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Clinical paper

One-year cognitive and neurologic outcomes in survivors of paediatric extracorporeal cardiopulmonary resuscitation

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Abstract

Objective: To describe one-year cognitive and neurologic outcomes among extracorporeal cardiopulmonary resuscitation (ECPR) survivors enrolled in the Therapeutic Hypothermia after Paediatric Cardiac Arrest In-Hospital (THAPCA-IH) trial; and compare outcomes between survivors who received ECPR, later extracorporeal membrane oxygenation (ECMO), or no ECMO.

Methods: All children recruited to THAPCA-IH were comatose post-arrest. Neurobehavioral function was assessed by caregivers using the Vineland Adaptive Behaviour Scales, 2nd edition (VABS-II) at pre-arrest baseline and 12 months post-arrest. Age-appropriate cognitive performance measures (Mullen Scales of Early Learning or Wechsler Abbreviated Scale of Intelligence) and neurologic examinations were obtained 12 months post-arrest. VABS-II and cognitive performance measures were transformed to standard scores (mean = 100, SD = 15) with higher scores representing better performance. Only children with broadly normal pre-arrest function (VABS-II ≥70) were included in this analysis.

Results: One-year follow-up was attained for 127 survivors with pre-arrest VABS-II ≥70. Of these, 57 received ECPR, 14 received ECMO later in their course, and 56 did not receive ECMO. VABS-II assessments were completed at 12 months for 55 (96.5%) ECPR survivors, cognitive testing for 44 (77.2%) and neurologic examination for 47 (82.5%). At 12 months, 39 (70.9%) ECPR survivors had VABS-II scores ≥70. On cognitive testing, 24 (54.6%) had scores ≥70, and on neurologic examination, 28 (59.5%) had no/minimal to mild impairment. Cognitive and neurologic score distributions were similar between ECPR, later ECMO and no ECMO groups.

Conclusions: Many ECPR survivors had favourable outcomes although impairments were common. ECPR survivors had similar outcomes to other survivors who were initially comatose post-arrest.

Keywords: Extracorporeal cardiopulmonary resuscitation, Paediatric, Outcome, Neurobehavioral, Cognitive, Neurologic

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Introduction

Extracorporeal cardiopulmonary resuscitation (ECPR) is an advanced rescue therapy increasingly used among children with refractory in-hospital cardiac arrest. During ECPR, an extracorporeal circuit is established to maintain vital organ perfusion until potentially reversible causes of cardiac arrest are identified and treated. Survival to hospital discharge after ECPR is about 40%[1,2]; however, long-term cognitive and neurologic outcomes among survivors are largely unknown.[3–6] Knowledge regarding these outcomes is important for clinical decision-making, counselling parents, and planning rehabilitation and educational services during recovery.

The Therapeutic Hypothermia after Paediatric Cardiac Arrest In-Hospital (THAPCA-IH) trial was a randomized trial comparing two targeted temperature management interventions in children who were comatose after in-hospital arrest.[7] Neurobehavioral function was assessed longitudinally by caregiver report using the Vineland Adaptive Behaviour Scales, 2nd edition (VABS-II).[8] The primary outcome measure was one-year survival with good/favourable neurobehavioral function defined as VABS-II score $\geq$70 (population mean = 100, SD = 15). Results of the THAPCA-IH trial showed the primary outcome did not differ between temperature management groups.

We previously reported that about a third of children receiving ECPR in the context of the THAPCA-IH trial survived with good neurobehavioral function at one year based on caregiver responses to the VABS-II.[3] Benefits of using a caregiver-report measure included the ability to collect data in-person or by telephone, and to obtain a retrospective assessment of each child's pre-arrest functional status. Despite benefits, caregiver-report measures of functional status may lack the sensitivity of performance-based measures in identifying global and selective impairments. In the THAPCA-IH trial, performance-based cognitive evaluation and neurologic examination were obtained at follow-up in addition to the VABS-II in order to provide complementary, objective outcomes for one-year survivors. The purpose of this study was to describe detailed one-year performance-based cognitive and neurologic outcomes in paediatric ECPR survivors enrolled in the THAPCA-IH trial, and to compare outcomes between survivors who received ECPR, later extracorporeal membrane oxygenation (ECMO), or no ECMO.

Methods

Study design

This study is a secondary analysis of the THAPCA-IH trial.[7] Thirty-seven children's hospitals in the United States, Canada, and the United Kingdom recruited children between September 1, 2009 and February 27, 2015. Details of the trial were previously published.[7,9,10] Institutional review boards at the University of Utah Data Coordinating Centre, the Kennedy Krieger Institute, and all study sites approved the study. Caregiver permission was obtained for all participants.

