



Clinical paper

Neurobehavioural outcomes in children after In-Hospital cardiac arrest



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ABSTRACT

Aim: Children who remain comatose after in-hospital cardiac arrest (IH-CA) resuscitation are at risk for poor neurological outcome. We report results of detailed neurobehavioural testing in paediatric IH-CA survivors, initially comatose after return of circulation, and enrolled in THAPCA-IH, a clinical trial that evaluated two targeted temperature management interventions (hypothermia, 33.0 °C or normothermia, 36.8 °C; NCT00880087).

Methods: Children, aged 2 days to <18 years, were enrolled in THAPCA-IH from 2009 to 2015; primary trial outcome (survival with favorable neurobehavioural outcome) did not differ between groups. Pre-IH-CA neurobehavioural functioning, measured with the Vineland Adaptive Behavior Scales, Second Edition (VABS-II) was evaluated soon after enrollment; this report includes only children with broadly normal pre-IH-CA scores (VABS-II composite scores ≥ 70 ; 269 enrolled). VABS-II was re-administered 3 and 12 months later. Cognitive testing was completed at 12 months.

Results: Follow-ups were obtained on 125 of 135 eligible one-year survivors. Seventy-seven percent (96/125) had VABS-II scores ≥ 70 at 12 months; cognitive composites were $\geq 2SD$ of mean in 59%. VABS-II composite, domain, and most subdomain scores declined between pre-IH-CA and 3-month, and pre-IH-CA and 12-month assessments (composite means declined about 1 SD at 3 and 12 months, $p < 0.005$); 3 and 12-month scores were strongly correlated ($r = 0.72$, $p < 0.001$).

Conclusions: In paediatric IH-CA survivors at high risk for unfavorable outcomes, the majority demonstrated significant declines in neurobehavioural functioning, across multiple functional domains, with similar functioning at 3 and 12 months. About three-quarters attained VABS-II functional performance composite scores within the broadly normal range.

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Abbreviations: IH-CA, In-hospital cardiac arrest; OH-CA, Out-of-hospital cardiac arrest; VABS-II, Vineland Adaptive Behavior Scales-Second Edition; THAPCA-IH, Therapeutic hypothermia after paediatric cardiac arrest, in-hospital; FAD, Family Assessment Device; PCPC, Paediatric Cerebral Performance Category; POPC, Paediatric Overall Performance Category; SD, Standard deviation; WASI, Wechsler Abbreviated Scale of Intelligence; Mullen, Mullen Scales of Early Learning.

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Introduction

Children who survive in-hospital cardiac arrest (IH-CA) are at risk for poor neurobehavioural outcome, although outcomes are generally better than for out-of-hospital CA (OH-CA) survivors.[1] Many factors differ between IH-CA and OH-CA paediatric populations, including pre-existing medical conditions, initial cardiac rhythm, etiologies, response times, and resuscitation skills of initial responders.[1] Despite these differences, studies of long-term outcomes following CA often include both IH-CA and OH-CA cases or those with CA in unspecified location.[2,3] Studies of detailed neurobehavioural outcomes following paediatric IH-CA are limited

by small samples [4] or focus on specific subpopulations such as those with underlying cardiac disease.[5]

Most paediatric IH-CA studies have focused on survival and global outcomes, described as “favorable,” “unfavorable” or “unchanged” from pre-IH-CA functioning.[1,6–12] Recently, the Therapeutic Hypothermia after Paediatric Cardiac Arrest In-Hospital Trial (THAPCA-IH) evaluated two targeted temperature management strategies, hypothermia or normothermia, in children who were comatose after IH-CA resuscitation. One-year later, 37% displayed favorable outcomes, defined as survival and broadly normal functioning [score ≥ 70 on Vineland Adaptive Behavior Scales, Second Edition (VABS-II), a caregiver reported neurobehavioural outcome measure]. Outcomes did not differ between treatment groups.[13] This analysis of data, collected for THAPCA-IH, reports neurobehavioural and cognitive outcomes one year after IH-CA in surviving children with broadly normal pre-IH-CA function.

