications. However, they did not specifically focus on the neurological outcomes based on cannulation sites (Ankola et al., 2021; Buyukgoz et al., 2023; Javidfar et al., 2012; Lorusso et al., 2019). Cui et al. (2022) found no significant difference in neurological complications between VA-ECMO compared to venovenous (VV)-ECMO with several combination of different cannulation sites (Cui et al., 2022).

This study aimed to assess the neurodevelopmental status of children treated with central VA-ECMO in a tertiary center.

Material and Methods

Participants: Between 2013 and 2020, all children supported with cardiac ECMO in a tertiary center were searched for the initial assessment. Only those who were supported by cardiac ECMO with central cannulation were included. The survivors were called by telephone and invited to the hospital for a developmental assessment besides their routine hospital checks. All survivors were included regardless of indications and interval after weaning from ECMO. Between April 2013 and December 2020, 129 children received extracorporeal life support. Among them, three children were supported by a left ventricular assist device, 31 underwent VV-ECMO, and 11 had peripheral cannulation for cardiac ECMO. Eighty-four children were supported by cardiac ECMO with central cannulation (right atrium to the aorta). Forty-three children survived at hospital discharge (51,1%). Four of them were excluded because they had reached adulthood. Following Institutional Review Board review and child informed assent, 17 children participated (see Fig 1).

Data collection: Clinical data (age at ECMO initiation, gender, ECMO indication, cannulation type and site, duration of ECMO, pre-existing disorders, use of other extracorporeal treatments, history of seizure and electroencephalography (EEG) findings, neuroimaging during and/or after ECMO, pediatric risk of mortality score (PRISM) and predicted death rate (PDR) on admission to pediatric intensive care unit (PICU)) was recorded from medical files retrospectively.

Developmental assessments: All assessments were employed by a child development specialist when the child had rested appropriately before the test and had no acute illness. To

eradicate the bias of age heterogeneity, we used age-appropriate assessment tools, which were revised and validated forms of the Bayley Scales of Infant and Toddler Development-III test for children below the age of 3, Stanford-Binet Intelligence Test (SBIT) for children between the ages of 3 and 6, and Wechsler Intelligence Scale for Children-Revised (WISC-R) for children between the ages of 6 and 16 (Balasundaram & Avulakunta, 2024; Petrosko, 2018; Roid & Pomplun, 2012). The results were scored with a mean of 100 and a standard deviation (SD) of 15. Based on test results, children were subcategorized into three cognitive groups; children with no disability were defined as having 'normal functional status,' with a delay between 1 and 2 SD were defined as 'mild to moderate disability,' and those with below 2 SD were defined as severe disability (Wagner et al., 2007). Motor functions were assessed as normal or delayed based on the data obtained from the sub-categories of BSIT and SBIT. For children aged 6 to 16 years, a detailed neurological examination was conducted to identify any motor dysfunction. The time between ECMO and developmental assessment was calculated as the age at the test minus age at weaning from ECMO, shown in months, and defined as the test interval.

Statistical analysis: Statistical analysis was performed using the SPSSv23. Numerical data were shown as mean ± SD for the normally distributed variables and median (minimum-maximum) for the non-normally distributed variables. Categorical variables were presented as numbers (percent). Since there were three different types of tools, only the cognitive scales of Bayley and the verbal scale of WISC-R were used to evaluate the relationship between the variables. The overall SBIT scores were also included in the analysis of cognitive functions and the variables. The Spearman correlation test was used to analyze PRISM, PDR, duration of ECMO, age at ECMO, pre-ECMO maximum lactate levels, and cognitive scores. The univariate analyses to

identify variables associated with participants' developmental outcomes were investigated using Chi-square, Fisher's exact, Student's t, and Mann-Whitney U tests, where appropriate. While investigating the associations between cognitive scores and continuous variables such as age at ECMO, lactate levels, PRISM and PDR within the first 24 hours of admission, and duration of ECMO and mechanical ventilation, the correlation coefficients and their significance were calculated using the Spearman test. For the multivariate analysis, the possible factors identified with univariate analyses were further entered into the logistic regression analysis to determine independent predictors of patient outcome. Hoshmer-Lemeshow's goodness of fit statistics was used to assess model fit. A 5% type-I error level was used to infer statistical significance.