Study participants

Children eligible for the THAPCA-IH trial were >48 h and <18 years of age, had an in-hospital cardiac arrest with chest compressions for $\geq$ 2 min, and required mechanical ventilation after return of circulation.[7] Major exclusion criteria were a Glasgow Coma Scale motor subscale score of 5 or 6 (i.e., purposeful lateralizing response to painful stimulus),[11] inability to be randomized within 6 h of return of circulation, and a decision by the clinical team to withhold aggressive treatment. Additional inclusion criteria for this secondary analysis included having broadly normal pre-arrest neurobehavioral function defined as pre-arrest VABS-II $\geq$70, survival to 12 months, and completion of at least one 12-month follow-up measure. ECPR was defined as ECMO initiation during active chest compressions or before sustained return of spontaneous circulation >20 min was achieved.[12,13] Of 329 children recruited to the THAPCA-IH trial, 269 had broadly normal pre-arrest function. Of these 135 survived 12 months; of these, 127 had follow-up. Of those with follow-up, 57 received ECPR, 14 received ECMO later in their hospital course, and 56 did not receive ECMO.

Measures

The VABS-II is a caregiver-report measure of adaptive behaviour defined as performance on daily life activities necessary for personal and social independence.[8] The VABS-II provides age-corrected standard scores (mean = 100, SD = 15) in four domains (communication, daily living, socialization, and motor skills) and an overall adaptive behaviour composite. Each domain includes subdomains with developmentally sequenced items starting with skills typically observed in infancy. Subdomain raw scores are age-corrected and standardized as v-scores. The VABS-II has a caregiver rating form and a survey interview (using caregiver as informant) that yield comparable scores.

The Mullen Scales of Early Learning (Mullen) is a performance-based measure of cognitive function for young children.[14] The Mullen has 4 scales (visual reception, fine motor, receptive language, expressive language). Normative data are available from birth through age 5 years and 8 months. Age-corrected standardized scores are available for each scale and for an overall early learning composite.

The Wechsler Abbreviated Scale of Intelligence (WASI) measures intellectual or general cognitive functioning and includes verbal and visual reasoning subtests.[15] Normative data are based on a standardization sample highly representative of the English-speaking United States population aged 6–89 years. Age-corrected standardized scores are available for the verbal and visual reasoning subtests. When combined, these subtests yield age-corrected standard scores for general intellectual functioning (Full Scale IQ).

For this report, all standardized scores (VABS-II, Mullen, WASI) were transformed to standard scores (mean = 100, SD = 15) with higher scores representing better performance. Scores >115 are above average, 85–115 are average, 70–84 are below average, 50–69 are impaired, and <50 are severely impaired.

The Paediatric Resuscitation after Cardiac Arrest (PRCA) form was used to record and score detailed, conventional age-appropriate neurologic examinations.[16] The PRCA was developed as a modification of the Paediatric Stroke Outcome Measure (PROM).[17] Versions were developed for children <3 years old and $\geq$3 years, reflecting age-related items for assessing language and cognition. Paediatric neurologists performed detailed neurological examinations and scored neurologic function (0, normal to 3, severe impairment) in 6 domains. The sensorimotor domain was scored independently for each side of the body (so that scores ranged from 0–6). The five other scored domains included other non-lateralizing sensorimotor function (encompassing cranial nerve deficits, movement/tone disorder, global delays), language production, language comprehension, cognition, and behaviour. Total PRCA scores range from 0–21, with 0 indicating no deficits and 21 indicating maximal deficits. Scores were categorized as 0–3 (no/minimal impairment), 4–7 (mild impairment), 8–11 (moderate impairment), 12–16 (severe impairment), and 17–21 (profound impairment).

Paediatric Cerebral Performance Category (PCPC) measures neurologic functioning and Paediatric Overall Performance Category (POPC) measures overall health including neurologic functioning.[18] Both are 6-point scales with lower scores representing better function. PCPC and POPC lack detailed assessment but are often used in studies of cardiac arrest and facilitate comparison with other studies.

Procedures

Caregivers completed pre-arrest VABS-II assessments at the local sites within 24 h of randomization in the THAPCA-IH trial using the caregiver rating form. Research coordinators assisted caregivers with the pre-arrest VABS-II as needed. Research coordinators also rated PCPC and POPC using medical records or caregiver report, and collected child and cardiac arrest characteristics. Child characteristics included age, sex, race, ethnicity, pre-existing conditions and baseline technology dependence (tracheostomy or percutaneous feeding tube). Cardiac arrest characteristics included primary aetiology of cardiac arrest, initial rhythm at the start of chest compressions, whether the child was post-cardiac surgery at the time of arrest, and duration of chest compressions.

