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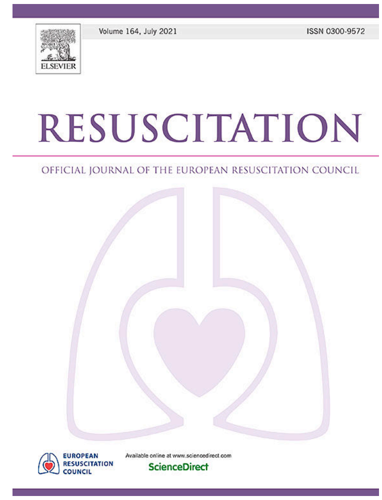

Clinical paper

Trends in community response and long term outcomes from paediatric cardiac arrest: A retrospective observational study

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Trends in community response and long term outcomes from paediatric cardiac arrest: A retrospective observational study.

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ABSTRACT

Aim: This study aimed to investigate trends over time in pre-hospital factors for pediatric out-of-hospital cardiac arrest (pOHCA) and long-term neurological and neuropsychological outcomes. These have not been described before in large

populations.
Methods: Non-traumatic arrest patients, 1 day-17 years old, presented to the Sophia Children's Hospital from January 2002 to December 2020, were eligible for inclusion. Favorable neurological outcome was defined as Pediatric Cerebral Performance Categories (PCPC) 1-2 or no difference with pre-arrest baseline. The trend over time was tested with multivariable logistic and linear regression models with year of event as independent variable.
Findings: Over a nineteen-year study period, the annual rate of long-term favorable neurological outcome, assessed at a median 2·5 years follow-up, increased significantly (OR 1·10, 95%-CI 1·03-1·19), adjusted for confounders. Concurrently, annual automated external defibrillator (AED) use and, among adolescents, initial shockable rhythm increased significantly (OR 1·21, 95% CI 1·10-1·33 and OR 1·15, 95% CI 1·02-1·29, respectively), adjusted for confounders. For generalizability purposes, only the total intelligence quotient (IQ) was considered for trend analysis of all tested domains. Total IQ scores and bystander basic life support (BLS) rate did not change significantly over time.
Interpretation: Long-term favorable neurological outcome, assessed at a median 2·5 years follow-up, improved significantly over the study period. Total IQ scores did not significantly change over time. Furthermore, AED use (OR 1·21, 95%CI 1.10-1·33) and shockable rhythms among adolescents (OR1·15, 95%CI 1·02-1·29) increased over time.

KEYWORDS

Pediatric out-of-hospital cardiac arrest, long-term outcome, Pediatric Performance Category, Intelligent Quotient, trends.

INTRODUCTION

Long-term neurological and neuropsychological outcome trends over time in large populations in pediatric out-of-hospital cardiac arrest (pOHCA) in combination with pre-hospital factors have not been described before. Reported pOHCA incidence rates are 8 per 100,000 person-years, peaking in the infant age group (1-5). The disease burden is high because of dismal survival rates (8-10%) and severe neurological sequelae (1, 2, 4-6). In the Netherlands, pOHCA accounts for 24% of pediatric mortality (7).

'Chain-of-survival' care has improved (8). Rates of bystander basic life support (BLS) have increased over time (9, 10). Automated external defibrillator (AED) use increased locally, depending on demographic and pre-hospital factors, especially first AED responder's presence (11-13). Furthermore, initial shockable rhythms seem to have increased, mainly in adolescents, through improved detection or incidence and are associated with favorable outcomes (1, 7, 14-16). Earlier advanced care was achieved through local system-based improvements such as a helicopter emergency medical service (HEMS) and text message-alerted lay rescuers (17, 18). Finally, post-return of circulation (ROC) care became more evidence-based and protocoled (19).

The data on whether these advances have resulted in increasing pOHCA survival trends are conflicting and may depend on methodological and regional differences (1, 14, 20). Long-term neurological outcome and neuropsychological outcome trends have not been studied before.

This study aimed to investigate trends in pre-hospital factors for pOHCA and long-term neurological and neuropsychological outcomes. We hypothesized that long-term outcome following pOHCA has improved over time.

METHODS

Design and setting

This cohort study was conducted at the Erasmus MC Sophia Children's Hospital, a tertiary-care university hospital in the Netherlands. The catchment area comprises approximately 5 million people (> 25% of the Dutch population) across 6000km². Data collection was approved, and informed consent requirement was waived by the Erasmus MC Ethics Review Board (MEC-2019-0440).

Inclusion criteria

Non-traumatic arrest patients, 1 day-17 years old, from January 2002-December 2020, admitted to the Erasmus MC Sophia Children's Hospital were eligible for inclusion. Neonates with perinatal asphyxia were excluded. Cardiac arrest (CA) was at least one minute of cardiopulmonary resuscitation (CPR). European Resuscitation Council guidelines definitions of CPR were used.

Data collection

The data collection process was similar to those previously described by Albrecht et al. (16). In short, different information sources (ambulance, HEMS, electronic patient files) were used to form one single-center cohort (17, 21, 22). Collected data comprised of A) basic patient characteristics (age, gender, parent's Social Economic Status (SES), pre-existing health status). B) CA features (year, location, first documented rhythm, witnessed, cause, bystander CPR, AED application, CPR duration, extracorporeal CPR, targeted temperature management, first blood lactate and pH after ROC, regional transport, re-arrest). C) outcome (ROC (either spontaneous or through extracorporeal membrane oxygenation (ECPR), different from 'return of spontaneous circulation' (ROSC)), mortality and neurological and neuropsychological outcome). Neurological outcomes were obtained using one of four outpatient clinic sources (in preferred order): prospective longitudinal follow-up (2012-2020 cohort), cross-sectional follow-up (2002-2011 cohort), regular visits (to medical specialists or psychologists) or hospital discharge letters (21, 22). Neuropsychological outcome was obtained similarly except not at hospital discharge.