This research has been approved by the local ethics committee, and written informed consent for participation and publication has been obtained from the participants.

Results

The characteristics of the participants are shown in Table 1. Fifteen participants were born on time and with normal birth weight for age. Two were born preterm, and one of them also had a low birth weight. The median age was 26 months (0-14 years). Most of the diagnoses were congenital heart defects (CHD) (n=11), three were cardiomyopathy, two were congenital hernia (CDH), and one was multisystem inflammatory syndrome (MISC). Four children had a comorbidity before ECMO (Down syndrome, cleft palate, pulmonary hypertension, tracheostomy).

Four children underwent ECMO with extracorporeal cardiopulmonary resuscitation (ECPR), and two children had cardiac arrest, which ended with the return of spontaneous circulation before ECMO initiation. The children with CDH had the surgery for diaphragm repair under ECMO support within the first 24 hours postnatally. Five of the 11 CHD participants went

through ECMO support in the operating room because of failure to wean from the bypass machine. The median PRISM score was 11 (5-44), and the median PDR was 66,8 (1,4-97). The median lactate level before ECMO support was 10,5 (2,1-17) mmol/L.

The median duration of ECMO was six days (2-74), and the median duration of mechanical ventilation was 20 days (5-87). The extracorporeal life support of Participant 13 was switched to a biventricular assist device, and then he underwent a heart transplantation in another center. In Participant 14, ECMO bridged to a heart transplant. Six participants had clinical seizures while in PICU, and seven had antiepileptic treatment other than benzodiazepines, which were used for sedation. Eight participants had neuroimaging, and seven had EEG after the PICU course.

During developmental assessment, two participants were under mechanical respiratory support through a tracheostomy tube. None of them had a diagnosis of epilepsy or used antiepileptic drugs during test assessments. Three children were found to have normal developmental status in all test domains (Table 2). The overall incidence of developmental delay was 82.7% (14/17), the motor dysfunction rate was 58.8% (10/17), and the cognitive dysfunction rate was 70.6 (12/17). Five children showed no impairment in cognitive functions, while seven had severe cognitive impairment. Seven participants had normal motor functions. No significant correlation was found between the duration of ECMO, age at ECMO, PRISM, PDR, pre-ECMO maximum lactate levels, and cognitive scores. Participants with motor dysfunction were significantly younger than those without (p=0.04). PRISM scores of those with an abnormal developmental status were significantly higher than those with a normal status (p=0.03). Three of the four ECPR participants had normal cognitive functions. However, none of the ECPR participants had an overall normal developmental status (Table 3). There was no significant

difference between the incidence of developmental delay of participants with or without ECMO in the operating room and the presence of seizure or comorbidity at test time. One participant was already under mechanical respiratory support through a tracheostomy tube before ECMO support, and three participants underwent tracheostomy and continued to be supported by mechanical ventilation because of extubation failure after ECMO support. The median length of mechanical ventilation was 20 (5-87) days, and it did not differ across groups. After adjusting covariates, the logistic regression did not show a significant increase in the risk of neurodevelopmental delay. Seven participants had cranial magnetic resonance imaging after ECMO; two showed no abnormalities, and the others showed the following findings: minimal diffusion restriction, thin corpus callosum, and periventricular micro-hyperintensities. One participant had multiple millimetric hemorrhages on bilateral cerebral areas. Seven participants had electroencephalography records, which were normal in two, which showed a slowdown in ground cerebral activity. No epilepsy sign was found in EEGs.

Discussion

This study has shown that the overall developmental delay rate was over 80% among the cardiac central ECMO survivors. While some studies have reported mental delay in 38% of children, others have reported cognitive scores above average in 33% (Joffe et al., 2012). Cashen et al. (2017) conducted a study on neonates and children treated with ECMO, which found that among survivors, 32% had a good functional status while others had varying levels of abnormality. Although the study did not focus specifically on neurological outcomes, it provided insights into the overall functional status of children treated with ECMO (Cashen et al., 2017).