One year after cardiac arrest, an interviewer from the Kennedy Krieger Institute, unaware of treatment group assignment, completed the VABS-II with caregivers by telephone. Subsequently, children underwent cognitive testing and neurologic examination at the local sites. Children were tested with the Mullen up through 5 years, 8 months and 30 days. Children who were $\geq$5 years and 9 months but $<$6 years were tested after their sixth birthday. Children $\geq$6 years of age completed the WASI. Spanish-speaking caregivers completed 12-month VABS-II interviews in Spanish. Spanish-speaking children were tested by a Spanish-speaking examiner. Paediatric neurologists trained in the use of the PRCA performed the neurologic examinations.

Statistical analyses

Twelve-month VABS-II composite scores were compared between children who completed 12-month Mullen/WASI and PRCA and those who did not in order to evaluate whether children completing the Mullen/WASI and PRCA were representative of all children included in the study. Wilcoxon rank-sum tests and Fisher's exact tests were used for these comparisons. Baseline child characteristics and cardiac arrest characteristics were compared between survivors who received ECPR, later ECMO, or no ECMO using Fisher's exact tests. Change in VABS-II scores was calculated as difference scores between pre-arrest baseline and 12 months post-arrest. Change in VABS-II scores was evaluated using signed-rank tests. Twelve-month outcomes were compared between survivors who received ECPR, later ECMO, or no ECMO using Fisher's exact tests. Analyses were performed using SAS software, version 9.4 (SAS Institute).

Results

ECPR survivor characteristics

Of 57 ECPR survivors, 46 (80.7%) were $<$6 years old, 37 (64.9%) were male and 26 (45.6%) were White (Table 1). ECPR survivors were more likely to have a cardiovascular event as the primary aetiology of arrest, post-operative cardiac surgery status, and longer duration of chest compressions than survivors who received later ECMO or no ECMO (Table 1). ECPR survivors were more likely to have a pre-existing cardiac condition and less likely to have neurologic conditions, respiratory conditions or technology dependence than other survivors. Twelve-month VABS-II scores were similar between ECPR survivors who completed 12-month Mullen/WASI and PRCA and those who did not (Supplemental material 1).

Neurobehavioral function at one year for ECPR survivors

Of 57 ECPR survivors, caregivers of 55 (96.5%) completed 12-month VABS-II adaptive behaviour assessment. Table 2 shows baseline and 12-month VABS-II composite, domain and subdomain scores for ECPR survivors. Mean baseline scores ranged from 93 to 109, mean 12-month scores from 77 to 96, and mean change from -21 to -2. Larger declines were observed in the daily living and motor function domains than the communication or socialization domains.

Cognitive performance at one year for ECPR survivors

Of 57 ECPR survivors, cognitive performance-based testing was attained for 44 (77.2%) (34 Mullen, 10 WASI). Table 3 shows the cognitive performance composite and domain scores for ECPR survivors. For survivors $<$6 years old, 1 (2.9%) had a Mullen composite score in the above average range, 8 (23.5%) average, 6 (17.6%) below average, 9 (26.5%) impaired and 10 (29.4%) severely impaired. For survivors $\geq$6 years old, 8 (80.0%) had WASI Full-Scale IQ in the average range, 1 (10.0%) below average, and 1 (10.0%) impaired. The degree of impairment was similar to the respective composite scores for all Mullen scales and WASI subsets. Fig. 1, shows distributions of VABS-II and cognitive performance scores for ECPR survivors.

Neurologic examination at one year for ECPR survivors

Of 57 ECPR survivors, neurologic examination was performed in 47 (82.5%). Table 4 shows the PRCA total and domain scores for ECPR survivors. Median total PRCA score was 4.0 (IQR 0.0, 12.0). Impairment was none/minimal for 23 (48.9%), mild for 5 (10.6%), moderate for 5 (10.6%), severe for 9 (19.1%), and profound for 5 (10.6%).

Comparisons of ECPR, later ECMO and no ECMO groups

Table 5 shows VABS-II adaptive behaviour composite, cognitive performance composite and PRCA total scores for ECPR, later ECMO and no ECMO groups. Caregiver-report 12-month VABS-II composite scores were broadly normal ($\geq$70) for 39 (70.9%) ECPR survivors, 10 (71.4%) later ECMO survivors, and 47 (83.9%) no ECMO survivors; 12-month VABS-II scores were not statistically significantly different across groups. Performance-based cognitive evaluation composite scores $\geq$70 were achieved for 24 (54.5%) ECPR survivors, 8 (72.7%) later ECMO survivors, and 27 (61.4%) no ECMO survivors; cognitive evaluation scores were not statistically significantly different across groups. Neurologic examination scores in the none/minimal impairment to mild impairment range were observed for 28 (59.5%) ECPR survivors, 10 (83.3%) later ECMO survivors, and 33 (73.3%) no ECMO survivors; neurologic examination scores were also not statistically significantly different across groups.