Outcome measures

The primary outcome measure was survival, with favorable neurological outcome at the longest available follow-up measurement. Neurological outcomes were based on the Pediatric Cerebral Performance Category score (PCPC, ranging from 1 to 6) and the Functional Status Scale score (FSS, ranging from 6 to 30) (23, 24). A favorable neurological outcome was PCPC 1-2 or no difference from the pre-arrest baseline. No ROC, mortality after ROC or survival with a deteriorated PCPC >2 were unfavorable outcomes. Two physicians (MA) and (MH, pediatric neurologist) scored outcomes separately. Consensus decisions were made in case of disagreement through arbitration. The secondary outcome was the neuropsychological outcome at the most extended available follow-up moment, which could differ from the primary outcome. Four neuropsychological domains were evaluated using validated, age-appropriate tests and questionnaires compared to Dutch normative test data: 1. Development and intelligence in children (all ages): Bayley Scales of Infant Development or the Wechsler Scales (BSID-II, Bayley-III, WPPSI-III, WISC-III, WISC-V or WIAS-IV) (25-30). 2. Processing speed: from the Wechsler Scales (WPPSI-III, WISC-III or WAIS-IV) (≥4 years) (27, 29, 30). 3. Visual-motor integration: Beery Developmental Test of Visual Motor Integration (Beery-VMI) (≥2 years) (31). 4. Parent-reported executive function (≥2 years): Behaviour Rating Inventory of Executive Function questionnaires (BRIEF-P or BRIEF) (32).

Statistical analysis

Baseline characteristics and survival outcomes are evaluated by their respective changes over four periods (2002-2005, 2006-2010, 2011-2015, 2016-2020). Categorical variables are reported as frequencies and percentages, and continuous variables, depending on the distribution, as means with standard deviations (SD) or medians with first and third quartiles (Q1; Q3). The standardized neuropsychological outcome was calculated into Z-scores by subtracting the test mean divided by the SD. BRIEF Z-scores were multiplied by -1 for comparability, as a higher score reflects a worse outcome. In this way, for all domains, a worse score than the norm ($Z = 0$) is reflected by a negative Z-score. Differences to the normative Z-score were tested using one-sample t-tests or sign tests depending on the distribution.
Pre-hospital factors, CA features and outcomes, further stratified by initial rhythm, are presented as frequencies over

four periods. To analyze the association with time, neuropsychological outcome data was studied as continuous and dichotomous outcome (≥-1 or ≥-2 SD from the median). Depending on the outcome measure, multivariable logistic and linear regression models were developed, including the event year as the most important independent variable to test for time trends. To adjust for possible confounding, covariates were considered for the model based on existing literature (age, gender, socio-economic status, bystander BLS, witnessed arrest, initial rhythm, CPR duration, first lactate after ROC, first pH after ROC, any medical history, follow-up duration and pre-existing conditions related to the event). Metrics for post-ROC care or withdrawal of life-sustaining therapies (WLST) rules in-hospital were unavailable. Confounding was tested by effect estimate change on the primary determinant with the crude model (>10% change) before inclusion in the model. Furthermore, collinearity was tested using a >0·7 cut-off correlation. Odds ratios (OR) or beta's (B) and 95%-confidence intervals (CI) are presented. Stratified analysis by age group (infant; 1< year, child; 1–11 years and adolescent; 12–17 years) and initial rhythm (non-shockable, shockable and unknown) were performed. In case missing information was less than 10% for all covariates, missing variables were calculated by IBM statistics with the multiple imputation (*n*=5 imputations) function based on the distribution of existing data. Statistical significance was considered based on a two-tailed p-level<0·05. All analyses were conducted using Statistical Package of Social Sciences software, version 28·0 (IBM Corp, Armonk, New York).

RESULTS

Inclusion and basic characteristics

Figure 1 depicts the overview of inclusion, and Table 1 shows the basic characteristics. Of 628 HEMS attended pOHCA's, 154 children (25%) were pronounced deceased at scene after attempted resuscitation and 82 children (13%) were transported to other hospitals. Three hundred ninety-two children presented to the Erasmus MC Sophia Children's Hospital, nine with missing data (2%). The median age at the time of arrest was 3.4 years (Q1; Q3 0·7–10·9), and 237 children (67%) were male. Of arrests, 43% were witnessed, in 68%, bystander BLS was performed, and in 9%, an AED was used. Detected rhythms were shockable in 14%, non-shockable in 67% and unknown (i.e., ROSC before EMS arrival) in 18%.

Outcomes

CPR was discontinued in the emergency department in 107 (28%) of the 383 included children. And 127 children (33%) with ROC did not survive hospital admission, of whom 84 (22%) due to WLST. One hundred and forty-nine children (39%) survived to hospital discharge, of whom 8 (2%) died after discharge due to the consequences of severe hypoxic encephalopathy. The median follow-up duration for neurological outcome was 2.4 years (Q1; Q3 0·5–6·1) at a median age of 8·3 years (Q1; Q3 3·7–15·5). One hundred and seventeen children (31%) had a favorable neurological outcome. Neuropsychological testing was performed in 71 children (48% of survivors), whereas 78 were not tested. Twenty-two patients were discharged, of whom two had unfavorable neurologic outcome (i.e., PCPC 3) without subsequent follow-up, and 45 patients attended an outpatient clinic without a neuropsychological testing program (Figure 1). The median neuropsychological outcome follow-up duration was 2·2 years (Q1; Q3 1·6–7·3), at a median age of 10.6 years (Q1; Q3 4·7–15·3). Significantly lower scores than norm data were found for total IQ, verbal IQ, performance IQ, processing speed, and visual motor integration. Over the four time periods, total IQ and processing speed were significantly lower than the norm test scores from 2000-2005, 2010-2015 and 2016-2020.

Trend analysis

Figure 2 shows pre-hospital, CA features and outcome trends (by rhythm) over time. The yearly median number of inclusions (final sample) was 20 (Q1; Q3 16-24, p for trend over time = 0·550). The crude associations of pre-hospital factors and neurological outcomes over time were adjusted for witnessed arrest, bystander BLS, age at arrest, first lactate after ROC, pre-existing conditions related to the event, CPR duration, initial rhythm and SES (Table 2). After adjustment, a more recent event year was significantly associated with long-term favorable neurological outcome (OR 1·10, 95%CI 1·03-1·19), AED use (OR 1·21, 95%CI 1·10-1·33) and ROC rate (OR 1·13, 95%CI 1·06-1·22). For generalizability purposes based on the number of tested children, only total IQ was considered for trend analysis. No significant changes over time were found for total IQ, as continuous or dichotomous variable, in the crude and adjusted analysis after adjustment for gender, age at arrest, duration to follow-up moment, and initial rhythm (Table 3).