The long-term neurological problems could be linked to three distinct periods. The pre-ECMO period is influenced by factors such as pre-existing comorbidities, the severity of the illness before ECMO, cardiac arrest, and the length of time with poor perfusion. Polito et al. (2013) analyzed Extracorporeal Life Support Organization registry data. They found that the need for cardiopulmonary resuscitation (CPR) prior to ECMO cannulation increased the incidence of neurologic complications, including ischemic brain injury, in ECMO patients of all ages. They specifically found higher odds of neurologic complications in newborns requiring pre-ECMO CPR (Polito et al., 2013). Kane et al. (2010) examined the survival and early neurological outcomes of children with heart disease who received a rapid response for ECPR and found that survival to discharge was 51%, and factors associated with mortality included noncardiac structural or chromosomal abnormalities and the use of a blood primed ECMO circuit (Kane et al., 2010). Lequier et al. reported that lactate levels on admission to the PICU were predictive of death and abnormal mental scores in patients less than five years of age. They also concluded that ECPR was not associated with an increased incidence of death or neurologic morbidity (Lequier et al., 2008). In a study in which 24 ECMO survivors underwent neurologic assessment at five years of age, it was found that 12 (50%) had a normal neurologic outcome. Lower gestational age and birth weight were found to be associated with an abnormal outcome, as was septic shock as an indication for extracorporeal membrane oxygenation initiation (Waitzer et al., 2009). Although invasive and implemented in critically ill infants, half of the newborns undergoing extracorporeal membrane oxygenation might have a normal neurologic outcome at school age. Preexisting factors, rather than those related to the ECMO itself, appear to be greater determinants of later neurologic outcomes. Regarding the patient with Down syndrome, upon reviewing the data, it

was discovered that this individual was experiencing severe cognitive and motor dysfunction. Despite this, we chose to include the patient in our study to observe if there was any potential for improvement in their neurological outcome. None of the participants who underwent ECPR had a normal functional status, although three participants were found to have normal cognitive functions. This result might be affected by the preexisting comorbidities, reason for ECMO, and duration of ECMO. Because of the small sample size and the heterogeneity of the participants and test intervals, it was impossible to evaluate these risk factors properly. The intraoperative measures of cardiac surgery were not also available for the study. Nevertheless, there could be various risk factors for neurological complications and long-term outcomes that are related to ECMO itself. A study by Nasr & Rubinstein (2015) identified several risk factors for central nervous system complications, including the use of vasopressor/inotropic medications, infection, pulmonary failure, acidosis, and elevated creatinine during ECMO initiation. The study found that approximately 13% of patients developed acute severe central nervous system complications, with the rate of complications and mortality increasing with age (Nasr & Rabinstein, 2015). Joffe et al. (2012) found that cumulative survival after cardiac ECMO was 45%, and factors such as renal dysfunction, neurologic complications, lactate, and ECMO duration consistently predicted this outcome (Joffe et al., 2012). Mehta & Ibsen (2013) highlighted the acute central nervous system complications that can occur with ECMO, including seizures, hemorrhage, infarction, and brain death. The risk of neurologic complications appears to vary by the age of the patient, with neonates having the highest risk. Acute central nervous system injuries are associated with an increased risk of death in patients receiving ECMO support (Mehta & Ibsen, 2013). Our results showed similar mortality and hospital discharge rates compared to previous reports.