Table 1 – Descriptive characteristics.

	ECPR (N = 57)	Later ECMO (N = 14)	No ECMO Use (N = 56)	P-value*
Age at time of 12-month follow-up				0.378
<3 years	43 (75.4%)	9 (64.3%)	34 (60.7%)	
3–<6 years	3 (5.3%)	1 (7.1%)	8 (14.3%)	
≥6 years	11 (19.3%)	4 (28.6%)	14 (25.0%)	
Sex				0.153
Male	37 (64.9%)	6 (42.9%)	28 (50.0%)	
Female	20 (35.1%)	8 (57.1%)	28 (50.0%)	
Race				0.156
Asian	3 (5.3%)	1 (7.1%)	0 (0.0%)	
Black or African American	20 (35.1%)	4 (28.6%)	13 (23.2%)	
White	26 (45.6%)	9 (64.3%)	35 (62.5%)	
Other/unknown	8 (14.0%)	0 (0.0%)	8 (14.3%)	
Hispanic or Latino	9 (15.8%)	2 (14.3%)	15 (26.8%)	0.341
Primary aetiology of cardiac arrest				0.002
Cardiovascular event	47 (82.5%)	8 (57.1%)	29 (51.8%)	
Respiratory event	10 (17.5%)	6 (42.9%)	22 (39.3%)	
Other	0 (0.0%)	0 (0.0%)	5 (8.9%)	
Initial cardiac arrest rhythm				0.812
Asystole	1 (1.8%)	1 (7.1%)	2 (3.6%)	
Bradycardia	28 (49.1%)	6 (42.9%)	33 (58.9%)	
Pulseless electrical activity	16 (28.1%)	5 (35.7%)	12 (21.4%)	
Ventricular fibrillation or tachycardia	11 (19.3%)	2 (14.3%)	8 (14.3%)	
Unknown	1 (1.8%)	0 (0.0%)	1 (1.8%)	
Duration of chest compressions (minutes)				<0.001
≤ 15	5 (8.8%)	12 (85.7%)	44 (78.6%)	
16–30	7 (12.3%)	1 (7.1%)	9 (16.1%)	
31–45	20 (35.1%)	1 (7.1%)	3 (5.4%)	
46–60	13 (22.8%)	0 (0.0%)	0 (0.0%)	
>60	12 (21.1%)	0 (0.0%)	0 (0.0%)	
Post-operative cardiac surgery	36 (63.2%)	3 (21.4%)	10 (17.9%)	<0.001
Technology dependence	2 (3.5%)	1 (7.1%)	11 (19.6%)	0.019
Any pre-existing condition	53 (93.0%)	13 (92.9%)	47 (83.9%)	0.279
Pre-existing conditions				
Cardiac condition	50 (87.7%)	7 (50.0%)	29 (51.8%)	<0.001
Congenital heart disease	42 (73.7%)	5 (35.7%)	27 (48.2%)	0.004
Single ventricle	16 (28.1%)	2 (14.3%)	9 (16.1%)	0.257
Acquired heart disease	7 (12.3%)	2 (14.3%)	5 (8.9%)	0.777
Arrhythmia	22 (38.6%)	2 (14.3%)	8 (14.3%)	0.008
Pre-existing heart transplant	5 (8.8%)	0 (0.0%)	1 (1.8%)	0.254
Respiratory condition	10 (17.5%)	6 (42.9%)	22 (39.3%)	0.022
Neurologic condition	5 (8.8%)	3 (21.4%)	20 (35.7%)	0.002
Gastrointestinal condition	10 (17.5%)	5 (35.7%)	14 (25.0%)	0.290
Prenatal condition	11 (19.3%)	1 (7.1%)	19 (33.9%)	0.065
Pulmonary hypertension	2 (3.5%)	0 (0.0%)	1 (1.8%)	1.000
Immunocompromised	7 (12.3%)	1 (7.1%)	8 (14.3%)	0.866
Renal condition	7 (12.3%)	2 (14.3%)	5 (8.9%)	0.777
Other pre-existing condition	13 (22.8%)	3 (21.4%)	18 (32.1%)	0.486
Pre-cardiac arrest PCPC				0.080
Normal = 1	35 (61.4%)	11 (78.6%)	40 (71.4%)	
Mild disability = 2	18 (31.6%)	1 (7.1%)	8 (14.3%)	
Moderate disability = 3	3 (5.3%)	2 (14.3%)	8 (14.3%)	
Severe disability = 4	1 (1.8%)	0 (0.0%)	0 (0.0%)	
Pre-cardiac arrest POPC				0.089
Good = 1	22 (38.6%)	9 (64.3%)	25 (44.6%)	
Mild disability = 2	27 (47.4%)	2 (14.3%)	20 (35.7%)	
Moderate disability = 3	6 (10.5%)	2 (14.3%)	11 (19.6%)	
Severe disability = 4	2 (3.5%)	1 (7.1%)	0 (0.0%)	

Data are counts and percentages.