Methods

Study population

THAPCA-IH enrolled 329 children, ages 2 days to 18 years. Full inclusion and exclusion criteria, randomization, and enrollment details are published.[13] Two-hundred-sixty-nine children with broadly normal pre-IH-CA neurobehavioural functioning (defined as VABS-II ≥ 70 or Paediatric Overall Performance Category and Paediatric Cerebral Performance Category scores of normal or mild disability when VABS-II was unavailable) were eligible for the primary outcome (135 randomized to hypothermia, 134 to normothermia). Of 135 survivors, 125 had 12-month neurobehavioural assessments (supplemental Fig. 1).

Assessment measures

Pre-IH-CA

Family Functioning. Pre-IH-CA family functioning was measured using the General Functioning Scale of the Family Assessment Device (FAD), scored 0–4; scores ≥ 2 indicate abnormal functioning.[14]

Global Functioning. Pediatric Cerebral Performance Category (PCPC) provides a measure of neurological functioning and Pediatric Overall Performance Category (POPC) measures overall health (including neurological functioning).[15,16] These clinician-rated scales have been recommended for reporting paediatric CA outcomes;[17] they provide no age-specific data.

Pre and post-IH-CA

Neurobehavioural Functioning. The VABS-II [18] measures functional skills and provides age-corrected standard scores [mean = 100, standard deviation (SD) = 15] for overall adaptive behavior composite and four domains (communication, daily living, socialization, motor skills) and v-scores (mean = 15, SD = 3) for subdomains. Subdomains include developmentally-sequenced items, starting with skills typical of infancy. The VABS-II parent/caregiver rating form and survey interview versions yield comparable scores.[18] Telephone administration of VABS-II is validated [19] and a Spanish translation is available.[18] Supplemental Table 1 describes developmental skills typical of score ranges at different ages.

Post-IH-CA

Cognitive Performance. The Wechsler Abbreviated Scale of Intelligence (WASI) [20] measures intellectual or general cognitive functioning and includes verbal and visual reasoning subtests.

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 subtests [t-scores (mean = 50, SD = 10)] and combined Full Scale IQ [standard score (mean = 100, SD = 15)].

The Mullen Scales of Early Learning, [21] a measure of cognitive functioning for younger children, has four scales (visual reception, fine motor, receptive language, expressive language). Normative data and age-corrected standard scores are available from birth through age 5-years-8-months. Age-corrected standardized scores are available for each scale (t-scores) and overall early learning composite (standard score).

All t-scores (Mullen, WASI)[20,21] and v-scores (VABS-II) [18] were transformed to standard scores (> 115 above average, 85–115 average, 70–84 below average, 50–69 well below average).

Procedures

Each THAPCA site's institutional review board approved the study; caregiver informed consent was obtained prior to enrollment. Within 24 h of enrollment, a primary caregiver completed the VABS-II rating form to determine pre-IH-CA functioning. Site research coordinators reviewed responses and in some cases read items to caregivers and recorded responses, collected demographic and CA-related variables, and rated pre-IH-CA neurological (PCPC) and overall functioning (POPC).

Three and twelve months following IH-CA, a research assistant (Kennedy-Krieger Institute, Baltimore, MD), trained by a neuropsychologist (BS), conducted a semi-structured telephone interview to assess neurobehavioural function (including VABS-II). Throughout the study, administration and scoring questions were reviewed with the supervising neuropsychologist. The first four interviews, followed by every 10th were audio-recorded and reviewed to ensure reliability. VABS-II interviews for Spanish-speaking caregivers were completed in Spanish.

After 12-month VABS-II assessments, 99 children participated in on-site cognitive testing; 26 families declined testing. Children ≥ 6 years with no consistent means of functional communication based on the 12-month VABS-II did not undergo cognitive testing and were assigned lowest possible WASI scores. Spanish-speaking children were tested by Spanish-speaking examiner; for those ≥ 6 years, only the nonverbal subtest (WASI Matrix Reasoning) was administered.

Data analysis

Change in VABS-II scores was calculated as difference scores between later and earlier time points (3-month vs. pre-IH-CA, 12-month vs. pre-IH-CA, 12-month vs. 3-month). Rank-Sum tests evaluated distributions of continuous variables between age groups. T-tests compared VABS-II scores between treatment and age groups. Signed-Rank tests evaluated change in VABS-II scores. Categorical variables were examined using Chi-squared test. Standard linear regression models were fit with 12-month VABS-II score as the outcome with pre-IH-CA and post-CA continuous and categorical factors as predictors. Multivariable regression models were fit using baseline predictors which showed association trends ($p < 0.10$) in univariate models. Spearman's rank correlation coefficients were used to measure relationships between VABS-II overall and domain scores and Mullen overall and scale scores. Analyses were performed using SAS software, version 9.4 (SAS Institute).