Among adolescents, the initial shockable rhythm was significantly associated with a more recent event year after adjustment (OR 1·15, 95%CI 1·02-1·29) (Supplementary Table 1). Long-term favorable neurological outcome significantly increased after adjustment for confounders in children (OR 1·21). AED use increased significantly in children and adolescents (OR 1·19 and OR 1·19, respectively). When split by rhythm (Supplementary Table 2), shockable and unknown rhythm sample sizes were too small for reliable regression analysis and, therefore, are not presented. Non-shockable rhythms, AED use, ROC and long-term favorable neurological outcome were associated with a more recent event year (OR 1·18, OR 1·11 and OR 1·14, respectively, after adjustment).

DISCUSSION

Over nineteen years, the annual rate of long-term favorable neurological outcome, assessed at median 2·5 years follow-up, increased significantly (OR 1·10, 95%CI 1·03-1·19) in a region covering over 25% of the Dutch population. Total IQ scores did not significantly change over time. Furthermore, AED use (OR 1·21, 95%CI 1.10-1·33) and shockable rhythms among adolescents (OR1·15, 95%CI 1·02-1·29) increased over time.

From previous reports, early recognition and treatment of shockable pOHCA by bystanders at scene are crucial in improving the globally low pOHCA survival rates (16, 33-35). Aiding these goals could be the implementation of text-message-alerted lay rescuers and early advanced care organizations in other countries (17, 18, 33). However, some contributing factors, such as short distances and the high population density specific to the Netherlands, cannot be replicated.

The findings of our study on actual long-term neurological outcome trends are not directly comparable to the literature. However, one-month favorable neurological outcome and AED use trends were shown to increase by Japanese OHCA registry data as per our findings (11, 36). Children achieved favorable outcomes in 10% compared to 31% in our study (11, 36). The inclusion of traumatic arrest and the disallowance of pre-hospital termination of resuscitation, selecting more children futile to resuscitative efforts, could explain the difference (37).

No previous pOHCA studies have reported longitudinal trend analyses on neuropsychological outcome. The finding that total IQ scores remained below population norm contradicts the favorable neurological outcomes increase (23). There could be multiple explanations. Possible explanatory variables such as pre-existing IQ levels and parents' educational and occupational status were unknown. Furthermore, the sample size of tested children (45% of survivors) could be too small to find a time trend. The prospective follow-up program (standard of care since 2012) boasts high response rates, making it likely to assume that the rate of tested survivors will increase over time (6). Our results emphasize that children have neuropsychological deficits despite 'good' neurological (PCPC) outcome (6).

Survival rates (inclusion starting in-field) are slightly lower than 26% in our cohort based on inclusions and pre-hospital HEMS data (1, 14, 20). No data are available for regionally transported patients. Data on trends are conflicting (1, 14, 20). In our study, survival to hospital discharge increased over time for non-shockable rhythms (OR 1·08, 95%CI 1·00-1·16) in adjusted analysis. Longitudinal (>15 years) Swedish (including trauma) and Australian (excluding trauma) cohorts found similar improving trends (14, 20). Fink et al. found unchanged survival rates after EMS-treated non-traumatic pOHCA over five years (1). Differences can be attributed to pre-hospital distances and the design, i.e., the inclusion of traumatic arrests, inclusion at scene instead of upon admission and the shorter inclusion period (1). Inclusion at scene is reflected by the lower number of pre-hospital ROC: 22·5% (Australia) and 16·2% (America) versus 41% in our cohort based on included patients and pre-hospital HEMS data, excluding regionally transported patients (no data available) (1, 20).

Estimated pre-hospital mortality rates were presented based on HEMS data. The rate increased significantly over time ($p < 0·001$). The HEMS, unlike ground ambulance crew with a physician on board, is primarily activated since 2013 in vitally compromised children 24 hours a day (17). Data from ambulance services, especially before 2013, are unavailable to determine whether the rise in HEMS activations drives the increase in pre-hospital mortality. However, this seems reasonable to assume because pOHCA incidence has not changed over time (1). Termination of resuscitation rules remained unchanged, and pronunciation of death is reserved for physicians in the Netherlands, making ground ambulance crews less likely to cease (38).

Moreover, the AED use and bystander BLS rates in the Netherlands, both associated with improved outcomes, play an essential role in achieving higher rates of ROC and, subsequently, favorable neurological outcomes (10, 12). Our cohort's bystander BLS rate is comparable to cohorts from Japan, Australia, the United States and Sweden (1, 11, 14, 20, 36). From the AED trend course, it seems apparent that the 2005 ERC guideline advising the safe use of AEDs in children <8 years and subsequently <1 year in 2010 positively affected AED use (39, 40). Our AED use rates are comparable to the

CARES registry (12). Neighborhood characteristics probably play an essential role in the regional variance in using AEDs in pediatrics (12).

How should our results be interpreted?

First, the combination of Dutch pre-hospital circumstances and care is unique. The country is small and densely populated. And over time, multiple advancements in early care delivery have been made. Police and firefighters are utilized as first AED responders (since 2011). HEMS is activated per protocol (since 2013) (17). And local lay rescuers are text-message alerted (since 2013) (18). Second, the favorable neurological outcome increase over time was most apparent for shockable rhythms. This concurs with the association between shockable rhythms and favorable neurological outcome (16). Over time, shockable rhythms increased among adolescents, possibly due to higher bystander BLS rates and increased use of AEDs. This may have prevented malignant ventricular arrhythmias from progressing to asystole. The rise in shockable rhythms is likely a result of improved detection rather than a genuine increase. Third, the rate of WLST increased (OR 1·06), leading to lower survival to discharge numbers and less severe neurologically damaged children surviving long-term. However, using a composite outcome (survival and neurological performance), WLST (i.e., PCPC 6) does not bias the neurological outcome trend. The increase was potentially influenced by stricter brain death (BD) criteria introduced in 2016 and standardized care for comatose non-BD children (21, 41). Yet, the time from hospital admission to WLST did not change. No studies report the number of WLST (1, 11, 14, 20, 36). Fourth, improved post-ROC care, including targeted temperature management, may have contributed to better outcomes (19). Fifth, the overall healthcare improvement during the study period, represented by the event year, likely involves various unmeasured factors positively impacting outcomes, such as blood pressure management during resuscitation (42).