Abbreviations: ECPR, extracorporeal cardiopulmonary resuscitation; ECMO, extracorporeal membrane oxygenation; PCPC, Paediatric Cerebral Performance Category; POPC, Paediatric Overall Performance Category.

* P-values from Fisher's Exact Test.

Table 2 – Vineland adaptive behavior scales, second edition, mean adaptive behavior composite, domain, and subdomain scores for paediatric extracorporeal cardiopulmonary resuscitation survivors.

	N[a]	Baseline	Month 12	Baseline to month 12 change	P-value[*]
Adaptive Behavior Composite	55	95 (16)	82 (19)	−13 (22)	<0.001
Communication	55	96 (16)	86 (19)	−10 (22)	<0.001
Receptive	55	100 (13)	92 (16)	−8 (17)	<0.001
Expressive	55	95 (15)	85 (21)	−9 (24)	0.006
Written	13	98 (15)	90 (12)	−8 (11)	0.035
Daily Living	55	97 (20)	80 (20)	−18 (26)	<0.001
Personal	55	98 (18)	77 (21)	−21 (25)	<0.001
Domestic	18	101 (14)	93 (10)	−9 (15)	0.022
Community	18	106 (19)	89 (14)	−10 (20)	0.014
Socialization	55	94 (18)	90 (16)	−4 (23)	0.139
Interpersonal Relationship	55	93 (16)	91 (20)	−2 (25)	0.461
Play and Leisure	55	94 (14)	88 (14)	−7 (20)	0.024
Coping Skills	17	109 (13)	96 (12)	−10 (16)	0.030
Motor Functioning	55	97 (15)	79 (21)	−18 (20)	<0.001
Gross	55	94 (10)	77 (19)	−17 (19)	<0.001
Fine	55	103 (15)	87 (23)	−15 (21)	<0.001

Data are means and standard deviations.
[a] N is the number of children with both baseline and 12-month assessment.
[*] P-value from the Signed Rank test. Data are means and standard deviations.

Discussion

This is the first multicentre study to report detailed one-year cognitive and neurologic outcomes among paediatric ECPR survivors. All children included in this study had broadly normal pre-arrest neurobehavioral function and were comatose in the early post-arrest period. Among ECPR survivors, 70.9% had caregiver-reported VABS-II adaptive behaviour composite scores ≥70 at 12 months post-arrest. Using performance-based cognitive evaluation, 54.5% ECPR survivors had standardized total scores ≥70. On neurologic examination, 59.5% ECPR survivors had impairment in the range of none/minimal to mild. Overall, these findings suggest that many ECPR survivors in our study had a broadly favourable functional outcome. These findings also suggest that performance-based testing may reveal impairments not readily identified by caregiver report. Outcomes based on caregiver report, performance testing, or neurologic examination were similar among survivors who were comatose post-arrest and who received ECPR, later ECMO, or no ECMO during their hospital course.

Although many ECPR survivors in our study had a favourable functional outcome at one-year follow-up, impairments were common

Table 3 – Cognitive performance at 12-month follow-up for children treated with extracorporeal cardiopulmonary resuscitation.

Mullen scales of early learning composite and domain scores (Age < 6 years)

	Early learning composite	Visual reception	Fine motor	Receptive language	Expressive language
Score category (N = 34)					
<50 (severely impaired)	10 (29.4%)	10 (29.4%)	10 (29.4%)	9 (26.5%)	10 (29.4%)
50–69 (impaired)	9 (26.5%)	7 (20.6%)	6 (17.6%)	7 (20.6%)	8 (23.5%)
70–84 (below average)	6 (17.6%)	4 (11.8%)	5 (14.7%)	8 (23.5%)	5 (14.7%)
85–115 (average)	8 (23.5%)	13 (38.2%)	13 (38.2%)	9 (26.5%)	11 (32.4%)
>115 (above average)	1 (2.9%)	0 (0%)	0 (0%)	1 (2.9%)	0 (0%)

Wechsler Abbreviated Scale of Intelligence full scale IQ composite and subtest scores (Age ≥ 6 years)

	Full-scale IQ score	Vocabulary	Matrix reasoning
Score Category (N = 10)			
50–69 (impaired)	1 (10.0%)	2 (20.0%)	1 (10.0%)
70–84 (below average)	1 (10.0%)	1 (10.0%)	1 (10.0%)
85–115 (average)	8 (80.0%)	7 (70.0%)	6 (60.0%)
>115 (above average)	0 (0%)	0 (0%)	2 (20.0%)

Scores were transformed to correspond to a scale with mean 100 and standard deviation 15.
Data are counts and percentages.