The neurological outcomes based on the cannulation site of ECMO in children had been investigated separately. The reports from children's and adult literature have investigated the technical utilities, bleeding, and infectious complications but did not specifically focus on the neurological outcomes based on cannulation sites (Ankola et al., 2021; Buyukgoz et al., 2023; Javidfar et al., 2012; Lorusso et al., 2019). Cui et al. (2022) compared VV and VA ECMO in infection-associated severe pediatric acute respiratory distress syndrome and did not find a significant difference in neurological complications between carotid and femoral cannulation for VA ECMO (Cui et al., 2022). On the other hand, Johnson et al. have reported that carotid artery cannulation was associated with higher rates of stroke and overall neurologic complications (Johnson et al., 2018). The available literature is limited and does not comprehensively compare neurological outcomes based on cannulation sites in the pediatric population. Thus, we included only those who underwent central cannulation to eliminate the bias regarding the cannulation site.

It is important for children who underwent ECMO to receive proper multidisciplinary post-ECMO support. The guidelines suggest that all ECMO survivors should have long-term follow-up in a structured and standardized approach tailored to their needs. Depending on the availability of resources, the indication for ECMO, the nature of the underlying disease, and the presence of other comorbidities, some may require more active investigation and intervention, and referral to other sub-specialties such as neurology may be necessary. This can help to ensure that children achieve the desired neurological outcomes and receive the best possible care (Ijsselstijn et al., 2021).

In summary, while some studies have reported significant neurodevelopmental problems in a subset of ECMO-treated children, others have found that ECMO is not a risk factor for poor

long-term neurological outcomes. Further research is needed to understand better the long-term neurological outcomes and factors influencing them in children treated with ECMO.

The current study's limitations included the small sample size, heterogeneity of age, and intervals between developmental assessments and hospital discharge.

Conclusion

The long-term neurological outcomes of children treated with cardiac ECMO can vary. Factors such as underlying cardiac disease, ECMO duration, renal dysfunction, and neurologic complications can influence these outcomes. After eliminating the possible effect of the cannulation site, the participants showed a certain rate of neurodevelopmental delay, which might be affected mostly by age and the disease severity, as well as ECMO itself. It is important to continue monitoring these children for possible neurodevelopmental delays using a multidisciplinary approach, even after they have been discharged from the hospital following ECMO support. Early initiation of developmental support with a specialized team should be encouraged.

Statements and Declarations

Conflict of interests: The authors have stated that they had no interests, which might be perceived as posing a conflict or bias**.**

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Table and Figure Legends

Table 1. The characteristics of participants

Table 2 The results of developmental assessments

Table 3 The possible risk factors related to developmental impairment

Figure 1 The selection of the participants

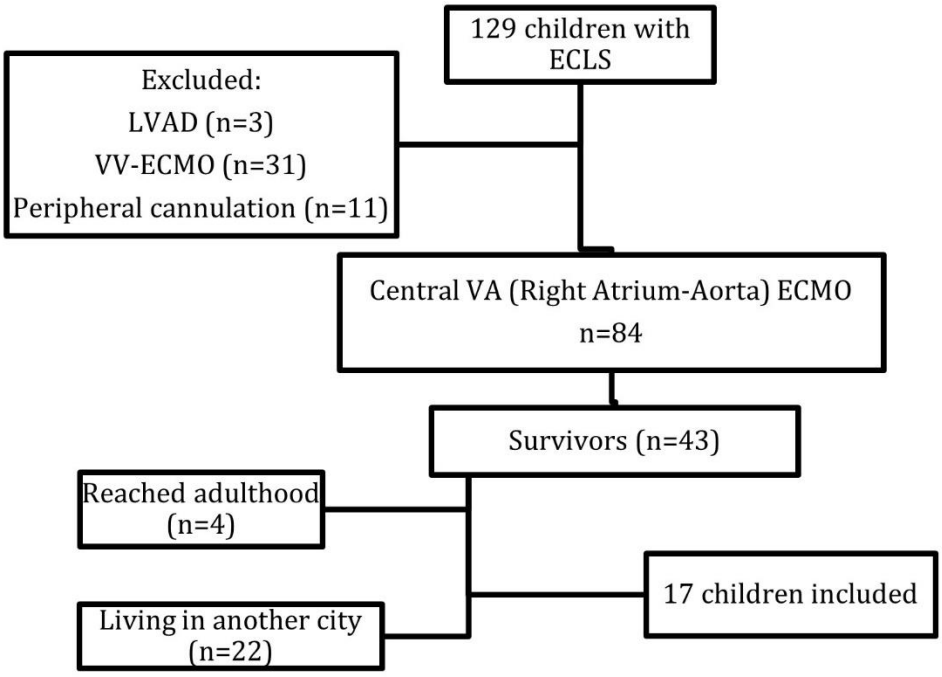

Figure 1 The selection of the participants. (ECLS; extracorporeal life support, ECMO; extracorporeal membrane oxygenation, LVAD; left ventricular assist device, VV; venovenous, VA; venoarterial)