Table 1
Characteristics of Study Population (Survivors with Pre-Cardiac Arrest VABS-II ≥ 70)

	Overall (N = 125)	Age Group at time of 12-month VABS-II Follow-Up		P-value
		0 – < 3 (N = 84)	3+ (N = 41)	
Age at Randomization (years)				
N	125	84	41	
Median [Q1, Q3]	1 [0,4]	0 [0,1]	9 [4,13]	
Sex: Male	70 (56%)	51 (61%)	19 (46%)	0.13 ²
Race				0.18 ²
White	69 (55%)	44 (52%)	25 (61%)	
Black or African American	36 (29%)	23 (27%)	13 (32%)	
Other/Unknown	20 (16%)	17 (20%)	3 (7%)	
Ethnicity				0.052 ²
Hispanic or Latino	26 (21%)	21 (25%)	5 (12%)	
Not Hispanic or Latino	94 (75%)	58 (69%)	36 (88%)	
Stated as Unknown	5 (4%)	5 (6%)	0 (0%)	
Caregivers highest education received				0.25 ²
Some high school or less	22 (18%)	13 (15%)	9 (22%)	
High school graduate or GED	34 (27%)	28 (33%)	6 (15%)	
Vocational school or some college	35 (28%)	22 (26%)	13 (32%)	
College degree	24 (19%)	14 (17%)	10 (24%)	
Graduate or doctoral degree	10 (8%)	7 (8%)	3 (7%)	
Average FAD score				0.69 ¹
N	123	82	41	
Mean (SD)	1.5 (0.5)	1.5 (0.4)	1.5 (0.5)	
Pre-cardiac arrest VABS Adaptive Behavior Composite Score				0.026 ¹
N	125	84	41	
Median [Q1, Q3]	94 [84,104]	94 [84,101]	101 [84,118]	
Pre-cardiac arrest PCPC				0.018 ¹
Normal = 1	84 (67%)	50 (60%)	34 (83%)	
Mild disability = 2	27 (22%)	24 (29%)	3 (7%)	
Moderate disability = 3	13 (10%)	9 (11%)	4 (10%)	
Severe disability = 4	1 (1%)	1 (1%)	0 (0%)	
Pre-cardiac arrest POPC				0.065 ¹
Good = 1	54 (43%)	31 (37%)	23 (56%)	
Mild disability = 2	49 (39%)	37 (44%)	12 (29%)	
Moderate disability = 3	19 (15%)	13 (15%)	6 (15%)	
Severe disability = 4	3 (2%)	3 (4%)	0 (0%)	
Total number of doses of epinephrine				0.66 ¹
N	124	83	41	
Median [Q1, Q3]	3 [2,7]	3 [2,7]	4 [1,6]	
Time between start of compressions and ROSC/ROC (minutes)				0.27 ¹
N	121	80	41	
Median [Q1, Q3]	19 [5,40]	21 [5,43]	13 [4,32]	
Primary etiology of cardiac arrest				0.85 ²
Cardiovascular event	62 (50%)	41 (49%)	21 (51%)	
Respiratory event	38 (30%)	25 (30%)	13 (32%)	
Other	23 (18%)	17 (20%)	6 (15%)	
Unknown	2 (2%)	1 (1%)	1 (2%)	
ECMO used post qualifying CA and prior to randomization	66 (53%)	49 (58%)	17 (41%)	0.076 ²
Treatment Assigned				0.91 ²
Hypothermia	68 (54%)	46 (55%)	22 (54%)	
Normothermia	57 (46%)	38 (45%)	19 (46%)	
Post-cardiac arrest length of stay (days)*				0.44 ¹
N	124	83	41	
Median [Q1, Q3]	37 [21,66]	37 [20,70]	34 [21,63]	

* One patient remained in the hospital at the time of 12 month follow-up and no discharge date was recorded.

¹ P-value is based on the Wilcoxon rank-sum test.