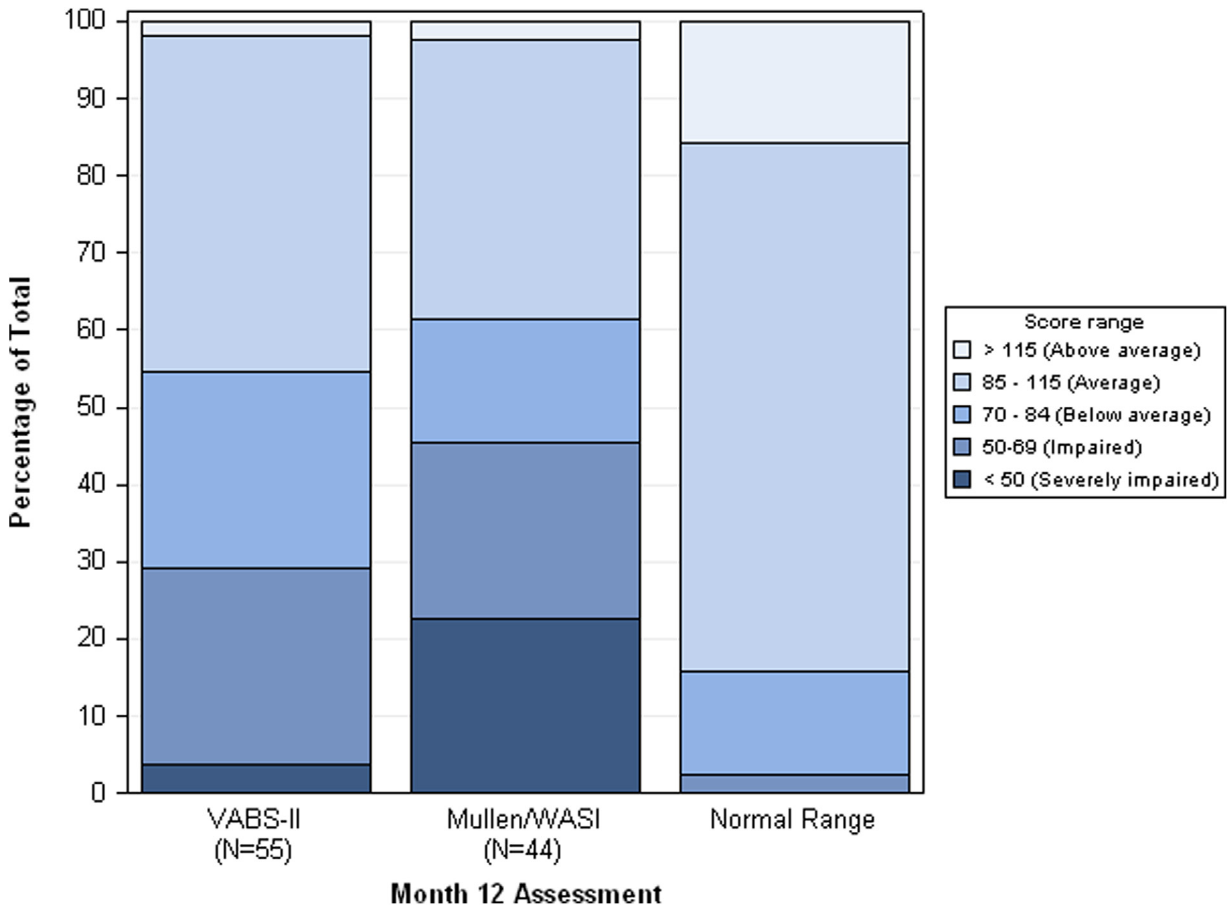

Fig. 1 – Percent of survivors with above average, average, below average, impaired, and severely impaired adaptive behaviour and cognitive performance 12 months after extracorporeal cardiopulmonary resuscitation for in-hospital cardiac arrest, and expected population norms.
***Abbreviations*: Mullen, Mullen Scales of Early Learning; WASI, Wechsler Abbreviated Scale of Intelligence.**

and the range of outcomes was wide. Overall, functional outcomes for our cohort of ECPR survivors were shifted below population norms. Caregiver-reported adaptive behaviour declined from pre-arrest baseline in all domains; declines were greater in daily living and motor functioning than socialization and communication domains. Differential impairment among adaptive behaviour domains may reflect a specific pattern of brain injury. On the other hand, caregivers may more accurately recognize their child's physical impairments, and tend to minimize deficits in social and communication skills. Greater decline in daily living and motor function domains of adaptive behaviour were also observed in the overall THAPCA-IH study population[19] as well as the Therapeutic Hypothermia after Paediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) population.[20]