The results of our study highlight the importance of early recognition and treatment of shockable pOHCA together with evidence-based post-CA care to improve outcomes (16, 19, 33, 34). Volunteer responder systems should be implemented by dispatching trained volunteer responders to start CPR using AEDs (18, 43). International collaboration is warranted for implementing pre-hospital and post-ROC care bundles and reliably measuring its effects with standardized data collection and follow-up programs in a large patient sample (44). Timing and cause of death should also be considered, forming an important selection bias on outcome (21).

Our study describes trends over a long period in crude neurological and neuropsychological outcomes assessed after a lengthy follow-up period (> 2 years). The single-center setup might benefit the uniformity of neuropsychological testing. Furthermore, by using different sources, data quality could be optimized. Limitations of our study are the retrospective design and the relatively low annual sample size, resulting in restrictions in our statistical approach of explanatory variables. Besides, not all contributing variables for outcome trends could be considered. Furthermore, PCPC is a crude measure of neurological outcome, although a PCPC score of 1-2 is correlated with daily independence (23, 45). The follow-up duration of 2·5 years was insufficient to account for the consequences of "growing into deficit", potentially overestimating favorable outcome (6). Also, choosing the most prolonged available follow-up moment development of children over time was not monitored. Besides, there is a risk of selecting better-performing children that can more easily attend the outpatient clinics with neuropsychological evaluation. Lastly, we might have selected a prognostically more favorable group of children by starting inclusion upon admission.

In conclusion, this study showed long-term favorable neurological outcomes after pOHCA increased significantly over nineteen years. Increased AED use could have led to increased capture of shockable rhythms, which increased over time for adolescents before degeneration to asystole, resulting in improved outcomes and advances in post-ROC care. Future goals should focus on pre-hospital EMS organization, such as AED use and implementation of post-ROC care guidelines (19). International collaboration with standardized data collection and follow-up programs into young adulthood is needed to perform interventional studies on post-ROC care.