Figure

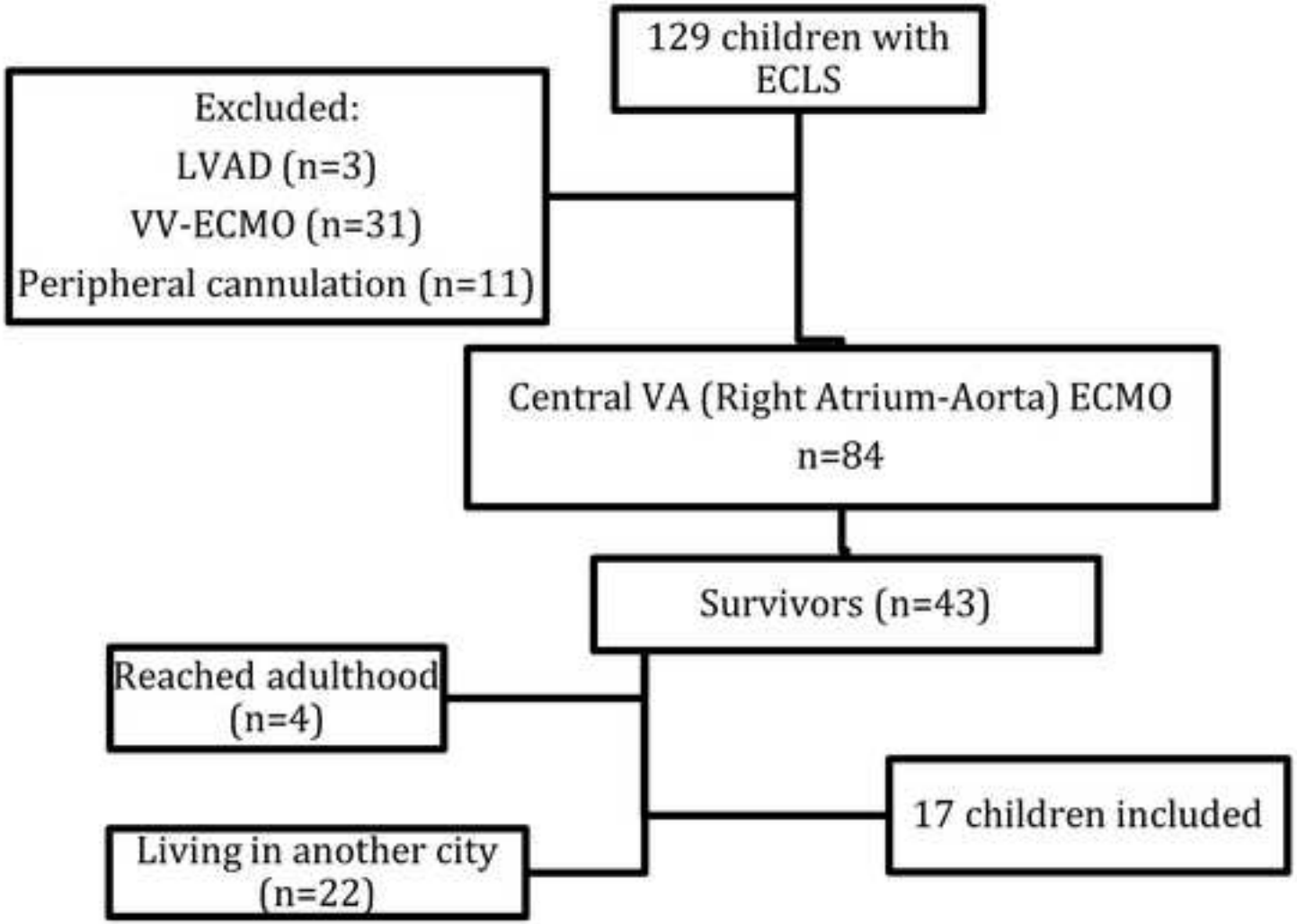

Table 1. The characteristics of participants

No	Sex	Primary diagnosis	Indication for ECMO	Age at ECMO (month)	Time before ECMO (days)	CPR time (min)	ECPR	Duration of ECMO (days)	Duration of MV (days)	Extubation
1	Male	CHD (TOF)	Cardiac stun	6	0	3	no	6	24	Yes
2	Female	CHD (AVSD)[1]	LCOS	26	2	0	no	5	8	Yes
3	Female	CHD (PAPVR)[2]	Cardiac stun	3	0[t]	0	no	20	27	Yes
4	Female	CHD (DORV-TOF)[3]	ARDS, Cardiac failure	5	0	45	yes	5	*	Tracheostomy
5	Female	CHD (DORV-TOF)	Cardiac stun	22	0[t]	0	no	5	19	Yes
6	Female	CHD (DORV)	LCOS	40	0	0	no	4	7	Yes
7	Male	CHD (TOF)	LCOS	11	3	0	no	6	10	Yes
8	Male	CHD (PA-SV)	Cardiac stun	79	0	0	no	6	21	Yes
9	Male	CHD (TOF)	Cardiac stun	24	0[t]	0	no	14	33	Tracheostomy
10	Female	CHD (TOF)[4]	Cardiac stun	63	0[t]	42	no	2	39	Tracheostomy
11	Male	CHD (bicuspid aorta)	Cardiac stun	125	0[t]	0	no	3	5	Yes
12	Male	Noncompaction CMP	LCOS	34	30	50	yes	42	87	Yes
13	Male	Dilated CMP	Arrhythmia, Cardiac failure	110	30	40	yes	27	27	Yes
14	Male	Dilated CMP	Cardiac arrest	98	4	80	yes	25	32	Yes
15	Female	CDH	PPH	0	0	0	no	8	33	Yes
16	Female	CDH	PPH	0	0	0	no	74	130	Tracheostomy
17	Female	MISC	LCOS	171	2	0	no	6	14	Yes

Time before ECMO refers to the interval between hospitalization and ECMO initiation.

[t]These participants underwent ECMO directly after cardiopulmonary bypass in the operating room.

*This participant was already under mechanical ventilatory support via tracheostomy cannula.

ECMO; extracorporeal membrane oxygenation, CHD; congenital heart disease, CPR; cardiopulmonary resuscitation, ECPR; extracorporeal cardiopulmonary resuscitation, MV; mechanical ventilation, TOF, tetralogy of Fallot, AVSD; atrioventricular septal defect, LCOS; low cardiac output syndrome, PAPVR; partial anomaly of pulmonary venous return, DORV; double outlet right ventricle, ARDS; acute respiratory distress syndrome, PA-SV; pulmonary atresia-single ventricle, CMP, cardiomyopathy, CDH; congenital diaphragmatic hernia, PPH; primary pulmonary hypertension, MISC; multisystem inflammatory syndrome in children.

Table 2 The results of developmental assessments.

Participants	Age at test (months)	Test interval (months)	Comorbidity during test	Test	Cognitive disability	Intellectual quotient	Motor functions	Overall development
1	47	41		SBIT	None	111	normal	normal
2	51	25	Down syndrome	SBIT	Severe	49	delayed	abnormal
3	21	17	Pulmonary Hypertension	BSIT-III	Mild to moderate	85	delayed	abnormal
4	20	15	Tracheostomy	BSIT-III	Mild to moderate	85	normal	abnormal
5	29	7	Attention deficit disorder	BSIT-III	Severe	75	delayed	abnormal
6	72	32	Fanconi aplastic anemia	SBIT	Severe	65	delayed	abnormal
7	33	18		BSIT-III	Severe	65	delayed	abnormal
8	118	39	ADHD	WISC-R	Mild to moderate	85	normal	abnormal
9	34	10	Tracheostomy	BSIT-III	Mild to moderate	75	delayed	abnormal
10	102	39	ADHD	WISC-R	Severe	49	delayed	abnormal
11	156	31	Learning disability	WISC-R	None	94	normal	normal
12	48	12		SBIT	None	94	delayed	abnormal
13	114	4		WISC-R	Severe	69	normal	abnormal
14	110	12		WISC-R	Mild to moderate	75	normal	abnormal
15	21	20		BSIT-III	None	95	delayed	abnormal
16	28	25		BSIT-III	Mild to moderate	80	delayed	abnormal
17	179	8		WISC-R	None	103	normal	normal

ADHD; attention deficit and hyperactivity disorder, SBIT; Stanford-Binet Intelligence Test, BSIT-III; Bayley Scales for infants and toddlers, WISC-R; Wechsler Intelligence Scale for Children-Revised.

Table 3 The possible risk factors related to developmental impairment.

	Cognitive dysfunction			Motor functions			Overall developmental status		
	none	yes	p	normal	delayed	p	Normal	Abnormal	p
PRISM score	30 (16-40)	23.5 (12-31)	0.32	30 (12-40)	18 (12-30)	0.36	18 (12-30)	40 (30-44)	0.03
PDR (%)	71 (18.70-90.0)	49 (7.3-81.5)	0.38	71 (5.1-92.1)	24.95 (7.7-78.0)	0.54	24.95 (7.4-78.0)	90 (71-97)	0.07
Pre-ECMO max lactate level	7.5 (6.19-15.0)	10.9 (8.5-12.7)	0.80	10.5 (6.1-14.6)	10.45 (7.7-12.0)	0.89	6.19 (4.3-15.0)	10.9 (7.8-13.5)	0.51
Age at ECMO (months)	34 (6-125)	25 (8-71)	0.65	98 (6-125)	23 (3-34)	0.04	125 (6-171)	25 (5-63)	0.20
Duration of ECMO (days)	6 (6-8)	6 (5-23)	0.96	6 (5-25)	7 (5-20)	0.89	6 (3-6)	7 (5-25)	0.36
ECPR			0.670			0.250			0.541
No	4 (80)	9 (75)		4 (57.1)	9 (90)		3 (100)	10 (71.4)	
Yes	1 (20)	3 (25)		3 (42.8)	1 (10)		0 (0)	4 (28.5)	
CHD			0.28			0.644			0.72
No	3 (60)	3 (25)		3 (42.8)	3 (30)		1 (33.3)	5 (35.7)	
Yes	2 (40)	9 (75)		4 (57.1)	7 (70)		2 (66.6)	9 (64.2)	
ECMO in OR			0.727			0.545			0.727
No	1 (50)	5 (55.6)		3 (75)	3 (42.9)		1 (50)	5 (55.6)	
Yes	1 (50)	4 (44.4)		1 (25)	4 (57.1)		1 (50)	4 (44.4)	
Seizure			0.102			0.625			0.515
No	5 (100)	6 (50)		5 (71.4)	6 (60)		3 (100)	8 (57.1)	
Yes	0 (0)	6 (50)		2 (28.6)	4 (40)		0 (0)	6 (42.9)	
Comorbidity during test			0.140			0.442			0.290
No	5 (100)	8 (66.7)		6 (85.7)	7 (70)		3 (100)	10 (71.4)	
Yes	1 (0)	4 (33.3)		1 (14.3)	3 (3)		0 (0)	4 (28.6)	

PRISM: pediatric risk of mortality, PDR: pediatric death rate, ECMO: extracorporeal membrane oxygenation, ECPR: Extracorporeal cardiopulmonary resuscitation, CHD: congenital heart disease,