In spite of broadly normal pre-arrest functioning, 55.9% of ECPR survivors <6 years old had Mullen composite scores in the impaired or severely impaired range (i.e., <70), and 10% of ECPR survivors ≥ 6 years had WASI composite scores in the impaired range. These findings might suggest that younger ECPR survivors have worse cognitive outcomes than older survivors. However, these findings must be interpreted with caution due to the small number of ECPR survivors ≥6 years old (n = 11); only ten underwent performance-based cognitive testing and one declined participation in this particular aspect of follow-up. Younger children enrolled in THAPCA-IH may have been more likely to have complex congenital anomalies and multisystem disorders at baseline that contribute to lower cognitive performance at follow-up. Cognitive performance is also inherently more difficult to assess formally in a single out-patient visit in young children with antecedent prolonged hospitalization.

A small number of single centre studies have reported functional outcomes among ECPR survivors. Guerra et al.[4] prospectively evaluated neurocognitive outcomes of 17 paediatric ECPR survivors at 4.5 years of age and at least 6 months after ECPR admission to a single Canadian centre using the Wechsler Preschool and Primary Scales of Intelligence. Paediatric ECPR survivors had a mean (SD) Full Scale IQ score of 76.5 (15.9) with 4 (24%) children having intellectual disability defined as a Full Scale IQ over two standard deviations below the population mean (i.e., <70). In a recent retrospective study, Beshish et al.[5] reported functional outcomes of 38 paediatric ECPR survivors from a single US centre using the Functional Status Scale (FSS)[21] assessed at hospital admission and discharge. The FSS assesses function in 6 domains (mental, sensory, communication, motor, feeding and respiratory) with total scores ranging from 6 to 30; higher scores represent more dysfunction. Beshish et al. found that half of ECPR survivors had a new functional morbidity defined as an increase in FSS by ≥3 points from baseline and 68% had a favourable outcome defined as an increase in FSS by

Table 4 – Neurologic examination: Paediatric Resuscitation after Cardiac Arrest scores at 12-month follow-up for children treated with extracorporeal cardiopulmonary resuscitation.

	Overall (N = 47)
Global assessment score (range 0–21)	4.0 [0.0, 12.0]
Global assessment score category	
0–3 (none/minimally impaired)	23 (48.9%)
4–7 (mildly impaired)	5 (10.6%)
8–11 (moderately impaired)	5 (10.6%)
12–16 (severely impaired)	9 (19.1%)
17–21 (profoundly impaired)	5 (10.6%)
Sensorimotor deficit (range 0–6)	2.0 [0.0, 4.0]
Other motor or sensory deficits (includes cranial nerve deficits) (range 0–3)	0.0 [0.0, 2.0]
Language, cognition, and behaviour (range 0–12)	1.0 [0.0, 7.0]
Language deficit — production (including dysarthria) (range 0–3)	0.0 [0.0, 2.0]
Language deficit — comprehension (range 0–3)	0.0 [0.0, 2.0]
Cognitive deficit (range 0–3)	0.0 [0.0, 2.0]
Behavioural deficit (range 0–3)	0.0 [0.0, 1.0]

Data are counts and percentages or medians and interquartile ranges.

<5 points from baseline. Small sample sizes and variation in outcome measures and study designs make comparisons between studies difficult.

ECPR survivors in our study had similar cognitive and neurologic outcomes to in-hospital cardiac arrest survivors who received ECMO later in their course or who did not receive ECMO. Although all children were comatose post-arrest, ECPR survivors were different from other survivors for important pre-arrest and arrest characteristics such as greater likelihood of pre-existing cardiac conditions, post-cardiac surgery status, cardiovascular events as the primary aetiology of arrest, and longer durations of chest compressions. Many ECPR survivors might have died without ECPR as failure to achieve sustained return of spontaneous circulation often prompts ECMO initiation. In a study based on the American Heart Association's Get with the Guidelines-Resuscitation Registry, Lasa et al.[2] evaluated children with in-hospital CPR ≥10 min duration using propensity-score matching to compare outcomes from ECPR and conventional CPR. Children receiving ECPR had greater odds of survival to hospital discharge and survival with favourable neurologic status based on PCPC scores. Although the ECPR, later ECMO and no ECMO groups in our study are difficult to compare due to baseline differences and small sample size in each group, our findings and those of Lasa et al suggest that ECPR can result in functional outcomes as favourable as those observed among other in-hospital cardiac arrest survivors. However, small samples in our comparison groups make it possible that differences were missed.