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The contributions of the authors were as follows: M. Albrecht, R. De Jonge and C. Buysse had the original idea for the study. M. Albrecht, as the first author, participated in its design, performed the statistical analysis, interpreted the data, and drafted and critically revised the article. C. Buysse, R. De Jonge and V. Nadkarni provided supervision. All authors read and approved the final article. All co-authors revised the manuscript critically for important intellectual content. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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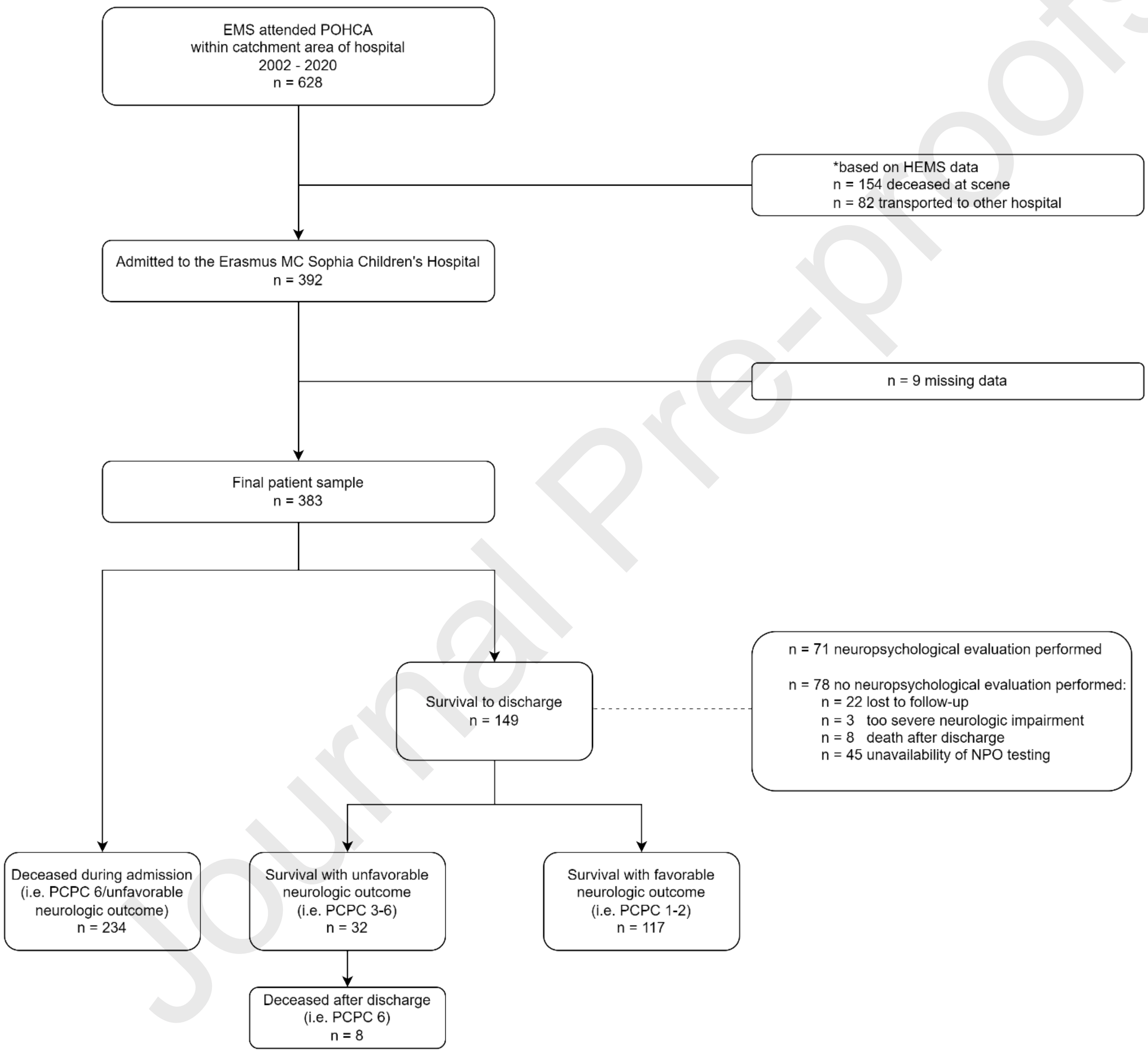
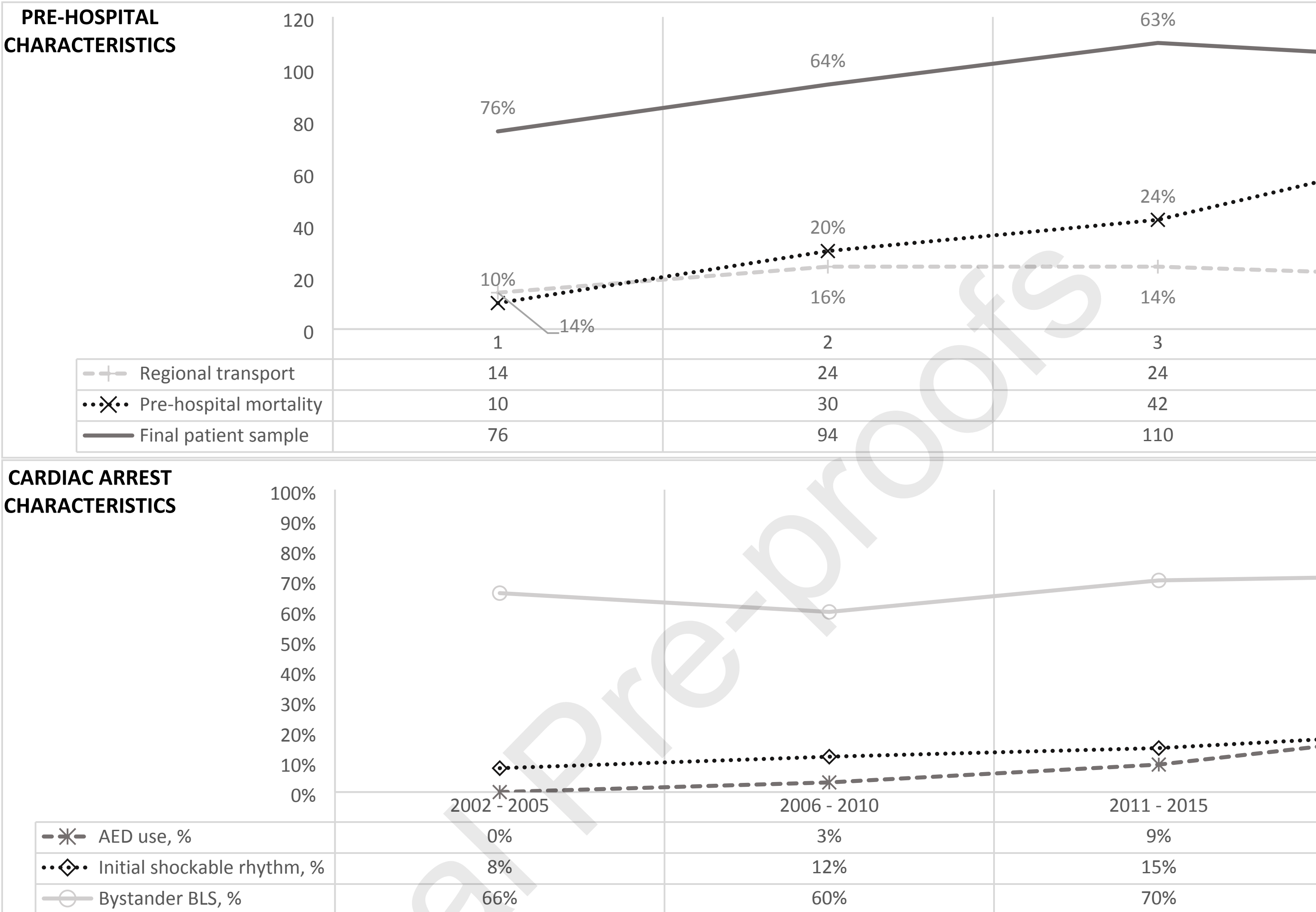
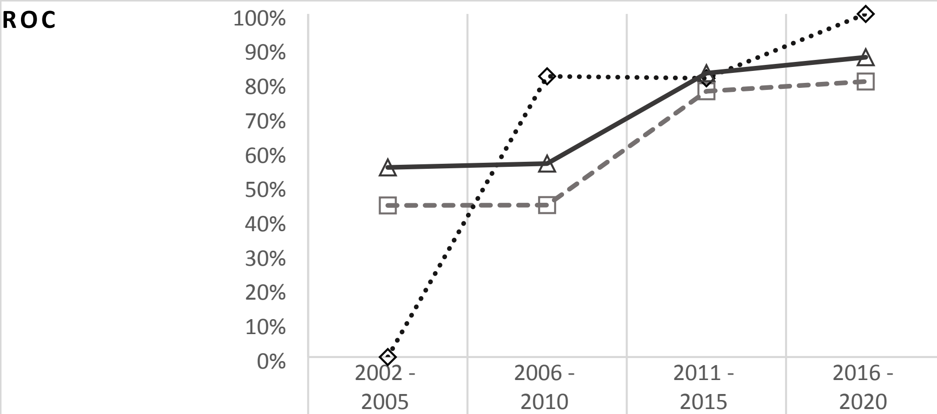
Figure 1. Overview of patient inclusion.



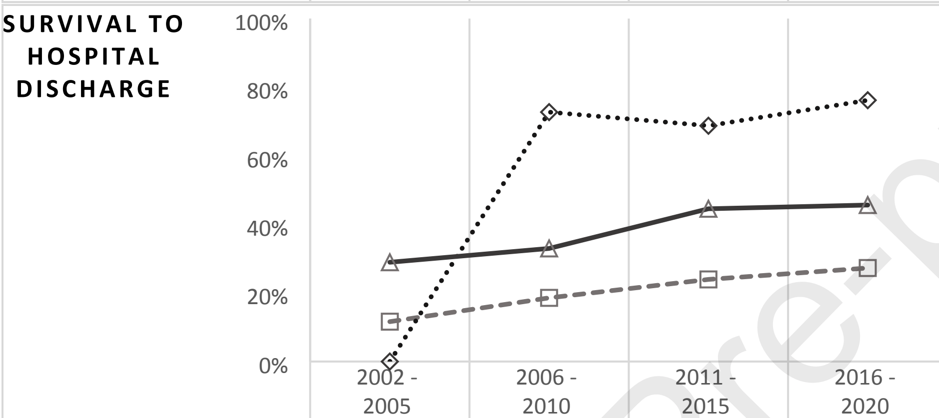
Abbreviations: EMS = Emergency Medical Services, POHCA = Pediatric Out-of-Hospital Cardiac Arrest, HEMS = Helicopter Emergency Medical Services, PCPC = Pediatric cerebral performance category.