² Chi-squared test of no association.

Results

Demographics and pre-IH-CA functioning

The majority (84/125) were <3 years at 12-month follow-up. Since demographic factors vary by age⁷ and also because we were concerned the pre-IH-CA function measures might be less precise in younger children, we compared infants and toddlers <3 years with children ≥ 3 years (Table 1). IH-CA aetiology was cardiovascular in about half. Average family functioning fell within the “normal” range. Mean pre-IH-CA VABS-II scores were average, although young children had lower pre-IH-CA mean VABS-II scores and

greater impairment on PCPC. Most children obtained normal PCPC ratings, but some disability on POPC.

Neurobehavioural functioning

Table 2 displays mean pre-IH-CA, 3-month, and 12-month VABS-II composite, domain and subdomain scores. All scores differed significantly between pre-IH-CA and 3-months, and between pre-IH-CA and 12-months. Most domain and subdomain scores did not differ between 3 and 12 months; significant improvements were noted for Daily Living domain and Community subdomain scores, and interpersonal subdomain of Socialization. Mean differences from pre-IH-CA to 3 or 12-month follow-ups ranged from

Table 2
Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite, Domain, and Subdomain Scores: Means and Standard Deviations.

	N ¹	Pre-CA	Month 3	Month 12	Pre-CA to month 3 change ²	Pre-CA to month 12 change ²	Month 3 to month 12 change ³
Adaptive Behavior Composite	125	96 (16)	82 (18)	83 (18)	-14 (21)	-12 (20)	1 (13)
Communication	125	99 (16)	89 (23)	87 (18)	-10 (25)	-11 (20)	-2 (17)
Receptive	125	102 (14)	95 (19)	92 (16)	-8 (20)	-10 (18)	-2 (16)
Expressive	125	98 (15)	90 (24)	88 (21)	-7 (25)	-9 (22)	-2 (19)
Written	36	99 (18)	86 (15)	87 (15)	-14 (18)	-11 (18)	2 (9)
Daily Living	125	97 (18)	79 (19)	83 (20)	-18 (24)	-15 (24)	4 (15)
Personal	125	98 (17)	79 (19)	81 (21)	-19 (24)	-18 (24)	1 (14)
Domestic	54	98 (16)	87 (19)	92 (13)	-12 (22)	-9 (18)	4 (15)
Community	54	104 (16)	88 (17)	90 (15)	-16 (21)	-10 (21)	5 (16)
Socialization	125	96 (16)	88 (18)	91 (15)	-8 (23)	-5 (20)	3 (15)
Interpersonal Relationship	125	96 (15)	89 (18)	92 (17)	-7 (21)	-4 (21)	3 (15)
Play and Leisure	125	94 (14)	89 (15)	88 (14)	-6 (20)	-6 (18)	-1 (16)
Coping Skills	53	107 (16)	95 (16)	95 (13)	-12 (24)	-11 (19)	1 (15)
Motor Functioning	124	95 (17)	79 (20)	80 (20)	-17 (22)	-15 (22)	2 (18)
Gross	124	92 (13)	79 (18)	78 (18)	-13 (20)	-14 (20)	-0 (19)
Fine	124	103 (16)	90 (20)	90 (21)	-14 (22)	-13 (22)	0 (18)

Pre-CA = Pre-Cardiac Arrest. All *p*-values from the Signed Rank test.

¹ N with both Pre-CA and month 12 assessment. Three subjects with the Pre-CA assessment did not complete the month 3 assessment.

² All *p*-values < 0.005 except for Pre-CA to month 3 Expressive subdomain score (*p* = 0.01) and Pre-CA to month 12 Interpersonal Relationship subdomain score (*p* = 0.04).

³ All *p*-values > 0.05 except for Daily Living domain score (*p* = 0.01), Community subdomain score (*p* = 0.02), and Interpersonal Relationship subdomain score (*p* = 0.04).

-4 to -19, whereas mean changes from 3 to 12-month follow-ups ranged from -2 to 5. Three and 12 month scores were strongly correlated ($r = 0.72$, $p < 0.001$).

Supplemental Table 2 displays the percentage of children within each outcome range for VABS-II composite and domain scores. Seventy-seven percent of children had broadly normal VABS-II composite score (≥ 70 , within 2 SD of mean); percentages varied across domains [Communication, 104/125(83%); Daily Living, 89/125(71%); Socialization, 115/125(92%); Motor, 85/125 (68%)].