Strengths of our study include the prospective multicentre design and the use of well-validated measures to assess many domains of functioning both by caregiver report and by performance-based testing. Another strength is the inclusion of a broad paediatric age range from >48 h to <18 years of age. However, important limitations to the generalizability of our findings exist. Children included in this study were those recruited to the THAPCA-IH trial and therefore were subject to all THAPCA-IH inclusion and exclusion criteria. In addition to these known

Table 5 – Outcomes at 12-month follow-up by extracorporeal membrane oxygenation use.

	ECPR	Later ECMO	No ECMO Use	P-value[*]
Total with month 12 VABS-II	55	14	56	
Adaptive behaviour composite				0.208
<50 (severely impaired)	2 (3.6%)	0 (0.0%)	1 (1.8%)	
50–69 (impaired)	14 (25.5%)	4 (28.6%)	8 (14.3%)	
70–84 (below average)	14 (25.5%)	1 (7.1%)	19 (33.9%)	
85–115 (average)	24 (43.6%)	8 (57.1%)	28 (50.0%)	
>115 (above average)	1 (1.8%)	1 (7.1%)	0 (0.0%)	
Total with Month 12 Mullen/WASI	44	11	44[a]	
Mullen or WASI score category (all ages combined)				0.435
<50 (severely impaired)	10 (22.7%)	1 (9.1%)	5 (11.4%)	
50–69 (impaired)	10 (22.7%)	2 (18.2%)	12 (27.3%)	
70–84 (below average)	7 (15.9%)	5 (45.5%)	11 (25.0%)	
85–115 (average)	16 (36.4%)	2 (18.2%)	14 (31.8%)	
>115 (above average)	1 (2.3%)	1 (9.1%)	2 (4.5%)	
Total with Month 12 PRCA	47	12	45	
Global assessment score category				0.727
17-21 (Profoundly impaired)	5 (10.6%)	1 (8.3%)	2 (4.4%)	
12-16 (Severely impaired)	9 (19.1%)	1 (8.3%)	5 (11.1%)	
8-11 (Moderately impaired)	5 (10.6%)	0 (0.0%)	5 (11.1%)	
4-7 (Mildly impaired)	5 (10.6%)	2 (16.7%)	9 (20.0%)	
0-3 (None/minimally impaired)	23 (48.9%)	8 (66.7%)	24 (53.3%)	

Data are counts and percentages.

Abbreviations: VABS-II, Vineland Adaptive Behaviour Scales, Second Edition; Mullen, Mullen Scales of Early Learning; WASI, Wechsler Abbreviated Scale of Intelligence; PRCA, Paediatric Resuscitation after Cardiac Arrest.

[*] P-values from Fisher Exact Test.

[a] One child ≥6 years in the No ECMO Use group had no consistent means of functional communication based on the 12-month VABS-II assessment and did not undergo cognitive testing.

criteria, children whose caregivers agree for their child to participate in a randomized trial may be different from those whose caregivers refuse participation in ways that are unknown. Children recruited to this study had broadly normal caregiver-reported pre-arrest baseline function and were comatose in the early post-arrest period. Thus, this study excludes children recognized by their caregivers as significantly impaired at baseline and children who rapidly regained consciousness following cardiac arrest. Additionally, this study includes only those children who survived in-hospital arrest and participated in at least one form of 12-month follow-up. Poor neurologic prognoses formulated during the hospital course would have led to withdrawal of life support for some children who might otherwise have survived with severe deficits. Detailed cognitive and neurologic outcomes among survivors who did not participate in 12-month follow-up are unknown. However, participation in the follow-up cognitive and neurologic examinations was similar for the ECPR, later ECMO and no ECMO groups: for ECPR 44/57 and 47/57; for later-ECMO 11/14 and 12/14; and for no-ECMO 44/56 and 45/56. Another limitation is our inability to explore age-related differences in cognitive and neurologic outcomes due to the small number of participants ≥6 years old.

Conclusion

We conclude that many paediatric ECPR survivors have favourable cognitive and neurologic outcomes one year after in-hospital cardiac arrest. However, impairments are common and the range of deficits is wide. Overall, functional outcomes for our cohort of ECPR survivors were shifted below population norms. ECPR survivors appear to have similar outcomes to other in-hospital cardiac arrest survivors who are comatose in the early post-arrest period.

Conflict of interest statement

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.resuscitation.2019.02.023.

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