Figure 2. Pre-hospital, cardiac arrest and outcome characteristics over the study period by period. Rates of ROC, survival to hospital discharge and favourable long-term neurological outcome presented overall and by initial rhythm.

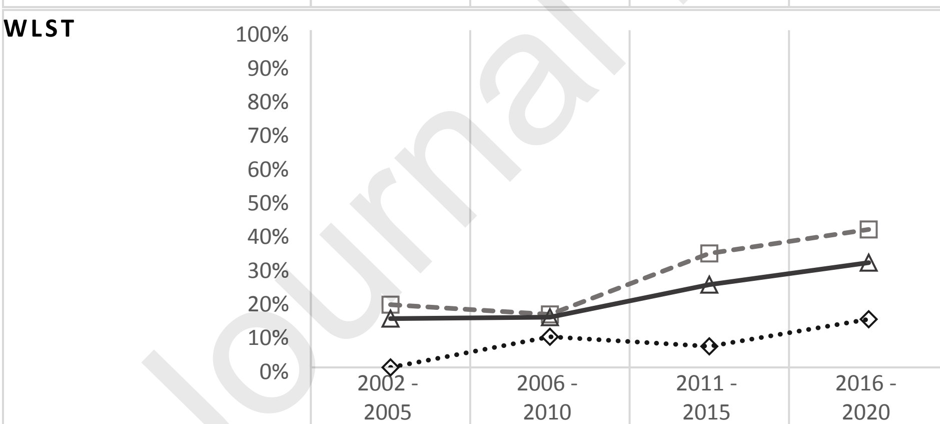




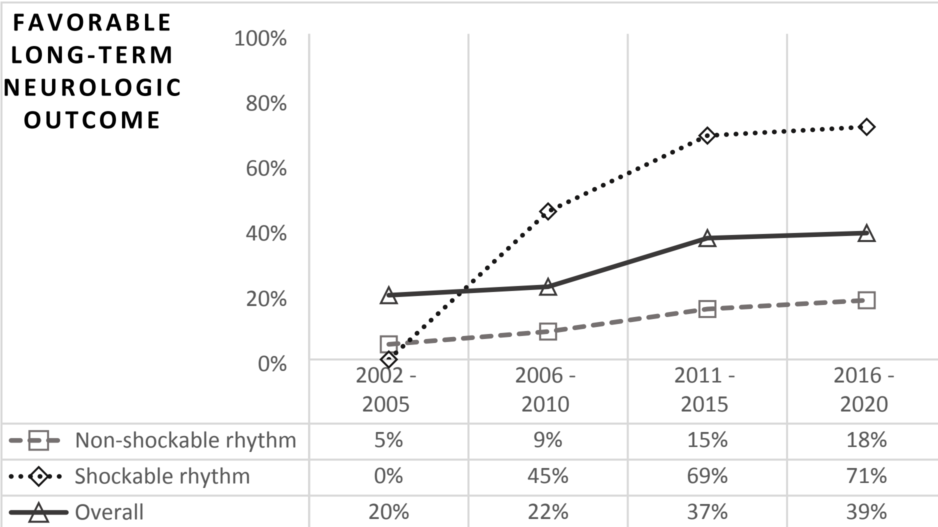
	2002 - 2005	2006 - 2010	2011 - 2015	2016 - 2020
Non-shockable rhythm	44%	44%	77%	80%
Shockable rhythm	0%	82%	81%	100%
Overall	55%	56%	83%	87%



	2002 - 2005	2006 - 2010	2011 - 2015	2016 - 2020
Non-shockable rhythm	12%	19%	24%	27%
Shockable rhythm	0%	73%	69%	76%
Overall	29%	33%	45%	46%



	2002 - 2005	2006 - 2010	2011 - 2015	2016 - 2020
Non-shockable rhythm	19%	16%	34%	41%
Shockable rhythm	0%	9%	6%	14%
Overall	14%	15%	25%	31%



Abbreviations: BLS = Basic life support, AED = Automatic external defibrillator, ROC = Return of circulation, WLST = Withdrawal of life sustaining therapy.

Table 1. Patient, cardiac arrest, post-cardiac arrest and outcome (neurological outcome and Z-scores neuropsychological outcome per domain) characteristics by period.

	Overall			2002 - 2005			2006 - 2010			2011 - 2015			2016 - 2020		
	n = 383			n = 77			n = 93			n = 110			n = 103		
	n[a]			n[a]			n[a]			n[a]			n[a]		
Patient characteristics															
Age (years)[d]	383	3.4	0.7;10.9	77	2.5	0.7;6.0	93	2.5	0.4;8.0	110	4.0	0.5;12.1	103	4.4	1.4;14.2
Male gender[e]	383	237	62%	77	44	57%	93	59	63%	110	71	65%	103	64	62%
Pre-existing conditions[e]	383	170	44%	77	29	38%	92	31	34%	110	31	28%	103	55	53%
Respiratory		43	25%		9	31%		3	10%		15	48%		16	29%

Cardiac		36	21%		5	17%		9	29%		11	35%		11	20%
Neurological		43	25%		2	7%		8	26%		13	42%		20	36%
Metabolic		4	2%		0	0%		0	0%		2	6%		1	2%
Congenital malformation (non-cardiac)		39	23%		9	31%		5	16%		8	26%		17	31%
Renal		4	2%		0	0%		0	0%		2	6%		1	2%
Genetic/Chromosomal		28	16%		4	14%		5	16%		10	32%		9	16%
Other		77	45%		8	28%		8	26%		28	90%		33	60%
SES parents[e]	373			74			91			108			100		
1		138	37%		34	46%		41	45%		32	30%		31	31%
2		160	43%		25	34%		28	31%		54	50%		53	53%
3		75	20%		15	20%		22	24%		22	20%		16	16%
CA characteristics															
Event location – public (versus private)[e]	383	133	35%	77	36	47%	93	33	35%	110	28	25%	103	36	35%
Witnessed arrest[e]	381	163	43%	76	37	49%	93	36	39%	109	52	48%	103	38	37%