At 12-months, 60% (75/125) had composite scores within 1 SD (15 points) of their pre-IH-CA baselines. Similar fractions had follow-up domain scores within 1 SD of baselines [Communication, 77/125(62%); Daily Living, 72/125(58%); Socialization, 94/125(75%); Motor, 66/124 (53%)].

Table 3 provides VABS-II composite scores classified by age and temperature-treatment group. Follow-up scores did not differ between age groups; however, overall mean declines to 3 and 12-month follow-ups (incorporating data from both treatment groups) were greater in older children. Although younger children randomized to hypothermia had significantly lower VABS-II total scores than the normothermia group, the magnitudes of change from pre-IH-CA did not differ between the temperature management interventions for either age group.

Table 4 presents cognitive test performance [WASI ($n = 24$) for age 6 years and over, Mullen for children up to 5-years-8-months ($n = 76$, including one without 12-month VABS-II data)]. On Mullen Scales, 50% displayed broadly normal functioning (within 2 SD of mean, ≥ 70), including 26% with average to above average functioning (within 1 SD of mean, ≥ 85); half obtained scores well below average (29%) or the lowest possible score (21%). Twenty-three children completed the WASI; an additional child, deemed ineligible for testing, was assigned the lowest possible score. Of these 24, 87% displayed broadly normal functioning and 67% performed in the average to above average range.

Fig. 1 compares the percentage of children within each range for VABS-II and cognitive composite scores. Sample sizes differ (VABS-II, $n = 125$; Cognitive testing, $n = 100$). Of note, VABS-II scores did not differ between participants and those whose caregivers declined onsite testing (means 82 vs 87, $p = 0.15$). To examine cognitive measures across age ranges, cognitive composite scores (Mullen early

learning composite or WASI 2-subtest composite) were combined. While 77% of children had broadly normal neurobehavioural functioning on the VABS-II based on caregiver report, 59% displayed broadly normal cognitive performance on standardized testing.

Predictors of neurobehavioural outcome

Exploratory analyses evaluated outcome predictors. In univariate analyses, the only pre-IH-CA subject variable associated with 12-month VABS-II was pre-IH-CA VABS-II. No IH-CA characteristics were associated with outcome. Among interventions, randomization to hypothermia was significantly associated with worse outcome. Discharge variables (greater neurological impairment based on PCPC and having a tracheostomy or gastrostomy) were associated with worse outcome. In the multivariate analysis that included predictor variables available during acute care (Model 1), lower pre-IH-CA VABS-II and randomization to hypothermia were associated with worse outcome; this model accounted for only 16% of variance. Even Model 2, including predictors available at hospital discharge, explained only 38% of variance; lower pre-IH-CA VABS-II, randomization to hypothermia, tracheostomy or gastrostomy, and worse PCPC scores were also associated with worse outcome. (Supplemental Table 3)

Discussion

This is the first detailed, prospective study of long-term neurobehavioural outcomes in paediatric IH-CA survivors who were comatose following resuscitation. Results revealed significant declines in all domains of neurobehavioural functioning, including communication, daily living, socialization, and motor skills 3 and 12 months later. Younger children had greater neurological impairment and lower VABS-II scores prior to IH-CA and smaller functional declines from pre-IH-CA to follow-up. In surviving infants/toddlers, those randomized to hypothermia had lower 3 and 12-month VABS-II scores than the corresponding normothermia group, but the magnitudes of score declines did not differ between treatment groups. Comparison of a relatively early (three month) outcome assessment with the primary outcome scoring at 12 months revealed few changes over this time interval. Overall,

Table 3
Mean Vineland Adaptive Behavior Scales, Second Edition (VABS-II) Adaptive Behavior Composite Scores by age group and treatment group.

	0–<3 years				3+ years			
	Overall (N = 84)	TH (N = 46)	TN (N = 38)	P-value ¹	Overall (N = 41)	TH (N = 22)	TN (N = 19)	P-value ¹
Pre-CA Adaptive Behavior Composite ³	93	91	95	0.12	102	103	100	0.69
Adaptive Behavior Composite at Month 3 ²	83	79	87	0.047	81	80	81	0.95
Adaptive Behavior Composite at Month 12	82	78	87	0.013	86	84	89	0.33
Change in composite score (Pre-CA to Month 3) ^{2,3}	–10	–12	–8	0.36	–21	–23	–20	0.72
Change in composite score (Pre-CA to Month 12) ³	–11	–13	–8	0.20	–16	–19	–11	0.24
Change in composite score (Month 3 to Month 12) ²	–1	–1	0	0.64	5	2	8	0.13

Pre-CA = Pre-Cardiac Arrest.

¹ P-value from a *t*-test comparing Therapeutic Hypothermia (TH) to Therapeutic Normothermia (TN).

² There was one subject in the 0–<3 years group and two in the 3+ years group that did not complete the month 3 assessment.

³ T-tests between age groups showed significant differences between baseline scores ($p = 0.011$), change from baseline to month 3 ($p = 0.022$), and change from baseline to month 12 ($p = 0.020$).

Table 4
Cognitive Performance at 12-month Follow-Up (N = 100).

4a Mullen Scales of Early Learning Composite and Scale Scores (<6 years old at Follow-Up)					
Score Range	Early Learning Composite (N = 76)	Visual Reception* (N = 76)	Fine Motor* (N = 76)	Receptive Language* (N = 76)	Expressive language* (N = 75)
Lowest possible score/49	16 (21%)	13 (17%)	14 (18%)	14 (18%)	18 (24%)
50–69 (well below average)	22 (29%)	20 (26%)	21 (28%)	21 (28%)	13 (17%)
70–84 (below average)	18 (24%)	15 (20%)	13 (17%)	17 (22%)	18 (24%)
85–115 (average)	17 (22%)	25 (33%)	26 (34%)	22 (29%)	25 (33%)
>115 (above average)	3 (4%)	3 (4%)	2 (3%)	2 (3%)	1 (1%)

4b Wechsler Abbreviated Scale of Intelligence Full Scale IQ Composite and Subtest Scores (≥6 years at Follow-Up)			
Score Range	Full Scale IQ Composite (N = 24)	Vocabulary* (N = 24)	Matrix Reasoning* (N = 24)
Lowest possible score	1 (4%)	1 (4%)	1 (4%)
55–69 (well below average)	2 (8%)	4 (17%)	2 (8%)
70–84 (below average)	5 (21%)	3 (13%)	2 (8%)
85–115 (average)	15 (63%)	15 (63%)	16 (67%)
>115 (above average)	1 (4%)	1 (4%)	3 (13%)

* Scores were transformed to correspond to a scale with mean 100 and standard deviation 15.

both on caregiver-reported neurobehavioural outcome measures and performance-based cognitive testing, the majority of survivors displayed broadly normal functioning (i.e. within 2 SD of population means).

Study strengths include the prospective design, large sample size, broad paediatric age range, high follow-up rate, and use of well-validated, detailed outcome measures that assess multiple domains of functioning, including caregiver-report and objective performance. Our THAPCA IH-CA cohort was restricted to a well-characterized and high disability risk group of children who were comatose for several hours after resuscitation (pain localization or responsiveness to commands were THAPCA-IH exclusion criteria). While our results can help clinicians tasked with early prognostication to better understand the range of outcomes in children at high risk for neurobehavioural morbidity after IH-CA, results cannot be generalized to all paediatric IH-CA survivors. Our exploratory multivariate analyses illustrate that understanding of the factors that influence outcome remain limited, and our data do not provide criteria for early individualized predictors of long-term outcome.

We found significant declines in all domain and subdomain of VABS-II mean scores at 3 and 12 months. Outcomes varied from above average to severely deficient with 77% functioning broadly within normal limits based on VABS-II composite score and 59% functioning similarly well on cognitive testing. In the correspond-

ing secondary analysis of THAPCA-OH survivors, [22] 49% had broadly normal functioning on VABS-II and 36% on cognitive testing and our retrospective cohort study found a higher rate of favorable outcome at hospital discharge in children after IH-CA compared to OH-CA.[1] Qualitatively, similar to our examination of OH-CA survivors, [22] performance was most impaired on the motor and daily living domains and least impaired on the socialization domain of the VABS-II.

Apart from our THAPCA-IH trial outcome report,[13] only two other studies have reported long-term neurobehavioural outcomes (both at least one year after IH-CA) in children;[4,5] both had small samples and limited description of IH-CA characteristics. In a retrospective study of 16 children with cardiac disease who received chest compressions for IH-CA, the average VABS composite was 82. In a prospective study including 25 children surviving an IH-CA, mean VABS composite was 87 at least one year later. These reports are similar to the average 12-month VABS-II composite score of 83 in our IH-CA group. These smaller studies likely included children who regained consciousness more rapidly following return of circulation.

In this report, which is restricted to children with broadly normal pre-IH-CA functioning, 16% obtained lowest possible Mullen scores, and of the children ≥6 years, only 1/24 (4%) lacked a means of functional communication and was assigned the lowest possible

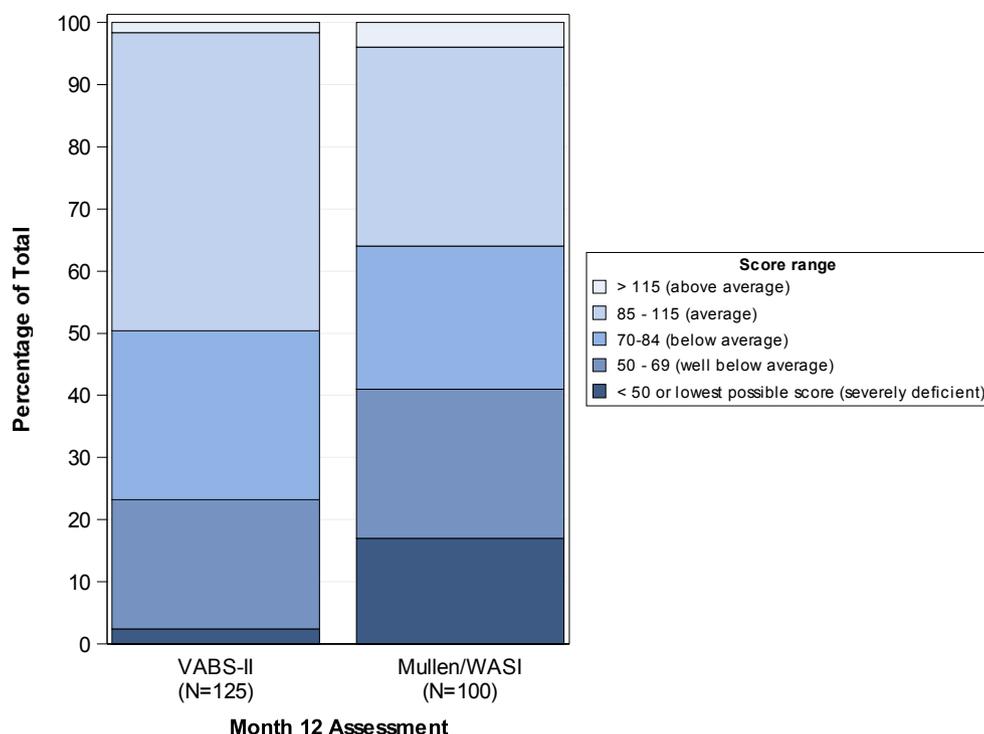


Fig. 1. Title: Neurobehavioral Functioning and Cognitive Performance at 12-month Follow-Up.

score. In contrast, THAPCA-OH trial survivors with broadly normal pre-OH-CA functioning had substantially greater cognitive impairment; 43% of THAPCA-OH survivors obtained the lowest possible Mullen scores and 51% of those ≥ 6 years old had no functional communication and were assigned the lowest possible score.[22] However, in comparison with other reports that included IH-CA cases, cognitive outcomes in THAPCA-IH survivors (mean cognitive composite score of 76) were worse. A recent study that included children who had been admitted to intensive care after either IH-CA or OH-CA² reported a mean IQ score of 87. In two small studies of children who survived IH-CA, cognitive composites were also higher (mean of 86⁵ and 87⁴). These studies likely included cases with more rapid post-CA neurological improvement than those who met criteria for enrollment in THAPCA-IH.

Results need to be considered from a developmental perspective. IH-CA is more common in very young children [7,11] and two-thirds of our sample was <3 years at 12-month follow up. Younger children with IH-CA may be likely to have complex congenital and multisystem disorders.[7] In our sample, infants/toddlers had lower mean pre-IH-CA VABS-II scores, more functional impairment due to neurological disease, and smaller declines in neurobehavioural functioning relative to pre-IH-CA functioning than older children. Yet, VABS-II absolute outcomes did not differ between age groups at 3 and 12-month follow-ups and age was not associated with VABS-II composite scores at 12 months. The smaller magnitude of decline in infants/toddlers relative to older children could reflect sensitivities of the test measures used to identify impairments. Specifically, outcome measures may not fully capture the degree of impairment in younger children. However, delineation of age-related trends is limited due to the large number of very young children, challenges inherent in assessment of young children, and higher rate of pre-existing neurological conditions in young children.

Our results reveal outcomes that ranged from severe to no impairment, which highlights the challenges in predicting

neurobehavioural outcome acutely after IH-CA resuscitation in comatose children. Consistent with other reports of paediatric IH-CA,[11] few variables known at hospital discharge were associated with later outcomes in the multivariate analysis. Since only data from THAPCA-IH trial survivors were evaluated, analyses of factors associated with outcome must be viewed cautiously.

Although hypothermia was associated with lower composite VABS-II scores, the clinical significance of this trend is challenging to interpret. This analysis was restricted to long-term survivors (rather than entire THAPCA-IH cohort), there was a trend for lower pre-IH-CA scores in 0–3 year olds in the hypothermia group, and magnitudes of declines in scores between groups did not differ. In the corresponding analysis of THAPCA-OH survivors we found no differences in neurobehavioural outcomes between temperature treatment arms.[22] Importantly, the results from the primary analysis of the THAPCA-IH Trial, that took into account survival, did not find differences between treatment groups.

Similar to the THAPCA-OH survivors, [23] we found that outcomes at 3 and 12 months were highly correlated ($r=0.72$) for survivors enrolled in THAPCA-IH. Although we found no compensatory accelerated skill acquisition during this recovery period, VABS-II scores are age-corrected, and therefore stable scores between 3 and 12 months indicate that children are developing new skills at similar rates as same-aged peers. These findings have important implications for both clinicians and investigators planning future studies in this population. Clinicians who care for children after IH-CA can cautiously use 3-month assessments to guide treatment planning and counseling. Investigators may consider an earlier time-point to be justifiable as an intervention study outcome end-point in similar study populations. That said, 3-month outcomes may not be as useful for trials involving primarily very young children, as neurodevelopmental measures in infants may not accurately predict later performance, [24] and the full extent of impairments may only be evident at school age.

This study should be interpreted in the context of several limitations. Pre-IH-CA functioning was assessed by caregiver report during a time of crisis within 24 h of their child's IH-CA. The young age of the study sample also needs to be highlighted, as it was particularly challenging to accurately assess pre-IH-CA functioning in young infants, many of whom had pre-existing illnesses. Age-related trends could not be fully examined with the smaller number of older children. Additionally, it is possible that the full extent of deficits in young children may not become evident until school age. In view of small sample sizes and multiple comparisons, subgroup analyses (e.g., age, treatment group) are considered exploratory. Data collection did not include several variables that might influence outcome (e.g. neuroimaging abnormalities, seizure burden, coma duration, medications after discharge, rehabilitation services, medical stability/impact of pre-existing conditions over the follow-up period). Lastly, given the limited number of older children, we could not examine functioning in specific neuropsychological domains (e.g., executive functions, memory).

Conclusion

In this population of children who incurred IH-CA and were comatose after resuscitation, we found a broad range of outcomes, with no substantial improvement between 3 and 12 months. Although the majority of survivors demonstrated significant declines in neurobehavioural functioning, across multiple functional domains at 3 and 12-month assessments, about three-quarters attained VABS-II functional performance composite scores within the broadly normal range. Results illustrate the broad range of outcomes in pediatric IH-CA survivors at high risk for neurological morbidity.

Conflict of interest

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Beth Slomine: Dr. Slomine contributed substantially to study design and data interpretation, oversaw neurobehavioural data collection, drafted the manuscript, and approved the final manuscript as submitted.

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Clinical trial registration

THAPCA-IH ClinicalTrials.gov number, NCT00880087

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