Bystander BLS[e]	379	257	68%	75	51	68%	92	55	60%	109	77	71%	103	74	72%
Bystander AED use[e]	383	35	9%	77	0	0%	93	3	3%	110	10	9%	103	22	21%
EMS defibrillation[e]	383	65	17%	77	13	17%	93	13	14%	110	18	16%	103	21	20%
CPR duration (minutes)[d]	314	30.0	8.0;75.0	59	60.0	7.0;90.0	67	50.0	20.0;75.0	92	20.0	5.0;72.3	96	20.0	8.0;45.0
Initial rhythm[e]	381			76			92			110			103		
Shockable (VF)		54	14%		6	8%		11	12%		16	15%		21	20%
Unknown/ROSC before EMS		70	18%		21	28%		11	12%		22	20%		16	16%
Non-shockable		257	67%		49	64%		70	76%		72	65%		66	64%
Asystole		185	72%		34	69%		61	87%		44	61%		46	70%
PEA		24	9%		3	6%		3	4%		13	18%		5	8%
Bradycardia		40	16%		6	12%		6	9%		13	18%		15	23%
Other		1	0%		0	0%		0	0%		1	1%		0	0%
Cause of arrest[e]	383			77			93			110			103		
Unknown		32	8%		7	9%		6	6%		6	5%		13	13%

ALTE/SIDS		54	14%		10	13%		16	17%		22	20%		6	6%
Airway obstruction		45	12%		4	5%		16	17%		12	11%		13	13%
Arrhythmia		53	14%		4	5%		11	12%		19	17%		19	18%
Drowning		101	26%		32	42%		21	23%		21	19%		27	26%
Electrolyte abnormality		3	1%		0	0%		0	0%		3	3%		0	0%
Elevated ICP		10	3%		2	3%		2	2%		4	4%		2	2%
Hypotension/Shock		33	9%		8	10%		7	8%		7	6%		11	11%
Ingestion/Toxin		2	1%		0	0%		0	0%		2	2%		0	0%
Other respiratory failure		38	10%		6	8%		12	13%		9	8%		11	11%
Seizures		12	3%		4	5%		2	2%		5	5%		1	1%
ECPR[e]	383	16	4%	77	0	0%	93	1	1%	110	5	5%	103	10	10%
First pH after ROSC or after hospital arrival[d]	357	6.95	6.74;7.21	73	6.83	6.6;7.2	86	6.89	6.57;7.18	104	7.04	6.76;7.26	94	7.02	6.77;7.22
First lactate (mmol/L) after ROC or after hospital arrival[d]	348	12.7	5.0;16.0	69	15.0	6.1;15.0	84	14.4	5.6;20.0	104	10.0	4.9;16.9	91	10.8	3.7;17.0
Post-CA characteristics															
Post-ROSC ECMO[e]	383	13	3%	77	0	0%	93	1	1%	110	5	5%	103	7	7%

Temperature management[e]	378	166	44%	76	3	4%	92	35	38%	107	63	59%	103	65	63%
Re-arrest[e]	383	17	4%	77	1	1%	93	4	4%	110	5	5%	103	7	7%
Neurological outcome															
ROC[e]	383	276	72%	77	43	56%	93	52	56%	110	91	83%	103	90	87%
Before arrival at hospital		221	58%		32	42%		37	40%		73	66%		79	77%
After arrival at hospital		55	14%		11	14%		15	16%		18	16%		11	11%
Withdrawal of life-sustaining therapies[e]	379	84	22%	75	11	15%	91	14	15%	110	27	25%	103	32	31%
Survival to hospital discharge[e]	383	149	39%	77	23	30%	93	30	32%	110	49	45%	103	47	46%
Follow-up (years)[d]	148	2.4	0.5;6.1	23	5.3	0.0;11.0	30	3.4	0.3;6.3	49	2.4	0.5;6.9	47	2.2	0.8;2.8
Age at follow-up (years)[d]	148	8.3	3.7;15.5	23	6.5	3.2;13.0	30	9.6	3.8;13.6	49	8.3	3.7;14.2	47	8.3	3.9;17.3
Deceased after discharge[e]	148	8	5%	23	4	17%	30	2	7%	49	1	2%	47	1	2%
Pre-arrest PCPC[d]	148	1.0	1.0;1.0	23	1.0	1.0;1.0	30	1.0	1.0;1.0	49	1.0	1.0;1.0	47	1.0	1.0;1.0
Post-arrest FSS[d]	140	6.0	6.0;7.0	19	6.0	6.0;7.0	28	6.0	6.0;7.0	48	6.0	6.0;7.0	46	6.0	6.0;6.0

Post-arrest PCPC[d]	149	2.0	1.0;3.0			23	2.0	1.0;3.0		30	2.0	1.0;3.0		49	2.0	1.0;2.5		47	2.0	1.0;3.0
Favourable neurological outcome (PCPC 1-2) at longest available follow-up date[e]	383	117	31%			77	16	21%		93	20	22%		110	41	37%		103	40	39%
Neuropsychological outcome				p vs norm[b]	z ≤ -1[c]				p vs norm[b]				p vs norm[b]				p vs norm[b]			p vs norm[b]
Neuropsychological testing performed[e]	148	71	48%			23	9	39%		30	9	30%		49	25	51%		47	28	60%
Favourable neurological outcome[e]	71	60	85%			9	7	78%		9	7	78%		25	22	89%		28	24	86%
Follow-up (years)[d]	71	2.2	1.6;3.7			9	11.1	10.4;11.7		9	3,7	3.3;4.8		25	2.1	1.4;2.4		28	2.1	0.5;2.3
Age at follow-up (years)[d]	71	10.5	4.6;15.1			9	13.0	12.3;16.4		9	11.8	3.8;12.5		25	8.3	4.8;14.3		28	7.4	3.8;16.4
Total IQ (all)[e,f,g]	62	-0.9	-2.1;-0.2	<0.001	41%	8	-0.9	-2.1;-0.2	0.017	9	-0.9	-2.0;-0.1	0.023	21	-0.3	-1.6;0.7	0.126	24	-0.3	-1.3;0.1	0.002
Verbal IQ (all)[e,f,g]	40	-0.4	-1.7;0.3	0.002	40%	5	-0.4	-1.7;0.3	0.228	8	-0.5	-1.9;-0.1	0.054	16	-0.9	-1.6;0.4	0.069	11	-0.1	-1.1;0.4	0.453
Performance IQ (all)[e,f,g]	38	-1.2	-2.2;0.0	<0.001	50%	5	-1.2	-2.2;0.0	0.101	8	-1.1	-1.5;-1.1	0.003	15	-0.7	-2.0;0.0	0.015	10	-0.4	-0.8;0.0	0.137
Processing speed (≥4 years)[e,f,g]	45	-1.1	-1.1;-0.6	<0.001	49%	7	-1.1	-1.1;-0.6	0.005	4	-1.6	-2.7;-0.7	0.046	15	-0.2	-1.3;0.4	0.148	19	-0.8	-1.8;-0.4	<0.001

VMI (Beery ≥2 years) [e,f,g]	43	-1.4	-2.3;-0.8	0.007	37%	6	-1.4	-2.3;-0.8	0.017	6	-0.3	-1.2;-0.1	0.111	14	-0.1	-0.8;0.5	0.607	17	-0.8	-1.9;-0.2	<0.001
BRIEF Total score (≥2 years) [e,f,g]	42	0.1	-0.6;0.7	0.827	19%	8	0.5	-1.0;1.3	0.512	5	-0.5	-1.2;0.0	0.170	14	0.2	-0.2;0.7	0.940	16	0.0	-0.7;1.0	0.815

Abbreviations: SES = Social economic class, BLS = Basic life support, AED = Automatic external defibrillator, EMS = Emergency medical support, CPR = Cardiopulmonary resuscitation, VF = Ventricular fibrillation, RO(S)C = Return of (spontaneous) circulation, PEA = Pulseless electrical activity, ALTE/SIDS = Apparent life-threatening event/Sudden infant death syndrome, ICP = Intracranial pressure, ECPR = Extracorporeal cardiopulmonary resuscitation, ECMO = Extracorporeal cardiopulmonary support, PCPC = Pediatric cerebral performance category, FSS = Functional status score, IQ = Intelligence Quotient, VMI (Beery) = Beery Developmental Test of Visual Motor Integration, BRIEF = Behavior Rating Inventory of Executive Function.
[a] Number of subjects from whom the variable was obtained.
[b] All neuropsychological tests were converted into Z-scores and compared with norm test data. A one-sample T-test was used. A higher Z-score means a better outcome.
[c] Expected % in general population with Z-score ≤ -1 = 16%
[d] Median (interquartile range).
[e] Number of subjects (%).
[f] All neuropsychological tests were converted into Z-scores and compared with norm test data. A one-sample T-test was used. A higher Z-score means a better outcome.
[g] Numbers of patients differ for neuropsychological tests due to different age ranges and diversity of tests when children were tested elsewhere.

Table 2. Univariable and multivariable logistic regression analysis of all children with different cardiac arrest characteristics and outcomes as dependent variable and year of event for a linear time trend.

	Year of event for linear time trend			
	Crude		Adjusted	
Dependent variable	OR [95%CI]	p-value	OR [95%CI]	p-value
Bystander BLS[a]	1.03 [0.99 - 1.07]	0.148	1.02 [0.98 - 1.07]	0.258
AED use[b]	1.24 [1.13 - 1.35]	<0.001	1.21 [1.10 - 1.33]	<0.001
Rhythm[c]				
Initial shockable rhythm	1.06 [1.00 - 1.13]	0.029	1.03 [0.95 - 1.10]	0.511
Initial non-shockable rhythm	0.99 [0.95 - 1.03]	0.720	1.02 [0.98 - 1.07]	0.366
Initial unknown rhythm	0.96 [0.92 - 1.01]	0.123	0.96 [0.91 - 1.01]	0.112
ROC[d]	1.14 [1.09 - 1.20]	<0.001	1.13 [1.06 - 1.22]	<0.001
WLST[d]	1.08 [1.03 - 1.13]	0.003	1.06 [1.00 - 1.12]	0.029
Survival to hospital discharge[d]	1.06 [1.02 - 1.10]	0.006	1.06 [0.99 - 1.12]	0.082
Long-term favorable neurological outcome at the longest follow-up interval[d]	1.07 [1.03 - 1.12]	<0.001	1.10 [1.03 - 1.19]	0.006

Abbreviations: BLS = Basic life support, AED = Automatic external defibrillator, ROSC = Return of spontaneous circulation, WLST = Withdrawal of life-sustaining therapies, PCPC = Pediatric cerebral performance category, OR = Odds ratio.
[a] Adjusted for witnessed arrest, age at arrest, and socio-economic status.
[b] Adjusted for witnessed arrest, bystander basic life support, age at arrest and socio-economic status.
[c] Adjusted for witnessed arrest, bystander basic life support, age at arrest, pre-existing conditions related to the event and socio-economic status.
[d] Adjusted for witnessed arrest, bystander basic life support, age at arrest, first lactate after ROSC, pre-existing conditions related to the event, CPR duration, initial rhythm (non-shockable (referent), shockable or unknown) and socio-economic status.

Table 3. Univariable and multivariable linear and logistic regression analysis of children with neuropsychological outcome ad a dependent variable and year of event for a linear) time trend.

	Year of event for linear time trend

	(n = 62)			
	Crude		Adjusted	
Dependent variable	B / OR [95%CI]	p-value	B / OR [95%CI]	p-value
Neuropsychological continuous outcome*				
Total IQ (all)[b]	0.35 [-0.50 ; 1.19]	0.417	1.55 [-0.25 ; 2.13]	0.122
Neuropsychological dichotomous				
≥ -1 SD from median Total IQ[a]	1.02 [0.92 ; 1.13]	0.658	1.07 [0.90 ; 1.26]	0.455
≥ -2 SD from median Total IQ[a]	1.06 [0.93 ; 1.20]	0.389	1.16 [0.91 ; 1.46]	0.220

Abbreviations: OR = Odds Ratio, IQ = intelligence coefficient, VMI = Visual Motor Integration, SD = Standard Deviation.
**Univariable and multivariable linear regression analysis performed.*
***Univariable and multivariable logistic regression analysis performed.*
[a] Adjusted for gender, age at arrest, duration to longest available neuropsychological follow-up moment and initial rhythm (non-shockable (referent), shockable or unknown).

CRediT author statement

The contributions of the authors were as follows: M. Albrecht, R. De Jonge and C. Buysse had the original idea for the study. M. Albrecht, as first author, participated in its design, performed the statistical analysis, interpreted the data, drafted and critically revised the article. C. Buysse, R. De Jonge and V. Nadkarni provided supervision. All authors read and approved the final article. All co-authors revised the manuscript critically for important intellectual content. All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: