If Life Ends?

out-of-hospital cardiac arrest in children

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If Life Ends?

out-of-hospital cardiac arrest in children

Wanneer het leven eindig is?

Hartstilstand buiten het ziekenhuis bij kinderen

Thesis

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Chapter 1.

General introduction

General introduction

Pediatric cardiac arrest (CA) is a life threatening condition. A child's heart suddenly stops pumping blood around the body with an abrupt loss of vital signs and consciousness. Without cardiopulmonary resuscitation (CPR), mortality is nearly always 100%.

In the United States, with a population of approximately 300 million people, each year 15.000 children experience an in-hospital cardiac arrest (IHCA) and approximately 6000 an out-of-hospital cardiac arrest (OHCA) (1-4).

In The Netherlands, with a population of approximately 17 million people the incidence of pediatric CA is unknown, due to lack of a national pediatric CA registry. In the Erasmus MC-Sophia Children's hospital (referral area 4 million inhabitants), a total of 474 pediatric CA events, both IHCA and OHCA, were documented between 2002 and 2011, which equates to 50 CAs per year (5).

Only one study described the incidence of pediatric OHCA in the Netherlands; Bardai et al reported an incidence of 9 per 100,000 pediatric person-years with a mortality rate of 95% (6). In 2020, there were 3.775.258 Dutch residents between 0-20 years old (7). Based on Bardai's paper, this means that approximately 340 children and adolescents experienced an OHCA in 2020.

During CA, cessation of cerebral oxygen delivery occurs resulting in cerebral hypoxic ischemia with different effects on the central nervous system (8). In case of return of circulation (ROC), post-cardiac arrest syndrome can arise causing secondary global brain injury due to reperfusion and the frequently used high inspirational oxygen supply with additional hyperoxic damage (9-13). Areas most vulnerable to ischemic hypoxic injury are vascular end zones, hippocampus, insular cortex, cerebellar Purkinje cells and basal ganglia (14-18). The extent of initial brain injury combined with the therapeutic modalities determines

the overall neurological outcome of children after CA and can vary from no neurological deficits to, at the other end of the spectrum, brain death.

By starting immediate adequate basic life support (BLS) or advanced pediatric life support (APLS), the lack of oxygen delivery to the brain (resulting in direct brain ischemia) can be reduced. Guidelines have been developed to optimize BLS, APLS and pediatric post-CA care with the purpose to increase survival rates and prevent (or limit) the occurrence of secondary brain injury (19-21).

CAs are categorized into two separate groups depending on the location of the arrest: IHCA and OHCA. Whereas children with IHCA are already hospitalized prior to the arrest with actual underlying diseases such as sepsis, pneumonia, cardiac failure and/or multi-organ failure or need for support, children with OHCA are more likely to be previously healthy with a sudden unexpected arrest. This makes children with OHCA a more homogeneous group. For this reason, we focus on OHCA in this thesis.

Causes of Out-of-hospital cardiac arrest

Whereas in adults OHCAs are predominantly caused by cardiac diseases, pediatric OHCAs are more attributable to non-cardiac causes. In a retrospective multi-center cohort study by Moler et al. with 138 pediatric OHCA patients, main causes were respiratory (81%), followed by cardiac causes (19%)(22). A large Japanese prospective nationwide cohort study including 5758 children with OHCA showed that 70% of OHCAs had a non-cardiac origin and only 30% a presumed cardiac origin (23).

Causes of death after Out-of-hospital cardiac arrest

The overall survival rate of children with OHCA is low. The vast majority die pre-hospital (no return of circulation (ROC), cessation of CPR) or during hospital admission (24, 25).

Causes of non-survival during hospital admission are mostly: no ROC after arriving at the emergency department, re-arrest with no ROC, brain death, multiple organ failure due to additional hypoxic damage to organs other than the brain such as heart and kidneys, severe neurological injury, withdrawal of life sustaining therapy (WLST).

In a large American/Canadian cohort including 1738 children experiencing OHCA, ROC was achieved in 36%. In another study from the United States with 599 children with OHCA, the percentage of ROC was comparable (24, 26).

In a study by Moler et al., describing outcome in children with OHCA and subsequently ROC, survival to hospital discharge was 38% (22).

Only in one study from the United States by Du Pont et al., the causes and timing of death are described in 191 children admitted to a Pediatric Intensive Care Unit (PICU) with ROC after OHCA (27). Neurological injury was the most common cause of death in their tertiary care center. Forty-five percent died before PICU discharge. Of those, 47% was declared brain death, 34% died after WLST because of poor neurologic prognosis. Re-arrest occurred in 9% and 10% died due to WLST for refractory circulatory failure. Median time from OHCA to death after WLST because of poor neurologic prognosis was 4 days (IQR 1-5 days) (figure 1).

Actual research question: In the absence of nationwide data from The Netherlands, we wondered what the causes of death were in children with OHCA who presented in our hospital.
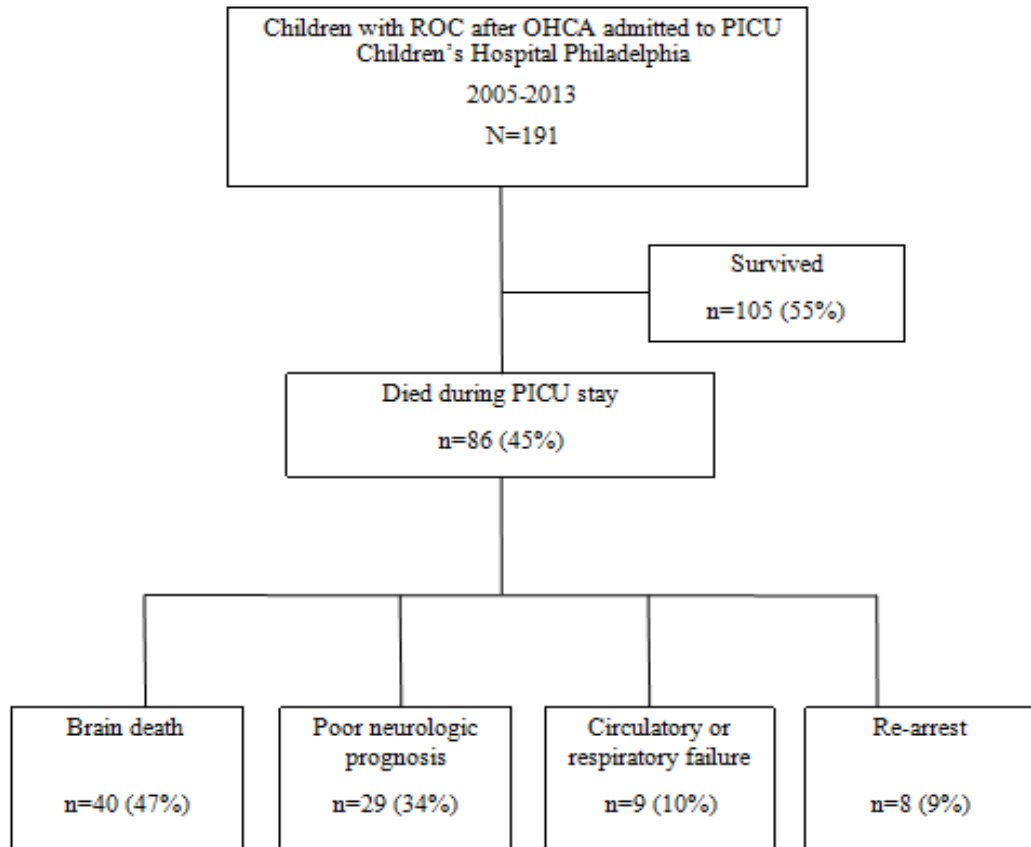
Figure 1. Causes of death by Du Pont et al. (27)
OHCA= Out-of-hospital cardiac arrest; PICU= Pediatric Intensive Care Unit; ROC= Return of circulation

Survival trends of Out of hospital cardiac arrest

Studies reporting outcome after pediatric OHCA show conflicting results.

Some studies showed that survival rates of children with OHCA did not significantly improve

in recent years (24, 28, 29). In a study of Fink et al. non-survival was associated with

unwitnessed CA, initial rhythm of asystole and region in North America. Regions with the

highest survival had more children with Emergency Medical Service (EMS)-witnessed

OHCA, bystander CPR, and increased EMS-defibrillation (24).

Other studies concluded that survival following pediatric OHCA did increase over the years

(30-33). Nehme et al. described improved outcomes for patients with an initial shockable

rhythm and ascribed higher survival rates to better CPR quality at scene (30). Mitani et al. and

Fukuda et al. found an increase in survival after implementation of public access defibrillation for children with witnessed OHCA and bystander CPR (31, 32).

If survival does increase, what does this mean for long-term consequences among survivors? Namachivayam et al. showed increased morbidity in pediatric CA survivors, suggesting that the price of survival of OHCA may be lifelong neurological sequelae which cause a serious burden for the survivor, families and society (34).

Long-term outcome after Out-of-hospital cardiac arrest

The occurrence and severity of neurological sequelae in pediatric OHCA survivors, both short-term and long-term, is one of the major concerns of pediatric intensivists and neurologist. Most studies describing survival/outcome after pediatric OHCA are limited to neurological outcome at hospital discharge. Furthermore, there are no clear agreements on the definition of short or long-term. Obviously, outcome at hospital discharge is short-term, but in literature one year post-CA is used both as short and long-term.

Pediatric cerebral performance category (PCPC) is often used as an outcome measure in studies describing neurological outcome after pediatric OHCA (35, 36). PCPC is a gross physical outcome scale ranging from 1 to 6 (normal; mild, moderate, or severe disability; comatose; or brain death, table 1). A recent study including 1980 children with OHCA showed that 77% of children who survived to hospital discharge had a relatively favorable outcome expressed in PCPC (PCPC 1 or 2) (28).

As part of the Therapeutic Hypothermia after Pediatric Cardiac Arrest (THAPCA) trial in which therapeutic hypothermia was compared with therapeutic normothermia in comatose children after IHCA and OHCA, Silverstein et al. examined PCPC scores of pediatric OHCA survivors at hospital discharge, 3-6 months and 1 year post-arrest (37).Thirty-six percent of survivors had a PCPC score of 1 or 2 at hospital discharge with no significant difference

between groups. PCPC score at discharge was significantly correlated with PCPC score at 3-6 and 12 months post-OHCA.

There are other methods to determine physical outcome such as general health assessment, neurological exam findings and the assessment of the functional status scale (FSS) (38). In a cohort with 179 children 1 year after IHCA and OHCA, neurological impairments (ranging from mild to profound), detected with neurological exam, were reported in 55% (39).

Score	Category	Description
1	Normal	Normal; at age-appropriate level;
2	Mild disability	Conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom, but grade perhaps not appropriate for age; possibility of mild neurologic deficit
3	Moderate disability	Conscious; sufficient cerebral function for age-appropriate independent activities of daily life; school-age child attending special education classroom and/or learning deficit present.
4	Severe disability	Conscious; dependent on others for daily support because of impaired brain function
5	Coma or vegetative state	Any degree of coma without the presence of all brain death criteria; unaware, even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles
6	Brain death	Apnea, areflexia, and/or electroencephalographic silence

Table 1. PCPC Score

Besides physical outcome, other outcome domains also inform us about the outcome of a child: neurocognitive functioning, psychosocial functioning and quality of life.

Table 2 gives an overview of literature on neuropsychological outcome after pediatric IHCA and OHCA published over the past 10 years. It illustrates the lack of studies on this topic.

In a cross-sectional cohort of 47 children surviving CA in our hospital between 2002-2011 (both IHCA and OHCA), with a median follow-up interval of 5.6 years (range 1.8-11.9 years), lower scores were found on all intelligence sub-scales. In addition, neuropsychological tests revealed lower scores on visual memory. Somewhat surprisingly, compared with norms, better scores were found on verbal memory (5). In this same cohort also long-term emotional and behavioral functioning of children was assessed with validated questionnaires for

children, parents/caregivers and teachers (Youth Self-Report, Child Behavior Checklist and Teacher's Report Form). In the reports of parents and teachers, deficits in attention and somatic complaints in children were reported (40).

Additionally, long-term health status and health related quality of life was assessed. Parents reported poorer health status in their children (Health Utilities Index Mark). Health related quality of life (Child Health Questionnaire) was significantly worse on general health perception, physical role functioning, parental impact and overall physical summary . In contrast parents reported better family cohesion.

Parents themselves scored better health related quality of life (quality of life of parents measured with 36 item Short Form Health Survey) on most scales (41).

Slomine et al. assessed neurobehavioral outcome by using the Vineland Adaptive Behavior Scale-second edition (VABS-II) in 85 children one year after OHCA (cohort of THAPCA trial) (42). They all had been temporarily unresponsive and required mechanical ventilation after return of spontaneous circulation (ROSC). All children had a broadly normal baseline functioning (based on VABS-II). Forty nine percent had a VABS-II score $\geq$ 70 (mean= 100, SD= 15) 12 months after OHCA. Significant declines were found in all domains of caregiver-reported neurobehavioral functioning, including communication, daily living, socialization, and motor skills. Declines were greatest in older children. On objective cognitive measures (<6 years Mullen Scales of Early Learning, $\geq$ 6 years Wechsler Abbreviated Scale of Intelligence), most children displayed significant deficits (42).

In a larger (partly overlapping cohort with the previous study) cohort of Slomine et al. neuropsychological assessments were done one year after pediatric IHCA and OHCA in initially unresponsive children requiring mechanical ventilation after ROSC (n=160) (43). In children younger than 6 years (n=119), scores were significantly lower on Mullen Scales of Early Learning (describing visual perception, fine motor, receptive and expressive language)

compared with normative reference group. In children 6 years and older (n=41), full-scale IQ was significantly lower as were scores on processing speed, attention, learning and memory skills, visuo-motor functioning and executive functioning, compared with normative data.

In a small cohort with 23 children, Manglick et al. investigated long-term neurocognitive outcome in children after near drowning who seemed neurologically intact on hospital discharge (44). Assessments were done 3-6 months, 1 year, 3 years and 5 years after near drowning. All children had CPR, except one. In 22% abnormalities in behavior as well as poor communication, executive dysfunction and learning problems were found (44).

In summary: Studies describing long-term outcome after OHCA in children are few and only five peer-reviewed studies were published.

All above mentioned neuropsychological outcome studies (see table 2) showed lower intelligence scores compared with the norm population. Additionally, as to subdomains, lower scores were found in visual memory, processing speed, attention and executive functions, also compared with norms.

Regretfully in some studies, part of neuropsychological assessments were done by telephone interview with parents/caregivers (42, 43). Also, few studies included children with both IHCA and OHCA (5, 43). No structured repeated neuropsychological assessments were done and inclusion criteria were different in all studies.

Two studies were cross-sectional (5, 45), both sub-studies of the THAPCA trial had a follow-up interval 1 year post-arrest without repeated measures (42, 43). Only Manglick et al. had a follow-up interval up to 5 years after event, but they included only children post-drowning who were neurologically intact at hospital discharge (44).

Actual research question: What is the long-term longitudinal (with repeated measures) physical and neuropsychological outcome of pediatric OHCA survivors?

Author Journal	Year	N	Age at arrest (range)	Inclusion criteria	Follow-up interval	Outcome
Suominen *Resuscitation* (45)	2014	20	Median 2.4 years (IQR 1.8-5.5 years)	near-drowning with cardiac arrest	Cross-sectional, median 8 years after arrest	Full scale IQ 40% below 80
Slomine *Pediatrics* (42)	2015	< 6 years n=42 ≥ 6 years n=18	0-17.9 years	OHCA Unresponsive and mechanical ventilation after ROC	1 year	**< 6 years:** Mullen scale: -Early learning composite 82% below 85 -Visual reception 70% below 85 -Fine motor 71% below 85 -Receptive language 71% below 85 -Expressive language 79% below 85 **≥ 6 years:** Full-scale IQ 38% below 85 **All ages:** VABS II: Worse all domains compared with baseline, 49% ≥ 70
Van Zellem *Intensive Care Medicine* (5)	2016	47	0-16.1 years	IHCA/OHCA	Cross-sectional, median 5.6 years after arrest	Full scale-IQ, VIQ, PIQ lower than norm data Worse scores on long-term visual memory Better scores on long-term verbal memory
Slomine *Jama Neurology* (43)	2018	< 6 years n=119 ≥ 6 years n=41	Median 2.5 years (IQR 1.3-6.1 years)	IHCA/OHCA Unresponsive and mechanical ventilation after ROC	1 year	**< 6 years:** Mullen scale: -Early learning composite sign lower than norm -Visual reception sign lower than norm -Fine motor sign lower than norm -Receptive language sign lower than norm -Expressive language sign lower than norm **≥ 6 years:** -Full-scale IQ significantly lower than norm -Lower scores on processing speed, attention, learning and memory skills, executive functioning, visuo-motor functioning than norm **All ages:** VABS II: 71.2% ≥ 70
Manglick *Archives of Disease in Childhood* (44)	2018	23	< 2-9 years	near-drowning Neurological intact at hospital discharge	6 months, 1, 3 and 5 years after near drowning	Only BRIEF was used: 22% abnormalities in behavior, poor communication, executive dysfunction and learning problems

Table 2. Literature overview of neuropsychological outcome after pediatric cardiac arrest over the past 10 years

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BRIEF= Behaviour Rating Inventory of Executive Function; IHCA= In-hospital cardiac arrest; IQ= Intelligence quotient; IQR= Interquartile range; OHCA= Out-of-hospital cardiac arrest; PIQ= Performance intelligence quotient; ROC= Return of circulation; VABS II= Vineland adaptive behavior scales-second edition; VIQ= Verbal intelligence quotient

Early prediction of outcome

In children with an optimal Glasgow Coma Scale (GCS) after OHCA, it is clear that the gross neurological outcome is favorable, at least at short-term. On the other hand, when a child is brain death, there is no doubt that the prognosis is futile.

However, when a child remains comatose in the first days after OHCA, prediction of long-term neurological outcome becomes a challenge. Early identification of those children who have a poor long-term neurological prognosis is crucial. An accurate individualized outcome prediction model would help clinicians in making important decisions regarding treatment (or WLST) and in counseling families on their child's prognosis/future prospects. It would help limit the so intense emotional period of uncertainty for the families. Furthermore, it could reduce health care costs (also on the long-term) when medical professionals are accurately informed on a disastrous patient outcome early after hospital admission. In contrast to adult literature, no prognostic guidelines exist for children post-CA. The adult guidelines combine findings on neurological exam together with ancillary tests (electroencephalography (EEG), somatosensory evoked potentials (SSEP) and cerebral plasma biomarkers) in order to predict gross outcome within a few days after CA (46, 47).

It is inappropriate to extrapolate these adult guidelines to children, because children have age-dependent anatomy and physiology relevant to central nervous system injury and its repair (48).

Many factors will influence the long-term outcome varying from pre-arrest to post-CA arrest factors, which makes prediction even more complex (figure 2):

1) Pre-CA: Pre-arrest neurocognitive functioning and already existing co-morbidities may play a role in outcome after OHCA. E.g., a child with already a developmental delay (e.g. due to a genetic disease) would be expected to have a more unfavorable outcome than a normal developing child. However, on this specific topic no studies could be found. Furthermore, socioeconomic status (SES) may contribute to outcome; a lower SES is associated with a risk for developmental problems/lower intelligence scores (49, 50).

The relationship between age and neurocognitive outcome received much attention in brain injured children, in particular traumatic brain injured children (51, 52). The immature brain appears to be more vulnerable to injury. Further, the phenomenon of growing into deficit causes more significant long-term neurocognitive deficits in infants and young children than in school-age children (51-54) .

2) CA: Known factors associated with favorable outcome after CA are etiology of CA, initial arrest rhythm of ventricular fibrillation or tachycardia, witnessed arrest, shorter duration of CPR, and BLS quality (55).

3) Post-CA: In a recent American Heart Association (AHA) statement by Topijan et al., state of the art recommendations are made in order to improve outcome by improving post-ROSC care. The most important are: pursue normoxemia and normocapnia, avoid hypoglycemia, prevent hypotension, maintain normothermia and prevent fever (56). However, scientific evidence for these statements is mostly lacking. As to neuroprognostication, few studies describe the association between outcome and neurological exam and ancillary tests (imaging and electrophysiological assessments) in children after OHCA. In a review by Abend et al. (2008), the absence of pupillary reflexes and motor score as well as a bilateral absent N20 wave on SSEP, electrocerebral silence or burst suppression patterns on EEG and diffusion

restriction in the cortex and basal ganglia on magnetic resonance imaging (MRI) are each highly predictive of poor outcome, at least 24 hours after the arrest (57). In the AHA statement, it is recommended to consider multiple modalities (e.g. neurological exam, neuroimaging, EEG, plasma biomarkers) when predicting outcome in children after CA (56).

4) Rehabilitation: Although there is insufficient evidence that after OHCA a specific rehabilitation program is associated with a better outcome, it is plausible that early and intensive rehabilitation may have a positive effect on outcome. This assumption is based on previous studies regarding rehabilitation after pediatric traumatic brain injury and severe brain injury otherwise (58, 59).

5) It is likely that there are factors associated with a good or poor outcome we are not yet aware of or have not been studied in detail yet.

As described above, many factors are supposed to be associated with outcome. Unfortunately evidence is often lacking and it is unknown what the predictive value for each factor is for prognosis for each individual patient.

Actual research question: Is it possible to develop a prediction outcome model for children post-cardiac arrest based on the above mentioned factors, in particular with the use of neuromonitoring methods such as neurological exam, imaging and electrophysiology post-OHCA?

Factors associated with outome

pre-event

unknown

cardiac arrest

outcome

rehabilitation

post-ROSC care and ancillary tests: PICU
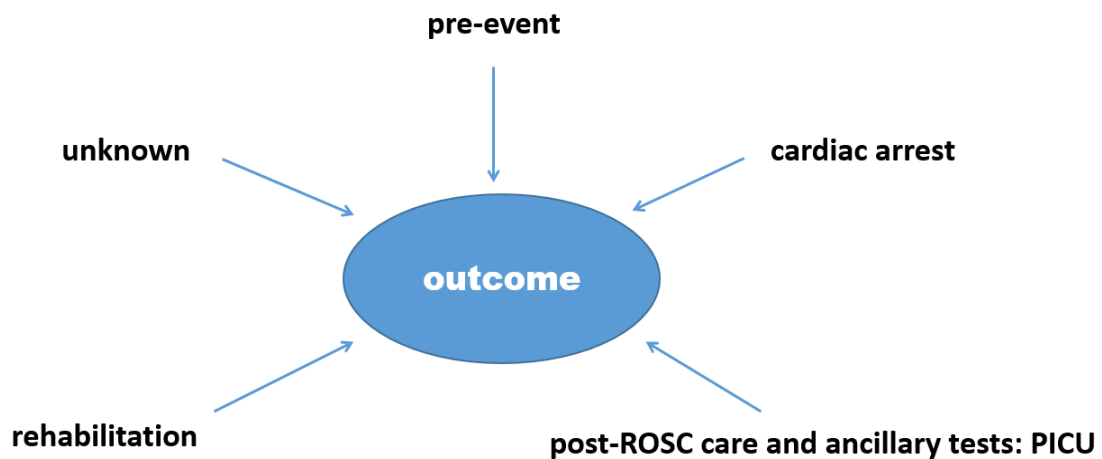
Figure 2. Factors associated with outcome
PICU= Pediatric Intensive Care Unit; ROSC= Return of spontaneous circulation

Aims and outline of this thesis

Background

In 2012, a standardized multidisciplinary follow-up program including pediatric OHCA survivors was set up in our PICU as standard of care. Children and their parents/caregivers are invited to our outpatient clinic 3-6, 12 and 24 months after the event and subsequently, dependent on the age at time of arrest, at the ages of 5, 8, 12 and 17 years. During these visits a pediatric neurologist and pediatric intensivist interview these children and their parents/caregivers in a semi-structured way. Both physical and neurological exam are performed, as well as extended neuropsychological assessments by a pediatric psychologist using validated instruments on different domains.The primary goal of this follow-up program is patient care. However, data are also used for research purposes with the ultimate goal to improve outcome of critically ill children.

The aim of this thesis:

- To investigate the current practice regarding neuro-prognostication and decision making in children after CA.

- To study the short- and long-term neurocognitive outcome in a homogeneous cohort of children after OHCA, in a prospective longitudinal way, using repeated and validated measures

Chapter 2 provides an overview of several neuromonitoring methods (neurological exam, brain imaging, neurophysiology and biomarkers) and their potential role in neuro-prognostication in children early after IHCA and OHCA.

Chapter 3 describes the results of a survey, performed among European pediatric intensivists and pediatric neurologists, regarding the treatment, prediction and decision making in children with a depressed level of consciousness after IHCA and OHCA.

In **chapter 4** the timing and causes of death are evaluated in children following ROC after OHCA in our hospital between 2012 and 2017.

Chapter 5 investigates whether early MRI with diffusion weighted imaging (DWI) contributes to the prediction of a favorable long-term outcome in the individual patient after OHCA.

In **chapter 6** the association between shockable rhythms and long-term outcome after pediatric OHCA in Rotterdam, over an 18-year period, is explored.

Chapter 7 presents the neuropsychological outcome of OHCA survivors 3 and 24 months after the arrest.

In **chapter 8** the results of the studies are discussed and placed in a broader perspective.

In **chapter 9** the results are summarized in English and Dutch.

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Chapter 2.

A systematic review of neuromonitoring modalities in children beyond neonatal period after cardiac arrest

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Dremmen; Wichor Bramer; Enno Wildschut; Dick Tibboel; Corinne Buysse

Abstract

Objective Postresuscitation care in children focuses on preventing secondary neurological injury and attempts to provide (precise) prognostication for both caregivers and the medical team. This systematic review provides an overview of neuromonitoring modalities and their potential role in neuroprognostication in post-cardiac arrest children.

Data resources Databases EMBASE, Web of Science, Cochrane, Medline Ovid, Google Scholar and PsycINFO Ovid were searched in February 2019.

Study Selection Enrollment of children after in- and out-of-hospital cardiac arrest between 1 month and 18 years and presence of a neuromonitoring method obtained within the first 2 weeks post cardiac arrest. Two reviewers independently selected appropriate studies based on the citations.

Data extraction Data collected included study characteristics and methodologic quality, populations enrolled, neuromonitoring modalities, outcome and limitations. Evidence tables per neuromonitoring method were constructed using a standardized data extraction form. Each included study was graded according to the Oxford Evidence-Based Medicine scoring system.

Data synthesis Of 1195 citations, 27 studies met the inclusion criteria. There were 16 retrospective studies, nine observational prospective studies, one observational exploratory study and one pilot randomized controlled trial. Neuromonitoring methods included neurological examination, routine electroencephalography and continuous electroencephalography, transcranial Doppler, MRI, head CT, plasma biomarkers, somatosensory evoked potentials, and brainstem auditory evoked potential. All evidence was graded 2B-C.

Conclusions The appropriate application and precise interpretation of available modalities still needs to be determined in relation to the individual patient. International collaboration in standardized data collection during the (acute) clinical course together with detailed long-term

outcome measurements (including functional outcome, neuropsychological assessment and health-related quality of life) are the first steps towards more precise, patient-specific neuroprognostication after pediatric cardiac arrest.

Introduction

Each year 15.000 children experience an in-hospital cardiac arrest (IHCA) and approximately 6000 an out-of-hospital cardiac arrest (OHCA) in the United States (1-4). The survival rate after cardiac arrest (CA) has increased due to early bystander basic life support, improved availability of automated external defibrillators, increased use of air medical services on site, the use of extracorporeal cardiopulmonary resuscitation (ECPR) and standardized care during the post-resuscitation phase (5-7).

However, mortality reduction has led to an increase in morbidity due to hypoxic-ischemic brain injury with an impact on quality of life (8). Predicting outcome in children who have reached return of circulation (ROC) remains challenging, particularly in those who do not regain consciousness within 24 hours (9). Early adequate neuroprognostication is important, especially for this group, to individualize prediction of long-term outcome and assist in decision making concerning withdrawal of life-sustaining therapies or rehabilitation planning.

To date, no guidelines exist for prognostication of children post-CA in contrast to adults (6). Extrapolating these adult guidelines to children is inappropriate, since children have age-dependent anatomy and physiology relevant to CNS injury (10). A recent scientific statement from the American Heart Association recommends considering multiple modalities (e.g. neurological examination, neuroimaging, electroencephalopgraphy (EEG), plasma biomarkers) when predicting outcome in children after CA (11).

The aim of this systematic review is to summarize the literature of the last 20 years on neuromonitoring modalities in children after CA and to evaluate their potential prognostic value in predicting neurological outcome at an early stage.

Methods

Search strategy

A search of the literature published between 1998 and March 2019 was performed in Embase.com, MEDLINE Ovid, PsycINFO Ovid, Web of Science Core Collection, Cochrane CENTRAL registry of trials, and Google Scholar using a combination of controlled vocabulary terms and words in title or abstract to define concepts such as pediatric CA, hypoxic-ischemic brain injury, and neuromonitoring (Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/PCC/B351).

Inclusion and exclusion criteria

Studies eligible for the present review met the following criteria:

Enrollment of children after IHCA and OHCA between 1 month and 18 years and presence of a neuromonitoring method obtained within the first 2 weeks post CA. Studies including only neonates were excluded as well as neuromonitoring studies without clinical correlates: case reports, reviews, abstract only and studies not written in English.

Selection of studies, data extraction and quality assessment

Two reviewers (M.H., N.K.) reviewed all citations independently, and disagreements were resolved by discussion. Each study was assigned a grade using the Oxford Evidence-Based Medicine scoring system (12) . We designed evidence tables by neuromonitoring method. Study quality was assessed by screening for clear reporting of methods and results.

Results

The database search yielded 1195 citations, nine additional citations were found by cross reference check. One-hundred two articles were eligible for full-text review ((Supplemental Table 1, Supplemental Digital Content 1, http://links.lww.com/ PCC/B351) (**fig. 1**).

Twenty-seven articles met the inclusion criteria (for specification of included articles, see

Supplemental Tables 2–8, Supplemental Digital Content 2, http://links.lww.com/PCC/B352).

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│                             │ 2 reviews                 │
│ 27 included in study review │ 1 animal study            │
│                             │ 6 neuromonitoring         │
└─────────────────────────────┘ studies, CA results not   │
                       │ specified                 │
                       │ 4 neuromonitoring ≥ 2      │
                       │ weeks after CA            │
                       │ 4 studies without CPR     │
                       │ 4 adults and children     │
                       │ included, but results     │
                       │ children not specified    │
                       │ 7 not related to          │
                       │ neuromonitoring           │
                       │ 1 clinical application    │
                       │ 1 neuromonitoring         │
                       │ study without clinical    │
                       │ correlates                │
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                       │ 1 part of thesis, not     │
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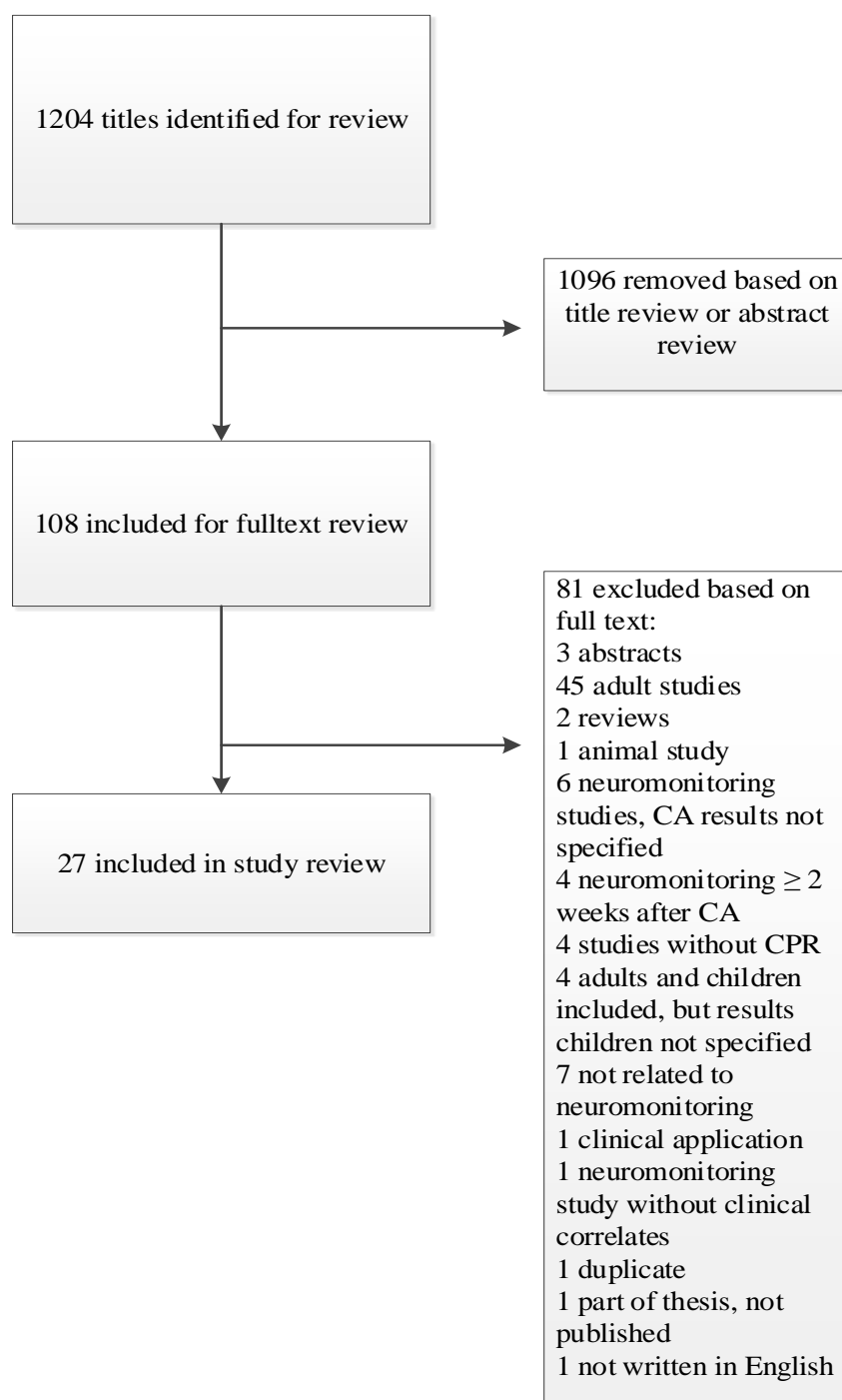
Figure 1. Study selection flowchart
CA=cardiac arrest, CPR=cardiopulmonary resuscitation

Neuromonitoring methods included neurological examination, routine EEG and continuous

EEG (cEEG), transcranial Doppler (TCD), MRI, head CT, plasma biomarkers, somatosensory

evoked potential (SEP) and brainstem auditory evoked potential (BAEP), and one included repeated routine EEG as well as SEP and BAEP (**table 1**).

All evidence was graded 2B-2C. Details on study type and population as well as outcome scores and definitions are specified in Supplemental Table 2-6 (Supplemental Digital Content 2, http://links.lww.com/PCC/B352).

Neuromonitoring method	Number of articles
Neurological examination	6
Electroencephalography (EEG)	10
Transcranial doppler	1
Neuro imaging	7
Plasma biomarkers	4
Evoked potentials	2

Table 1. Article categories
(n=27, 3 articles are listed twice, as they described more neuromonitoring modalities (Neurological examination, EEG monitoring and Evoked Potentials)

Neuromonitoring methods

Neurological examination

Six studies were included in our review (Supplemental Table 2, Supplemental Digital Content 2, http://links.lww.com/ PCC/B352). Three were prospective and three retrospective. In a prospective cohort including 44 children with hypoxic ischaemic encephalopathy (HIE) and impaired consciousness, a Glasgow Coma Scale of less than 5, absence of pupillary responses or lack of spontaneous respiratory activity at 24 hours from admission had a positive predictive value (PPV) of 100% for poor outcome in the third year after event (13). In another prospective cohort of 36 children with HIE the sensitivity and specificity for absent motor responses during the first 9 days for a poor outcome at 5 years were 93% and 50% respectively. This was 47% and 100% for the absence of pupillary responses (14).

Abend et al showed that absent motor and pupillary responses after normothermia in children post CA and therapeutic hypothermia (TH) are highly predictive for a poor outcome at PICU discharge (n=35, PPV 100%)(15). Brooks et al evaluated motor responses, pupillary responses and brainstem reflexes in 41 children after CA and found that all patients with the absence of one of these responses had a poor outcome (p<0.001), the majority within 12 hours post-ROSC (16).

In two retrospective studies of children after IHCA and OHCA (n=353 and 138), bilateral equal responsive pupils at 12 hours post-ROC were associated with survival (p<0.01) (17, 18).

However, these studies have limitations. First, clinicians were unblinded to neurological examination findings, which may have influenced treatment decisions (13-16). Furthermore, most studies included small patient numbers with crude outcome scales (13-16). Meert et al and Moler et al both included a large cohort (n=353 and 138 respectively). However they only assessed survival up to hospital discharge. Long-term outcome was not investigated (17, 18). In some studies patients received sedatives or analgesics at time of neurological examination which could have influenced neurologic findings (14, 16).

Electroencephalography

Ten studies explored the prognostic value of routine and cEEG after pediatric CA; four were prospective observational and six were retrospective (Supplemental Table 3, Supplemental Digital Content 2, http://links.lww.com/PCC/B352).

A summary of six studies including only patients after cardiac arrest and more than 20 patients is given below. The other four studies can be found in Supplemental Table 3 (Supplemental Digital Content 2, http://links.lww.com/PCC/B352) (13, 19-21).

Topjian et al evaluated short-term outcome in 128 children after CA treated with controlled normothermia by early cEEG background features (within 24 hr after CA) (22). Worse

background categories (discontinuous, discontinuous-burst suppression, attenuated-flat) and absence of EEG reactivity were associated with mortality and poor outcome at hospital discharge. The odds of death increased with each progressively worse background pattern. Status epilepticus was also associated with poor neurologic outcome, not with mortality.

Ostendorf et al also showed an association between burst suppression or flat cEEG and poor outcome and a continuous EEG within 12 hours post ROSC with good outcome (n=73) (23).

In a retrospective cohort (n=34), routine EEG was employed within 7 days after CA. Ninety percent of children with a discontinuous or isoelectric EEG had a poor outcome at hospital discharge whereas 91% of children with a continuous EEG had a good outcome at hospital discharge (24).

Kessler et al (n=35) demonstrated that an unreactive or discontinuous EEG, burst suppression or flat EEG during hypothermia or rewarming was associated with poor outcome (25).

Another retrospective study (n=34), demonstrated that the presence of sleep spindles within 24 hours post-ROSC was associated with a good outcome (p=0.001) (26).

In a recent retrospective study (n=41) EEG background suppression (<10 μV) was associated with poor outcome (16).

There are important limitations. First, many studies were retrospective (16, 21-24, 26) with often a small cohort (median n=34, interquartile range (IQR) 28-56) and all studies were single center. Second, clinicians were not blinded for the EEG results which might have influenced the decision to withdraw treatment (21-26). Third, most studies had a short-term follow-up (ranging from hospital/PICU discharge in eight studies up to 3 years in one study) with crude outcome scores (i.e. Pediatric Cerebral Performance Category (PCPC)). These studies labeled different PCPC scores as good outcome; PCPC 1 and 2 where defined as good outcome in some studies, other studies used a PCPC score of 1, 2 and 3 as good outcome. When outcome was nonsurvival, cause of death was not specified (did patient die due to withdrawal of life

sustaining therapies based on a poor neurological prognosis, or due to refractory circulatory failure?). No neuropsychological assessments were performed. Fourth, different studies used different EEG classifications, restricting comparability.

Fifth, timing of the EEG was not always fully specified. This should be taken into account as studies in adults after CA suggest that EEG patterns at 12 hours after ROSC have the best predictive value for good outcome and patterns at 24 hours post ROSC have the best predictive value for poor outcome (27).

Finally, although a normal EEG is associated with a good outcome, there were children with a normal EEG and poor outcome and vice versa (22, 25).

Transcranial Doppler

A retrospective study by Lin et al (n=17) showed that TCD can serve as a prognostic tool in children post CA receiving hypothermia (28) (Supplemental Table 4, Supplemental Digital Content 2, http://links.lww.com/PCC/B352). A normal mean flow velocity of the middle cerebral artery (MCA) in the rewarming phase led to a better outcome compared with a low peak flow velocity (p=0.009). A normal pulsatility index (PI) value led to a significantly better outcome than a high PI value in the hypothermia and rewarming phases (p=0.002 and 0.003, respectively).

However, this was a retrospective study with a small cohort. Also, autoregulation is often impaired in children after CPR which might influence TCD values (29).

Brain MRI

We included four retrospective studies and one observational exploratory study on brain MRI made within 2 weeks after pediatric CA in relation to outcome (Supplemental Table 5, Supplemental Digital Content 2, http://links.lww.com/PCC/B352).

A summary of four studies including more than 20 patients is given below. The other study can be found in Supplement Table 5 (Supplemental Digital Content 2, http://links.lww.com/PCC/B352) (30).

A retrospective analysis of MRIs post CA in 22 children after near-drowning concluded a strong significant correlation between high signal on T2 weighted images (cortical and basal ganglia) or the presence of edema (occipital or generalized) at day 3-4 and outcome. The PPV and negative predictive value (NPV) for abnormal MRI for a poor outcome was 100% (T2 abnormalities cortex or basal ganglia, brain stem infarction or generalized or occipital edema) (31).

In a retrospective cohort of 28 patients who underwent brain MRI after CA, an association was found between signal abnormalities in multiple brain lobes on T1/T2 or diffusion weighted imaging (DWI) and worse outcome ($p < 0.01$ and $P = 0.02$ respectively) (32).

Another retrospective study of 20 patients after CA showed an association of DWI abnormalities in cortex, basal ganglia or cerebellum with poor outcome ($p < 0.05$). All five patients with a normal DWI on MRI had a good outcome ($p = 0.05$) (33).

A recent study of Yacoub et al (2019) showed that in 26 pediatric patients post CA remaining comatose or with neurological deficits, specific quantitative values of DWI MRI correlate with outcome. An apparent diffusion coefficient (ADC) threshold of less than 600×10^{-6} mm^2/s in greater than or equal to 7% of brain volume and less than 650×10^{-6} mm^2/s in greater than or equal to 11% of brain volume both showed a specificity of 1.0 and a sensitivity of 0.8 for poor outcome (34).

Limitations of these neuroimaging studies are multiple.

All studies included small patient groups (median n=22, IQR 17-27), were single center and the majority were retrospective (31-33). The study of Dubowitz et al dates from 1998 when DWIs

were not available (31). Yacoub et al used specific quantitative values of DWI MRI and tried to determine ADC thresholds in order to predict outcome. However, validation of the two found thresholds is impossible due to a small and retrospective cohort (34) and variability in these measurements between different MRI scanners. At least four studies only performed MRI when clinically indicated by the treating clinicians, this might have caused a selection bias and influenced the decision process to continue or withdraw treatment (30, 32-34). Temperature management was different in the studies: three studies did not implement TH (30, 31, 34) and in one study the initiation of TH was at the discretion of the treating clinician (32). Different gross outcome scales were used with varying follow-up intervals. When outcome was non-survival, the cause was not clarified. Long-term follow-up studies with neuropsychological tests, evaluation of quality of life and social participation are lacking. Finally, the timing of MRI was different within the cohorts (ranging from 1 up to 14 d post CA) (30, 32-34). If MRI is obtained too soon after CA (within 2 d after CA), DWI changes might not be visible (31, 35). In addition if imaging is obtained after 7 days, pseudo-normalization can occur (35). Neuroimaging outside this time window might have influenced DWI results.

Head CT

Two retrospective studies were included in this review including children after CA (n=78 and n=64) (Supplemental Table 6, Supplemental Digital Content 2, http://links.lww.com/PCC/B352) (36, 37), concluding that patients with a normal early CT (median time 3.3 hr post ROSC, IQR 1-6 hr) survived with good outcome (36).

Loss of gray-white matter differentiation, in particular in the basal ganglia and effacement of the basilar cistern, ambient cistern and sulcal effacement were significantly associated with poor outcome (36, 37).

However, both studies were single site studies and retrospective. Similar to most MRI studies, CTs were obtained if clinically indicated, creating a selection bias, and the results might have influenced the medical team in the decision to withdraw or continue treatment.

Finally PCPC was used as outcome scale in both studies, determined at hospital discharge.

Evoked potentials

This review contains two observational prospective studies (Supplemental Table 7, Supplemental Digital Content 2, http://links.lww.com/PCC/B352). Carter et al described SEP findings in a cohort of 105 children with severe brain injury (HIE n=38, unclear how many children after CA) performed within 7 days after the injury (38). At 5 years follow-up using Glasgow outcome scale (GOS) and Health Utilities Index Mark 1 (HUI:1, a questionnaire to assess quality of life) as outcome measurements, a normal SEP had a PPV for a good outcome of respectively 85.4% (sensitivity 61.2%, specificity 87.8%) and 85.4% (sensitivity 68.6%, specificity 88.9%); A bilateral absent SEP had a PPV of respectively 90.9% (sensitivity 61.2%, specificity 94.6%) and 93.9% (sensitivity 57.4%, specificity 96.1%).

Mandel et al performed a SEP in 57 HIE patients within 5 days after event. All children with a bilateral absent SEP had a poor outcome (severe disability, persistent vegetative state or death in the third year after event) (p=0.001). Of 13 patients with a normal SEP, three had poor outcome. BAEP did not have a predictive value (13).

Both studies were single center and had heterogeneous inclusion criteria, including children after CA. However, the exact number of CA patients was unclear and no subanalysis was done for this subgroup. Although the strength in Carters cohort was the follow-up interval (5 yr after event), the outcome assessment (HUI:1 and GOS) was done by telephone interview making bias by caregivers possible.

Biomarkers

One pilot randomized controlled trial, two observational prospective studies and one retrospective study are published in children after CA (Supplemental Table 8, Supplemental Digital Content 2, http://links.lww.com/PCC/B352).

Kramer et al ((39), n=95), Fink et al ((40), n=43) and Topjian et al ((41), n=35) found a significant correlation between high levels of neuron specific enolase (NSE) post ROSC and death 24 hours post ROSC.

Topjian et al found no significant differences in S-100b levels in patients with good versus poor outcome, however in the study by Fink et al S-100B levels were increased in the poor outcome group from 48 hours after ROSC (p<0.05). For S-100B, in both the study by Topjian et al and in the study by Fink et al, increased levels from 48 hours and 24 hours respectively post ROSC were significantly associated with nonsurvival (40, 41).

Fink et al concluded that S-100B and NSE are superior in predicting outcome at 6 months compared to clinical predictors (duration CPR, first lactate, first blood pH) (40).

Recently Fink et al (2018) described biomarker trajectories in patient groups with different duration of targeted temperature management, but no association with outcome was shown (42). The most important limitations of these studies are as follows:

Only one study was a pilot randomized controlled trial (42). However, the purpose of this randomized controlled trial was not neuroprognostication but rather to test the hypothesis that 72 versus 24 hours of hypothermia would produce more favorable serum biomarkers after pediatric CA. All studies were single center with mostly a small cohort (median n=39, IQR 34-82). Kramer et al also included neonates (39).

As already described in other neuromonitoring modalities, outcome scales were gross (no neuropsychological assessments) and short term, ranging from hospital discharge up to 6 months post CA. When outcome was nonsurvival, the cause was not specified.

Discussion

This systematic review describes several methods of neuromonitoring in children after CA with the purpose of early neuroprognostication. It is noteworthy that even with generous inclusion criteria, the total number of patients in the (included) studies is only 1564, which is a fraction of the total number of CAs over a 20-year period. This review shows us that the described neuromonitoring methods must be interpreted with extreme caution in the context of the patient's clinical neurological status. Even for EEG, with the majority of studies in this review, patients with 'poor' patterns may have a 'good' outcome' and vice versa. It must be emphasized that the value of predicting 'short-term' outcome is itself dubious since the long-term trajectory of outcome after CA is not well studied and subject to a complex interaction of socioeconomic factors and value judgements about meaningful quality of life. Also the data on MRI, SEP and biomarkers is sparse and almost uninterpretable. Furthermore, the current available data, which is mostly retrospective and heterogeneous, has small to moderate sample sizes (median pediatric sample size post-CA n=35, IQR 28-64) using often crude outcome measures. Therefore, no evidence-based statement can be given on which neuromonitoring method should be implemented. However this does not reduce the potential of current neuromonitoring modalities and we discuss their promise below.

The current studies provide insight into the challenges in performing outcome studies after pediatric CA. First, the pediatric population is a developing group. The different ages (ranging from 1 mo to 17 yr) hamper meaningful outcome comparison. Children of varying age have age-specific (cerebral) physiology and are in different developmental stages. In children (especially preschool) with brain damage, growing into deficit can occur later in life. Second, many additional investigations (e.g. EEG, MRI) in multiple studies were only done when clinically indicated and clinicians were unblinded to the results. This can lead to selection bias

and self-fulfilling prophecies in relation to patient outcome (e.g. decision-making regarding withdrawal of life-sustaining therapies). Third, the majority of neuromonitoring studies included both OHCA and OHCA with different etiologies, resulting in heterogeneous patient groups. Finally, in the majority of studies, outcome was measured using gross outcome scales (e.g. PCPC, GOS). But how to define outcome? Can we express this using only a crude functional measure such as a PCPC score and how does this reflect the health-related quality of life? Furthermore, could the meaning of quality of life vary among health care professionals, parents and patients due to differences in cultural aspects, beliefs and socio-economic factors? In this review, we could only identify one study that investigated quality of life (38). The same applies to neuropsychological assessment and social participation which also contribute to overall outcome. Equally important is the follow-up interval. In most studies, follow-up was short term (i.e. evaluation at hospital or PICU discharge). We must emphasize that long-term follow-up (in adolescents at least 1 yr after the event and in pre-school children at least 5 to 10 yr) is extremely important as outcome often changes within the first years after CA (38) and patients may grow into deficit as they become older and are increasingly expected to participate in society.

In summary: given the above mentioned challenges, possibilities and increased awareness and in line with the scientific statement from Topjian et al (11), we would like to recommend the following approach for clinical practice: If a child remains comatose after CA, clinicians should combine individual patient information (medical history, etiology of cardiac arrest, CPR variables like duration, witnessed arrest, bystander CPR etc) with the results of the neurologic examination (serial exams for at least 72 hr) and ancillary tests (at least EEG and MRI) in order to attempt outcome prediction as accurately as possible.

In order to take the next step in understanding how best to implement and interpret available neuromonitoring modalities in terms of neuroprognostication, international collaboration is

warranted. Although recognizing challenges with this concept due to different financial resources and expertise (between countries and even between hospitals around the world), this approach will enable a larger, more homogenous patient dataset as a starting point. Such standardized data collection with a large patient sample size could finally enable us to design international guidelines that can be implemented for the individual patient. This standardized data set should comprise information on patient characteristics, clinical (neurologic) examination, care and neurological ancillary tests. Outcome measures should include both mortality and long-term follow-up of survivors after CA (> 1 yr and preferably up until adulthood). As stated, long-term follow-up as standard of care (not feasible in research setting) should include both detailed functional and neuropsychological testing as well as health-related quality of life (43).

Conclusion

A complex condition such as HIE after pediatric CA warrants multimodal neuromonitoring to understand pathophysiology and subsequently predict prognosis. The appropriate application and precise interpretation of available modalities still needs to be determined in relation to the individual patient. The current literature is too heterogeneous, underpowered and lacking long-term, detailed follow-up to draw any conclusions. International collaboration in standardized data collection during the (acute) clinical course together with detailed long-term outcome measurements (including functional outcome, neuropsychological assessment and health-related quality of life) is the first steps towards more precise, patient-specific neuroprognostication after pediatric CA.

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Supplemental table 1

Resuscitated comatose children neuromonitoring

19-06-2018, updated on 08-02-2019 and 07-01-2020

Embase.com	731	724
Medline Ovid	490	235
Web of science	139	63
Cochrane	6	2
PsycINFO Ovid	41	18
Google scholar	200	153
Total	**1607**	**1195**

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('unconsciousness'/exp OR 'consciousness disorder'/de OR 'minimally conscious state'/de OR 'comatose patient'/exp OR (unconscious* OR coma OR comatous OR comatose OR semicoma* OR stupor OR ((loss OR low* OR reduc* OR level* OR disorder* OR minimal* OR state* OR depress* OR alter* OR disturb*) NEAR/6 conscious*) OR awaken* OR nonawaken*):ab,ti) AND ('resuscitation'/exp OR 'heart arrest'/exp OR hypoxia/de OR 'brain hypoxia'/de OR 'anoxia'/de OR 'hypoxemia'/de OR 'pediatric advanced life support'/exp OR (resuscitat* OR anox* OR hypox* OR posthypoxic* OR postanoxic* OR postresuscitat* OR 'cardiac life support' OR CPR OR ((Heart OR cardiac) NEAR/3 Massage*) OR reanimat* OR ((heart OR cardi*) NEAR/3 arrest) OR Asystole* OR 'life support' OR ACLS OR BLS):ab,ti) AND ('neuromonitoring'/exp OR 'neurologic examination'/exp OR 'electroencephalogram'/exp OR 'EEG abnormality'/de OR 'electroencephalography'/exp OR 'evoked somatosensory response'/de OR 'evoked response'/de OR (('nuclear magnetic resonance imaging'/exp OR 'near infrared spectroscopy'/exp) AND 'brain'/exp) OR 'biological marker'/de OR 'neuron specific enolase'/de OR 'protein S100B'/de OR (neuromonitor* OR (Neurophysiolog* NEAR/3 test*) OR ((brain OR cerebral OR neuro*) NEAR/3 (monitor* OR examination* OR exam)) OR electroencephalogr* OR (evoked NEAR/6 (somatosensor* OR sensor*) NEAR/6 (response* OR potential*)) OR eeg OR aeeg OR sep OR (('magnetic resonance' OR mr OR mri OR 'near infrared spectroscopy' OR nirs) NEAR/6 (brain* OR cerebral* OR cranial*)) OR bio*-marker* OR biomarker* OR ct-cerebrum* OR bispectral-index* OR neuron-specific-enolase OR nse OR S100B OR S100-B OR S-100B OR S-100-B):ab,ti) AND (child/exp OR adolescent/exp OR adolescence/exp OR 'child behavior'/de OR 'child parent relation'/de OR pediatrics/exp OR childhood/exp OR 'child nutrition'/de OR 'infant nutrition'/exp OR 'child welfare'/de OR 'child abuse'/de OR 'child advocacy'/de OR 'child development'/de OR 'child growth'/de OR 'child health'/de OR 'child health care'/exp OR 'child care'/exp OR 'childhood disease'/exp OR 'child death'/de OR 'child psychiatry'/de OR 'child psychology'/de OR 'pediatric ward'/de OR 'pediatric hospital'/de OR (adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu OR picus):ab,ti)

Medline Ovid

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Cochrane

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OR postresuscitat* OR 'cardiac life support' OR CPR OR ((Heart OR cardiac) NEAR/3 Massage*) OR reanimat* OR ((heart OR cardi*) NEAR/3 arrest) OR Asystole* OR 'life support' OR ACLS OR BLS):ab,ti) AND ((neuromonitor* OR (Neurophysiolog* NEAR/3 test*) OR ((brain OR cerebral OR neuro*) NEAR/3 (monitor* OR examination* OR exam)) OR electroencephalogr* OR (evoked NEAR/6 (somatosensor* OR sensor*) NEAR/6 (response* OR potential*)) OR eeg OR aeeg OR sep OR (('magnetic resonance' OR mr OR mri OR 'near infrared spectroscopy' OR nirs) NEAR/6 (brain* OR cerebral* OR cranial*)) OR bio-marker* OR biomarker* OR ct-cerebrum* OR bispectral-index* OR neuron-specific-enolase OR nse OR S100B OR S-100B):ab,ti) AND ((adolescen* OR infan* OR newborn* OR (new NEXT/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEXT/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu OR picus):ab,ti)

Web of science

TS=(((unconscious* OR coma OR comatous OR comatose OR semicoma* OR stupor OR ((loss OR low* OR reduc* OR level* OR disorder* OR minimal* OR state* OR depress* OR alter* OR disturb*) NEAR/5 conscious*) OR awaken* OR nonawaken*)) AND ((resuscitat* OR anox* OR hypox* OR posthypoxic* OR postanoxic* OR postresuscitat* OR "cardiac life support" OR CPR OR ((Heart OR cardiac) NEAR/2 Massage*) OR reanimat* OR ((heart OR cardi*) NEAR/2 arrest) OR Asystole* OR "life support" OR ACLS OR BLS)) AND ((neuromonitor* OR (Neurophysiolog* NEAR/2 test*) OR ((brain OR cerebral OR neuro*) NEAR/2 (monitor* OR examination* OR exam)) OR electroencephalogr* OR (evoked NEAR/5 (somatosensor* OR sensor*) NEAR/5 (response* OR potential*)) OR eeg OR aeeg OR sep OR (("magnetic resonance" OR mr OR mri OR "near infrared spectroscopy" OR nirs) NEAR/5 (brain* OR cerebral* OR cranial*)) OR bio*-marker* OR biomarker* OR ct-cerebrum* OR bispectral-index* OR neuron-specific-enolase OR nse OR S100B OR S100-B OR S-100B OR S-100-B)) AND ((adolescen* OR infan* OR newborn* OR (new NEAR/1 born*) OR baby OR babies OR neonat* OR child* OR kid OR kids OR toddler* OR teen* OR boy* OR girl* OR minors OR underag* OR (under NEAR/1 (age* OR aging)) OR juvenil* OR youth* OR kindergar* OR puber* OR pubescen* OR prepubescen* OR prepubert* OR pediatric* OR paediatric* OR school* OR preschool* OR highschool* OR picu OR picus))) AND DT=(article) AND LA=(english)

Google scholar

unconsciousness|unconscious|coma|comatose|stupor resuscitation|resuscitated|"life support"|CPR|"heart|cardiac arrest" neuromonitoring|"brain|cerebral monitoring"|eeg|"evoked somatosensory|sensory response|potential" children|infants|pediatric|paediatric

Supplemental table 2-8: Study description and results

2. Neurological examination

Source/Year Inclusion period	Study type	Number of centers	N	Age	Hypothermia	Outcome score Follow up interval	Neurological examination Timing	Results	Mortality (%)	Limitations	EBM Grade
Mandel 2002 (13) 1993-1996	Prospective Observational	1	N=57 with HIE (N=44 CA 77%)	Total cohort: Median 28 mo (2 mo-15yrs)	No	PCPC and POPC score 24 hours and in third year after event in group with uncertain prognosis 1-2-3 defined as good outcome	At admission: GCS, pupillary reactivity and spontaneous respiratory activity 24 hours after admission: GCS, pupillary reactivity and spontaneous respiratory activity	Admission: GCS, pupillary reactivity and spontaneous respiratory activity were not predictive for outcome. 24 hrs: In 42 children with impaired consciousness: GCS was lower in unfavourable group (5 ± 2 vs 10 ± 3; P<0.0001). In 42 children with impaired consciousness: GCS< 5, absence of spontaneous respiratory activity and PR have a 100% PPV for poor outcome	45 % (children with uncertain prognosis)	-Heterogeneous population (no subgroup analysis possible for CA) Crude outcome	2B
Carter 2005 (14) Inclusion period not specified	Prospective Observational	1	N=102 with acute brain injury and coma (N=36 with HIE)	Total cohort: Median age 4.46 yrs (0.08-14.67yrs)	Unknown	GOS 5 years after event 4-5 defined as good outcome	Serial motor and pupillary responses in the first 9 days	-In HIE patients: Sensitivity and specificity for absent motor response and poor outcome is 93%/50% Sensitivity and specificity for absent pupillary responses is 47%/100% 7 patients with absent motor response had good outcome (sedatives)	39 % (total cohort)	-Missing data -HIE included, unclear if and how many CA patients are included. -Clinician not blinded for findings motor and pupillary responses -Multiple patients used sedatives and or analgesics -Timing of motor response and pupillary responses are unclear -Crude outcome	2B/C
Abend 2012 (15) 2007-2009	Prospective Observational	1	N=35	Median age 1.02 yrs (0.18-16.6yrs)	Yes	PCPC discharge PICU 4-6 defined as poor outcome (death defined as secondary outcome)	Pupillary responses Motor responses Assessments: final hour of HT, 1 hour after HT, 1 hour after NT, 1 day after NT, 3 days after NT	Absent motor and pupil responses after normothermia predicted poor outcome (PPV 100%) Paralytic drugs lowered the predictive value	43%	-Short term and crude outcome -Clinician not blinded for findings motor responses and pupillary responses	2B/C
Brooks 2018 (16) 2011-2015	Retrospective	1	N=41	Mean age 59 months	Not specified	PCPC Discharge Increase in PCPC ≤ 1 = good outcome	Motor responses Pupillary responses Brainstem reflexes Assessments: final hour of HT, 1 hour after HT, 1 hour after NT, 1 day after NT, 3 days after NT	-All patients with absent pupillary responses (N=14), absent motor response to pain (N=10) or absent brain-stemreflexes (N=9) had a poor outcome (all P<0.001). -Among patients with absent pupillary responses 12 were first documented within 12 hrs post ROSC, for absence of motor responses 6 were documented < 12 hrs post-ROSC	18% (IHCA) 47% (OHCA)	-Retrospective -Short term and crude outcome -Clinicians not blinded for findings motor responses and pupillary responses -No information about sedatives/analgesics administration	2C

Meert 2009 (17) 2003-2004	Retrospective	15	N=353	Median age survivors 0.7 yrs (0.1-3.7yrs) Median age non-survivors 1.3 yrs (0.3-8.7yrs)	N=13 received therapeutic hypothermia	Survival to hospital discharge	Pupillary responses: 0-6 hrs and >6-12 hrs post-ROC	Bilateral equal responsive pupils at 12 hrs post-ROC were associated with survival (P<0.01)	51 %	-Retrospective -Neonates included (N=6) -Survival as sole outcome measure	2C
Moler 2011 (18) 2003-2004	Retrospective	15	N=138 OHCA	Median age survivors 3.1 yrs (0.9-10 yrs) Median age non-survivors 2.7 yrs (0.5-12yrs)	N=3 received therapeutic hypothermia	Survival to hospital discharge	Pupillary responses 0-6 hrs and >6-12 hrs post-ROC	Bilateral equal responsive pupils at 12 hrs post-ROC were associated with survival (P<0.01)	62%	-Retrospective -Neonates included, (N=5) -Survival as sole outcome measure	2C

CA=cardiac arrest, GCS=Glasgow coma scale, HIE=hypoxic ischemic encephalopathy, HT=hypothermia, IHCA=in hospital cardiac arrest, NT= normothermia, OHCA= out of hospital cardiac arrest, ROC=return of circulation

3. EEG

Source/Year Inclusion period	Study type	Number of centers	N	Age	Hypothermia	Outcome score Follow up interval	EEG classification EEG timing	Results	Mortality (%)	Limitations	EBM Grade
Mandel 2002 (13) 1993-1996	Prospective Observational	1	N=57 (HIE) (N=44 CA 77%)	Total cohort: Median 28 mo (2mo-15yrs)	No	PCPC and POPC score in third year after event in group with uncertain prognosis 24 hrs after injury (1-2-3 = good)	-Continuous -Discontinuous -Reactivity: no, high voltage δ slower than 2 Hz or faster than 2 Hz Routine EEG daily day 1-3, first < 24 hrs post ROSC Together with SEP and BAEP (see EP table)	-In children with uncertain prognosis at 24 hrs initial discontinuous EEG, spikes or epileptiform discharges are associated with unfavorable outcome (PPV 100%, sensitivity 27%, 54%) -Other factors predictive of unfavourable outcome (expressed in PPV): 1.CPR duration > 10 min, GCS < 5 after 24 hrs 2.Bilateral absence N20 wave (SEP)	45 % (children with uncertain prognosis)	-Heterogeneous population (no subgroup analysis possible for CA) -Crude outcome	2B
Nishisaki 2007 (24) 2001- 2004	Retrospective Chart review	1	N=34	Median 12.5 mo (IQR 4-57 mo)	Not specified	PCPC score Change > 1 compared to admission or death = poor outcome Hospital discharge	1=Continuous, not low voltage, not slow 2= Continuous, low voltage or slow 3=Continuous, low voltage and slow 4=Discontinuous 5=Isoelectric Routine EEG < 7 days post ROSC. median 1 day (IQR 0-2 days	-90% of pts with EEG scale of 4 or 5 had poor outcome -91% of pts with EEG scale of 1 or 2 had good outcome -EEG scale ≥ 2: PPV 53% NPV 100% EEG scale ≥ 3: PPV 73%, NPV 91% EEG scale ≥ 4: PPV 90%, NPV 65% EEG scale ≥ 5: PPV 100%,NPV 55%	41%	-Retrospective -Only IHCA -EEG only if clinically indicated -Clinician not blinded for EEG results. -Different timing EEG -Short term and crude outcome -PCPC by chart review	2B

Study	Study type		N	Age		Outcome	EEG categories / timing	Results	Mortality	Limitations	LoE
Abend 2009 (19) 2007-2008	Prospective Observational	1	N=19	Median 10.7 ± 50 mo (2.2mo-16yrs)	Yes	Unclear Hospital discharge	1= Normal for age 2=Attenuation/slowing 3=BS, excessive discontinuity Onset cEEG within 5 hrs for > 24 hrs	47% electrographic seizure 32% electrographic status epilepticus. 9 poor outcome (7 with severe EEG background abnormalities)	26%	-Small cohort -Not focusing on outcome -Short term non defined follow up	2B
Kessler 2011 (25) 2007-2009	Prospective Observational	1	N=35	Median 1.02 yrs (0.18 -16.6yrs)	Yes	PCPC (1-2-3 = good outcome) Hospital Discharge	1=Continuous/reactive 2=Continuous but unreactive 3=Discontinuous tracing, BS, or low voltage Onset cEEG: mean 9.3±0.3hrs post ROSC for > 24 hrs	-PPV for poor outcome of EEG score of 2/3 during hypothermia 88% (95%CI 77-98%) -PPV for poor outcome of EEG score of 2/3 during normothermia 91% (95%CI 81-100%). -Continuous but unreactive EEG, discontinuous EEG, BS or no cerebral activity during hypothermia and rewarming were far more likely to have a poor outcome -All deaths in EEG categories 2 or 3	37%	-Small cohort -Non blinded physicians -Seizures not evaluated in prognostication. -N=1 with discontinuous EEG good outcome -N=1 with normal EEG poor outcome -Only short and crude outcome -N=9 had pre-CA neurological abnormalities	2B
Topijan (20) 2013 2008-2011	Prospective Observational	1	N=200 Acute encephalopathy (N=50 HIE)	Median 3.7 yrs (0.8-10yrs)	Not specified	PCPC (worsening score form pre admission or death = poor outcome) PICU discharge	1=No seizures 2=Electrographic seizures 3=Electrographic status epilepticus cEEG in pts with acute encephalopathy at least 24 hrs up to 72 hrs (in pts with therapeutic hypothermia). In pts with NCSE until 24hrs after last ES.	Of 50 HIE pts: -64% no seizures, 20% electrographic seizures, 16% electrographic status epilepticus -electrographic status epilepticus in children with acute encephalopathy including HIE is associated with mortality and worse short term outcome (OR resp 5.1, P 0.01, 17.3 (P<0.001)	18% (total cohort)	-Unclear how many pts CA -Unclear relation with EEG findings and outcome in pts after CA. -cEEG only when clinically indicated -Only short en crude outcome -Differences in use of anticonvulsants in pts with seizures	2B
Nenadovic 2014 (21) 2000-2010	Retrospective	1	N=84 with acute brain injury (N=30 CA)	Mean 5.7 yrs (0.02-17yrs)	Not specified	PCPC (1-2-3=good) Hospital discharge	- EEG phase synchrony - Spatio-temporal variability - Electrode location analysis Routine EEG Timing unclear, dependent on treating physician	-Poor outcome (vs good outcome): 1.higher magnitude phase synchrony (R-index), lower spatial complexity and temporal variability 2.frontal and parietal EEG electrodes show less spatial complexity (at 15 Hz)	36% (total cohort)	-Retrospective -EEG findings and outcome not specified for pts after CA, but for total cohort -Different timing EEG -only short and crude outcome -Influence of Rx (heterogeneity) led to choice of band widths 3 and 15 Hz	2B
Topjian 2016 (22) 2010-2013	Retrospective	1	N=128	Median 2.6 yrs (0.4 -10.7yrs)	Controlled normothermia	PCPC (1-2 = good) Hospital discharge	-Normal -Slow-disorganized -Discontinuous-BS -Attenuated-flat cEEG onset: within 1 day of ROSC for > 24 hrs	-Worse background EEG and absence of reactivity early after CPR associated with mortality and poor neurologic outcome (P<0.001) -Each incrementally worse background score led to an odds of death of 3.63 (95% CI 2.18-6.0, p<0.001) and an odds of unfavourable NO of 4.38 (95% CI 2.51-7.17, p = 0.001) -IHCA vs OHCA: no difference in seizures or survival to discharge. IHCA more likely to have a slow and disorganized background category and favourable neurological outcome	42%	-Retrospective -Non-blinded physicians -PCPC by chart review -EEG report review instead of EEG tracings -Some children with initial flat or BS EEG had a good outcome. -Only short and crude outcome	2B

Ostendorf 2016 (23) 2009-2014	Retrospective	1	N=73	Median 31 mo (1.6-242mo)	Hypothermia or normothermia	PCPC (1-2-3 = good) Hospital discharge	0=Normal 1=Slow organized 2=slow, disorganized, 3=discontinuous 4=BS 5=Suppression Onset cEEG: mean 18hrs post ROSC (good outcome) , 10 hrs (poor outcome) post ROSC for > 24 hrs post ROSC	-EEG score 0 or 1, normal voltage, reactivity and variability within 12 hrs post ROSC with CA < 20 minutes significantly associated with good outcome (P<0.05) -EEG score 4 or 5 within 12 hrs post ROSC associated with poor outcome (P?) -Association between poor outcome and moderate seizure burden and status epilepticus (not sign, P=0.17)	Unspecified	-Retrospective -Non-blinded -Short and crude outcome -18-21% of children with normal EEG poor outcome -Duration of EEG monitoring epochs varied	2B
Ducharme 2017 (26) 2010- 2015	Retrospective	1	N=34	Median 6.1 yrs (1.5-12.5yrs)	Targeted temperature	PCPC (1-2=good) 6 months	1= Normal 2=Nearly continuous 3=Discontinues traces 4=Burst-attenuation, BS, suppression Onset cEEG < 24 hrs after ROSC: median 9.3 hrs post (5.8-14.9)up to 16 hrs	-The presence of sleep spindles was associated with a good neurological outcome (P=0.001) -Spindles absent in all patients with severely abnormal EEG background -EEG background is associated with good neurological outcome	Unspecified	-Retrospective -Small cohort -Non-blinded -N=1 with spindles poor outcome -N=2 without spindles good outcome -Crude outcome	2B
Brooks 2018 (16) 2011-2015	Retrospective	1	N=41	Mean age 59 months	Not specified	PCPC Increase ≤ 1 = good outcome Discharge	No classification, looked at: -Seizures -BS -Background suppression -Myoclonic status epilepticus -GPEDs -α coma -Continuous slow vEEG <10 days after CA Timing not specified, duration not specified.	Background suppression (<10 µV) significantly associated with poor outcome (P0.005) (N=8 in poor outcome group vs N=0 in good outcome group) Duration of CA, out of hospital CA, arterial pH, arterial lactate, lack of pupil reactivity to light, absent motor response to noxious stimuli and absent brainstem reflexes were all predictors of poor neurological outcome	18% (IHCA) 47% (OHCA)	-Retrospective -Small cohort -Short and crude outcome -vEEG when clinical suspicion of seizers or as a part of therapeutic hypothermia -timing and duration vEEG not specified -Clinicians non blinded for vEEG results -Neonates included? -ROSC > 20 min excluded	2B

BAEP=brainstem auditorial evoked potential, BS =burst suppression, CA=cardiac arrest, cEEG=continuous EEG, CPR=cardiopulmonary resuscitation, EP=evoked potentials, GCS=Glasgow coma scale, GPEDS=generalized periodic epileptiform discharges, HIE=hypoxic ischemic encephalopathy, IHCA =in hospital cardiac arrest, OHCA=out of hospital cardiac arrest, ROSC=return of spontaneous circulation, SEP=somatosensory evoked potentials, vEEG=video EEG.

4. TCD

Source/Year Inclusion period	Study type	Number of centers	N	Age group	Hypothermia	Outcome score Follow up interval	Timing TCD	Results	Mortality (%)	Limitations	Grade
Lin 2015 (28) 2011- 2012	Retrospective	1	N=17	Median unknown (1mo-16yrs)	Yes	PCPC (1-2= good outcome) 3 months	TCD at pre hypothermia, Hypothermia and rewarming measuring bilateral MCA (peak flow velocity , end diastolic velocity, mean flow velocity and pulsatility index)	-All pts with reversal diastolic flow or undetectable flow died. -Normal pulsatility index led to better outcome during hypothermia and rewarming (P= 0.002 and 0.0003) -Normal mean flow velocity during rewarming led to better outcome (P=0.009)	29%	-Retrospective -Small cohort -Probable impaired autoregulation with influence on TCD. -Non blinded clinicians -Only 1 TCD operator -Confounders not investigated -Crude outcome scale	2B

TCD=trans cranial Doppler, MCA=middle cerebral artery.

5. MRI Brain

Source/Year / Inclusion period	Study type	Number of centers	N	Age group	Hypothermia	Timing MRI / MRI sequences	Outcome score / Follow up interval	Results	Mortality (%)	Limitations	Grade
Dubowitz 1998 (31) / 1991-1997	Retrospective	1	N=22	Mean 3.5 yrs (6mo-11yrs)	no	-MRI performed mean 2.2 days (1-6) post ROSC / N=17 second MRI mean 2.9 days (2-5) / N=6 third MRI mean 8.90 days MRI (4-16) / -Axial spin-echo, T1, repetition time/echo, Gradient echo and T2. MR spectroscopy	CPC (1-2 = good outcome) / Timing not specified	-Strong significant correlation between abnormalities (cortical or basal ganglia T2 or presence of edema occipital or generalized) at day 3-4 and outcome (P<0.001). T2 changes did not reverse and sign correlated with poor outcome / -Best correlation with outcome was MRI day 3-4. PPV and NPV of abnormal MRI for a poor outcome 100% (T2 abnormalities cortex or BG, brain stem infarction or generalized/occ edema) / -Spectroscopy in good outcome normal, in vegetative outcome abnormal (3 out of 4 at first MRI and 1 out of 4 day 3), in death abnormal (10 out of 12 at first MRI and 2 at day 4) / -A sign correlation between abnormal MR spectra and abnormal MRI on day 3-4 (P<0.0001)	55%	-Retrospective / -Only near drowning / -Small cohort / -Were clinicians blinded? / -Crude and adult outcome scale / -Timing outcome unclear / -Wide age range	2B/C (unclear timing outcome)
Fink 2013 (32) / 2002-2008	Retrospective	1	N=28	Median 1.9 yrs (IQR 0.4-13)	68 % (Depended on PICU physician)	-MRI performed median 6 days (IQR 4-11) post ROSC / -T1, T2 and DWI/ADC	GOS (4-5 = good outcome) / Hospital discharge	-N=16 with normal MRI all survived, N=6 had decrease in GOS score / -T1/T2: Association between multiple brain lobes affected and worse outcome (P<0.01) / -Occipital lobe and lenticular nucleus lesions on T1 and lesions in lenticular and caudate nucleus on T2 associated with (unfavorable outcome (P<0.05) / -DWI/ADC: Lesions in multiple brain lobes associated with poor outcome (P=0.02) / -No effect therapeutic hypothermia Infrequent follow-up MRI scan showed evolution of lesions	18%	-Retrospective / -Small cohort / -MRI only performed when clinically indicated / -Crude and unusual short term outcome scale / -Hypothermia not standard / -Possible secondary insults like fever or hypotension not analyzed / -Timing MRI different	2B
Oualha 2013 (33) / 2003-2010	Retrospective	1	N=20	Median 20 mo (1.5-185mo)	N=3 received hypothermia	MRI performed mean 3 days (1-7) after CA / DWI/ADC	PCPC score (1-2-3 = good outcome) / Up to 24 months	-All 5 patients with normal DWI good outcome (P=0.05) N=15 abnormal DWI: 7 good outcome / -High intensity on DWI in cortex, basal ganglia and cerebellum associated with poor outcome (P<0.05) / -Degree of ADC decrease proportional to degree of cytotoxic oedema and poor prognosis	30%	-Retrospective / -Small cohort / -MRI only performed when clinically indicated / -Crude outcome scale / -Hypothermia in N=3 and no temperature management in n=17 / -Timing MRI different	2B/C ('hypothesis-generating study on outcome')
Manchester 2016 (30) / 2011-2013	Observational, exploratory	1	N=14	Mean 5.8 yrs (± 6.5)	Prevention of fever	MRI performed mean 6 (±4) days after CA / ADC and ASL	PCPC score (1-2-3 = good outcome) / Hospital discharge	-Global decreased ADC values are associated with poor outcome (P=0.02) / -No difference in CBF by ASL between outcome groups / -Brain regions with decreased ADC frequently had an increase in CBF	36%	-Small cohort / -No ADC or CBF data are known from healthy controls / -Values can vary over development, this is not compensated in this study	2B/C

Source/Year Inclusion period	Study type	Number of centers	N	Age group	Hypothermia	Timing MRI	Outcome Score Follow up interval	Results	Mortality (%)	Limitations	Grade
										-Short and crude outcome -Timing MRI different -MRI only if clinically indicated	
Yacoub 2018 (34) 2014- 2017	Retrospective	1	N=26	Median 8.5 yrs (IQR 2.2-14yrs)	Normothermia	MRI performed within 14 days after CA, median 4 days after CA (IQR 2-7) Quantitative ADC in survivors remaining neurologically impaired after CA	PCPC score (-1-2 = good outcome OR -no worsening from baseline score if baseline was ≥ 3 = good outcome) 6 months	2 ADC thresholds were found: -If ≥7% of brain volume had an ADC <600 X10 $^{-6}$ mm^2/s or if ≥11% of brain volume had an ADC <650 X 10 $^{-6}$ mm^2/s the odds ratio of poor outcome was 112 (95% CI 5-2611), specificity 1.0 (0.76-1.0 95% CI), sensitivity 0.8 (0.44-0.96 95% CI) -ROC analysis: ADC thresholds of <600 X10 $^{-6}$ mm^2/s and <650 X10 $^{-6}$ mm^2/s are good predictors of poor outcome with AUC of resp 0.95 (95% CI 0.88-1.0) and 0.95 (95% CI 0.87-1.0) Duration of CPR, witnessed CA and cause of CA were individually predictors of outcome	27%	-Retrospective -Small cohort -MRI only performed when neurologically impaired -Crude outcome scale at 6 months - 19% pre arrest PCPC score of 3-4 -Clinicians non blinded for qualitative MRI results -No validated thresholds -Timing MRI varies which might cause variability in ADC results	2B?

ADC=apparent diffusion coefficient, ASL=arterial spin labeling, CA=cardiac arrest, CBF=cerebral blood flow, DWI=diffusion weighted imaging, MRI=magnetic resonance imaging, ADC=apparent diffusion coefficient, ASL=arterial spin labeling, CBF=cerebral blood flow.

6. Head CT

Source/Year Inclusion period	Study type	Number of centers	N	Age group	Hypothermia	Timing CT	Outcome Score Follow up interval	Results	Mortality (%)	Limitations	Grade
Starling 2015 (36) 2005-2012	Retrospective	1	78	Median 2.3 yrs (IQR 0.4-9.5yrs)	33%	Median 3.3 hrs post ROSC (IQR 1.0hrs - 6.0 hrs)	-Primary: Mortality -Secondary: PCPC (-1-2-3= good and no worsening from baseline score=good outcome) Hospital discharge	-All 28 patients with normal CT survived with good outcome (P<0.001, PPV 86%, NPV 70%) -At least 1 CT abnormality associated with mortality and poor outcome (P<0.001) -Quantative and qualitative loss of GWM differentiation associated with mortality and poor outcome (P<0.001, PPV mortality 91% and poor outcome 100%) -Basilar cistern effacement and sulcal effacement associated with mortality and poor outcome (resp P=0.001 and P<0.001, PPV mortality resp 97% and 100% and poor outcome resp 93% and 100%) -reversal sign associated with mortality and poor outcome (P=0.011, PPV mortality and poor outcome 100%)	50%	-Retrospective -CT performed when clinically indicated -Crude secondary outcome scale at hospital discharge -Clinicians non blinded for CT results	2B
Yang 2019 (37) 2000-2018	Retrospective	1	64	Median 4.1 yrs (IQR 0.5-11.9yrs)	23.4% (Depended on PICU physician)	Median 1.9 hrs form CPR (IQR 1.2-2.9)	PCPC (1-2-3=good outcome) Hospital discharge	-Decrease in GWR-basal ganglia and average associated with poor outcome (rep P 0.005 and 0.04) -Decrease in GWR- CN/PIC, CN/CC and PU/CC (resp P0.03, 0.006 and 0.004) -Ambient cistern effacement associated with poor outcome(P<0.001)	Unspecified	-Retrospective -CT performed when clinically indicated -Crude secondary outcome scale at hospital discharge -Clinicians non blinded for CT results	2B

CC=genu of corpus callosum, CN= caudate nucleus, CT=Computed Tomography, GWM=gray-white matter, GWR=gray to white matter ratio, PIC=posterior limb of the internal capsule, PU=putamen

7. Evoked potentials

Source/Year Inclusion period	Study type	Number of centers	N	Age group	Hypothermia	Timing EP	Outcome Score Follow up interval	Results	Mortality (%)	Limitations	Grade
Carter 1999 (38) 1991-1993	Prospective Observational	1	N=105 with severe brain injury (n=38HIE)	Median 4.4 yrs (0.1-14.7yrs)	unspecified	**SEP** classification 1= bilateral normal 2= unilateral delayed N20 3= bilateral delayed N20 4= Unilateral absent N20 5= Bilateral absent N20 SEP < 7 days after event, median 16.8 h (1-163.5 h)	-GOS (good and moderate = good outcome) 1 and 5 years after event -HUI:1 HSUV 1.00-0.70 = good outcome HSUV 0.69-0.30 = moderate outcome HSUV 0.29-0.00= Poor outcome HSUV <0.00 = 'worse than death' 5 years after event	Normal SEP (grade 1) and GOS 5 yrs: Pos pred power 85% neg pred power 67% Normal SEP (grade 1 and HUI:1 5 yrs: Pos pred power 85% neg pred power 75% Bil absent SEP (grade 5) and GOS 5 yrs: pos pred power 91%, neg pred power 74% Bil absent SEP (grade 5) and HUI:1 5 yrs: Pos pred power 94%, neg pred power 68% In 12 pts outcome improved between 1 and 5 yrs.4	42% (total cohort at 5 yrs)	-Unclear how many pts with HIE had CA -Outcome by telephone interview -N=3 with absent SEP had good outcome - N=6 with normal SEP had poor outcome	2B
Mandel 2002 (13) 1993-1996	Prospective Observational	1	N=57 pts HIE (N=44 CA 77%)	Total cohort: Median 28 mo (2mo-15yrs)	No	**SEP** classification 1 = normal 2 =unilateral increased interpeak N13-N20 3=bilateral increased interpeak N13-N20 4= unilateral absence 5=bilateral absence Mean 2 days after admission (1-5 days) and in 10 pts second SEP mean 4 days after admission (2-11 days) **BAEP** Timing unclear Together with EEG (See EEG table)	1. dead, brain-dead, awake or uncertain at 24 hrs post admission. 2. PCPC and POPC in third year after event (1-2-3 = good outcome)	All 12 children with bilateral absent SEP had poor outcome (P=0.001) Of 13 pts with normal SEP, 3 had poor outcome BAEP had no predictive value Other factors predictive of unfavourable outcome (expressed in PPV): - CPR duration > 10 min, GCS < 5 after 24 hrs - EEG: discontinuous pattern, spikes, epileptiform discharges	45 % (children with uncertain prognosis)	Heterogeneous population (no subgroup analysis possible)	2B

BAEP=brainstem auditorial evoked potential, CPR=cardiopulmonary resuscitation, EEG=electroencephalography, HIE=hypoxic-ischemic encephalopathy, HUI:1=Health Utilities Index Mark 1, HSUV=overall health state utility value, SEP=somatosensory evoked potentials.

8. Biomarkers

Source/Year Inclusion period	Study types	Number of centers	N	Age group	Hypothermia	Type of Biomarkers (plasma, CSF, other) Timing biomarkers	Outcome score Follow up interval	Results	Mortality (%)	Limitations	Grade
Topjian 2009 (41) 2002-2004	Prospective, Observational	1	N=35	Median 4 yrs (IQR 0.8 –10yrs)	Variable (5 received ht 32-34ºC)	-Plasma NSE and S100b 4, 12, 24, 48, 72 and 96 hrs -Plasma PAI-1 24 hrs	Primary: PCPC (change <2 = good outcome) Hospital discharge Secondary: survival	Primary: -NSE higher in pts with poor outcome at 48 hrs, 72 hrs and 96 hrs, all P<0.001 -S100b no sign difference with poor outcome. -Total and active PAI-1 no sign difference Secondary: -Correlation between higher NSE and death at 24 hrs (P=0.004), 48 hrs (P<0.001), 72 hrs (P<0.001) and 96 hrs (P<0.001) -S100b sign associated with death at 48 hrs (p=0.002), 72 hrs (P=0.001) and 96 hrs (p=0.007) in children ≥ 2 yrs -Total and active PAI-1 no sign difference	43%	-Samples are missing (died, early discharge, initially other hospital) - No accepted individual cut offs -Heterogeneous pts which may alter baseline levels of biomarkers -Biomarker sampling from peripheral access -Short and crude outcome scale	2B/C
Fink 2014 (40) 2009-2011	Prospective Observational	1	N=43	Mean 5.87 yrs (IQR 0.33-11.52yrs)	Variable (81% received ht 33 ºC)	Plasma NSE, S100b and MBP twice day 1-4 and once day 7	Primary: accuracy biomarker concentration to predict PCPC score (1-2-3 = good outcome) Hospital discharge and at 6 months Secondary: Mortality Hospital discharge and 6 months post-CA Additional: -Clinical variables for prediction	Primary: -NSE and S100B concentrations increased in the poor vs. good outcome group at 48 and 72 hrs post-ROSC (All P<0.05) -MBP predicted good vs poor outcome at 72 hours (P0.08) Secondary: -All 3 biomarkers predicted mortality at 24 hrs (p < 0.05) -NSE and S-100B increased in subjects who died at all time points (p < 0.05) Additional: -S100B and NSE superior in predicting poor vs good outcome at 6 mo compared to clinical predictors (CPR-ROSC time, first lactate, blood pH) -MBP positive correlation with subject temperature -Initial NSE and s-100B inversely correlated with age	40%	-Small sample size -No cut off values are available -PI was part of medical team - Not all subjects survived to day 7 -Crude outcome scale	2B
Fink 2018 (42) 2009-2013	Pilot randomized controlled trial	1	N=34	Median 1.5 yrs (IQR (0.3-9.8yrs)	50% 24 hrs ht 32-34 ºC 50% 72 hrs ht 32-34 ºC	Plasma NSE, S100b and MBP twice day 1-4 and once day 7	Primary: biomarker concentrations day 7 (post-ROSC/post-rewarming) by HT group Secondary: PCPC (1-2-3 = good outcome, increase >1 poor outcome) Hospital discharge and 6 months	Primary: NSE sign increased in 24 hrs ht group vs 72 hrs HT group at 84-96 hrs and day 7 S100B sign increased in 24 hrs ht group vs 72 hrs HT group at 12- 24hrs, 36-84 hrs and day 7 MBP sing increased in 24 hrs ht group vs 72 hrs HT group at 36-48 hrs Secondary: No outcome difference between 24 hrs ht group and 72 hrs HT group	35%	-Small sample - PCPC non blinded and often by telephone interview -Crude outcome scale -time to randomization was up to 24 hrs	2B
Kramer 2018 (39) 2010-2016	Retrospective	1	N=95	Median 0.51 yrs (IQR 0.0-17.1yrs)	Variable, 68% targeted temperature (34-35 ºC)	Plasma NSE and S100b 12hrs, 24 hrs, 48 hrs and 72 hrs	Primary: PCPC score (Good outcome= change of PCPC ≤ 1) Hospital discharge Secondary: in-hospital mortality	Primary: -NSE peaked 24 hrs and remained elevated until 72 hrs in pts with poor outcome -NSE sign higher in pts with poor outcome at 24 hrs, 48 hrs and 72 hrs -S100b peaked at 12 hrs with decline afterwards in pts with poor outcome -S100b sign higher in pts with poor outcome immediately, at 12 hrs, 24hrs and 48 hrs -NSE and S100b peaked later in poor group compared to good outcome group Secondary:	38%	-Retrospective -13% abnormal baseline neurological status -Physician not blinded for biomarker results -neonates included -Narrow spectrum of arrest etiologies -Missing biomarker analysis -Short and crude outcome scale	2B/C

							N=37 died			

CA=cardiac arrest, HT=hypothermia, MBP=myelin basic protein, NSE=neuron-Specific Enolase, PAL1=plasminogen activator inhibitor-1, ROSC=return of spontaneous circulation, S100B=S100 Calcium-Binding-Protein B.

Supplemental Table 6. Clinical characteristics associated with poor outcome.

	duration CPR	GCS	blood pressure	unwitnessed arrest	amount epinephrine	Lactate	pH	initial rhythm	hypo-thermia	ECMO	AST titer	ALT titer	location CPR	NE	cause CA	pupil reflexes	absent brainstem reflexes
Mandel 2002 (8)	x	x														x	
Nishisaki 2007 (14)		x	x														
Abend 2009 (9)																	
Kessler 2011 (15)																	
Topjian 2013 (10)																	
Nenadovic 2014 (11)																	
Topjian 2016 (12)	x			x									x		x		
Ostendorf 2016 (13)	x							x	x	x	x						
Ducharme 2017 (16)	x																
Brooks 2018 (17)	x	x				x	x						x		x		x
Lin 2015 (19)																	
Dubowitz 1998 (22)																	
Fink 2013 (23)																	
Oualha 2013 (24)																	
Manchester 2016 (21)	x												x				
Yacoub 2019 (25)	x			x												x	
Starling 2015 (27)	x					x	x										
Yang 2019 (28)							x				x	x					

Study																	
Carter 1999 (29)																	
Topjian 2009 (32)														x			
Fink 2014 (31)		x				x	x									x	
Fink 2018 (33)																	
Kramer 2018 (30)	x					x	x			x							

'x' indicates a significant association with poor outcome. When box is empty there was nog correlation with clinical outcome or it wasn't been analyzed. ALT=Alanine aminotransferase, AST=aspartate transaminase, CPR=cardiopulmonary resuscitation, GCS=Glasgow Coma Scale, NE=neurological exam, CA=cardiac arrest

Infographic

Pediatric Critical Care Medicine

Society of Critical Care Medicine — The Intensive Care Professionals

World Federation of Pediatric Intensive & Critical Care Societies

A Systematic Review of Neuromonitoring Modalities in Children Beyond Neonatal Period After Cardiac Arrest

Children after IHCA or OHCA aged 1 month-18 yrs + presence of neuromonitoring within the first 2 weeks post cardiac arrest
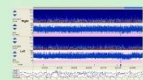
1204 articles identified

108 included for full-text review

27 included in study review

All evidence = grade 2B-2C

Neurological Examination 6 studies

EEG 10 studies

Neuroimaging 7 studies

Transcranial Doppler 1 study

Biomarkers 4 studies
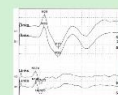
Evoked Potentials 2 Studies

The appropriate application and precise interpretation of available modalities still need to be determined in relation to the individual patient. International collaboration is required.

Data from Hunfield M, et al: *Pediatr Crit Car Med* 2020.

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Chapter 3.

The current practice regarding neuro-prognostication for comatose children after cardiac arrest differs between and within European PICUs: A survey

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Corinne Buysse

Abstract

Purpose To describe current practices in European Paediatric Intensive Care Units (PICUs) regarding neuro-prognostication in comatose children after cardiac arrest (CA).

Methods An anonymous online survey was conducted among members of the European Society of Paediatric and Neonatal Intensive Care (ESPNIC) and the European Paediatric Neurology Society (EPNS) throughout January and February 2019. The survey consisted of 49 questions divided into 4 sections: general information, cardiac arrest, neuro-prognostication and follow-up.

Results The survey was sent to 1310 EPNS and 611 ESPNIC members. Of the 108 respondents, 71 (66%) (23 countries, 45 PICUs) completed the "neuro-prognostication" section. Eight PICUs (20%) had a local neuro-prognostication guideline. The 3 methods considered as most useful were neurological examination (92%), magnetic resonance imaging (MRI) (82%) and continuous electroencephalography (cEEG) (45%). In 50% a Pediatric Cerebral Performance Category (PCPC) score ≥ 4 was considered as poor neurological outcome. In 63% timing of determining neurological prognosis was based on the individual patient. Once decided that neurological prognosis was futile, 55% indicated that withdrawing life-sustaining therapy (WLST) was (one of) the options, whereas 44% continued PICU treatment (with or without restrictions). In 28 PICUs (68%) CA-survivors were scheduled for follow-up visits.

Conclusion Local guidelines for neuro-prognostication in comatose children after CA are uncommon. Methods to assess neurological outcome were mainly neurological examination, MRI and cEEG. Consequences of poor outcome differed between respondents. Inaccuracies in neuro-prognostication can result in premature WLST, thereby biasing outcome research

and creating a self-fulfilling cycle. Further research is needed to develop scientifically based

international guidelines for neuro-prognostication in comatose children after CA.

Introduction

Both in-hospital cardiac arrest (IHCA) and out-of-hospital cardiac arrest (OHCA) are uncommon in children. The incidence of paediatric OHCA ranges from 9.0 to 19.7 per 100,000 persons/year, including traumatic cardiac arrest (CA)(1-3). The incidence of paediatric IHCA widely ranges from 0.77 to 21 per 1000 hospital admissions (4-7). Whereas CA in adults is mostly of cardiac origin, in children it is commonly due to hypoxia (8). In our retrospective cohort study, 33% of 401 children with IHCA or OHCA had no return of spontaneous circulation (ROSC), whereas 34% died in the paediatric intensive care unit (PICU) due to severe neurological injury, brain death or respiratory/cardiovascular failure (9). Prognosis of CA in children is grim but over the past decades survival rates after CA have improved. This may be due to the combined effect of availability of early basic life support (BLS), the use of automated external defibrillators (AED) and improved post-ROSC care (10-13). However due to the improved survival rates numbers of survivors with neurological impairments due to hypoxic ischemic brain injury may increase (10, 14, 15). Predicting long-term outcome in children after ROSC remains challenging, especially for children who remain comatose for more than 24 hours (16). Different methods may be used in these comatose children in order to determine the neurological prognosis (neuro-prognostication): neurological examination (17, 18), routine and continuous electroencephalography (EEG) (16, 18-20), neuroimaging by computed tomography (CT) (21, 22) and magnetic resonance imaging (MRI) (23-26), serum biomarkers: Neuron-Specific Enolase (NSE) and S100 calcium-binding protein B (S100B) (27-29), and somatosensory evoked potential (SSEP) (17, 30). But the value for prognostication for these different methods is lacking. International guidelines for neuro-prognostication after CA are available for adults (31, 32), but not for children. Therefore, current practices may vary worldwide. It is crucial to predict neurological outcome as accurately as possible in these children in order to discuss further steps of

treatment and to inform parents correctly. An inaccurate prediction of long-term outcome could lead to premature withdrawing of life-sustaining treatment (WLST) or at the other end of the spectrum severely disabled children with persistent vegetative state and high impact on resources and caregivers (33). The aim of our survey was to describe current practices in European PICUs regarding neuro-prognostication in comatose children after CA, in particular, the methods used, their timing, and end-of-life decision making. Due to the lack of international guidelines, we hypothesized that practices not only differ between various PICUs, but also may vary within PICUs. With this survey we aim to identify relevant research questions and priorities across Europe in order to optimize and standardise neuro-prognostication in European PICUs.

Methods

We conducted a cross-sectional anonymous electronic survey (using LimeSurvey, supplemental data 1) across European Society of Paediatric and Neonatal Intensive Care (ESPNIC) members and European Paediatric Neurology Society (EPNS) members. The survey was carefully designed by the authors in order to address all aspects of the research question and hypothesis (34). The questions in our survey were clear and straightforward, with an appropriate length of the questionnaire and check questions. The survey was reviewed by 4 ESPNIC section chairs (Neuro critical Care, Ethics, Outcome, Resuscitation) and an expert board member of EPNS. Subsequently, the survey was piloted on a paediatric neurologist, paediatric intensivist and fellow intensivist for clarity and face validity. The questionnaire was written in English; it consisted of 49 questions divided into 4 sections: general information, cardiac arrest, neuro-prognostication and follow-up (see appendix A) requiring 15 minutes on average to complete. The specific points of interest were practices concerning post-resuscitation care, neuro-prognostication and end-of-life decision making.

The survey has been approved by the ErasmusMC Medical Review Ethics Committee (MEC 2019-0095).

Paediatric (fellow) intensivists, paediatric neurologist and other healthcare professionals being a member of ESPNIC or EPNS received a link (by email or newsletter) to the online survey. The survey started in January 2019. After 3 weeks, a reminder to fill out the survey was sent. All valid responses received before the 8th of March were included for analysis. For inclusion, a completed neuro-prognostication section was mandatory. Also surveys completed by physicians active in non-European PICUs were excluded (According to the geographic scheme of the United Nations).

Descriptive statistics were used to analyse all answers. Most questions were analysed on individual level. However, questions concerning PICU characteristics were analysed on PICU-level. In case contradictory answers were given within one PICU, it was classified as intra PICU variability.

Results

The survey was sent to 1310 EPNS members representing 47 European countries and 611 ESPNIC members, representing 31 European and 28 non-European countries (exact number of PICUs unknown).

Of the 108 respondents, 71 (66%) completed the "neuro-prognostication" section (Figure 1).

3.1 General information

The respondents represented 23 European countries and 45 different PICUs with most respondents from the Netherlands (N = 26) (Table 1). The survey was completed mainly by paediatric intensivists (N = 32) and paediatric neurologists (N = 31). Fifty-three respondents (75%) worked in a University (Children's) Hospital. Thirty-five respondents (50%) had more

than ten years work experience (Appendix B, supplementary table S1). PICU characteristics are described in Appendix B, supplementary table S2.
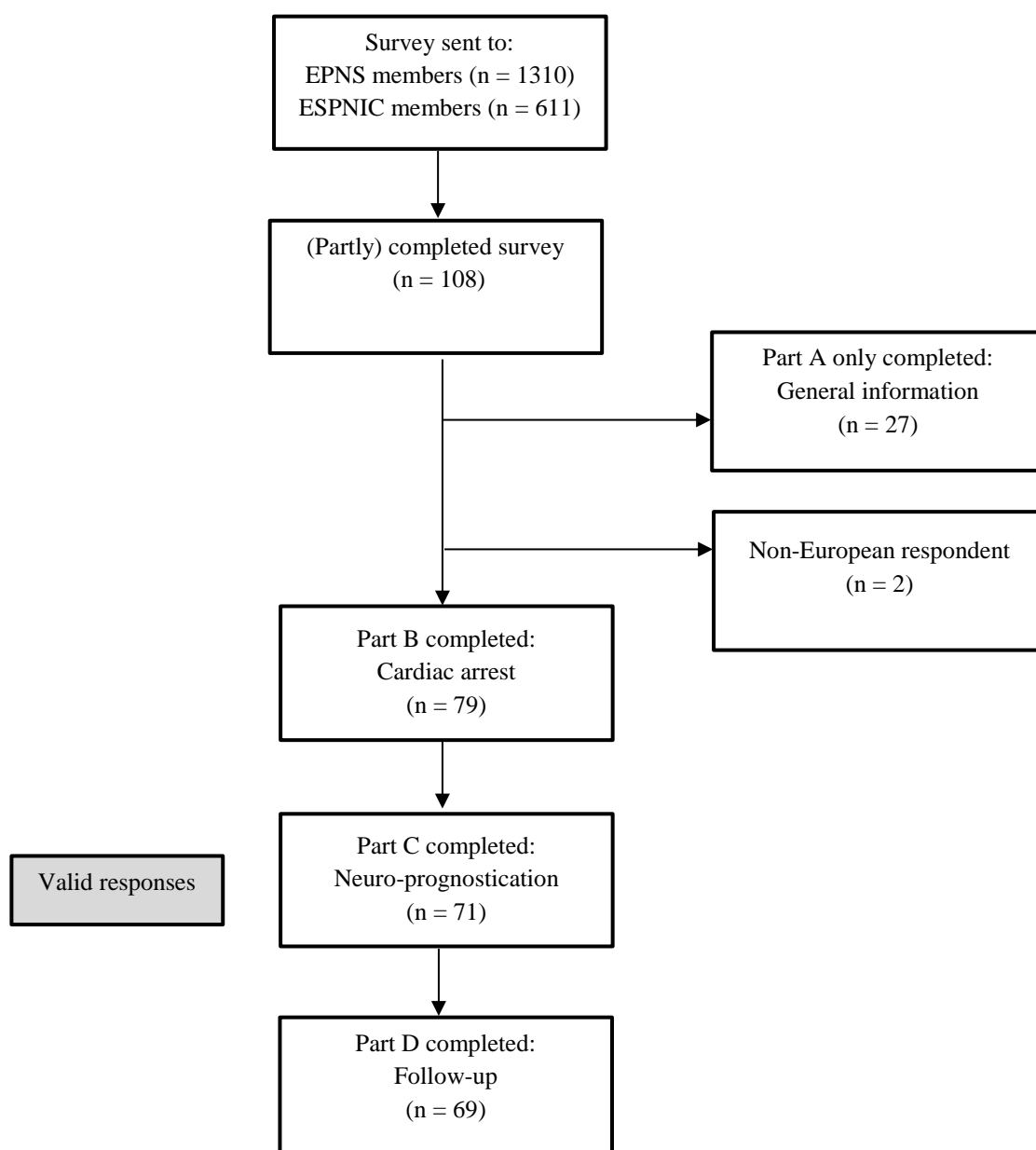

Figure 1. Flowchart of surveys included for analysis

EPNS= European Paediatric Neurology Society, ESPNIC= European Society of Paediatric and Neonatal Intensive Care

Country	European Region[1]	No. respondents (%)	No. PICUs (%)
Andorra	Southern	1 (1.4)	1 (2.2)
Austria	Western	1 (1.4)	1 (2.2)
Belarus	Eastern	1 (1.4)	1 (2.2)
Belgium	Western	4 (5.7)	4 (8.9)
Croatia	Southern	1 (1.4)	1 (2.2)
Denmark	Northern	3 (4.2)	2 (4.5)
Finland	Northern	1 (1.4)	1 (2.2)
France	Western	3 (4.2)	3 (6.7)
Georgia	Eastern	1 (1.4)	1 (2.2)
Germany	Western	1 (1.4)	1 (2.2)
Hungary	Eastern	1 (1.4)	1 (2.2)
Italy	Southern	2 (2.8)	2 (4.5)
Kazakhstan	Eastern	3 (4.2)	2 (4.5)
Latvia	Northern	1 (1.4)	1 (2.2)
Malta	Southern	1 (1.4)	1 (2.2)
Netherlands	Western	26 (36.7)	5 (11.1)
Slovakia	Eastern	1 (1.4)	1 (2.2)
Slovenia	Southern	1 (1.4)	1 (2.2)
Spain	Southern	3 (4.2)	3 (6.7)
Switzerland	Western	3 (4.2)	1 (2.2)
Turkey	Southern	3 (4.2)	3 (6.7)
Ukraine	Eastern	2 (2.8)	2 (4.5)
United Kingdom	Northern	7 (10)	6 (2.2)
Total		71	45

Table 1. Number of respondents and PICUs per country
[1]According to the WHO definition and geographic scheme of the United Nations.

3.2 Cardiac arrest

Fifteen PICUs (38%) had a post-ROSC guideline. A local, national and international database

was available in respectively 15 (47%), 8 (25%) and 5 (16%) PICUs (Appendix B,

supplementary table S2 and S3).

3.3 Neuro-prognostication

One nation had a national guideline for neuro-prognostication after paediatric CA, whereas 8

PICUs (20%) had a local guideline (Appendix B, supplementary table S2).

To assess the level of consciousness, 92% of respondents used at least the Glasgow Coma

Score (GCS) (Appendix B, supplementary table S4) and 75% brainstem reflexes. Sixty-seven

percent of the respondents performed neurological examination more than once a day. Both

physicians and nurses performed neurological examination (Appendix B, supplementary table

S4.).

Sixty-six percent performed a brain MRI in routine clinical practice between day 1-7 after

CA. Eight respondents (11%) replied not to use MRI (Table 2). Thirty-four percent used a

routine EEG and 38% a continuous EEG (cEEG) in order to prognosticate, the timing of EEG

registrations differed (Table 2). Ninety-four percent of the respondents used at least one test

besides neurological examination for neuro-prognostication. The three methods considered as

most useful to predict neurological outcome, according to paediatric intensivist and paediatric

neurologist, were: neurological examination (resp 91% and 90%), MRI brain (resp 78% and

87%) and cEEG (resp 53% and 39%) (figure 2).

No. of respondents			Frequency (%)
EEG[1]	(N=71)	No	19 (27)
		Routine[2] < 24 hours	10 (14)
		Routine > 24 hours	14 (20)
		Continuous[3] < 24 hours	18 (25)

		Continuous > 24 hours	9	(13)
		Depends on treating physician	12	(17)
		Other	3	(4)
		Unknown	1	(1)
MRI[1]	(N=71)	No	8	(11)
		< 24 hours	5	(7)
		Between day 1 – 3	18	(25)
		Between day 4 – 7	29	(41)
		> 7 days	4	(6)
		Timing differs	15	(21)
		Depends on treating physician	4	(6)
		Unknown	1	(1)
CT[1]	(N=71)	No	43	(61)
		< 24 hours	7	(10)
		Between day 1 – 3	4	(6)
		Between day 4 – 7	1	(1)
		> 7 days	1	(1)
		Timing differs	10	(14)
		Depends on treating physician	10	(14)
		Other	6	(8)
		Unknown	1	(1)
Biomarker[1]	(N=71)	No	57	(80)
		NSE	9	(13)
		S-100B	4	(6)
		Depends on treating physician	6	(8)
		Unknown	2	(3)
SSEP[1]	(N=71)	No	46	(65)
		After rewarming	6	(8)
		> 24 hours	1	(1)
		> 48 hours	1	(1)
		> 72 hours	2	(3)
		Timing differs	6	(8)
		Depends on treating physician	7	(10)
		Other	3	(4)
		Unknown	1	(1)
NIRS[1]	(N=71)	Yes	21	(30)
		No	44	(62)
		Depends on treating physician	8	(11)
		Other	1	(1)
		Unknown	1	(1)

Table 2. Tests for neuro-prognostication: type and timing

CT=computed tomography, EEG=electroencephalography, MRI= magnetic resonance imaging
NIRS=near infrared spectroscopy NSE=Neuron-Specific Enolase in serum,
SSEP= somato sensory evoked potential, S-100B=Calcium Binding Protein B
[1] Multiple answers possible
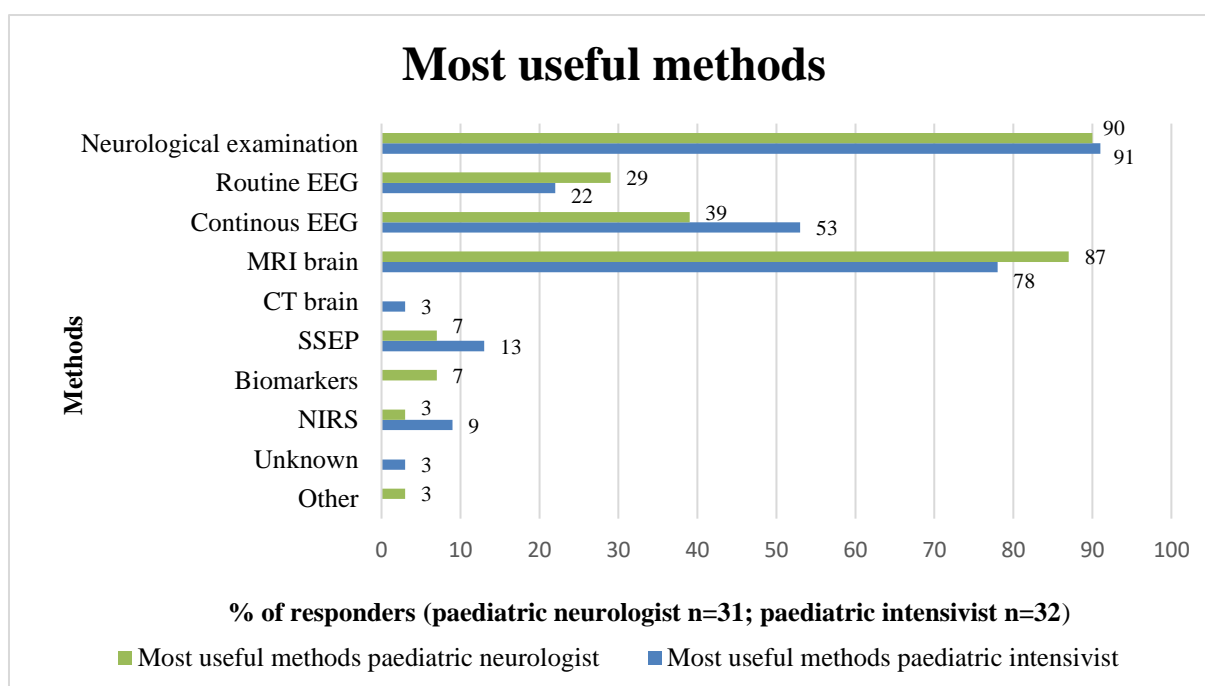[2] 30 minutes
[3] At least several hours

Figure 2. Methods considered as most useful in order to prognosticate
CT=computed tomography, EEG=electroencephalography, MRI= magnetic resonance imaging, NIRS=near infrared spectroscopy, SSEP= somato sensory evoked potential.

Thirty-five respondents (50%) considered a Pediatric Cerebral Performance Category (PCPC) score of ≥ 4 (at least severe neurological disability) at hospital discharge as a poor outcome and 8 (11%) a PCPC score of ≥ 3 (Table 3a). Eleven respondents (15%) considered a difference of ≥ 2 between PCPC score at baseline and after CA as poor neurological outcome. Timing of determining neurological prognosis varied from within 48 h after CA (8%) up to beyond 14 days (10%), whereby 63% indicated that individual patient characteristics were also taken into account (Table 3a). Both intensivist and paediatric neurologist were mostly primary responsible (resp. 69% and 83%) for determining neurological prognosis. Once decided that neurological prognosis was futile, 55% of the respondents (N=39) indicated that WLST was one of the options, whereas 44% continued PICU treatment with or without restrictions (Table 3a). The practices in PICUs in the different areas of Europe regarding WLST or continuing treatment when prognosis is futile are shown in figure 3.

Ten percent answered that an ethicist was routinely involved in cases in which an end-of-life decision was discussed and 70% answered that an ethicist was consulted on individual basis (Table 3a).

The differences in opinion between paediatric intensivists and paediatric neurologists regarding the definition of a poor outcome, timing of determining prognosis, consequences of a poor outcome and involvement of an ethicist are shown in table 3b.

No. of respondents			Frequency (%)
Poor prognosis [1]	(N = 71)	PCPC ≥ 3 (moderate overall disability or worse)	8 (11)
		PCPC ≥ 4 (severe overall disability or worse)	35 (50)
		PCPC ≥ 5 (death, coma or vegetative state)	17 (24)
		PCPC difference ≥ 1	2 (3)
		PCPC difference ≥ 2	11 (15)
		It depends on treating physician	15 (21)
		Other	5 (7)
		Unknown	5 (7)
Timing prognosis[1]	(N = 71)	< 48 hours	6 (8)
		Day 3	6 (8)
		Day 4 – 5	11 (15)
		> 5 days	4 (6)
		> 14 days	7 (10)
		Based on individual patient	45 (63)
		Other	2 (3)
		Unknown	2 (3)
Consequence[1]	(N = 71)	WLST	39 (55)
		Intensive care is continued without any restrictions	4 (6)
		Intensive care support is continued with restrictions	27 (38)
		There is no standard policy	20 (28)
		Depends on the parents' wishes	26 (37)
		Other	5 (7)
Ethicist[1]	(N = 71)	No	14 (20)
		Yes, always in case of end-of-life decision making	7 (10)
		Yes, but it happens on individual basis	50 (70)

Table 3a. Practices concerning decision-making: definition, timing and consequence, all responders
PCPC= Pediatric Cerebral Performance Category, WLST= withdrawing life-sustaining therapy
[1]Multiple answers possible

	No. of respondents		Frequency I (%)	Frequency N (%)
Poor prognosis [1]	(I;N=32)	PCPC ≥ 3 (moderate overall disability or worse)	3 (9)	4 (13)
	(N;N=31)	PCPC ≥ 4 (severe overall disability or worse)	16 (50)	17 (55)
		PCPC ≥ 5 (death, coma or vegetative state)	10 (31)	6 (19)
		PCPC difference ≥ 1	0 (0)	1 (3)
		PCPC difference ≥ 2	9 (28)	1 (3)
		It depends on treating physician	6 (19)	7 (23)
		Other	1 (3)	3 (10)
		Unknown	4 (13)	1 (3)
Timing prognosis[1]	(I;N=32)	< 48 hours	1 (3)	2 (6)
	(N;N=31)	Day 3	3 (9)	3 (10)
		Day 4 – 5	3 (9)	6 (19)
		> 5 days	2 (6)	2 (6)
		> 14 days	2 (6)	4 (13)
		Based on individual patient	22 (69)	20 (65)
		Other	2 (6)	0 (0)
		Unknown	1 (3)	1 (3)
Consequence[1]	(I;N=32)	WLST	21 (66)	12 (39)
	(N;N=31)	Intensive care is continued without any restrictions	0 (0)	4 (13)
		Intensive care support is continued with restrictions	15 (47)	9 (28)
		There is no standard policy	8 (25)	8 (26)
		Depends on the parents' wishes	13 (41)	11 (35)
		Other	2 (6)	3 (10)
Ethicist[1]	(I;N=32)	No	4 (13)	8 (26)
	(N;N=31)	Yes, always in case of end-of-life decision making	5 (15)	1 (3)
		Yes, but it happens on individual basis	23 (72)	22 (71)

Table 3b. Practices concerning decision-making: definition, timing and consequence; divided into paediatric intensivist and paediatric neurologist

I= paediatric intensivist, N= paediatric neurologist, PCPC= Pediatric Cerebral Performance Category, WLST= withdrawing life-sustaining therapy

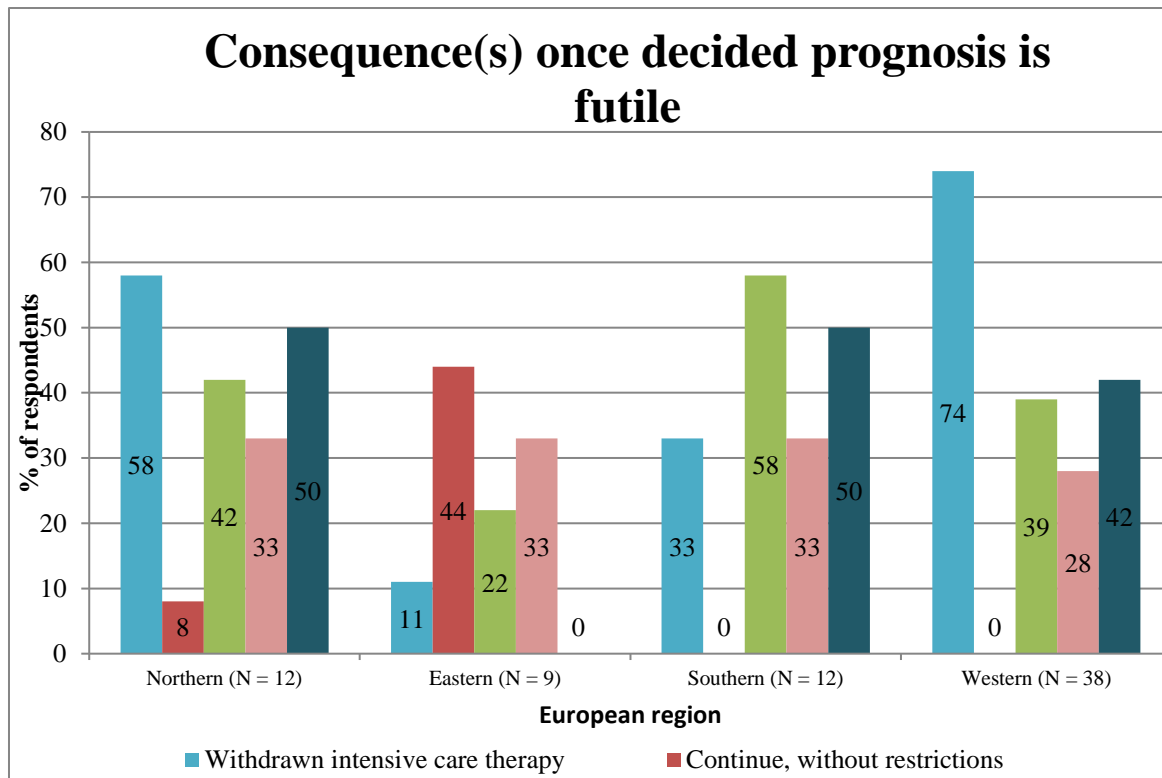[1]Multiple answers possible.

Figure 3. Treatment consequences across Europe once decided prognosis is futile

3.4 Follow-up

In 28 PICUs (68%) CA survivors were scheduled for regular follow-up visits as standard of care, mainly performed by paediatric neurologists (96%) and intensivists (40%). All first follow-up visits were scheduled within 6 months. Subsequent outpatient visits depended on the medical condition (42%) or the presence of a standardised follow-up program (27%) (Appendix B, supplementary table S5).

Fifty-six percent of respondents routinely performed neuropsychological assessment during follow-up.

Discussion

This survey among members of ESPNIC and EPNS showed that methods to assess neurological outcome in children surviving CA but in comatose condition were mainly neurological examination (GCS and brainstem reflexes), MRI and EEG. Local guidelines for

neuro-prognostication in comatose children after CA are uncommon in most European PICUs. Once decided that the prognosis is futile, consequences differed between respondents and countries.

In order to determine neurological prognosis the majority of respondents (94%) thought that ancillary tests were needed besides neurological examination, being MRI and EEG as most useful. In children, there are few studies suggesting that absent brainstem reflexes and low GCS motor score within 12-24 hours after CA predicts a poor outcome (17, 18). In the past, there have been a number of studies regarding the prognostic value of other neuromonitoring modalities (EEG, MRI, SSEP, CT, biomarkers) in to predict outcome. An EEG with early (after 24 h) normal or continuous background pattern or with sleep spindles is associated with a good outcome, whereas burst suppression, flat, discontinuous background patterns and early epilepsy with poor outcome (16, 18-20). A recent study by Fung et al. concluded that EEG findings in children after CA must be used in overall clinical context to prognosticate early (35). A normal MRI after paediatric CA seems a predictor of a favourable outcome (between day 3-7 post-CA), whereas damage in multiple brain lobes and basal ganglia on T1/T2 images, cytotoxic edema globally or in the basal ganglia or multiple cortical brain regions and low apparent diffusion coefficient (ADC) values on diffusion weighted imaging (DWI) MRI are associated with poor outcome (between day 3-7 post-CA) (23-26, 36). Loss of gray-white matter differentiation (in particular in basal ganglia) and basilar cistern plus sulcal effacement on CT are associated with poor outcome (21, 22).

Over the past 20 years, only two studies have been published regarding SSEP in children with hypoxic ischemic encephalopathy (17, 30) concluding that bilateral absence of the cortical N20 wave within 7 days after CA predicts poor outcome. However thresholds for SSEP are not defined yet.

Increased levels of NSE and S-100B from respectively 24-48 h and 12-48 h post ROSC are associated with unfavourable outcome, however thresholds are lacking (27-29).

All above mentioned studies were single center studies, mostly retrospective with small cohorts and clinicians that were not blinded for the results. Follow-up was mostly short-term (at hospital discharge) with gross outcome scales. Very recently (after the completion of this survey) a scientific statement has been published on paediatric post-cardiac arrest care by Topjian et al (37). They concluded that no single test (neurological examination, EEG, neuro-imaging, SSEP, biomarkers) was found to be sufficiently accurate and reliable for prognostication after paediatric CA. Multiple factors and ancillary tests should be considered when predicting outcome in children who achieve ROSC after CA. According to this statement we would like to recommend te next approach for clinical practice: When a child remains comatose after CA, clinicians should combine individual patient information (medical history, aetiology of CA, CPR variables like duration, witnessed arrest, bystander CPR etc) with the results of neurological examination (serial exams for at least 72 h) and ancillary tests (at least EEG (continuous or serial) and MRI) in order to in order to optimize neuro-prognostication at this moment.

The limitations and the lack of multimodal neuromonitoring studies create uncertainty in predicting outcome and the lack of evidence for many of the above mentioned modalities hampers the development of an evidence based guideline. In the vast majority of PICU practices strong supportive evidence is needed before therapy or diagnostics are applied or stopped. Each PICU cares for a relatively small number of patients with heterogeneous severe medical problems, which emphasises the need for international multicenter randomised controlled trials.

Timing of determining neurological prognosis after paediatric CA remains challenging and evidence is lacking. In our survey it varied from within 48 h after CA (8%) up to beyond 14

days (10%) and 63% indicated that individual patient characteristics were also taken into account. For comatose adults post-CA the guidelines from 2015 recommended to wait with prognostication using clinical examination (with or without EEG) for at least 72 h. A bilateral absence of the N20 SSEP wave 24 to 72 h after CA or after rewarming is a predictor of poor outcome (32).

In children, neuronal plasticity and capacity to recover function are poorly understood and ongoing brain development clouds neurodevelopmental prognostication. In addition, children with CA (often below the age of 10 years) may grow into their deficits as late as adolescence or young adulthood (more multitasking required on different domains)(38).

This makes evaluation of outcome beyond hospital discharge and even far beyond the first years after the CA event mandatory. Research in children with acquired brain injury from other causes demonstrate that outcome should continuously be evaluated on different domains at key moments such as at the start of high school or college. However, it is obvious that collecting these long-term outcome data are logistically very challenging (30).

In our survey, PCPC at hospital discharge was used as outcome measure. However we must realise that PCPC is a very gross tool with only 6 scores. It does not evaluate precisely how these children are really doing. Other validated scales of neurological function after paediatric CA used in literature include the King's Outcome Scale for Childhood (Koschi), the pediatric Stroke Outcome Measure (PSOM) and the Functional System Score (FSS). However, all scales do not precisely display the patient's clinical condition.

Recently an advisory statement has been published with a core outcome set for cardiac arrest (COSCA) clinical trials in adults (39). This set includes survival, neurological function and health-related quality of life. For children a similar set is mandatory and is under development.

Once decided that prognosis was futile the consequences differed between European regions. Although the number of respondents was limited, some patterns were identifiable. The majority of respondents from Western and Northern Europe indicated WLST as (one of) the consequence(s), as opposed to Eastern and Southern Europe. This is in line with a previous study showing that physicians from North European countries more often decide to WLST compared to Southern part of Europe (40). This is probably the result of personal beliefs and experiences, cultural and religious aspects and local policies. It would be interesting to study the long-term outcome of paediatric comatose CA survivors in countries where WLST is uncommon. At the other end, inaccuracies in neuro-prognostication can result in premature WLST, thereby biasing outcome research and creating a self-fulfilling cycle.

Our study has limitations.

To the best of our abilities, this survey was carefully designed and instrumentalised in order to address all aspects of the research question and hypothesis. However, we cannot guarantee that our instrument was fully in line with all quality conditions. This survey may not be representative for all PICUs in Europe, because representatives of only 23 European countries participated and the number of responders per nation varied widely (from 1 respondent to 26 responders per country). Seventy-one of 108 respondents completed the neuro-prognostication section and 69 the follow-up section. It is conceivable that responders (in particular paediatric neurologists) did not finish the survey due to the inability to answer the first en second section of the survey (general information and cardiac arrest). Also, questions regarding neuro-prognostication and decisions around WLST can be delicate topics making it complicated for responders to answer these questions.

Self-reporting bias, portraying daily practices differently from reality, may have arisen since we used a survey to conduct this study.

We asked as many as possible clinicians to respond per PICU in order to gain a clear overview of the local PICU policy. However, this resulted in an overrepresentation of respondents from our own center.

Conclusion

The current practice regarding neuro-prognostication for comatose children after CA differs between and within European PICUs. The 3 methods considered as most useful are neurological examination, MRI brain and EEG. National or local guidelines are uncommon, presumably resulting in suboptimal neuro-prognostication. Further profound research is required to eventually develop an international guideline for reliable determination of neurological prognosis in comatose children after CA. The ultimate aim is to establish an ESPNIC/EPNS neuro-prognostication guideline based on evidence and implementation of the guideline in European PICUs. Standard of care within European PICUs provides useful data which can lead to relevant research questions in future.

Conflict of interest statement

All authors declare no conflict of interest.

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Appendix A Questionnaire

Survey on current practices for neurological outcome prognostication after pediatric cardiac arrest

There are 49 questions in this survey.

Part A General information

What is your country of work? *

If you choose 'Other:' please also specify your choice in the accompanying text field.

Please choose **only one** of the following:

- ○ Albania
- ○ Andorra
- ○ Armenia
- ○ Austria
- ○ Azerbaijan
- ○ Belarus
- ○ Belgium
- ○ Bosnia and Herzegovina
- ○ Bulgaria
- ○ Croatia
- ○ Cyprus
- ○ Czech Republic
- ○ Denmark
- ○ Estonia
- ○ Finland
- ○ France
- ○ Georgia
- ○ Germany
- ○ Greece
- ○ Hungary
- ○ Iceland
- ○ Ireland
- ○ Italy
- ○ Kazakhstan
- ○ Kosovo
- ○ Latvia
- ○ Liechtenstein
- ○ Lithuania
- ○ Luxembourg
- ○ Macedonia
- ○ Malta
- ○ Moldova
- ○ Monaco
- ○ Montenegro
- ○ Netherlands
- ○ Norway
- ○ Poland
- ○ Portugal
- ○ Romania
- ○ Russia
- ○ San Marino
- ○ Serbia
- ○ Slovakia
- ○ Slovenia
- ○ Spain
- ○ Sweden
- ○ Switzerland
- ○ Turkey
- ○ Ukraine
- ○ United Kingdom
- ○ Vatican City
- ○ Other:

What is the name of your institution? *

Please write your answer here:

[text box]

What type of hospital do you work in? *

If you choose 'Other:' please also specify your choice in the accompanying text field.

Please choose **only one** of the following:

- ○ General hospital
- ○ University hospital
- ○ Children's hospital
- ○ University children's hospital
- ○ Other:

What is your profession? *

If you choose 'Other:' please also specify your choice in the accompanying text field.

Please choose **only one** of the following:

- ○ Pediatric intensivist
- ○ Pediatric anesthesiologist
- ○ Pediatrician
- ○ (Pediatric) neurologist
- ○ Pediatric cardiologist
- ○ Other:

How many years of experience do you have working/ clinical visits in a PICU (as a staff member and/or as a fellow)? *

Please choose **only one** of the following:

- ○ 1 - 5 years
- ○ 6 - 10 years
- ○ 11 - 20 years
- ○ >20 years

Is the PICU combined with an adult ICU or NICU? *

If you choose 'Other:' please also specify your choice in the accompanying text field.

Please choose **only one** of the following:

- ○ Not combined
- ○ PICU and adult ICU combined
- ○ PICU and NICU combined
- ○ PICU, NICU and adult ICU combined
- ○ Other:

Does your PICU care for children after pediatric cardiac surgery? *

Please choose **only one** of the following:

○ Yes
○ No
○ Unknown

What is the number of PICU beds in your unit? *

Please choose **only one** of the following:

○ 1 - 10
○ 11 - 20
○ 21 - 30
○ >30
○ Unknown

What is the average number of PICU admissions per year in your unit? *

Please choose **only one** of the following:

○ < 250
○ 251 - 500
○ 501 - 750
○ 751 - 1000
○ 1001 - 1500
○ >1500
○ Unknown

What is the average proportion of pediatric patients receiving invasive mechanical ventilation per year in your unit? *

Please choose **only one** of the following:

○ < 25%
○ 25 - 50%
○ 50 - 75%
○ >75%
○ Unknown

What is the average mortality of all PICU patients per year in your unit? *

Please choose **only one** of the following:

○ 0 - 3%
○ 4 - 5%
○ 6 - 10%
○ >10%
○ Unknown

Part B Cardiac arrest

The following questions regard the management in your PICU of children with cardiac arrest (both in-hospital and out-of-hospital) due to cardiac and non-cardiac causes. You can give an estimate if we ask for numbers or percentages.

How many children per year are admitted to the PICU after out-of-hospital **cardiac arrest? ***

Please choose **only one** of the following:

○ < 10
○ 10 - 30
○ 30 - 50
○ 50 - 100
○ > 100
○ Unknown

How many children per year are admitted to the PICU after in-hospital **cardiac arrest or have a cardiac arrest within the PICU?   ***

Please choose **only one** of the following:

○ < 10
○ 10 - 30
○ 30 - 50
○ 50 - 100

○   > 100
○   Unknown

Do you have a post 'return of spontaneous circulation' (ROSC) protocol at your PICU for comatose children after cardiac arrest? *

Please choose **only one** of the following:

○   Yes
○   No
○   Unknown

Do you applicate targeted temperature management (TTM) in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

○   Yes, regardless temperature on PICU admission, we pursue hypothermia ≤35 °C (95 °F)
○   Yes, regardless temperature on PICU admission, we pursue hypothermia ≤33 °C (91,4 °F)
○   Yes, we maintain the same temperature on PICU admission, between 32 °C and 36 °C (89,6 °F - 96,8 °F)
○   Only to prevent fever (> 37.5 °C - 99.5 °F)
○   It depends on the treating physician
○   No
○   Unknown
○   Other:

For how long do you continue TTM in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

○   Non-applicable
○   24 hours
○   48 hours
○   72 hours
○   It depends on the treating physician
○   Unknown
○   Other:

Do you have target values for blood pressure in comatose children after cardiac arrest? *

Please choose **only one** of the following:

○   Yes
○   No
○   Unknown

Please specify

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '17 [Code17]' (Do you have target values for blood pressure in comatose children after cardiac arrest?)

Please write your answer here:

Do you have target values for PaCO2 levels in comatose children after cardiac arrest? *

Please choose **only one** of the following:

○   Yes
○   No

     ○   Unknown

Please specifiy

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '19 [Code19]' (Do you have target values for PaCO2 levels in comatose children after cardiac arrest?)

Please write your answer here:

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Do you have target values for glucose levels in comatose children after cardiac arrest? *

Please choose **only one** of the following:

     ○   Yes
     ○   No
     ○   Unknown

Please specifiy

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '21 [Code21]' (Do you have target values for glucose levels in comatose children after cardiac arrest?)

Please write your answer here:

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Part C Neuroprognostication

Please answer the questions based on the practices in your PICU.

Do you have a national guideline for neuroprognostication after pediatric cardiac arrest? *

Please choose **only one** of the following:

     o   Yes
     o   No
     o   Unknown

Do you have a local guideline for neuroprognostication after pediatric cardiac arrest? *

Please choose **only one** of the following:

     o   Yes
     o   No
     o   Unknown

How do you perform neurological examination in comatose children after cardiac arrest?ⓘ
(multiple answers possible) *

Please choose **all** that apply:

     o   Glascow Coma score

- o Brainstem reflexes
- o FOUR score
- o It depends on the treating physician
- o Unknown
- o Other:

Who performs neurological examination in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

- o (Pediatric) neurologist
- O Pediatric intensivist/fellow
- O Pediatric anesthesiologist
- O Resident
- o Nurse practitioner
- o Nurse
- o Unknown
- o Other:

How often do you perform neurological examination in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

- o > once per day
- o Daily
- O Less than daily
- O Never
- o It depends on the treating physician
- o Unknown
- o Other:

Do you use EEG in routine clinical practice for neuroprognostication in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

- o No
- o Yes, routine EEG (30 minutes) within 24 hrs
- o Yes, routine EEG (30 minutes) after 24 hrs
- o Yes, continuous EEG (at least several hours) within 24 hrs
- o Yes, continuous EEG (at least several hours) after 24 hrs
- o It depends on the treating physician
- o Unknown
- o Other:

Do you use MRI brain in routine clinical practice for neuroprognostication in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

- o No
- o Yes, preferably within 24 hrs
- o Yes, preferably between day 1 - day 3
- o Yes, preferably between day 4 - day 7
- o Yes, preferably after 7 days
- o Yes, but timing differs
- O It depends on the treating physician
- O Unknown
- O Other:

Do you use CT brain in routine clinical practice for neuroprognostication in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

- o No
- o Yes, preferably within 24 hrs
- o Yes, preferably between day 1 - day 3
- o Yes, preferably between day 4 - day 7
- o Yes, preferably after 7 days
- o Yes, but timing differs
- o It depends on the treating physician
- o Unknown

o   Other:

Do you measure biomarkers in routine clinical practice for neuroprognostication in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

o   No
o   Yes, NSE
o   Yes, S-100B
o   It depends on the treating physician
o   Unknown
o   Other:

Do you use SSEP in routine clinical practice for neuroprognostication in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

o   No
o   Yes, after rewarming
o   Yes, preferably after 24 hrs
o   Yes, preferably after 48 hrs
o   Yes, preferably after 72 hrs
o   Yes, but timing differs
o   It depends on the treating physician
o   Unknown
o   Other:

Do you use near infrared spectroscopy (NIRS) in routine clinical practice for neuroprognostication in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

o   Yes
o   No
o   It depends on the treating physician
o   Unknown
o   Other:

Which investigation do you consider most useful in the neuroprognostication of comatose children after cardiac arrest? *

Please select between 1 and 3 answers.

Please choose **all** that apply:

o   Neurological examination
o   Routine EEG
o   Continuous EEG
o   MRI brain
o   CT brain
o   SSEP
o   Biomarker, NSE
o   Biomarker, S-100B
o   Biomarker, NSE and S-100B
o   NIRS
o   Unknown
o   Other:

How do you define a poor neurological outcome? (See below for explanation PCPC score, multiple answers possible) *

Please choose **all** that apply:

o   PCPC score ≥ 3 (moderate overall disability or worse) at hospital discharge
o   PCPC score ≥ 4 (severe overall disability or worse) at hospital discharge
o   PCPC score ≥ 5 (death, coma or vegetative state) at hospital discharge
o   Difference in PCPC score before and after cardiac arrest ≥ 1 at hospital discharge
o   Difference in PCPC score before and after cardiac arrest ≥ 2 at hospital discharge
o   It depends on the treating physician
o   Unknown
o   Other:

Score	Category	Clinical feature
1	Normal	• Normal at age appropriate level
		• School age child attends regular school classroom
2	Mild disability	• Conscious alert and able to interact at an age appropriate level
		• School age child attending regular school classroom but grade perhaps not appropriate for age
		• May have a mild neurologic deficit
3	Moderate disability	• Conscious
		• Sufficient cerebral function for age-appropriate independent activities of daily life
		• School age child attending special education classroom
		• May have learning deficit
4	Severe disability	• Conscious
		• Dependent on others for daily support because of impaired brain function
5	Coma or vegetative state	• Any degree of coma without any of the criteria for brain death
		• Unawareness even if awake in appearance without interaction with the environment
		• Cerebral unresponsiveness
		• No evidence of cortical function and not aroused by verbal stimuli
		• Possibly some reflexive responses spontaneous eye opening and/or sleep-wake cycles
6	Brain death	• Apnea OR
		• Areflexia OR
		• Electroencephalographic (EEG) silence

At what time do you, in general, determine the neurological prognosis in comatose children after cardiac arrest? (multiple answers possible) *

Please choose **all** that apply:

- o Within 48 hrs
- o Day 3
- o Day 4 - 5
- o >5 days
- o >14 days
- o Timing is based on the individual patient
- o Unknown
- o Other:

Who is primarily responsible in determining neurological prognosis? (multiple answers possible) *

Please choose **all** that apply:

- o Pediatric intensivist
- o Pediatric anesthesiologist
- o Pediatrician
- o (Pediatric) neurologist
- o Nurse/nurse practitioner
- o Unknown
- o Other:

What is the consequence once decided that the prognosis is futile (based on expected very poor neurological outcome)? (multiple answers possible) *

Please choose **all** that apply:

- o Intensive care support is withdrawn
- o Intensive care support is continued without any restrictions
- o Intensive care support is continued, with restrictions (e.g.: no resuscitation in case of re-arrest)
- o There is no standard policy for this
- o The decision to continue or withdraw intensive care support depends on the parents' wishes
- o Unknown
- o Other:

Do you have an ethicist in your hospital who you (can) consult? *

Please choose **only one** of the following:

- o No
- o Yes, always in case of end-of-life decision making
- o Yes, but it happens on individual basis
- o Unknown

Part D Follow up and database

Is every child admitted to PICU after cardiac arrest and who survived, scheduled for regular follow up visits? *

Please choose **only one** of the following:

- o Yes
- o No
- o Unknown

When is the first follow up visit scheduled? *

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '40 [Code40]' (Is every child admitted to PICU after cardiac arrest and who survived, scheduled for

regular follow up visits?) If you choose 'Other:' please also specify your choice in the accompanying text field.

Please choose **only one** of the following:

- o Within 3 months
- o Within 3 - 6 months
- o Within 6 - 9 months
- o Unknown
- o Other:

Will there be more follow up visits after the first visit? *

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '40 [Code40]' (Is every child admitted to PICU after cardiac arrest and who survived, scheduled for

regular follow up visits?) Please choose **only one** of the following:

- o Yes, but it depends on the medical condition of the patient
- o Yes, we have a standardized follow up program
- o No

Please specify at which intervals the patients are scheduled

Only answer this question if the following conditions are met:

Answer was 'Yes, we have a standardized follow up program' at question '42 [Code42]' (Will there be more follow up

visits after the first visit?) Please write your answer here:

Who performs the follow up visits? (multiple answers possible) *

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '40 [Code40]' (Is every child admitted to PICU after cardiac arrest and who survived, scheduled for

regular follow up visits?) Please choose **all** that apply:

- o   Pediatric intensivist
- o   Pediatric anesthesiologist
- o   Pediatrician
- o   (Pediatric) neurologist
- o   Nurse/nurse practitioner
- o   Pediatric cardiologist
- o   Psychologist
- o   Rehabilitation specialist
- o   Physiotherapist
- o   Other:

Is there a neuropsychological assessment during follow up visits? *

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '40 [Code40]' (Is every child admitted to PICU after cardiac arrest and who survived, scheduled for regular follow up visits?)

Please choose **only one** of the following:

- o   Yes
- o   No
- o   It happens on individual basis
- o   Unknown

Please specify at which visit (time interval after the event) the assessment will take place

Only answer this question if the following conditions are met:

Answer was 'Yes' at question '45 [Code45]' (Is there a neuropsychological assessment

during follow up visits?) Please write your answer here:

Does your PICU have a local database for children admitted after cardiac arrest? *

Please choose **only one** of the following:

- o   Yes
- o   No
- o   Unknown

Does your PICU have access to a national database for all children admitted after cardiac arrest? *

Please choose **only one** of the following:

- o   Yes
- o   No
- o   Unknown

Does your PICU have access to an international database for all children admitted after cardiac arrest? *

Please choose **only one** of the following:

- o   Yes
- o   No
- o   Unknown

Appendix B. Supplementary data

Table S1. Respondent characteristics

		Frequency (%)
Hospital Type (N=71)	General hospital	5 (7)
	Children's hospital	13 (18)
	University (children's) hospital	53 (75)
Profession (N=71)	Paediatric intensivist	32 (45)
	Paediatric anesthesiologist	1 (1)
	Paediatrician	4 (6)
	(Paediatric) neurologist	31 (44)
	Other	3 (4)
Work experience (N=71)	1 – 5 years	18 (25)
	6 – 10 years	18 (25)
	11 – 20 years	16 (23)
	>20 years	19 (27)

Table S2. **PICU characteristics**

	No. of PICUs		Frequency (%)
Cardiac surgery	(N=45)	Yes	19 (42)
		No	23 (51)
		Intra PICU variability[1]	3 (7)
Number of PICU beds	(N=44)	1 – 10	14 (32)
		11 – 20	22 (50)
		21 – 30	3 (7)
		Other	5 (11)
Overall PICU admissions/year	(N=35)	<250	6 (17)
		251 - 750	21 (60)
		751 – 1500	5 (14)
		Other	3 (9)
Overall PICU mortality/year	(N=29)	0 - 3%	18 (62)
		4 - 5 %	6 (21)
		6 - 10%	2 (7)
		Other	3 (10)
OHCA admissions/year	(N=39)	<10	28 (72)
		10 – 30	7 (18)
		Other	4 (10)
IHCA events/year	(N=38)	< 10	22 (58)
		10 - 30	12 (31)
		30 – 50	1 (3)
		Other	3 (8)
Post-ROSC guideline	(N=40)	Yes	15 (38)
		No	21 (52)
		Intra PICU variability[1]	4 (10)
Local CA database	(N=32)	Yes	15 (47)
		No	17 (53)
National CA database	(N=31)	Yes	8 (25)
		No	20 (65)
		Intra PICU variability[1]	3 (10)
International CA database	(N=31)	Yes	5 (16)
		No	26 (84)
Local neuro-prognostication guideline	(N=41)	Yes	8 (20)
		No	30 (73)
		Intra PICU variability[1]	3 (7)
National neuro-prognostication guideline	(N=23)[2]	Yes	1 (4)
		No	20 (87)
		Intra PICU variability[1]	2 (9)

Answers are given per PICU
[1] In case there were contradictory questions within one PICU, it was classified as intra PICU variability
[2] Per nation

Table S3. Post-ROSC care

	No. of respondents		Frequency (%)
TTM			
Use[1]	(N=63)	No	6 (10)
		Yes, ≤33 °C [2]	1 (2)
		Yes, ≤35 °C [2]	17 (27)
		Yes, 32 °C – 36 °C [3]	20 (32)
		Only to prevent fever (> 37.5 °C)	22 (35)
		It depends on treating physician	3 (5)
		Other	5 (8)
		Unknown	1 (2)
Timing[1]	(N=71)	NA	11 (15)
		24 hours	18 (25)
		48 hours	17 (24)
		72 hours	20 (28)
		It depends on treating physician	4 (6)
		Other	2 (3)
		Unknown	4 (6)
Target values			
Blood pressure	(N=71)	Yes	48 (68)
		No	14 (18)
		Unknown	9 (14)
$PaCO_2$	(N=71)	Yes	53 (75)
		No	11 (15)
		Unknown	7 (10)
Glucose	(N=71)	Yes	53 (75)
		No	11 (15)
		Unknown	7 (10)

NA= not applicable TTM= targeted temperature management
[1]Multiple answers possible
[2]Regardless temperature on PICU admission
[3]Maintain same temperature as on PICU admission

Table S4. Neurological examination

No. of respondents			Frequency (%)
Assessment[1]	(N=71)	GCS	65 (92)
		Brainstem reflexes	53 (75)
		FOUR	9 (13)
		It depends on treating physician	19 (27)
		Other	4 (6)
Professionals[1]	(N=71)	(Paediatric) neurologist	62 (87)
		Paediatric intensivist/fellow	60 (84)
		Paediatric anesthesiologist	6 (8)
		Resident	28 (39)
		Nurse practitioner	12 (17)
		Nurse	27 (38)
		Other	3 (4)
Frequency[1]	(N=70)	> once per day	47 (67)
		Daily	21 (30)
		< daily	4 (6)
		Never	1 (1)
		It depends on treating physician	6 (9)
		Other	3 (4)

GCS=Glasgow Coma Score FOUR=Full Outline of Unresponsiveness score
[1] Multiple answers possible

Table S5. Follow-up

	No. of respondents		Frequency (%)
Timing follow-up	(N=71)	Within 3 months	30 (42)
		Within 3 – 6 months	17 (24)
		Within 6 – 9 months	0 (0)
		No follow-up	17 (24)
		Unknown	7 (10)
>1 follow-up assessment	(N=71)	Depends on medical condition patient	30 (42)
		Standardized follow-up program	19 (27)
		No	1 (1)
		No follow-up	17 (24)
		Unknown	4 (6)
Discipline follow-up	(N=50)	Paediatric intensivist	20 (40)
		Paediatrician	12 (24)
		(Pediatric) neurologist	48 (96)
		Nurse/nurse practitioner	2 (4)
		Paediatric cardiologist	12 (24)
		Psychologist	18 (36)
		Rehabilitation specialist	17 (34)
		Physiotherapist	8 (16)
		Other	2 (4)
NPA	(N=53)	Yes	30 (56)
		No	5 (10)
		It happens on individual basis	14 (26)
		Unknown	4 (8)

Answers are given per PICU
NPA=neuropsychological assessment

Editorial commentory on our findings:

Can we improve prediction of neurological outcome in children after cardiac arrest?

Zvonka Rener-Primec
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Can we improve prediction of neurological outcome in children after cardiac arrest?

Cardiac arrest (CA) is rare in children however it occurs in out-of-hospital settings in up to 6000 children per year in USA; only 10-30% are successfully resuscitated and admitted to PICU [1]. Due to advances in intensive care medicine survival after paediatric CA has improved, but the reduction in mortality is reflected in the significant burden of living with lifelong neurological sequelae as a consequence of hypoxic-ischemic brain injury. It is therefore of utmost importance that accurate early prognostic guidelines after CA are made available for children, as they are for adults. In acute emergency situation all diagnostic and therapeutic procedures are focused maximally to save the child's life. Along with neurologic examination, urgent CT head scan or MRI is done, not only to assess the brain damage but mainly to rule out the potential aetiology of cardiac arrest (trauma, intracranial haemorrhage etc.), if the cause of CA is not obvious from the history. Duration of initial resuscitation/time to return of spontaneous circulation (ROSC), biomarkers and early electroencephalography may provide additional tools to the paediatric intensivist when giving initial information to the family regarding the possible outcome [1,2]. Although combining CT imaging with clinical examination may improve the ability to prognosticate, in the era of advanced postresuscitation care neurological assessment should be undertaken with caution acknowledging the impact of hypothermia, sedation and ventilator support. However when a child remains comatose for more than 24 hours predicting long-term neurological outcome is challenging, especially when being aware that no diagnostic tests are 100% sensitive nor specific for neurologic outcome.To address these dilemmas in this issue, Hunfeld and colleagues, report the results of an anonymous online survey about current practices in European PICUs regarding neuro-prognostication in comatose children after CA [2]. They found that among paediatric intensivists and paediatric neurologists three methods

were considered as most useful to predict neurological outcome: neurological examination (resp. 91% and 90%), brain MRI (resp. 78% and 87%) and cEEG (resp. 53% and 39%). In the literature there are a number of studies published about the prognostic value of these methods, but most of them are retrospective and single centre studies. Early head CT may to some extent help in prognosis of more unfavourable outcome: loss of gray-white matter (GWM) differentiation, in particular in basal ganglia or sulcal effacement had unfavourable neurologic outcomes as demonstrated by Starling et al., who analysed 78 patients with head CT performed within

24 hours of ROSC with a median time to CT of 3.3 hours [1]. Among children not treated with hypothermia after CA early electroencephalography (EEG) is routinely used in many PICUs as background activity reflects the degree of acute cerebral damage. In a study by Topijan 128 patients had EEG monitoring within one day of ROSC [3]. Normal background activity was associated with good prognosis while severely abnormal EEG background (burst suppression, flat, discontinuous background patterns and early epileptic seizures) carried increased odds of death and unfavourable neurologic outcome. They concluded that addition of EEG information to clinical criteria is more predictive of outcome than clinical criteria alone [3]. After cardiac arrest ischemic cytotoxic oedema develops due to hypoxia and is followed by neuronal necrosis (apoptosis). This process is ongoing within minutes to few hours after the acute event. MRI and DW-MRI are much more sensitive than CT and provide accurate and detailed insight into the level and regions of brain tissue damage. Timing of MRI is important as shown more than 2 decades ago by Dubowitz (1998) who found that lesions present on MRI on day 3 or 4 post-CA correlated best with patient outcome versus MRI on days 1 or 2 post-CA. A normal MRI between day 3e7 post-CA was associated with a favourable outcome whereas damage in multiple brain lobes, involvement of cortical regions and basal ganglia and low apparent diffusion coefficient (ADC) values on diffusion weighted

imaging (DWI) MRI were associated with poor outcome[4]. There is a need for prospective multicentre studies to better understand the variable individual susceptibilities to excitotoxicity and free radical stress, cellular metabolism and stage of brain development and the impact of specific treatment modalities.

Hunfeld et al., described the differing practices in European PICUs in relation to withdrawing of life-sustaining treatment (WLST) or continuing treatment when prognosis is futile. Respondents from Western and Northern Europe more often decide to withdraw life-sustaining treatment as compared to those from the Southern and Eastern part of Europe [2]. Many ethical dilemmas arise around the decisions to withdraw life-sustaining treatment. There are very few local or national guidelines. End of life care is a process of recognising that ongoing intensive treatment is prolonging the patient's life but may not be in the patient's best interest. For physicians in PICU one of the most difficult decisions is limiting life-sustaining treatment (LST) and moving from cure to prioritising comfort and palliative care [5]. This study helps to raise awareness of contemporary trends in medical ethics including the awareness of patients' autonomy (in case of paediatric populations through parents). International guidelines for reliable determination of neurological prognosis in comatose children after CA are needed to ensure patients receive optimal standards of care within European PICUs and are provided with ethically acceptable aspects of end of life care [5].

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Chapter 4.

Timing and cause of death in children following return of circulation after out-of-hospital cardiac arrest: A single center retrospective cohort study.

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Abstract

Objectives To determine timing and cause of death in children admitted to the PICU following return of circulation after out-of-hospital cardiac arrest.

Design Retrospective observational study.

Setting Single-center observational cohort study at the PICU of a tertiary-care hospital (Erasmus MC-Sophia, Rotterdam, the Netherlands) between 2012- 2017.

Patients Children younger than 18 years old with out-of-hospital cardiac and return of circulation admitted to the PICU.

Measurements and results Data included general, cardiopulmonary resuscitation and post-return of circulation characteristics. The primary outcome was defined as survival to hospital discharge. Modes of death were classified as brain death, withdrawal of life-sustaining therapies due to poor neurologic prognosis, withdrawal of life-sustaining therapies due to refractory circulatory and/or respiratory failure, and recurrent cardiac arrest without return of circulation.

One-hundred-thirteen children with out-of-hospital cardiac arrest were admitted to the PICU following return of circulation: median age 53 months, 64% male, most common cause of out-of-hospital cardiac arrest drowning (21%). In these 113 children, there was 44% survival to hospital discharge and 56% nonsurvival to hospital discharge (brain death 29%, withdrawal of life-sustaining therapies due to poor neurologic prognosis 67%, withdrawal of life-sustaining therapies due to refractory circulatory and/or respiratory failure 2%, recurrent cardiac arrest 2%). Compared with nonsurvivors, more survivors had witnessed arrest (p=0.007), initial shockable rhythm (p<0.001), shorter cardiopulmonary resuscitation duration (p<0.001) and more favorable clinical neurologic exam within 24 hours after admission. Basic, cardiopulmonary resuscitation event and postreturn of circulation (except for number of extracorporeal membrane oxygenation) characteristics did not significantly differ between

withdrawal of life-sustaining therapies due to poor neurologic prognosis and brain death patients. Timing of decision-making to withdrawal of life-sustaining therapies due to poor neurological prognosis ranged from 0 to 18 days (median: 0 days; interquartile range: 0-3) after cardiopulmonary resuscitation. The decision to withdrawal of life-sustaining therapies was based on neurologic examination (100%), electroencephalography (44%) and/or brain imaging (35%).

Conclusions More than half of children who achieve return of circulation after out-of-hospital cardiac arrest died after PICU admission. Of these deaths, two-thirds (67%) underwent withdrawal of life-sustaining therapies based on an expected poor neurologic prognosis and did so early after return of circulation. There is a need for international guidelines for accurate neuroprognostication in children after cardiac arrest.

Introduction

Nine out of 100,000 children in the Netherlands have an out-of-hospital Cardiac Arrest (OHCA) each year (1). Noncardiac causes are the most prevalent known causes of OHCA, in contrast with adults ((2-4). The incidence of OHCA is lower in children compared to adults (5).

A few studies suggest that survival rates of children with OHCA did not significantly improve in recent years (6-8). However, some other studies concluded that survival following pediatric OHCA did indeed increase (9-12).

Understanding the process of neuro-prognostication and withdrawal of life-sustaining therapies (WLST) following pediatric cardiac arrest (CA) is important. However, detailed information regarding the process of neuroprognostication (e.g., timing and basis for WLST) is often lacking. Furthermore, early after admission to the PICU, it may be difficult to predict prognosis based on the extent of the neurologic damage and the ability of the child to make a full or at least meaningful neurologic recovery. Many children survive OHCA with long-term moderate or severe disability due to hypoxic-ischemic brain injury (13). This knowledge combined with prior individual experience may bias health-care provider neuro-prognostication and decision-making regarding WLST.

A previous study characterizing the epidemiology of inhospital cardiac arrest (IHCA) and OHCA in our center revealed that 30% of the children had no return of circulation (ROC) and 34% died in the PICU, as a result of brain death (BD) or WLST due to serious neurologicdamage or respiratory/circulatory failure (14). A single-center study in the United States reported that BD (47%) was the most common cause of death in children who initially survived OHCA and received post-ROC care in the PICU. When patients died with WLST for poor neurologic prognosis (34%), timing of WLST varied from 1 to 29 days (15).

The aim of this study was to characterize timing and cause of death in children admitted to the PICU following ROC after OHCA. We hypothesized that the majority of hospital non-survivors, died after WLST based on neuroprognostication.

Materials and methods

This observational cohort study was performed at the PICU of the Erasmus MC – Sophia Children's Hospital, a tertiary-care university children's hospital in Rotterdam, the Netherlands. We included patients less than 18 years old with documented OHCA who were admitted to the PICU between January 2012 and December 2017 after achieving ROC. The Medical Ethical Committee Rotterdam approved the protocol (MEC-2019-0096).

CA was defined as unresponsiveness with absent palpable pulse, no signs of life, or healthcare provider perceived need for chest compressions for at least one minute. All data were collected from medical records and analyzed retrospectively. Data were derived from the electronic health record using an electronic case report form created in an OpenClinica database. A medical student, a pediatric intensivist and a pediatric neurologist were involved in data retrieval. We collected the following: 1) basic patient characteristics (e.g. age, gender, socioeconomic Status (SES), preexisting medical conditions, prearrest pediatric cerebral performance category score (PCPC)), 2) OHCA characteristics (e.g. initial rhythm (shockable/non-shockable), witnessed arrest, cause of arrest, bystander CPR, duration of CPR-event, first lactate and first pH after ROC), 3) post-ROC characteristics (e.g., neurologic examination at multiple time intervals during PICU admission (Glasgow Coma Scale score (GCS)), pupillary light reflexes and brainstem reflexes performed by pediatric neurologist, PICU physician and/or PICU nurse, temperature management, Electroencephalography (EEG) (routine or continuous), brain imaging (MRI, CT and ultrasound), somato sensory

evoked potential (SSEP)) and 4) outcome (e.g., survival to hospital discharge (SHD) and PCPC at PICU discharge for survivors).

The criteria for targeted temperature management (TTM) were children who remained comatose after ROC.

Between 2012-2016 imaging, EEGs and SSEPs were performed when clinically indicated (at the discretion of the treating physicians). In 2017 post-ROSC care guidelines were developed at our PICU recommending continuous EEGs (cEEG) in all children with an impaired consciousness after CA and performing MRI images in all children approximately 5 days after the arrest.

In patients following ROC after OHCA who died during PICU or hospital admission ('non-survivors'), cause of death was categorized as clinical BD, WLST due to poor neurologic prognosis (WLST-Neuro), WLST due to refractory circulatory shock and/or respiratory failure (WLST-Cardiopulmonary), or recurrent refractory cardiac arrest without ROC (recurrent CA) (15). Patients may have been classified as having more than one cause of WLST. WLST could consist of withdrawal or no escalation of mechanical ventilation, inotropic/vasoactive support or extracorporeal membrane oxygenation (ECMO). In our hospital (in absence of European BD criteria), clinical BD was defined as follows: GCS score of 3 without brainstem reflexes greater than 24 hours after CPR, no sedation (for at least 24 hr) or possible effects of neuromuscular blockade administration at time of neurologic examination by using the train of four (a peripheral nerve stimulator to assess neuromuscular transmission) and a temperature of at least 32 °C.

Timing of WLST decision making and rationale, and also timing of the actual WLST and death were retrieved for non-survivors. Timing was defined as number of days after the CPR-event: within 24 hours = 0 day, between 24-48 hours= 1 day, between 48-72 hours = 2 days, etc.

In our center (as in all PICUs of The Netherlands) WLST decision-making is done by the medical team, not the parents. In case parents do not agree, a second opinion is often organized (i.e., clinicians from another hospital, preferably an expert in this field).

To define prearrest neurologic functioning (in children > 6 mo), the PCPC score was used (16). Both the medical student (JH) and pediatric neurologist (MH) determined the PCPC score independently (based on notes in the medical records). In the case of disagreement, consensus was achieved.

The SES was estimated by using the 'Status Score' (17).

We used radiology reports to review MRI, CT and ultrasound brain imaging findings. SSEP results were obtained from the neurophysiology reports. An independent clinical neurophysiologist reviewed the EEGs (routine and or continuous) and was blinded to outcome. Neurologic examination findings were obtained from documentation in physician and nursing medical records.

Data analysis

Categorical variables were described using counts and percentages. Continuous variables were described with descriptive statistics presented as mean and SD, or as median and interquartile range (IQR, $25 - 75^{th}$ percentile) if data were not normally distributed. To determine differences between survivors and nonsurvivors, and between WLST-Neuro and BD patients, chi-square, Fisher's exact tests or linear-by-linear chi-square association tests were used for categorical variables, and Mann-Whitney tests or independent sample t tests were used for continuous variables. Missing data were handled by performing complete case analyses. All statistical tests were two-sided with a significance level of 0.05, but a Bonferroni-adjusted significance level of 0.017 was used for comparisons that were performed for each of three time points.

Results

Between January 2012 and December 2017, 113 children were admitted to the PICU of the Erasmus MC – Sophia Children's Hospital following ROC after OHCA (**Supplemental Fig. 1**, Supplemental Digital Content 1, http://links.lww.com/PCC/B538). The most common causes of OHCA were drowning (21%) and arrhythmia (17%) (**Table 1**).

The median age was 53 months and 64% were male. Of these 113 children, 51 (44%) survived to hospital discharge. Of the 62 (56%) nonsurvivors, 60 (97%) died in the PICU and 2 in the general ward. Causes of death were as follows: BD (18/62; 29%), WLST-Neuro (42/62; 67%), WLST-Cardiopulmonary (1/62; 2%) and recurrent CA (1/62; 2%). In twelve patients who died due to WLST-Neuro (12/42; 29%), other reasons contributed to the decision to withdraw treatment (Recurrent CA or WLST-Cardiopulmonary).

Of the 22 children on ECMO (n=11 Extracorporeal cardiopulmonary resuscitation, n=11 ECMO post-CA), 14 (64%) died. Causes of death were as follows: WLST-Neuro (7/14; 50%), WLST-Cardiopulmonary (1/14; 7%), and a combined cause of WLST-Neuro and WLST-Cardiopulmonary (6/14; 43%).

Survivors vs. Non-Survivors

Basic and CPR-event characteristics of survivors (n=51) and nonsurvivors (n=62) are presented in **table 1**.

Survivors more often had a witnessed arrest, a shorter CPR duration with lower number of epinephrine doses and more often an initial shockable rhythm compared with nonsurvivors, all statistically significant. The first pH was significantly higher in the survivors with a lower first lactate. Furthermore, arrhythmia as a cause of CPR occurred more commonly in survivors, whereas trauma was more common in nonsurvivors. Post-ROC characteristics of survivors and nonsurvivors are presented in **table 2**.

Between admission and 72 hours post-CA, there was a significant difference in the presence of pupillary light reflexes in favor of survivors and survivors scored higher on the GCS motor response. Although not always statistically significant, differences were found regarding triggering mechanical ventilator, elicitable corneal and oculocephalic reflexes between the two groups.

TTM was more often applied in nonsurvivors. Nonsurvivors more often had ischemia or edema on brain MRI or CT compared with survivors.

The median PCPC score of survivors at hospital discharge was 2 (IQR, 1-3).

Non-survivors

WLST-Neuro vs. BD: basic, CPR-event and Post-ROC Characteristics

Basic and CPR-event characteristics in WLST-Neuro (n=42) and BD patients (n=18) are presented in **table 1**. No significant differences were found. Post-ROC characteristics in WLST-Neuro (n=42) and BD (n=18) groups are presented in **table 2**.

The only significant difference between these two groups post-ROC was a higher number of ECMO procedures in the WLST-Neuro group (p=0.006). There were no differences between the two groups regarding neurologic examination, temperature management or results of ancillary tests (i.e., EEG, brain imaging, SSEP).

Variable	Survivors n = 51	number included patients	Non-survivors n = 62	number included patients	p-value	WLST-Neuro n = 42	number included patients	BD n = 18	number included patients	p-value
Basics										
Age (months)	48 (17-164)		57 (11-149)		0.695	62 (12-157)		48.5(5-147)		0.723
Male	35 (68)		37 (59)		0.432	22 (52)		14 (78)		0.088
PCPC pre-arrest		(n=42)		(n=50)	0.520		(n=35)		(n=13)	0.533
Normal	37 (88)		44 (88)			30 (86)		12 (92)		
Mild disability	1 (2)		2 (4)			2 (6)		0 (0)		
Moderate disability	3 (7)		1 (2)			0 (0)		1 (8)		
Severe disability	1 (2)		3 (6)			3 (9)		0 (0)		
SES parents *		(n=50)		(n=61)	0.844		(n=41)		(n=18)	0.813
1	11 (22)		12 (20)			7 (17)		5 (28)		
2	31 (62)		42 (69)			30 (73)		10 (56)		
3	8 (16)		7 (11)			4 (10)		3 (17)		
Medical history	23 (45)		32 (52)		0.572	20 (48)		12 (67)		0.259
CPR-event										
Witnessed arrest	28 (55)		19 (31)		0.013	15 (36)		4 (22)		0.375
Bystander CPR	41 (80)		41 (66)		0.137	28 (67)		11 (61)		0.771
CPR duration (min)	8 (3-20)	(n=41)	30 (15-50)	(n=51)	0.000	30 (17-65)	(n=33)	32.5(13-45)	(n=16)	0.820
Epinephrine doses					<0.001					0.805
No	28 (55)		11 (18)			9 (22)		1 (6)		
1	4 (8)		10 (17)			5 (13)		5 (29)		
2-4	12 (24)		22 (37)			13 (32)		9 (53)		
5+	7 (14)		17 (28)			14 (33)		2 (12)		
**First rhythm (shockable) **	17 (47)	(n=36)	4 (8)	(n=49)	<0.001	3 (10)	(n=31)	1 (6)	(n=17)	1.000
First pH after ROC *	7.15(6.95-7.26)	(n=47)	6.90 (6.75-7.11)	(n=54)	<0.001	6.9 (6.8-7.1)	(n=34)	6.9 (6.7-7.1)	(n=18)	0.788
First lactate after ROC* (mmol/L)**	5.8 (4.3-12.7)	(n=47)	14.2 (9.05-18.0)	(n=54)	0.000	15.5 (7-18)	(n=34)	13.5(10-19)	(n=18)	0.758
Cause of CPR event										
Arrhythmia	16 (31)		3 (5)		<0.001	2 (5)		1 (6)		1.000
Drowning	15 (30)		9 (15)		0.066	7 (17)		0 (0)		0.091
ALTE/SIDS	4 (8)		11 (18)		0.166	6 (14)		5 (28)		0.279
Hypotension/shock	4 (8)		9 (15)		0.377	7 (17)		2 (11)		0.710
Airway obstruction	4 (8)		5 (8)		1.000	2 (5)		3 (17)		0.154
Respiratory failure	4 (8)		5 (8)		1.000	4 (10)		1 (6)		1.000
Ingestion/toxin	2 (4)		0 (0)		0.201	0 (0)		0 (0)		
Unknown	1 (2)		7 (11)		0.071	3 (7)		4 (22)		0.182
Electrolyte abnormality	1 (2)		0 (0)		0.451	0 (0)		0 (0)		
Trauma	0 (0)		8 (13)		0.008	7 (17)		1 (6)		0.415
Elevated ICP	0 (0)		3 (5)		0.250	3 (7)		0 (0)		0.547
Seizures	0 (0)		2 (3)		0.500	1 (2)		1 (6)		0.514
ECPR	6 (12)	(n=51)	5 (8)	(n=62)	0.540	5 (12)	(n=42)	0 (0)	(n=18)	0.309
ROC at scene	42 (82)		42 (69)		0.207	27 (64)		14 (78)		0.174

Table 1. Survivors vs. Non-survivors and WLST-neuro vs BD: basic and CPR-event characteristics

Data are presented as n (%) or as median (IQR: 25th -75th percentile)

* 1= low SES , 3= high SES

** First documented rhythm

*** source blood gas and lactate was capillary, arterial or venous and timing of sampling varied from 10 min until 152 min after ROC

PCPC= Pediatric Cerebral Performance Category, SES= socioeconomic status, ALTE= Acute life threatening event, SIDS= Sudden Infant Death syndrome, ECPR= Extracorporeal cardiopulmonary resuscitation, ROC= return of circulation, ICP= intracranial pressure

Variable	Survivors n = 51	number included patients	Non-survivors n = 62	number included patients	p-value	WLST-Neuro n =42	number included patients	BD N=18	number included patients	p-value
Neurologic exam										
Pupils reactive PICU admission – 24 hrs	49 (100)	(n=49)	23 (38)	(n=61)	<0.001	17 (42)	(n=41)	5 (28)	(n=18)	0.449
Invasive mechanical ventilation	45 (90)		61 (99)		0.087	41 (98)		18 (100)		1.000
Triggering PICU admission – 24 hrs	28 (90)	(n=31)	17 (40)	(n=42)	<0.001	12 (41)	(n=29)	5 (39)	(n=13)	1.000
OCR present PICU admission – 24 hrs	6 (60)	(n=10)	5 (13)	(n=39)	0.005	4 (15)	(n=26)	1 (8)	(n=12)	1.000
CR present PICU admission – 24 hrs	8 (16)	(n=21)	1 (1)	(n=52)	<0.001	1 (3)	(n=36)	0 (0)	(n=15)	0.648
Best Motor response PICU admission – 24 hrs		(n=43)		(n=62)	<0.001		(n=41)		(n=18)	0.642
M1	12 (27)		55 (90)			36 (88)		17 (94)		
M2	3 (7)		2 (3)			2 (0)		0 (0)		
M3	2 (4)		0 (0)			0 (0)		0 (0)		
M4	12 (27)		4 (7)			3 (7)		1 (6)		
M5	6 (14)		0 (0)			0 (0)		0 (0)		
M6	9 (21)		0 (0)			0 (0)		0 (0)		
Pupils reactive PICU 24 – 48 hr	37 (100)	(n=40)	16 (40)	(n=37)	<0.001	11 (48)	(n=23)	4 (25)	(n=16)	0.115
Triggering PICU 24 – 48 hr	23 (95)	(n=24)	11 (42)	(n=26)	<0.001	10 (60)	(n=17)	1 (11)	(n=9)	0.036
OCR present PICU 24 - 48 hr	2 (50)	(n=4)	0 (0)	(n=18)	0.026	0 (0)	(n=6)	0 (0)	(n=12)	1.000
CR present PICU 24 - 48 hr	6 (86)	(n=7)	1 (4)	(n=25)	<0.001	0 (0)	(n=10)	1 (4)	(n=15)	1.000
Best Motor response 24 - 48 hr		(n=38)		(n=36)	<0.001		(n=21)		(n=16)	0.630
M1	31 (82)		9 (25)			17 (80)		14 (88)		
M2	2 (5)		1 (3)			2 (10)		0 (0)		
M3	2 (5)		2 (5)			0 (0)		2 (12)		
M4	3 (8)		3 (8)			2 (10)		0 (0)		
M5	0 (0)		11 (31)			0 (0)		0 (0)		
M6	0 (0)		10 (28)			0 (0)		0 (0)		
Pupils reactive PICU 48 – 72 hr	32 (100)	(n=32)	8 (33)	(n=24)	<0.001	6 (40)	(n=15)	1 (13)	(n=8)	0.251
Triggering PICU 48 - 72 hr	15 (88)	(n=17)	10 (59)	(n=17)	0.118	8 (62)	(n=13)	2 (50)	(n=4)	1.000
OCR present PICU 48 - 72 hr	3 (60)	(n=5)	1 (10)	(n=11)	0.016	1 (20)	(n=5)	0 (0)	(n=6)	0.455
CR present PICU 48 - 72 hr	3 (50)	(n=6)	1 (7)	(n=14)	0.061	1 (13)	(n=8)	0 (0)	(n=6)	1.000
Best Motor response 48 - 72 hr		(n=24)		(n=29)	<0.001		(n=15)		(n=9)	0.293
M1	17 (71)		3 (10)			10 (67)		7 (72)		
M2	1 (4)		0 (0)			0 (0)		1 (11)		
M3	0 (0)		2 (7)			0 (0)		0 (0)		
M4	5 (21)		3 (10)			4 (26)		1 (11)		
M5	1 (4)		10 (35)			1 (7)		0 (0)		
M6	0 (0)		11 (38)			0 (0)		0 (0)		
Post-ROC										
Targeted temperature management	36 (71)		55 (89)		0.018	37 (88)		16 (89)		1.000
ECMO (ECPR or post-ROC)	8 (16)		14 (23)		0.475	13 (31)		0 (0)		0.006
Seizures (clinical)	4 (6.1)		7 (12.7)		0.752	7 (17)		0 (0)		0.091
EEG	25 (49)		41 (67)		0.125	25 (60)		15 (83)		0.084
Seizures [*]	1 (5)	(n=22)	5 (14)	(n=37)	0.396	5 (24)	(n=21)	0 (0)	(n=15)	0.062
MRI brain	34 (67)		15 (24)		<0.001	11 (26)		4 (22)		1.000
Days after CPR event	4 (3-6)	(n=34)	3 (2-4)	(n=15)	0.033	3 (2-4)	(n=11)	3 (2.5-4)	(n=4)	0.903
Ischemia	12 (35)	(n=34)	13 (87)	(n=15)	0.001	11 (100)	(n=11)	2 (50)	(n=4)	0.057
Edema	5 (15)	(n=34)	11 (73)	(n=15)	<0.001	7 (64)	(n=11)	4 (100)	(n=4)	0.516
CT brain	20 (39)		34 (55)		0.130	26 (62)		7 (39)		0.156
Days after CPR event	0.00 (0-0)	(n=20)	0.00 (0.00-0.75)	(n=34)	0.5984	0 (0 - 0)	(n=26)	0 (0 - 0)	(n=7)	0.216
Ischemia or edema	2 (5)	(n=20)	23 (70)	(n=34)	<0.001	18 (70)	(n=26)	5 (71)	(n=7)	1.000
Ultrasound brain	7 (14)		11 (18)		0.614	6 (14)		5 (28)		0.279
Ischemia	1 (15)	(n=7)	6 (55)	(n=11)	0.151	4 (67)	(n=6)	2 (40)	(n=5)	0.567
Edema	0 (0)	(n=7)	2 (29)	(n=11)	0.497	1 (17)	(n=6)	1 (20)	(n=5)	1.000
Abnormal SSEP [**]	0 (0)	(n=1)	3 (75)	(n=4)	0.207	1 (100)	(n=1)	2 (67)	(n=3)	0.104

Table 2. Survivors vs. Non-survivors and WLST-neuro vs BD: post-ROC characteristics

Data are presented as n (%) or median (IQR: 25th -75th percentile)

[*] Seizures on rEEG and/or cEEG (regardless of time).

[**] Abnormal SSEP: bilateral absent N20 wave.

OCR= oculocephalic reflex, CR= corneal reflex, ROC= return of circulation, SSEP = somatosensory evoked potential

Cause of Death and Timing of WLST Decision-Making

Supplemental table 1 (Supplemental Digital Content 2, http://links.lww.com/PCC/B539) gives an overview of timing and decision-making of WLST in the WLST-Neuro group (n=30) and WLST-Neuro in combination with WLST-Cardiopulmonary or recurrent CA (n=12). Timing of WLST decision making varied from 0 to 18 days after CPR event (median, 0 d; IQR, 0-3). In 28 patients (67%) the decision to WLST was made within 72 hours after CPR event and in 22 (52%), within 24 hours after the CPR event. The decision-making in these 22 patients was always based on neurologic examination: Absence of brainstem reflexes in all patients but 1 and in all patients a GCS motor response of 1.

In 17 of these 22 patients this neurologic examination was combined with at least one additional investigation (EEG or brain imaging). In four children (18%) the prearrest medical condition contributed to the early WLST decision-making (two had severe pre-existent encephalopathy, one a brain tumor with no curative options and one a severe skeletal dysplasia with pulmonary hypoplasia). In eight children (36%), the presence of other severe injuries or organ failure was an important factor leading to early WLST decision-making (four had circulatory failure, two severe cervical spine and spinal cord injury, one severe traumatic brain injury, and one meningitis).

Supplemental table 2 (Supplemental Digital Content 3, http://links.lww.com/PCC/B540) summarizes the timing and rationale of WLST decision-making for each individual patient. Seventeen of the 22 patients (78%) had targeted TTM around the decision of WLST: (induced hypothermia n=15, with temperatures between 33-34° C, controlled normothermia n=2, with temperatures > 34 °C).

At the time of decision-making, 40% of these patients were either receiving a sedative or opioid infusion during the neurologic examination, or the infusion was discontinued within 24 hours prior to the neurologic examination.

Forty-eight percent of the total WLST-Neuro group (20/42), were monitored with regular or continuous EEG within 24 hours after CPR; isoelectric EEG 40%, low voltage 15%, burst suppression (BS) 30%, BS and low voltage 5% and electrographic seizures with generalized periodic discharges 10%.

Sixty-two percent had hypoxic ischemic injury on neuroimaging (MRI n=11, CT n=18, and ultrasound n=4).

The time between decision making and actual WLST (of the total WLST-Neuro group) ranged from 0 to 51 days (median, 0 d; IQR, 0-1).

Time between actual WLST and death ranged from 1 minute to 32 days (median, 13 min; IQR, 8-25; 8 missing). Two patients were discharged from the PICU but died in the general ward.

WLST included the following: withdrawal of (non-)invasive mechanical ventilation (39/42), discontinuation of inotropic/vasoactive drugs (23/42), no escalation of existing therapy (8/42), or ECMO withdrawal (11/42).

The decision to WLST was always made by the medical team. In all 42 patients, at least one pediatric intensivist was involved in the WLST decision making and in all but two, a (pediatric) neurologist. Four families (10%) initially did not accept the medical decision to withdraw life-sustaining treatment. However, after several discussions with the medical team/and or a second opinion, they all agreed. Therefore, among survivors, there were no children where the medical team decided to withdraw intensive care treatment due to poor neurologic prognosis but eventually continued treatment because parents did not agree.

Discussion

In this single-center observational cohort study, we found that more than half of the children who achieved ROC after OHCA died prior to hospital discharge. In the children that were admitted to PICU, the most common cause of death was WLST due to poor neurologic prognosis (WLST-Neuro 67%), whether or not combined with WLST due to refractory circulatory and/or respiratory failure or recurrent CA. In the majority of this WLST- Neuro group the decision-making took place within 72 hours after the CPR event, and in half of the patients, within 24 hours. Basic, CPR-event and post-ROC (except for number of ECMO) characteristics did not significantly differ between WLST-Neuro and BD patients.

Fifty-six percent of the children who initially achieved ROC and who were subsequently admitted to the PICU died before hospital discharge. This is comparable to other studies (8, 15, 18, 19). However in our cohort, WLST after neuroprognostication was the most important cause of death (67%). In a recent study by Du Pont et al in the United States, to the best of our knowledge the only study describing timing and cause of death in the PICU after pediatric OHCA, BD was the most common cause of death (47%)(15). How can this difference between the findings of Du Pont et al and our findings be explained?

First, the definition of BD is not identical in both studies and dependent from criteria that differ between countries, making a comparison difficult. In our study, we defined BD as clinically BD (see the 'Materials and Methods' section). Additionally, in 2016, the Dutch guideline was changed with one of the prerequisites not to determine BD until 12-24 hours after the CPR event (20). This implies that according to the previous guideline, patients admitted before 2016 may have been declared BD by clinicians, but did not fulfill the BD criteria of the present study (wait for at least 12-24 hr with neurologic examination). This may have given an underestimation of the total amount of BD patients in our cohort.

Second, were the children in our study initially in a better condition after ROC compared to the study in the United States, resulting in less BD? If so, this could be due to the setting in

the Netherlands: a higher incidence in Automatic External Defibrillator (AED) use and bystander CPR, the availability of Helicopter Emergency Medical Service (HEMS), short transfer time from the scene to the hospital (21-24). Indeed, as part of national protocol, in vitally compromised children a HEMS is activated consisting of a physician and specialized nurse for quick advanced pediatric life support at site. In addition, in the Netherlands, a text message CA response system exist for volunteers trained in resuscitation and AED use. However, we must emphasize this hypothesis is purely speculative, because documentation of these variables in both studies are lacking.

Although in our study cohort survivors were discharged from the PICU with favorable outcome (median PCPC= 2; IQR, 1-3), we didn't focus on long-term outcome in different domains (e.g., neuropsychological assessments and quality of life). Could it be possible that in the U.S. cohort of Du Pont et al survivors have more severe long-term neurologic deficits due to lower percentage of WLST (15)?

In all WLST-Neuro patients, the decision-making was based on neurologic examination. However, besides neurologic examination, there was great variability between other factors contributing to the decision-making (e.g., prearrest medical conditions, severity of other injuries/organ failure, brain imaging and type, EEG, SSEP). In most of these patients, at least one modality beside neurologic examination was used for decision making. Until 2017, there was no standardized care for comatose, non-BD children after CA at our PICU and ancillary tests (EEG, imaging) remained at the discretion of the treating physician (pediatric intensivist and pediatric neurologist). In 2017, we developed standardized post-CA care for these patients, both therapeutic and diagnostic. With regard to diagnostics, cEEG recordings are started as soon as possible after PICU admission and all children undergo imaging by MRI approximately 5 days after the arrest. When sedation or analgesics are administered or consciousness may be impaired by these drugs, one must wait to determine a prognosis. At

our PICU, we still do not have guidelines for comatose, non-BD patients regarding neurological examination, MRI and EEG findings (except when EEG is isoelectric) and what it means for the prognosis for each individual patient, due to te lack of evidence of the prognostic value of these modalities. A recent statement from the American Heart Association recommends to consider multiple factors (neurologic examination, neuroimaging, EEG, plasma biomarkers etc.) when predicting outcome in children after CA (22).

Could the decision to WLST have been made too early in some cases? Due to the retrospective design of our study, this is difficult to answer. As mentioned before, in contrast to adults, international evidence based neuroprognostication guidelines do not exist in children. The fact that no differences were found in basic, CPR event and post-ROC characteristics between the WLST-Neuro and BD group was quite reassuring and could implicate that the decision to WLST was accurate. However, we must remain cautious, since in the WLST-Neuro group, 40% were receiving a sedative or opioid infusion during the neurologic examination or the last dosage was administered within 24 hours at time of neurologic examination. Although the dosages of these sedatives or opioids were within normal ranges, we cannot exclude that they had an effect on the neurologic examination, also given the slower metabolism due to organ failure and cooling (TTM). Reasons for administering sedative drugs were to prevent the patient from shivering, to facilitate mechanical ventilation and for the treatment of seizures.

Clinicians should, if the patient's condition allows it, try to avoid the administration of sedatives and delay neuroprognostication.

The possible influence of sedatives/analgesics and hypothermia on neurologic examination and EEG makes the exact differences between the BD and WLST-Neuro group difficult with presumably an overlap. If the treating clinicians had waited with withdrawal in the WLST-Neuro group (to exclude the possible influence of sedatives/analgesics and to wait until the

patient had normal body temperature), more children could presumably have been classified as BD.

On the other hand, another possible consequence of decision making more than 72 hours after the CPR event, could mean less WLST due to change in neurologic examination and ancillary tests, spontaneous breathing, and recovery of multiple organ failure. This could lead to higher SHD numbers, but with more severe neurologically damaged children surviving long-term. For comatose adults post-CA the 2015 guidelines recommend to waiting to neuro-prognosticate using clinical examination) for at least 72 hours. A bilateral absence of the N20 SSEP wave 24-72 hours after CA or after rewarming is a predictor of poor outcome (25, 26). The prognostic role of early EEG in adults is becoming increasingly important; continuous EEG patterns at 12 hours post-CA are associated with a good outcome, whereas generalized EEG suppression and synchronous patterns with greater than or equal to 50% suppression between 6 hours and 5 days post-arrest are associated with a poor outcome (27)).

Our study has several limitations. First of all, it was a retrospective single-center study. Therefore, it may not represent the post-ROC and decision-making in other hospitals in the Netherlands. Second, there was a considerable number of missing data due to the incomplete documentation of the CPR event, post-ROC care, and the decision to WLST. Additionally, as mentioned before, during 2012-2017, post-ROC care in our PICU has been slightly changed. Finally, data were extracted from medical records. The role of parents, family, nurses or other healthcare professionals during the complex real-time decision-making process is likely not documented completely in the medical records, and therefore, may be underappreciated. Because of the uncertainty about the most accurate medical policy, not only with crucial consequences for patients and their caregivers, but also for the medical team, the hospital and health insurance companies, there is an urgent need for international collaboration with standardization of care, neurologic ancillary tests and long-term follow-up of children after

CA. This way, we can get more insight in how to interpret available neuromonitoring modalities. With standardized data collection with a large patient sample size, it could finally enable us to design international guidelines that can be implemented for the individual patient. However, we must realize that even if these neuroprognostication guidelines would be available, the question rises if physicians across the world would adhere to this guideline, in view of their personal beliefs, cultural and religious aspects, different financial resources and expertise.

Furthermore, an unambiguous definition of BD worldwide would facilitate accurate decision making. Besides neurologic examination including apnea testing, confirmatory tests (EEG, transcranial Doppler or CT-angiography) are required in the Netherlands to determine 'whole' BD (for the purpose of possible organ donation). Ancillary tests are only done when neurologic examination and apnea testing are performed reliably and completely (20).

However, in The United States and United Kingdom, only neurologic examination with apnea testing is sufficient for the determination of pediatric BD. Ancillary tests can be used when parts of neurologic examination or apnea testing cannot be completed safely. Also variability exists across countries in the number of physicians required, need for repeated examination, time intervals between examination and choice of ancillary tests (28, 29).

Additionally, we need to be informed about short- and long-term outcome, both physical and neuropsychologic, in OHCA survivors. Proper and precise documentation for every child is very important. Finally, recently, an advisory statement has been published with a core outcome set for cardiac arrest clinical trials in adults (30).This set includes survival, neurologic function and health-related quality of life. For children a similar set is mandatory for appropriate outcome research and is currently under development.

Conclusions

More than half of children who achieve ROC after OHCA died after PICU admission. Of these deaths, two thirds (67%) underwent WLST based on an expected poor neurologic prognosis and did so early after ROC. There is an urgent need for international collaboration to finally develop international guidelines regarding neuroprognostication after CA and a solid Core Outcome Set after CA in children.

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Supplemental figure 1. Flowchart of patient inclusion and cause of death
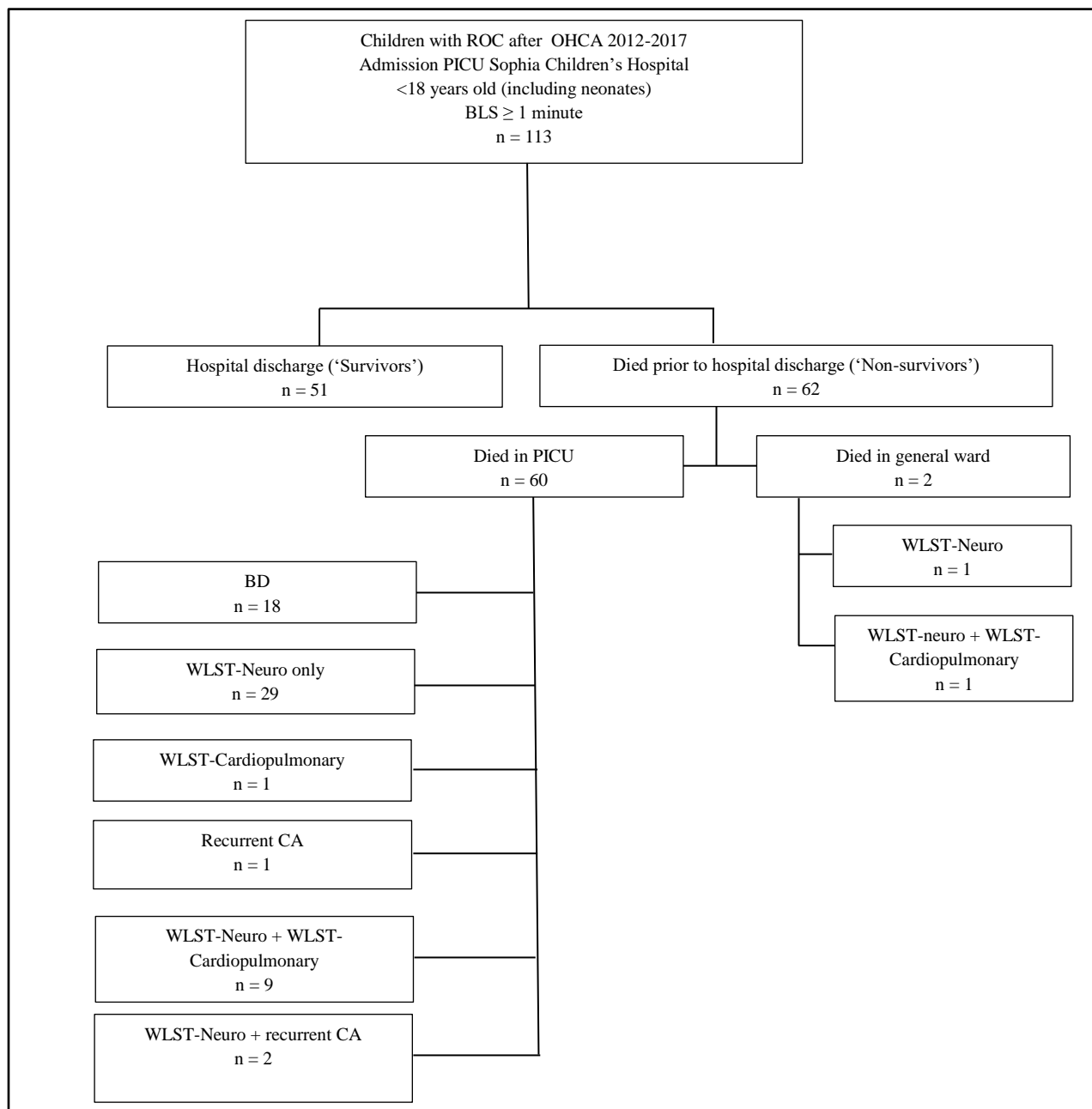
Supplemental table 1. Overview of timing and reasoning of WLST due to poor neurologic prognosis and the use of ancillary tests

Tests/ Reasons to WLST	WLST<24hrs N=22	WLST 24-48hrs N=4	WLST 48-72hrs N=2	WLST >72 hrs N=14
Neurologic exam + Medical condition pre-Arrest[1] + Other sever injury[2]	N=2	N=1		
Neurologic exam + Medical condition pre-arrest[1] + Imaging or EEG[3]	CT N=1			
Neurologic exam + Medical condition pre-arrest[1]	N=1			
Neurologic exam + Other severe injury[2] + Imaging or EEG[3]	CT N=2 MRI N=1	EEG+CT N=1	CT N=1	N=4
Neurologic exam + Other severe injury[2]	N=4			
Neurologic exam + Imaging	CT N=3			MRI N=5
Neurologic exam + EEG	N=4	N=1	N=1	
Neurologic exam + EEG + Imaging	CT N=3	CT N=1		CT N=1 MRI N=3
Neurologic exam + EEG + Imaging + SSEP				MRI N=1
Neurologic exam	N=1			
Total	N=22	N=4	N=2	N=14

[1]Medical conditions pre-arrest were: Metastatic brain tumor, pulmonary hypoplasia, preexistent severe encephalopathy

[2] Other severe injuries were: Circulatory failure or respiratory failure, severe damage cervical spine, fulminant meningitis, multi organ failure, severe traumatic brain injury with immeasurable high intracranial pressure

[3] Imaging or EEG could be: MRI brain or CT brain or ultrasound brain or EEG

EEG=Electroencephalography, SSEP=Somato Sensory Evoked Potential, WLST= Withdraw Life Sustaining Therapies

Supplemental table 2. W/D-Neuro: characteristics of patients with decision WLST (n=42)

Nr.	Sex (M/F)	Time decision WLST [a]	Pre-arrest PCPC	Neurological exam [b]	Sedative infusions [c]	Targeted Temperature[d]	EEG [e]	CT brain	MRI brain	Ultrasound brain	Decision WLST based on[f]
1	M	0	Mild disability	No reactive pupils; No CR; No OCR; Triggering ventilation present; Best Motor score M1	Fentanyl, Propofol	-	-	Hydrocephalus with diffuse swelling and brain herniation	-	-	Neurologic exam + imaging + metastatic brain tumor + re arrest
2	M	0	Normal	No reactive pupils; No CR; No OCR; Unknown triggering ventilation; Best Motor score M1	Propofol, Sufentanil	33°C	-	No ischemia; No edema	-	-	Neurologic exam + circulatory failure
3	F	0	Normal	Reactive pupils; No CR; OCR ND; No triggering ventilation; Best Motor score M1	No	-	-	Diffuse swelling and brain herniation	Diffuse ischemia cortex, BG	-	Neurologic exam + imaging + severe damage craniocervical junction
4	F	0	Normal	No reactive pupils; CR ND; OCR ND; triggering ventilation ND; Best Motor score M1	Midazolam, Rocuronium, Ketamine	-	-	Diffuse swelling and brain herniation	-	-	Neurologic exam + imaging + traumatic decapitation of the cervical spine with major dislocation of the dense
5	F	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	Fentanyl, Propofol	37°C	-	No ischemia; No edema	-	-	Neurologic exam + immeasurably high intracranial pressure
6	M	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	Propofol	34°C	-	No ischemia; No edema	-	-	Neurologic exam + fulminant meningitis
7	F	0	Normal	No reactive pupils; No CR; No OCR; triggering ventilation ND; Best Motor score M1	No	33°C	-	Diffuse swelling	-	-	Neurologic exam + imaging
8	F	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	Fentanyl	33°C	-	-	-	-	Neurologic exam + circulatory failure + poor ECMO output
9	F	0	Normal	No reactive pupils; No CR; No OCR; triggering ventilation ND; Best Motor score M1	Midazolam	34°C	-	Diffuse swelling and brain herniation	-	-	Neurologic exam + imaging
10	M	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	No	34°C	Low voltage	Diffuse swelling	-	-	Neurologic exam + EEG + imaging
11	F	0	Mild disability	No reactive pupils; Unilateral CR; OCR ND; triggering ventilation ND; Best Motor score M1	No	33°C	-	-	-	-	Neurologic exam + medical condition pre-arrest (pulmonary hypoplasia and skeletal dysplasia)
12	F	0	Unknown because of age	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	No	33°C	-	-	-	-	Neurologic exam
13	M	0	Normal	No reactive pupils; No CR; No OCR; triggering ventilation ND; Best Motor score M1	No	33°C	Iso electric	Diffuse swelling	-	-	Neurologic exam + EEG + imaging
14	F	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	Midazolam	-	Iso electric	No ischemia; No edema	-	-	Neurologic exam + EEG (BD volgens wet tot 2016)

#	Sex		Outcome	Clinical exam	Sedation	Temp	EEG				Determination
15	M	0	Normal	No reactive pupils; No CR; No OCR; triggering ventilation ND; Best Motor score M1	No	34°C	Iso electric	-	-	-	Neurologic exam + EEG
16	M	0	Normal	No reactive pupils; No CR; No OCR; triggering ventilation ND; Best Motor score M1	No	34°C	BS	-	-	-	Neurologic exam + EEG
17	M	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	No	33°C	Iso electric	-	-	-	Neurologic exam + EEG + re arrest
18	M	0	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	No	34°C	Iso electric	Diffuse swelling	-	-	Neurologic exam + EEG + imaging
19	M	0	Severe disability	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	No	34°C	-	-	-	-	Neurologic exam + circulatory failure and preexistent severe encephalopathy
20	F	0	Normal	No reactive pupils; No CR; No OCR; triggering ventilation ND; Best Motor score M1	No	34°C	-	Diffuse swelling	-	-	Neurologic exam + imaging + circulatory failure
21	M	0	Severe disability	Reactive pupils; No CR; No OCR; Triggering ventilation present; Best Motor score M1	Midazolam	-	-	-	-	-	Neurologic exam + preexistent severe encephalopathy + severe hypoxia with respiratory failure
22	F	0	Normal	Unilateral reactive pupil; No CR; No OCR; No triggering ventilation; Best Motor score M1	No	36°C	-	Diffuse swelling and brain herniation	-	-	Neurologic exam + imaging
23	M	1	Normal	No reactive pupils; No CR; OCR ND; No triggering ventilation; Best Motor score M1	Midazolam	-	Iso electric	Multiple ischemic areas cortical	-	-	Neurologic exam + EEG + imaging
24	F	1	Normal	Unknown reactive pupils*; CR*; Unknown OCR*; triggering ventilation ND; Best Motor score M1	No	-	Iso electric	Diffuse swelling	-	-	Neurologic exam + EEG + imaging + no improvement after laparotomy for abdominal compartment syndrome + persistent circulatory failure
25	M	1	Normal	No reactive pupils; No CR; OCR ND; No triggering ventilation; Best Motor score M1	Midazolam	-	Iso electric	-	-	-	Neurologic exam + EEG
26	F	1	Severe disability	No reactive pupils; CR ND; OCR ND; triggering ventilation ND; Best Motor score M1	No	-	-	-	-	-	Neurologic exam + circulatory failure+ preexistent severe encephalopathy
27	F	2	Unknown because of age	Reactive pupils; Unknown CR; Unknown OCR; Triggering ventilation present; Best Motor score M1	No	-	-	Diffuse swelling	-	Diffuse swelling	Neurologic exam + imaging + circulatory failure
28	F	2	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best Motor score M1	Midazolam	-	BS	No ischemia; No edema	-	-	Neurologic exam + EEG
29	M	3	Normal	Reactive pupils; CR ND ; OCR ND; triggering ventilation ND; Best Motor score M1	No	-	Low voltage; BS	No Ischemia; No edema	-	-	Neurologic exam + EEG + circulatory failure + multi-organ failure
30	M	3	Normal	No reactive pupils; No CR; No OCR; No triggering ventilation; Best motor score M1	Pentobarbital	-	BS	Diffuse swelling	-	-	Neurologic exam+ EEG+imaging
31	M	3	Normal	No reactive pupils: No CR; No OCR; Did trigger ventilation; Best motor score M2	No	-	Epileptiform; GPD's	-	Diffuse ischemia cortex, BG, brain herniation	-	Neurologic exam+ imaging

#	Sex	Age		Neurological exam	Medication		EEG	CT	MRI		Based on which characteristics[f]
32	F	3	Normal	No reactive pupils; No CR; OCR ND**; Trigger ventilation ND; Best motor score M1	Midazolam, Pentobarbital, Fentanyl	-		Diffuse swelling, brain herniation		-	Neurologic exam+imaging+ immeasurably high intracranial pressure and no cerebral perfusion pressure
33	M	3	-***	No reactive pupils; No CR; No OCR; No Trigger ventilation; Best motor score M1	No	-	Low voltage	-	Diffuse ischemia cortex, BG, brainstem	No ischemia	Neurologic exam+ EEG+ imaging
34	M	4	-***	No reactive pupils; No CR; No OCR; No trigger ventilation: Best motor score 4	No	-	BS	Multiple ischemic areas cortical, BG	Diffuse ischemia cortex, BG, brain herniation	No ischemia	Neurologic exam+ imaging
35	F	4	Normal	Reactive pupils; CR+/+; OCR ND; Did trigger ventilation; Best motor score 4	No	-	BS	-	Diffuse ischemia cortex, BG, brain herniation	-	Neurologic exam+EEG+imaging
36	F	4	Normal	No reactive pupils; No CR; No OCR; No trigger ventilation; Best motor score 1	Midazolam	-	-	No ischemia; No edema	Diffuse ischemia cortex, BG	-	Neurologic exam+imaging
37	F	5	Normal	Reactive pupils; No CR; OCR ND; No trigger ventilation; Best motor score 1	No	-	-	Cerebellar hematoma, brain herniation	Diffuse ischemia brainstem, cerebellum	-	Neurologic exam+imaging
38	M	6	Normal	Reactive pupils; CR +/+; OCR ND; Did trigger ventilation; Best motor score 1	Propofol	-	Epileptiform; GPD's	Diffuse swelling	Multiple ischemic areas cortical, BG	-	Neurologic exam+EEG+imaging+ SSEP
39	M	6	-***	No reactive pupils; No CR; No OCR; Did trigger ventilation; Best motor score 1	Midazolam, Morphine	-	BS	No ischemia; No edema	Multifocal ischemic areas cortex, subcortical	Ischemia thalami bilateral	Neurologic exam+imaging
40	F	7	-***	Pupils ND; CR ND; OCR ND; Did trigger ventilation; Best motor score 5	No	-	-	-	Ischemia thalami bilateral	Possible ischemia	Neurologic exam+imaging+ preexistent Turner syndrome and severe cardiac failure
41	F	12	-***	Unilateral reactive pupil*; CR ND; OCR ND; Trigger ventilation ND; Best motor score 3	No	-	-	-	-	Ischemia MCA L	Neurologic exam+ imaging+ circulatory failure
42	M	18	Normal	Reactive pupils; CR ND; OCR ND; Did trigger ventilation; Best motor score 1	No	-	Low voltage	-	Diffuse ischemia cortex, subcortical, BG, brainstem	-	Neurologic exam+imaging

[a] = hours after CPR-event 0=0-24 hrs, 1=24-48 hrs and 2= 48-72 hrs, [b] = around decision making WLST, [c] = during neurological exam or discontinued <24 hrs before neurological exam, [d] = temperature first 24 hrs, [e]= only EEG results PICU admission – 24 hrs, [f] based on which characteristics clinicians decided to withdraw treatment for each individual patient, based on the notes in the medical records.

Chapter 6.

Association between shockable rhythms and long-term outcome after pediatric out-of-hospital cardiac arrest in Rotterdam, the Netherlands: An 18-year observational study

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Abstract

Introduction Shockable rhythm following pediatric out-of-hospital cardiac arrest (pOHCA) is consistently associated with hospital and short-term survival. Little is known about the relationship between shockable rhythm and long-term outcomes (> 1 year) after pOHCA. The aim was to investigate the association between first documented rhythm and long-term outcomes in a pOHCA cohort over 18 years.

Methods All children aged 1 day-18 years who experienced non-traumatic pOHCA between 2002-2019 and were subsequently admitted to the emergency department (ED) or pediatric intensive care unit (PICU) of Erasmus MC-Sophia Children's Hospital were included. Data was abstracted retrospectively from patient files, (ground) ambulance and helicopter emergency medical service (HEMS) records, and follow-up clinics. Long-term outcome was determined using a Pediatric Cerebral Performance Category (PCPC) score at the longest available follow-up interval through august 2020. The primary outcome measure was survival with favorable neurologic outcome, defined as PCPC 1-2 or no difference between pre- and post-arrest PCPC. The association between first documented rhythm and the primary outcome was calculated in a multivariable regression model.

Results 369 children were admitted, nine children were lost to follow-up. Median age at arrest was age 3.4 (IQR 0.8-9.9) years, 63% were male and 14% had a shockable rhythm (66% non-shockable, 20% unknown or return of spontaneous circulation (ROSC) before emergency medical service (EMS) arrival). In adolescents (aged 12-18 years), 39% had shockable rhythm. 142 (39%) of children survived to hospital discharge. On median follow-up interval of 25 months (IQR 5.1-49.6), 115/142 (81%) of hospital survivors had favorable neurologic outcome. In multivariable analysis, shockable rhythm was associated with survival with favorable long-term neurologic outcome (OR 8.9 [95%CI 3.1-25.9]).

Conclusion In children with pOHCA admitted to ED or PICU shockable rhythm had significantly higher odds of survival with long-term favorable neurologic outcome compared to non-shockable rhythm. Survival to hospital discharge after pOHCA was 39% over the 18-year study period. Of survivors to discharge, 81% had favorable long-term (median 25 months, IQR 5.1-49.6) neurologic outcome. Efforts for improving outcome of pOHCA should focus on early recognition and treatment of shockable pOHCA at scene.

Introduction

Pediatric out of hospital cardiac arrest (pOHCA) is uncommon, with incidences ranging from 9.0 – 19.7 per 100,000 person-years (1-4). Whereas CA in adults is mostly of cardiac origin, in pediatrics it is commonly due to respiratory failure (5).

Survival following pOHCA is poor, especially among infants (6, 7), but increasing due to 'chain-of-survival' improvements (7-13). Children receive more bystander basic life support (BLS), more automated external defibrillators (AED's) are available and post-return of spontaneous circulation (ROSC) care has improved, despite AED use in children remaining low (6, 7, 9, 13, 14).

Shockable rhythms in children seem more common than once thought (15, 16), especially in adolescents with a prevalence of 19% (7). The positive association between shockable rhythm and short-term outcomes (ROSC, survival to hospital discharge (SHD) and outcome up to 1 year) has been reported but true long-term follow-up (> 1 year after event) is lacking (6, 17) . Is increased short-term survival rate after pOHCA associated with more children with severe long-term neurological sequelae due to hypoxic ischemic brain injury (18-20)? To be able to detect a child's full potential (neurologic) recovery, a statement from the American Heart Association recently recommended one year of follow-up minimally (21). Literature on outcomes beyond one-year following pOHCA is scarce, often small in sample size, using different and mostly crude measurements and mainly based on data prior to 2008 (17, 22-27). Since 2012 the Erasmus MC – Sophia Children's Hospital has a long-term follow-up program including all pOHCA, as part of standard of care, which led to the following subjective observations: 1) the incidence of shockable rhythms increased over time and 2) shockable pOHCA's achieve favorable long-term neurological outcome more frequently compared with non-shockable pOHCA's.

The aim of this study was to investigate the association of first documented cardiac arrest (CA) rhythm on true long-term outcome in non-traumatic pOHCA. We hypothesized that a shockable rhythm was positively associated with survival with long-term favorable neurologic outcome.

Methods

Study Design

This cohort study was performed at the PICU of the Erasmus MC – Sophia Children's Hospital, a tertiary-care university children's hospital in the Netherlands. The hospital and Helicopter Emergency Medical Service (HEMS) provide health care in the southwest of the Netherlands with approximately five million inhabitants, about 25% of the Dutch population. The Medical Ethics Review Board of the Erasmus MC approved the data collection and gave a waiver for the requirement of informed consent (MEC-2019-0440).

Inclusion criteria

All children aged 24 hours to 18 years with non-traumatic pOHCA, admitted to the Erasmus MC - Sophia Children's Hospital (ED or PICU) with or without CPR in progress between January 2002 and August 2019 were included. Arrests in neonates younger than 24 hours were excluded as they are generally caused by perinatal asphyxia. CA was defined as the need for chest compressions for at least one minute. Cardiopulmonary resuscitation was defined as 'basic life support', in line with the European Resuscitation Council Guidelines, and if needed, followed by 'advanced pediatric life support' (APLS) (5).

Data collection

Existing CPR databases were used to combine CPR data from 2002 until 2019 (23, 28). All

CPR data were derived from ground ambulance records, HEMS records and hospital health record systems. Because HEMS are always deployed in the Netherlands in (suspected) pOHCA, all HEMS records between 2002 and 2019 were also analysed to get an insight of pre-hospital mortality and potential transport to other hospitals. In some rare cases of conflict between data sources (ground EMS and HEMS) HEMS data was used as golden standard. Our CPR data is primarily based on two already existing CPR databases derived from ground EMS CPR data, HEMS data and health record systems from our hospital. In addition HEMS records were analyzed to report pre-hospital mortality and alternate destination.

Data included: A) basic child characteristics (age, gender, parent's Social Economic Status (SES), pre-existing health status). The SES was calculated using a 'Status Score' divided into tertiles to interpret a 'low status (1)', 'intermediate status (2)' and 'high status (3)' (29). The 'Status Score' is based on income, education level and unemployment rate by postal code. B) OHCA characteristics (year, location, first documented rhythm (shockable/non-shockable or unknown), witnessed, cause, bystander CPR, use of AED, CPR duration, extracorporeal CPR (ECPR), targeted temperature management, first blood lactate and pH after ROSC or at hospital arrival, regional transport, re-arrest). C) outcome (pre-hospital mortality, ROSC, SHD and neurologic outcome at the longest available follow-up interval).

At the longest available follow-up interval the neurologic outcome was determined using a Pediatric Cerebral Performance Category score (PCPC, ranging from 1 to 6) and a Functional Status Scale score (FSS, ranging from 6 to 30). The PCPC and FSS scores are internationally validated scores for assessing a child's overall cognitive and functional status after critical illness or injury (30, 31).

The PCPC and FSS scores were based on one of four possible sources: 1) the prospective longitudinal follow-up outpatient clinic database (2012-2019 cohort). 2) the cross-sectional outcome database (2002-2011 cohort) (23). 3) hospital letters from outpatient clinic visits. 4)

hospital discharge letters after the pOHCA.

Both cross-sectional and prospective follow-up databases included validated neurocognitive and daily functioning questionnaires. Hospital letters contained more crude descriptions. The PCPC and FSS were scored by two physicians and one pediatric neurologist independently and in case of disagreement (in less than 5% of cases) agreement was reached through a consensus meeting.

Outcome measures

The primary outcome measure was survival with favorable neurologic outcome at the longest available follow-up interval. Survival with favorable neurologic outcome was defined as a PCPC score of 1-2 or no difference between pre- and post-arrest PCPC, in hospital survivors at the longest available follow-up interval. Unfavorable outcome was defined as: no ROSC, no survival to hospital discharge despite ROSC and PCPC 3-6. Secondary outcome measures were survival and favorable neurological outcome in the group of hospital-survivors.
No universal definition of favorable neurologic outcome exists. The PCPC score is mostly based on daily activity and school performance so 'favorable outcome' largely depends on a country's school system. Favorable neurologic outcome has been defined in the literature as PCPC 1-2 as well as PCPC 1-3 (9, 21, 32). Because in the Netherlands, a high threshold for attending a special needs classroom exists, favorable neurologic outcome was defined as PCPC 1-2.

Statistical analysis

Baseline characteristics and survival outcome were reported using descriptive statistics. Categorical variables were reported as percentages and frequencies, and differences were analyzed with Chi-square test or Fisher's exact test when applicable. Continuous data was

presented as median and interquartile ranges (IQR) for skewed data, and mean and standard deviation (SD) for normal distributed data. Differences were tested using an independent sample t-test for continuous data or Mann–Whitney U test dependent on normality.

The associations of first documented rhythm, AED use, bystander BLS, year of event and the post AED guideline change period with long-term neurologic outcome were calculated with a multivariable logistic regression model. The choice of inclusion of covariates was made in three steps. First, the following covariates were considered based on existing literature: age, gender, pre-existing condition (yes or no and related to CPR event or not), SES (1, 2 or 3), event location (private or public), year of event (including before and after the AED guideline change), witnessed arrest (yes or no), bystander CPR (yes or no), bystander AED use (yes or no), CPR duration (in minutes), first documented cardiac arrest rhythm (shockable, non-shockable or unknown), cause of arrest (specific), ECPR (yes or no) and first lactate and pH after ROSC. Second, collinearity analysis to explore correlation between all covariates using a correlation matrix was performed. A cut-off value of >0.7 was used for the exclusion of variables in the model. Third, inclusion of the abovementioned potential confounders in the final models was based on >10% change of the effect estimate in the crude model. These covariates were entered one-by-one in the crude model to see the effect on the effect estimate. Results are presented as odds ratio (OR) and 95%-confidence interval (CI).

A sensitivity analysis comparing the different definitions of favorable neurologic outcome (PCPC 1-2 vs PCPC 1-3, or no pre-and post-arrest difference) was performed. Stratified analysis by age group (infant; aged <1 year, child; aged 1 to 11 years and adolescent; aged 12 to 18 years as well as below and above 8 years of age) was also done. Lastly, a propensity score analysis using 1:1 nearest-neighbor matching of shockable to non-shockable rhythm was performed. The propensity score was estimated using a multivariable logistic regression model including the following variables: gender, age at arrest and year of event. Both groups

were tested for association with long-term neurologic outcome using a multivariable logistic regression model.

Our data contained missing values for CPR duration (19%). Other covariates had < 10% missing data. Variables were imputed using multiple imputation (n = 5 imputations) function based on the distribution of existing data.

A two-tailed p-value < 0.05 was considered statistically significant. All analyses were conducted using SPSS software version 24 (IBM SPSS Statistics for Windows, Armonk, New York, USA).

Results

Child and CA characteristics

The target population consisted of 581 children, of whom 138 (24%) had termination of resuscitation and were pronounced deceased at scene and 74 (13%) were transported to other hospitals by HEMS. Of 369 eligible children admitted to the Erasmus MC-Sophia, 360 were included (9 children, 2%, had missing data). An overview of the inclusion is given in figure 1. The basic characteristics are presented in table 1.

Most important causes of arrest were drowning (28%), 'Sudden Infant Death Syndrome' (SIDS) (15%) and arrhythmia (13%). The median age at CA was 3.4 (IQR 0.8-9.9) years and 225 (63%) were male. 152 arrests (42%) were witnessed and in 241 (68%) bystander BLS was performed. Of first documented rhythms, 14% were shockable, 66% non-shockable, 20% unknown (i.e. ROSC before arrival of EMS).
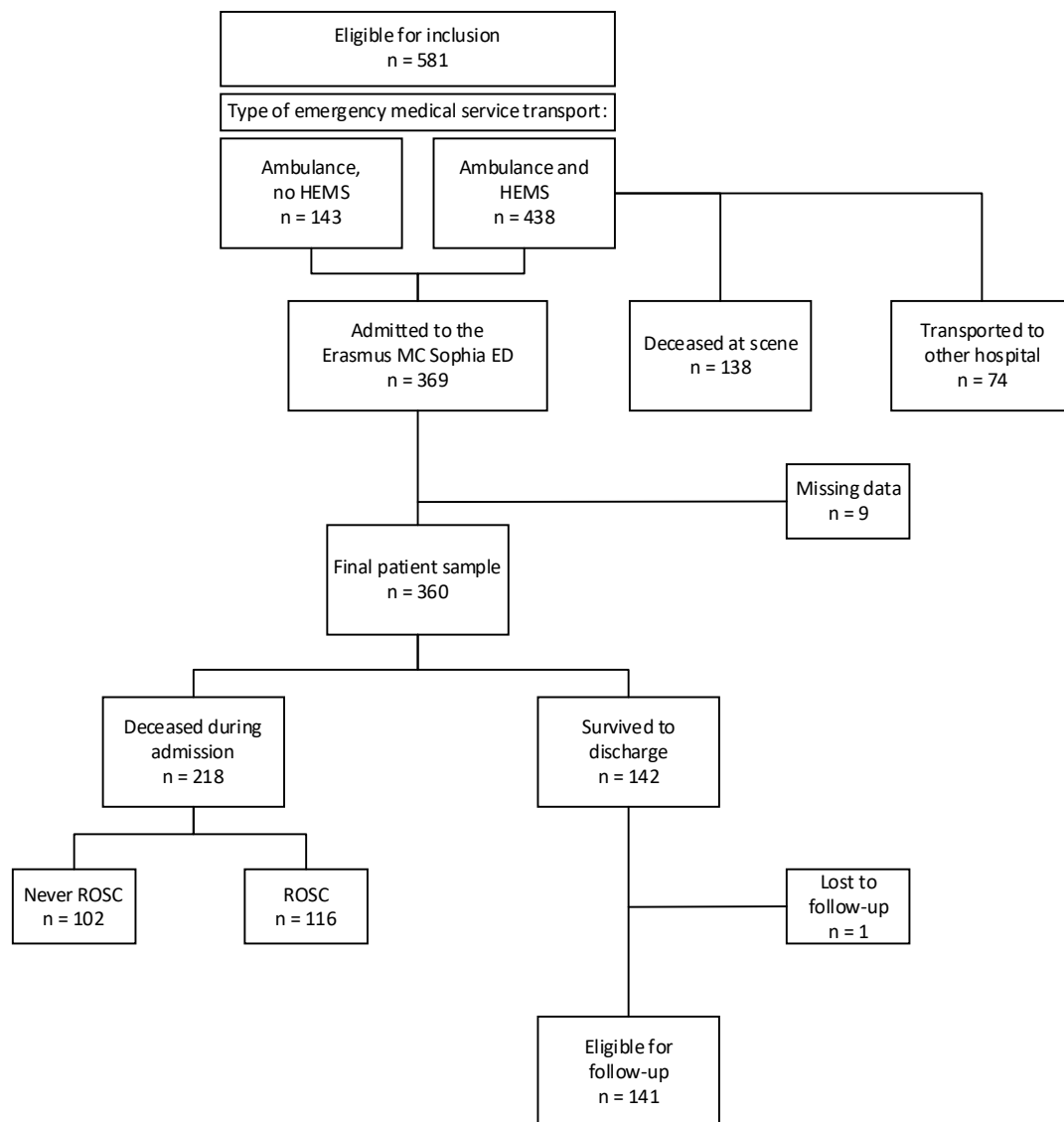
Figure 1. Overview of patient inclusion
ED = Emergency Department, HEMS = Helicopter Emergency Medical Service, ROSC = Return of Spontaneous Circulation.

	Overall (n = 360)			Favorable outcome (n = 115)			Non-favorable outcome (n = 244)			p-Value[d]	Missings[c]	
	n[a]			n[a]			n[a]					
Patient characteristics												
Age (years)[b]	360	3.4	0.8 - 9.9	115	3.4	1.2 - 12.1	245	3.2	0.7 - 8.6	0.429	0	
Male gender[c]	360	225	63%	115	74	64%	245	151	62%	0.489	0	
Pre-existings conditions[c]	358	155	43%	114	49	43%	244	106	43%	1.000	2	1%
- Respiratory		40	26%		12	24%		28	26%	1.000		
- Cardiac		31	20%		13	27%		18	17%	0.540		
- Neurologic		37	24%		8	16%		29	27%	0.354		
- Metabolic		3	2%		0	0%		3	3%	1.000		
- Congential malformation (non-cardiac)		32	21%		10	20%		22	21%	1.000		
- Renal		3	2%		1	2%		2	2%	1.000		
- Genetic/Chromosomal		25	16%		7	14%		18	17%	0.174		
- Other		70	45%		28	57%		42	40%	0.091		
SES parents[c]	352			112			240			0.006	8	2%
- 1		128	36%		28	25%		100	42%	0.003		
- 2		153	43%		61	54%		92	38%	0.008		
- 3		71	20%		23	21%		48	20%	0.888		
Cardiac arrest characteristics												
Event location – public (versus private)[c]	360	125	35%	115	56	49%	245	69	28%	0.197	0	
Witnessed arrest[c]	358	152	42%	114	54	47%	244	98	40%	0.256	2	1%
Bystander BLS[c]	356	241	68%	115	99	86%	241	142	59%	<0.001	4	1%
Bystander AED use[c]	360	30	8%	115	10	9%	245	20	8%	0.684	0	
EMS defibrillation[c]	360	59	16%	115	23	20%	245	36	15%	0.175	0	
CPR duration (minutes)[b]	291	30.0	8.0 - 75.0	89	4.0	2.0 - 8.0	202	57.0	25.0 - 83.0	<0.001	69	19%
Initial rhythm[c]	351			115			237			<0.001	9	3%
- Shockable (VF)		48	14%		27	23%		21	9%	<0.001		
- Unknown/ROSC before EMS arrival		70	20%		57	50%		13	5%	<0.001		
- Non-shockable		233	66%		31	27%		202	85%	<0.001		
Asystole		172	74%		11	35%		161	80%	<0.001		
PEA		23	10%		4	13%		19	9%	0.113		
Bradycardia		38	16%		15	48%		23	11%	0.373		
Other		1	3%		1	3%		0	0%	0.331		
Cause of arrest[c]	360			115			245			<0.001	0	
- Unknown/Not documented		27	8%		3	3%		24	10%	0.024		
- ALTE/SIDS		54	15%		17	15%		37	15%	1.000		
- Airway obstruction		41	11%		7	6%		34	14%	0.047		
- Arrythmia		47	13%		30	26%		17	7%	<0.001		
- Drowning		100	28%		45	39%		55	22%	0.002		
- Electrolyte abnormality		3	1%		0	0%		3	1%	0.554		
- Elevated ICP		10	3%		0	0%		10	4%	0.034		
- Hypotension/Shock		30	8%		2	2%		28	11%	0.001		

Characteristic	n	Value	% / IQR	n	Value	% / IQR	n	Value	% / IQR	p	Missing n	Missing %
- *Ingestion/Toxin*		2	1%		2	2%		0	0%	0.103		
- *Other repiratory failure*		33	9%		8	7%		25	10%	0.336		
- *Seizures*		13	4%		1	1%		12	5%	0.043		
ECPR[c]	360	13	4%	115	4	3%	245	9	4%	1.000	0	
First pH after ROSC or after hospital arrival[b]	336	6.95	6.71 - 7.21	109	7.24	7.09 - 7.33	227	6.79	6.60 - 7.03	<0.001	24	7%
First lactate (mmol/L) after ROSC or after hospital arrival[b]	328	12.7	5.1 - 16.0	105	4.4	2.4 - 7.6	223	15.0	10.7 - 19.0	<0.001	32	9%
Post cardiac arrest characteristics												
Post-ROSC ECMO[c]	360	12	3%	115	5	4%	245	7	3%	0.534	0	
Temperature management[c]	354	149	42%	115	47	41%	239	102	43%	0.819	6	2%
Re-arrest[c]	360	13	4%	115	6	5%	245	7	3%	0.364	0	
Outcome												
Sustained ROSC[c]	360	258	72%	115	115	100%	245	143	58%	<0.001	0	
- *Before arrival to hospital*		204	57%		108	94%		96	39%	<0.001		
- *After arrival to hospital*		54	15%		7	6%		47	19%	0.001		
Withdrawal of life sustaining therapies[c]	354	76	21%	115	0	0%	241	76	32%	NA	4	1%
Survival to hospital discharge[c]	360	142	39%	115	115	100%	245	27	11%	<0.001	0	
Deceased after discharge[c]	360	7	2%	115	0	0%	245	7	3%	NA	0	
Follow-up												
Follow-up (months)[b]	141	25.2	5.1 - 49.6	115	26.3	1.6 - 49.5	19	14.2	9.1 - 67.9	0.779		
Age at follow-up (years)[b]	141	6.6	3.4 - 13.4	115	8.1	3.5 - 14.7	19	5.3	3.0 - 12.1	0.300		

Table 1. Patient and cardiac arrest characteristics by primary outcome measure: survival with favorable neurological outcome.

AED = Automatic external defibrillator, BLS = Basic life support, EMS = Emergency medical support, CPR = Cardiopulmonary resuscitation, ECMO = Extracorporeal cardiopulmonary support, ECPR = Extracorporeal cardiopulmonary resuscitation, VF = Ventricular fibrillation, ICP = Intracranial, NA = Not applicable pressure, PEA = Pulseless electric activity, ROSC = Return of spontaneous circulation.

[a] Number of subjects in whom the variable was obtained.
[b] Median (interquartile range).
[c] Number of subjects (%).
[d] p-Value: independent sample t-test for continuous data or Mann–Whitney U test dependent on normality; Fisher's exact test for dichotomous data.

Outcome: ROSC, SHD, long-term outcome

Of the final sample of 360 children, 142 (39%) survived until hospital discharge, whereas 218 (61%) died in the ED (no ROSC, 102, 28%) or during hospital admission (116, 32%). The main cause of in-hospital mortality after ROSC was withdrawal of life-sustaining therapy (WLST) (76 children, 21%). Of the 142 survivors to hospital discharge, 7 (5%) died after discharge; 6 due to severe hypoxic encephalopathy, 1 cause unknown. The median follow-up duration was 25 months (IQR 5.1 - 49.6) and median age at follow-up was 6.6 years (IQR 3.4 - 13.4) (table 1). 89 of 142 children (63%) had a follow-up duration of longer than 1 year post-arrest.

Table 2 shows timing and source of the long-term neurological outcome. PCPC scores are presented per category (1-6) and FSS scores as median. PCPC scores were mostly scored either at regular hospital visit (n = 47) or at prospective follow-up (n = 46). Except for the group scored at hospital discharge, median follow-up duration for the other groups exceeded 2 years (regular hospital visit 2.7 years [IQR: 0.8-5.5]; cross-sectional 3.7 [IQR 2.5 – 10.5] and prospective 2.3 years [IQR 1.1 – 3.8].

	Deceased after discharge (n = 7)		Scored at hospital discharge (n = 23)		Scored at a regular hospital or clinic visit (n = 47)		Scored at cross-sectional follow-up (2013-2014) (n = 18)		Scored at prospective follow-up (2011 and onwards) (n = 46)	
	Pre-arrest	Post-arrest	Pre-arrest	Post-arrest	Pre-arrest	Post-arrest	Pre-arrest	Post-arrest	Pre-arrest	Post-arrest
PCPC score[a]										
1 – Normal	5	0	18	16	39	26	17	8	40	24
2 – Mild disability	1	0	3	5	3	6	0	6	1	11
3 – Moderate disability	1	0	2	2	3	7	1	3	5	8
4 – Severe disability	0	0	0	0	2	7	0	1	0	3
5 – Coma or vegetative state	0	0	0	0	0	1	0	0	0	0
6 – Brain death	0	7	0	0	0	0	0	0	0	0
FSS score[b]	NA	NA	NA	6.0 [6.0 - 6.0]	NA	6.0 [6.0 - 11.0]	NA	6.0 [6.0 - 6.3]	NA	6.0 [6.0 - 6.3]
Follow-up (years)[b]	NA	0.6 [0.5 - 1.7]	NA	0.0 [0.0-0.0]	NA	2.7 [0.8 - 5.5]	NA	3.7 [2.5 - 10.5]	NA	2.3 [1.1 - 3.8]
Age at follow-up (years)[b]	NA	NA	NA	4.2 [1.5 - 8.9]	NA	6.6 [2.6 - 12.1]	NA	12.6 [3.8 - 15.0]	NA	9.0 [4.6 - 16.0]

Table 2. Timing and source of long-term neurological outcome.

FSS = Functional Status Scale, PCPC = Pediatric Cerebral Performance Category.

[a] Number of subjects.

[b] Median (interquartile range).

For patients deceased after discharge follow-up duration represents the median duration to date of death.

Favorable outcome versus non-favorable outcome

A higher SES score, bystander BLS, shorter CPR duration, rhythm (shockable or unknown), cause of arrest (arrhythmia, drowning, shock and seizures), lower first pH, higher lactate and ROSC before arrival to hospital were all significantly associated with favorable neurologic outcome (table 1).

Multivariable analysis

The crude associations were adjusted for witnessed arrest, bystander CPR, age at arrest, year of arrest, first lactate, pre-existing conditions related to arrest and CPR duration. After adjustment, first documented shockable rhythm showed significantly improved odds of favorable outcome compared with non-shockable rhythm, with an OR of 8.9 [95% CI 3.1-25.9] (table 3). Also, first documented unknown rhythm (OR 6.1 [95% CI 2.2-16.5]), a more recent year of arrest (OR 1.2 [95% CI 1.1-1.2]) and the post-guideline change period (advising AED use in all ages) (2010-2017) (OR 2.6 [95% CI 1.3-5.1]) showed significantly improved odds of favorable outcome. In the sensitivity analysis with PCPC 1-3, first documented shockable rhythm showed a stronger relationship with favorable outcome than favorable outcome defined as PCPC 1-2 (OR 13.7 [95% CI 4.6-40.9]).

Variable	Survival with post-arrest PCPC 1-2 or ΔPCPC 0 at the longest follow-up interval[f] (n = 360)				Survival with post-arrest PCPC 1-3 or ΔPCPC 0 at the longest follow-up interval[g] (n = 360)			
	Crude		Adjusted		Crude		Adjusted	
	OR [95%CI]	p-Value	OR [95%CI]	p-Value	OR [95%CI]	p-Value	OR [95%CI]	p-Value
Initial non-shockable rhythm[a]	referent		referent		referent		referent	
Initial shockable rhythm[a]	8.4 [4.2 - 16.8]	<0.001	8.9 [3.1 - 25.9]	<0.001	9.4 [4.7 - 18.9]	<0.001	13.7 [4.6 - 40.9]	<0.001
Initial unknown rhythm[a]	29.6 [14.6 - 60.3]	<0.001	6.1 [2.2 - 16.5]	<0.001	31.5 [15.1 - 65.8]	<0.001	5.7 [2.1 - 15.8]	0.001
AED use[b]	1.1 [0.5 - 2.4]	0.873	0.3 [0.1 - 1.0]	0.049	1.1 [0.5 - 2.4]	0.798	0.2 [0.1 - 0.9]	0.035
Bystander BLS[c]	4.3 [2.4 - 7.8]	<0.001	1.9 [0.8 - 4.3]	0.137	3.6 [2.1 - 6.2]	<0.001	1.3 [0.6 - 3.0]	0.492
Year of arrest[d]	1.1 [1.1 - 1.2]	<0.001	1.2 [1.1 - 1.2]	<0.001	1.1 [1.0 - 1.1]	<0.001	1.2 [1.1 - 1.2]	<0.001
Post AED guideline change[e]	2.5 [1.6 - 4.1]	<0.001	2.6 [1.3 - 5.1]	0.007	2.3 [1.5 - 3.7]	<0.001	2.1 [1.1 - 4.1]	0.028

Table 3. Univariable and multivariable logistic regression analyses of all children with survival with favorable neurologic outcome as dependent variable.

AED = Automatic external defibrillator, BLS = Basic life support, CPR = Cardiopulmonary resuscitation, PCPC = Pediatric Cerebral Performance Category ROSC = Return of spontaneous circulation.

[a] Adjusted for witnessed arrest, bystander CPR, age at arrest, year of event, first lactate, pre-existing conditions related to event and CPR duration.

[b] Adjusted for initial rhythm (shockable/non-shockable/unknown), bystander CPR, age at arrest, year of event, first lactate, socio-economic status and CPR duration.

[c] Adjusted for initial rhythm (shockable/non-shockable/unknown), year of event, first lactate, socio-economic status and CPR duration.

[d] Adjusted for initial rhythm (shockable/non-shockable/unknown).

[e] Adjusted for initial rhythm (shockable/non-shockable/unknown), bystander CPR, age at arrest, socio-economic status and CPR duration.

[f] Favorable neurologic survival defined as a post-arrest PCPC of 1-2 or a ΔPCPC of 0.

[g] Favorable neurologic survival defined as a post-arrest PCPC of 1-3 or a ΔPCPC of 0.

Supplementary material

Stratified analysis for age are presented in the supplementary material. It proved unfeasible to create a nearest-neighbor propensity matching model (for 1:1 as well as 1 to many matching) because of the age distribution of shockable compared to non-shockable rhythm. The results are therefore not presented. The child and CA characteristics sorted by age group are presented in supplementary table 1. In adolescents (aged 12-18 years) the incidence of shockable rhythm was 39%. In the analysis stratified by age group an unknown rhythm was associated with favorable outcome in children < 8 years (OR 5.6 [95% CI 3.6-8.8]) and children 8 years and above (OR 25.1 [95% CI 7.5-84.1) (supplementary table 2). Shockable rhythm was statistically significantly associated with favorable outcome in children 8 years and above (OR 22.7 [11.6-44.8). Primary and secondary outcome measures were similarly associated with overall survival (supplementary table 3).

Discussion

Over an 18-year period and after a median follow-up of 25 months, this retrospective single-center study of pOHCA showed a nine times higher odds of shockable rhythms surviving with long-term favorable neurologic outcome compared to non-shockable rhythm, even after adjustment for confounders. First documented rhythms were 14% shockable (in adolescents aged 12-18 years 39%), 66% non-shockable and 20% unknown. SHD after pOHCA was 39%. 81% of hospital survivors achieved long-term favorable neurologic outcome and of all included children 32% survived with favorable neurologic outcome (17, 22, 24).

Only few studies have true long-term follow-up and are thus comparable with the present study. We will summarize these, beyond case reports or series (17, 22-24, 27).

The study of Meert et al., a secondary analysis of The Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital (THAPCA-OH) trial, has comparable methodology

as the present study as children were included after OHCA upon admission to hospital (17). They also found that shockable rhythm was associated with greater 12-month survival and greater 12-month survival with favorable neurobehavioral functioning, assessed using the Vineland Adaptive Behavior Scales.

However, there are important differences: 1. Inclusion criteria; in THAPCA children were included when unresponsive and mechanically ventilated after ROSC, creating a specific pOHCA population. 2. Furthermore; only a fraction of eligible children presenting to the hospital were included (295/1355, 22%). 3. THAPCA was a randomized trial comparing the efficacy of therapeutic hypothermia with therapeutic normothermia on survival with good neurobehavioral outcome in children 1 year after event. 4. Inclusion period; 2009-2012 in THAPCA versus 2002-2019 in present study. 5. Follow-up interval; 1 year in THAPCA versus cross-sectional with a median of 25 months in present study.

Additional cognitive evaluations of the THAPCA cohort were performed by Slomine et al. (25, 26). They found significant neuropsychological and neurobehavioral deficits in initially comatose pOHCA survivors although they were classified one year post-arrest as having favorable neurologic outcome. In addition they observed 3-month outcomes to be predictive of outcomes after 1 year (33). Van Zellem studying in- and out-of-hospital arrests et al. used different IQ tests, neuropsychological tests and questionnaires, incomparable with the PCPC scoring system (23). Lopez-Herce et al. found in 95 children (multicenter, 1998-1999), 17% favorable neurologic outcome after one year (24). Michiels et al. found in a 36-year inclusion period (1976-2007) and a median of 4 years of follow-up, 2% favorable neurologic outcome (22). Both described favorable neurologic outcome as PCPC scores of 1-2. Finally, Suominen et al. studied only arrests caused by drowning between 1985 and 2007 (27). Only 4 of 21 children had no neurologic or cognitive deficit after a median of 8 years of follow-up.

What are the implications of the present study?

First, shockable rhythm was shown to significantly and relevantly improve odds of true long-term favorable outcome. With favorable outcome defined as PCPC 1-3 the relationship was even stronger. And most notably in children eight years and above, shockable rhythm was statistically significantly associated with favorable outcome with OR 22.7 [11.6-44.8). This can be explained by the relatively high incidence of shockable rhythm in adolescents (aged 12-18 years) (39%). Also young children are less likely to have an AED used during CPR than older children, possibly because arrests are more often occurring at home rather than in public locations where AEDs are available. In a cohort study from an OHCA registry in Japan, the proportion of adults with a favorable neurological outcome 30 days after event was significantly higher in those who received public-access defibrillation than those who did not (845 [37.7%] *vs* 5676 [22.6%] (34).

Our results might implicate that the efforts for improving outcome of pOHCA should focus on early recognition and treatment of shockable OHCA at scene and the importance of improvements in the chain of survival (e.g. bystander BLS, public access to and use of AED and adequate EMS response) (35, 36).

Second, a remarkable finding was that 81% of survivors to hospital discharge achieved long-term favorable neurologic outcome beyond 1 year. This could be due to the setting in the Netherlands (e.g. high incidence in AED use and bystander CPR, the availability of HEMS 24/7, short transfer time from the scene to the hospital). Another possible explanation could be that in our study cohort the main cause of in-hospital mortality after ROSC was WLST (21%), probably due to poor neurologic prognosis. Less WLST could lead to higher survival to discharge numbers, but with more severe neurologically damaged children surviving long-term. Accurate neurological prognostication in a comatose child after OHCA remains challenging and no international pediatric guidelines exist (21, 37, 38). Potentially inaccurate prognostication and WLST may bias outcome (37, 39-40).

Third, the median age at time of follow-up was 6.6 years (IQR 3.4-13.4), which is relatively young in childhood and thus growing into deficits might not yet be present. Moreover, neurologic outcome was measured by PCPC, which is a crude outcome scale ranging from 1 to 6 (from no disabilities to brain death). It is unknown whether PCPC reflected how these children function in daily life and if it was associated with detailed neuropsychological functioning. In our opinion, it is crucial to identify how these pOHCA survivors will function on different physical and neuropsychological domains when reaching adolescence or young adulthood. Will they be able to live independently and happy, have a job and start a family? The importance to understand the influence of an arrest on long-term education and development as children grow into adulthood seems clear (21). True long-term follow-up is time and resource consuming, with the potential of losing children to follow-up (21). Long-term follow-up outpatient clinics have to be set up also beyond the 18 year boundary to support this group in maximizing outcome.

Our study has several limitations. First, it was an observational, retrospective single center study. Secondly, there were missing data due to the incomplete documentation of the CPR-event (e.g. CPR duration), which required imputation in up to 10% of the data. We minimized this potential bias by doing supplemental analyses with and without imputation. Additionally, we were not able to report and correct for some important CPR characteristics (e.g. quality of CPR, post-ROSC care). Finally, our study is not a complete regional or national pOHCA study since only children admitted to our hospital (with or without CPR in progress) were included. This could have led to selection bias by not including those children who died at scene or transferred to another hospital.

Conclusion

Shockable pOHCA had an almost nine times higher odds of long-term favorable neurologic survival compared to non-shockable rhythm, adjusted for confounding. The overall SHD after pOHCA was 39% over the 18-year study period, of which 81% of survivors achieved long-term (median 25 months, IQR 5.1-49.6) favorable neurologic outcome. This indicates the efforts for improving outcome of pOHCA should focus on early recognition and treatment of shockable pOHCA at scene.

Acknowledgements

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Supplementary Table 1. Patient and cardiac arrest characteristics by age group.

	Infants (n = 95)			Children (n = 187)			Adolescents (n = 78)			p-Value[d]
	n[a]			n[a]			n[a]			
Patient characteristics										
Male gender[c]	95	58	61%	187	119	64%	78	48	62%	0.887
Pre-existings conditions[c]	95	38	40%	186	69	37%	77	48	62%	0.001
- Respiratory		5	13%		20	29%		15	31%	0.015
- Cardiac		11	29%		13	19%		7	15%	0.405
- Neurologic		5	13%		16	23%		16	33%	0.004
- Metabolic		0	0%		1	1%		2	4%	0.182
- Congential malformation (non-cardiac)		14	37%		15	22%		3	6%	0.044
- Renal		2	5%		1	1%		1	2%	0.110
- Genetic/Chromosomal		11	29%		9	13%		5	10%	0.080
- Other		18	47%		30	43%		22	46%	0.165
SES parents[c]	93			182			77			0.254
- 1		38	41%		68	37%		22	29%	0.237
- 2		33	35%		80	44%		40	52%	0.099
- 3		22	24%		34	19%		15	19%	0.616
Cardiac arrest characteristics										
Event location – public (versus private)[c]	95	15	16%	187	78	42%	78	34	44%	<0.001
Witnessed arrest[c]	95	46	48%	185	63	34%	78	43	55%	0.003
Bystander BLS[c]	95	63	66%	185	123	66%	76	55	72%	0.617
Bystander AED use[c]	95	5	5%	187	11	6%	78	14	18%	0.005
EMS defibrillation[c]	95	4	4%	187	22	12%	78	33	42%	<0.001
CPR duration (minutes)[b]	71	38.0	10.0 - 75.0	160	35.0	8.0 - 75.0	60	15.0	6.0 - 60.0	0.141
Initial rhythm[c]	93			181			77			<0.001
- Shockable (VF)		4	4%		14	8%		30	39%	<0.001
- Unknown/ROSC before EMS arrival		23	25%		41	23%		6	8%	0.006
- Non-shockable		66	71%		126	70%		41	53%	0.025
Asystole		48	73%		91	72%		32	78%	0.356
PEA		6	9%		13	10%		4	10%	0.958
Bradycardia		12	18%		22	17%		4	10%	0.186
Other		2	17%		1	5%		1	25%	0.219
Cause of arrest[c]	95			187			78			<0.001
- Unknown/Not documented		7	7%		15	8%		5	6%	0.932
- ALTE/SIDS		49	52%		5	3%		0	0%	<0.001
- Airway obstruction		10	11%		20	11%		11	14%	0.687
- Arrythmia		3	3%		15	8%		29	37%	<0.001
- Drowning		1	1%		91	49%		8	10%	<0.001
- Electrolyte abnormality		0	0%		1	1%		2	3%	0.183
- Elevated ICP		0	0%		3	2%		7	9%	0.002
- Hypotension/Shock		12	13%		14	7%		4	5%	0.225
- Ingestion/Toxin		0	0%		2	1%		0	0%	0.725
- Other repiratory failure		10	11%		15	8%		8	10%	0.716
- Seizures		3	3%		6	3%		4	5%	0.701

	n			n			n			p
ECPR[c]	95	2	2%	187	9	5%	78	2	3%	0.568
First pH after ROSC or after hospital arrival[b]	87	6.87	6.61 - 7.14	175	6.94	6.72 - 7.19	76	7.11	6.86 - 7.28	0.001
First lactate (mmol/L) after ROSC or after hospital arrival[b]	85	15.0	9.1 - 19.0	173	13.1	5.4 - 16.0	72	6.4	4.0 - 15.0	0.001
Post cardiac arrest characteristics										
Post-ROSC ECMO[c]	95	12	13%	187	9	5%	78	3	4%	0.072
Temperature management[c]	92	33	36%	185	77	42%	77	39	51%	0.156
Re-arrest[c]	95	3	3%	187	6	3%	78	4	5%	0.701
Outcome										
Sustained ROSC[c]	95	63	66%	187	133	71%	78	62	79%	0.155
- *Before arrival to hospital*		51	54%		98	52%		55	71%	0.106
- *After arrival to hospital*		12	13%		35	19%		7	9%	0.109
Withdrawal of life sustaining therapies[c]	95	22	23%	187	32	17%	78	22	28%	0.312
Survival to hospital discharge[c]	95	29	31%	187	75	40%	78	31	40%	0.159
Deceased after discharge[c]	95	1	1%	187	6	3%	78	0	0%	0.238
Surival with favorable neurologic outcome at the longest follow-up[c]	95	26	27%	187	60	32%	77	29	38%	0.405
Follow-up										
Follow-up (months)[b]	30	28.3	5.7 - 57.3	81	23.1	3.6 - 49.5	31	25.7	8.1 - 32.0	0.647
Age at follow up (years)[b]	30	2.4	0.9 - 5.1	81	5.5	3.6 - 10.3	31	17.2	15.9- 18.8	<0.001

Abbreviations: VF = Ventricular fibrillation, PEA = Pulseless electric activity, AED = Automatic external defibrillator, EMS = Emergency medical support, CPR = Cardiopulmonary resuscitation, ICP = Intracranial pressure, ECMO = Extracorporeal cardiopulmonary support, ECPR = Extracorporeal cardiopulmonary resuscitation, ROSC = Return of spontaneous circulation.

a Number of subjects in whom the variable was obtained.

b Median (interquartile range).

c Number of subjects (%).

d p-Value: independent sample t-test for continuous data or Mann–Whitney U test dependent on normality; Fisher's exact test for dichotomous data.

Supplementary Table 2. Univariable and multivariable logistic regression analyses of all children with survival with favorable neurologic outcome as dependent variable by age.

	Survival with post-arrest PCPC 1-2 or ΔPCPC 0 at the longest follow-up interval[f]							
	Crude		Adjusted[a,b,c,d,e]		Crude		Adjusted[a,b,c,d,e]	
Variable	OR [95%CI]	p-Value	OR [95%CI]	p-Value	OR [95%CI]	p-Value	OR [95%CI]	p-Value
	Below 8 years (n = 256)				**8 years and above (n = 104)**			
Initial non-shockable rhythm[a]	referent		referent		referent		referent	
Initial shockable rhythm[a]	1.0 [0.4 - 2.4]	0.974	0.6 [0.2 - 1.7]	0.327	14.2 [9.2 - 21.8]	<0.001	22.7 [11.6 - 44.8]	<0.001
Initial unknown rhythm[a]	27.2 [20.0 - 37.1]	<0.001	5.6 [3.6 - 8.8]	<0.001	49.0 [19.3 - 124.3]	<0.001	25.1 [7.5 - 84.1]	<0.001
AED use[b]	0.2 [0.1 - 0.4]	<0.001	0.1 [0.0 - 0.2]	<0.001	2.6 [1.7 - 4.0]	<0.001	1.3 [0.5 - 2.9]	0.592
Bystander BLS[c]	4.7 [3.5 - 6.4]	<0.001	2.0 [1.3 - 3.1]	0.001	3.7 [2.5 - 5.6]	<0.001	2.1 [1.1 - 4.2]	0.022
Year of event[d]	1.1 [1.1 - 1.1]	<0.001	1.2 [1.1 - 1.2]	<0.001	1.1 [1.1 - 1.2]	<0.001	1.2 [1.1 - 1.2]	<0.001
Post AED guideline change[e]	2.6 [2.1 - 3.3]	<0.001	2.8 [2.0 - 3.9]	<0.001	2.1 [1.5 - 3.1]	<0.001	2.4 [1.4 - 4.3]	0.002

Abbreviations: AED = Automatic external defibrillator, BLS = Basic life support, CPR = Cardiopulmonary resuscitation, PCPC = Pediatric Cerebral Performance Category, ROSC = Return of spontaneous circulation.

[a] Adjusted for witnessed arrest, bystander CPR, age at arrest, year of event, first lactate, pre-existing conditions related to event and CPR duration.

[b] Adjusted for initial rhythm (shockable/non-shockable/unknown), bystander CPR, age at arrest, year of event, first lactate, socio-economic status and CPR duration.

[c] Adjusted for initial rhythm (shockable/non-shockable/unknown), year of event, first lactate, socio-economic status and CPR duration.

[d] Adjusted for initial rhythm (shockable/non-shockable/unknown).

[e] Adjusted for initial rhythm (shockable/non-shockable/unknown), bystander CPR, age at arrest, socio-economic status and CPR duration.

Supplementary Table 3. Univariable and multivariable logistic regression analyses of favorable neurologic outcome among hospital-survivors and total survival.

| Variable | Favorable neurologic outcome (PCPC 1-2 or ΔPCPC 0) among discharged patients at the longest follow-up interval[f] (n = 142) | | | | Total survival[g] (n = 360) | | | |
| | Crude | | Adjusted[a1.b.c.d] | | Crude | | Adjusted[a2,b,c,d] | |
	OR [95%CI]	p-Value	OR [95%CI]	p-Value	OR [95%CI]	p-Value	OR [95%CI]	p-Value
Primary outcome measure								
Initial non-shockable rhythm[aa,a2]	referent		referent		referent		referent	
Initial shockable rhythm[a1,a2]	5.5 [1.5 - 20.1]	0.011	1.8 [0.2 - 15.2]	0.589	7.4 [3.8 - 14.5]	<0.001	9.6 [3.5 - 26.2]	<0.001
Initial unkown rhythm[a1,a2]	8.7 [2.7 - 14.0]	<0.001	8.8 [1.6 - 48.3]	0.011	25.6 [12.1 - 54.1]	<0.001	5.1 [1.9 - 13.6]	0.001
Secondary outcome measure								
AED use[b]	0.7 [0.2 - 2.9]	0.652	0.1 [0.0 - 1.3]	0.087	1.2 [0.5 - 2.5]	0.672	0.3 [0.1 - 1.0]	0.051
Bystander BLS[c]	2.4 [0.9 - 6.7]	0.092	1.6 [0.4 - 6.7]	0.521	3.9 [2.3 - 6.7]	<0.001	1.6 [0.7 - 3.5]	0.221
Year of event[d]	1.1 [1.0 - 1.2]	0.018	1.2 [1.1 - 1.3]	0.003	1.1 [1.0 - 1.1]	<0.001	1.1 [1.1 - 1.2]	<0.001
Post AED guideline change[e]	3.5 [1.5 - 8.5]	0.005	4.5 [1.5 - 13.5]	0.007	2.3 [1.5 - 3.7]	<0.001	1.8 [0.9 - 3.4]	0.068

Abbreviations: AED = Automatic external defibrillator, BLS = Basic life support, CPR = Cardiopulmonary resuscitation, PCPC = Pediatric Cerebral Performance Category, ROSC = Return of spontaneous circulation.

[a1] Adjusted for follow-up duration, witnessed arrest, bystander CPR, age at arrest, year of event, first lactate, pre-existing conditions related to event and CPR duration.

[a2] Adjusted for witnessed arrest, bystander CPR, age at arrest, year of event, first lactate, pre-existing conditions related to event and CPR duration.

[b] Adjusted for initial rhythm (shockable/non-shockable/unknown), bystander CPR, age at arrest, year of event, first lactate, socio-economic status and CPR duration.

[c] Adjusted for initial rhythm (shockable/non-shockable/unknown), year of event, first lactate, socio-economic status and CPR duration.

[d] Adjusted for initial rhythm (shockable/non-shockable/unknown).

[e] Adjusted for initial rhythm (shockable/non-shockable/unknown), bystander CPR, age at arrest, socio-economic status and CPR duration.

[f] Favorable neurologic survival defined as a post-arrest PCPC of 1-2 or a ΔPCPC of 0.

[g] Total survival amongst the included study population.

Chapter 7.

Longitudinal two years evaluation of neuropsychological outcome in children after out of hospital cardiac arrest.

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Abstract

Aim To investigate longitudinal functional and neuropsychological outcomes 3-6 and 24 months after paediatric out-of-hospital cardiac arrest (OHCA). Further, to explore the association between pediatric cerebral performance category (PCPC) and intelligence.

Methods Prospective longitudinal single center study including children (0-17 years) with OHCA, admitted to the PICU of a tertiary care hospital between 2012 and 2017. Survivors were assessed during an outpatient multidisciplinary follow-up program 3-6 and 24 months post-OHCA. Functional and neuropsychological outcomes were assessed through interviews, neurological exam, and validated neuropsychological testing.

Results The total eligible cohort consisted of 49 paediatric OHCA survivors. The most common cause of OHCA was arrhythmia (33%). Median age at time of OHCA was 48 months, 67% were males. At 3-6 and 24 months post-OHCA, respectively 74 and 73% had a good PCPC score, defined as 1-2. Compared with normative data, OHCA children obtained worse sustained attention and processing speed scores 3-6 (n=26) and 24 (n=27) months post-OHCA. At 24 months, they also obtained worse intelligence, selective attention and cognitive flexibility scores. In children tested at both time-points (n=19), no significant changes in neuropsychological outcomes were found over time. Intelligence scores did not correlate with PCPC.

Conclusion Although paediatric OHCA survivors had a good PCPC score 3-6 and 24 months post-OHCA, they obtained worse scores on important neuropsychological domains such as intelligence and executive functioning (attention and cognitive flexibility). Follow-up should continue over a longer life span in order to fully understand the long-term impact of OHCA in childhood.

Introduction

Yearly, 9 out of 100.000 children in the Netherlands experience an Out-of-Hospital Cardiac Arrest (OHCA) [1]. In contrast to adults, non-cardiac causes are the most prevalent causes of OHCA [2-4]. The overall survival rate of OHCA children is low; approximately 90-92% die pre-hospital or during hospital admission [5, 6]. In our previous observational cohort study, 56% of the children who achieved return of circulation (ROC) died after PICU admission. Death was mainly due to withdrawal of life sustaining therapies based on poor neurological prognosis (67%) or brain death (29%)[7.]

In a recent study including 1980 children with OHCA, 125 of 162 survivors (77%) had a favorable outcome at discharge expressed in a good pediatric cerebral performance category (PCPC) [6].

PCPC is often used as an outcome measure in studies describing neurological outcome after paediatric OHCA [8, 9]. However, PCPC is a crude outcome on a scale ranging from 1 to 6 (normal; mild, moderate or severe disability; comatose; dead) (supplementary file 1). It is unknown whether PCPC at discharge reflects daily function at longer term and if it appropriately reflects the level of neuropsychological functioning. Neuropsychological deficits are expected as sequelae in children after cardiac arrest (CA), due to ischaemic changes in the brain during and around CA. Identification of cognitive deficits is of paramount importance as these deficits may delay or even prevent the development of academic and social skills, causing long-term restrictions in activities and participation in daily life. This phenomenon is known as growing into deficit [10].

Little is known about long-term neuropsychological functioning in OHCA survivors [11, 12].

In a cross-sectional cohort of in-and-out of hospital CA survivors (median follow-up interval 5.6 years), lower scores were found for intelligence and visual memory, compared with the general population [11].

In the THAPCA trial, 85 parents of OHCA children reported, during a single interview by phone at 1-year follow-up, neurocognitive problems in their children such as problems in adaptive behaviour, communication, daily living and motor skills [12]. In this same study, most children displayed significant deficits in intelligence domains of neuropsychological tests.

Since 2012, our hospital provides a standardised multidisciplinary follow-up program for paediatric OHCA survivors with structured and repeated outpatient clinic visits including functional and neuropsychological assessments. Within this context 1) we investigated functional and neuropsychological outcomes 3-6 and 24 months after paediatric OHCA and, 2). explored whether PCPC scores were associated with intellectual functioning in paediatric OHCA survivors.

Methods

Study design and participants

This prospective study was performed in children admitted to the paediatric intensive care unit (PICU) of Erasmus MC-Sophia Children's Hospital, the single tertiary-care University children's hospital providing health care to children in the southwest of The Netherlands (referral area 4 million inhabitants, 25% of the Dutch population). The Erasmus MC Ethical Review Board approved the study protocol (MEC-2019-0259). In accordance with the Dutch law, signed informed consent was not required at moment of inclusion

We included children (0-17 years) who experienced OHCA between 2012 and 2017 and survived to hospital discharge. OHCA was defined as unresponsiveness with absent palpable

pulse, no signs of life, or healthcare provider perceived need for chest compressions for at least one minute [7].

Exclusion criteria were a pre-arrest PCPC score > 3 and children diagnosed with a neurodegenerative disease.

Data collection

As part of standard care children were invited to our multidisciplinary follow-up program at the outpatient clinic 3-6 and 24 months post-OHCA. Functional outcomes were assessed by an experienced paediatric neurologist (MH) and paediatric intensivist (CB) through a semi-structured interview with children and their parents/caregivers and through physical and neurological exams. When no follow-up visit took place, these outcomes, if available, were collected from notes in the patient records (records of hospital visits with other physicians). Neuropsychological outcomes were assessed by an experienced psychologist. If neuropsychological testing was performed elsewhere, results were retrieved after parental consent.

Demographical and OHCA variables

The following variables were retrospectively collected from ambulance registration forms and in hospital electronic health records: 1. Baseline patient characteristics (e.g. gender, age, socioeconomic status (SES) parents, pre-arrest PCPC), 2. OHCA and post-OHCA characteristics (aetiology, first monitored rhythm, bystander cardiopulmonary resuscitation (CPR), duration CPR, first pH and lactate), and 3. Medical outcome (survival and PCPC at hospital discharge). The SES was calculated using a 'Status Score' divided into tertiles to interpret a 'low status', middle status' and 'high status' [13]. The 'Status Score' is based on income, education level and unemployment rate by postal code.

Outcomes measures

Functional outcomes

The following functional outcomes were assessed: PCPC score, school attendance, motor deficits and epilepsy. PCPC scores were dichotomised into 'good' outcome (score 1 and 2) or 'poor' outcome (scores 3 to 6) [6]. All PCPC scores were determined by a paediatric neurologist (MH).

Neuropsychological outcomes

Validated, age-appropriate neuropsychological tests and questionnaires with Dutch normative testdata were used to assess a broad range of neuropsychological domains, see supplementary file 2 for detailed description.

1. Development and intelligence in children (all ages): age-appropriate versions of the Bayley Scales of Infant Development or the Wechsler Scales (BSID-II, Bayley-III, WPPSI-III, WISC-III or WAIS-IV) [14-17].

2. Selective attention: Stroop Color Word Test ($\geq$8 years)[18].

3. Sustained attention: Bourdon-Vos cancellation test ($\geq$6 years)[19].

4. Processing speed: from the Wechsler Scales (WPPSI-III, WISC-III or WAIS-IV) ($\geq$4 years) [14-16].

5. Visual motor integration: Beery Developmental Test of Visual Motor Integration (Beery-VMI) ($\geq$2 years)[20].

6. Verbal memory: Rey auditory verbal learning test (Rey-AVLT), delayed recall ($\geq$6 years) [21, 22].

7. Visual memory: Rey-Osterrieth complex figure test (Rey-CFT) recognition (≥6 years)[23].

8. Executive functions (cognitive flexibility): Trail-Making Test part B (TMTB) (≥8 years)[24].

9. Parent-reported executive function: Behaviour Rating Inventory of Executive Function questionnaires (BRIEF-P or BRIEF) (≥2 years) [25].

Statistical analyses

Outcomes of participants and non-participants were compared with independent sample t-tests for normally distributed continuous data, Mann–Whitney U tests for non-normally continuous data and Fisher's exact test for dichotomous data. Normality of all data was examined with the Shapiro-Wilk test.

Neuropsychological outcome standard scores were converted into Z-scores by calculating the difference with the test-mean, divided by the test-SD. A negative Z-score reflects a worse score compared with the norm (for comparable interpretation, BRIEF z-scores were multiplied by -1). One-sample t-tests were performed to compare neuropsychological outcomes of OHCA survivors with the normative Z-score = 0.

Repeated measures of participants at 3-6 and 24 months were compared with non-parametric paired tests (Wilcoxon signed rank tests) for continuous Z-scores. Due to the explorative design of this study, no correcting for multiple testing was performed. Correlations between PCPC and intellectual functioning were analyzed using Kendall's tau-b.

All analyses were performed with SPSS 25.0 for Windows. Results were considered statistically significant at p values < 0.05.

Results

Between January 2012 and December 2017, 113 children were admitted to the PICU

following ROC post-OHCA (Fig. 1). Of these 113 children, 51 (45%) survived to hospital

discharge. Two were excluded due to pre-arrest PCPC > 3.

In the eligible sample of 49 children, the most common causes of OHCA were (33%)

arrhythmia and near-drowning (31%) (supplementary file 3). At time of OHCA, median age

was 48 months (IQR 17-166) and 67% were males. SES was low in 20%, middle in 61% and

high in 16%, which was significantly lower than the SES distribution in the Netherlands [26].

Median PCPC score at hospital discharge was 2 [IQR 1-3], with good outcome in 73%.

Demographical and OHCA variables between neuropsychological tested and non-tested

children were overall comparable (supplementary file 4). Except that tested OHCA children

were significantly older than non-tested children at 3-6 months (p=0.03).

Children with ROC after OHCA 2012-2017

Admission PICU Sophia Children's Hospital

<18 years old (including neonates)

BLS ≥ 1 minute

n=113

Died prior to hospital discharge ('Non-survivors') n=62

Hospital discharge ('Survivors') n=51

Exclusion:

Pre-arrest PCPC >3 n=2

Total eligible cohort n=49

No follow-up visit 3 months after OHCA n=13:

Living abroad/distance too far n=4

Still admitted in hospital or rehabilitation center n=2

Not invited for unknown reasons/lost to follow up n=4

Refused to visit outpatient clinic n=1

Died n=1[a]

Severe pre-arrest comorbidity n=1[b]

No follow-up visit 24 months after OHCA n=22:

Living abroad/distance too far n=5

≥ 18 years n=3

Not invited for unknown reasons/lost to follow up n=9

Refused to visit outpatient clinic n=2

Died n=1[a]

Severe pre-arrest comorbidity n=2[c]

Visit outpatient clinic 3-6 months after OHCA n=36:

Visit outpatient clinic 24 months after OHCA n=27:

No neuropsychological assessment 3-6 months after OHCA n=11:

Reasons unknown n=4

Follow-up neurology outpatient clinic n=3[c]

Not testable n=1

Refusal parents n=1

Delayed assessment n=2

Neuropsychological assessment 3-6 months after OHCA n=26[d:]

Erasmus medical center n=21

Rehabilitation center n=5

No neuropsychological assessment 24 months after OHCA n=3:

Reasons unknown n=2

Not testable n=1

Neuropsychological assessment 24 months after OHCA n=27[f:]

Erasmus medical center n=23

Rehabilitation center n=2

Youth psychiatry n=1

Other university hospital n=1

165

Both neuropsychological test 3 and 24 months after OHCA n=19

Figure 1. Flowchart of included patients

[a] Severe neurological sequelae, PCPC at hospital discharge 5, died 6 months post-OHCA due to a pneumonia in a pediatric nursing home
[b] Hematological malignancy
[c] At neurology outpatient clinic neuropsychological assessment is not standard care
[d] 1 patient didn't visit the follow-up outpatient clinic, but neuropsychological assessment was performed in rehabilitation center.
[e] One patient hematological malignancy and one patient genetic disorder (at 3-6 months nog diagnosed yet)
[f] 3 patients didn't visit the follow-up outpatient clinic, but neuropsychological assessment was performed in another university hospital or by a different department in Erasmus Medical Center
BLS= basic life support; ROC= return of circulation; OHCA= out of hospital cardiac arrest; PCPC= pediatric cerebral performance category; PICU= pediatric intensive care unit

Outcome 3-6 months after OHCA

Of the eligible 49 children, 36 (73%) visited the outpatient clinic. Twenty-six (53%) children underwent neuropsychological assessment. Reasons for no follow-up visits and testing are described in fig. 1. One child with severe neurological sequelae died 6 months post-OHCA due to pneumonia. One child could not be tested neuropsychologically due to severe neurological deficits post-OHCA.

Functional outcomes

Of the 49 children, 20/24 school-aged children (83%) returned to school. One patient attending secondary education changed to a lower education level due to cognitive problems related to OHCA. One child was diagnosed with epilepsy. Neurological exam revealed hemiparesis in 5 and tetraparesis in 2 children (14%) (Gross Motor Function Classification System (GMFCS) varying from I-V (27)). Median PCPC score was 2 [IQR 1-3]; 36 children (74%) had a good outcome (Table 1).

Neuropsychological outcomes

In the 26 children who underwent neuropsychological assessment, verbal, performance, and total IQ scores did not differ significantly from norm data (Table 2). Significantly lower

scores, compared with norm data, were found for sustained attention and processing speed; respectively 88% and 47% of the children scored >1 SD below the norm (in the general population 16% is expected), see Table 2. Median Z-scores for most neuropsychological domains were lower than zero, fig. 2.

Outcome 24 months after OHCA

Of 48 eligible children (one patient died 6 months post-OHCA), 27 children (56%) visited the outpatient clinic and 27 (56%) underwent neuropsychological assessment. One child who visited the outpatient clinic could not be tested due to severe neurological deficits post-OHCA, fig.1.

Functional outcomes

Of these 48 children, 26/32 school-aged children (81%) went back to school. Due to cognitive problems related to OHCA, 2 children at regular primary school changed to a different school with smaller groups and 2 secondary school children changed to a lower education level. Neurological exam revealed hemiparesis in 4 children, tetraparesis in 1 child and 1 child had ataxia (15%) (GMFCS varying from I-V (27)) (Table 1). Median PCPC score was 2 [IQR 1-3.5]; 35 children (73%) had good outcome.

Neuropsychological outcomes

In the 27 children with neuropsychological assessment, total, verbal, and performance IQ scores were lower compared with normative data; respectively 46%, 46%, and 38% of the children scored >1 SD (15 IQ points) below the mean norm score (Table 2). They also obtained worse scores for selective attention, sustained attention, processing speed, and cognitive flexibility compared with norm data; respectively 70%, 83%, 58% and 60% scored >1 SD lower than the norm (Table 2). Median z-scores for most domains were lower than zero, fig. 2.

	All patients		Tested 3-6 months		Tested 24 months	
	n=49		**n=26**		**n=27**	
Characteristics						
Age at admission (months)	48	(17-166)	90	(31-177)	88	(32-164)
Gender male	33	(67)	19	(73)	18	(67)
Bystander CPR	39	(80)	22	(85)	22	(73)
Initial rythm shockable	17/34	(50)	12/19	(63)	12/21	(57)
Duration CPR (min)	10	(3-20)	10	(3.5-20)	8	(3-44)
Missing, n	10		5		6	
First lactate	6.3	(4.5-12.8)	6.0	(4.5-13.4)	5.6	(4.4-13.3)
Missing, n	3		1		3	
First pH	7.1	(7.0-7.3)	7.2	(7.0-7.3)	7.2	(7.1-7.3)
Missing, n	4		1		4	
Etiology arrest						
Cardiac	20	(41)	12	(46)	10	(37)
Respiratory	21	(43)	11	(42)	13	(48)
Other	8	(16)	3	(12)	4	(15)
PCPC discharge	2	(1-3)	2	(1-2)	2	(1-3)
SES						
Low	10	(20)	6	(23)	8	(30)
middle	30	(61)	16	(62)	17	(63)
high	8	(16)	4	(15)	2	(7)

Functional outcome	**All patients at 3-6 months n=49**		**Tested patients at 3-6 months n=26**		**All patients at 24 months n=48[a]**		**Tested patients at 24 months n=27**	
PCPC								
Poor	7	(14)	2	(8)	3	(6)	2	(8)
Good	36	(74)	24	(92)	35	(73)	24	(92)
Missing, n	6	(12)	0		10	(21)	0	
Return to school[b]	20	(83)	14	(88)	26	(81)	22	(96)
Missing, n	2	(10)	0		5	(16)	1	
Epilepsy	1	(2)	0	(4)	0		0	
Missing, n	8		0		16		2	
Neurological motor deficits[c]	7	(14)	5	(19)	6	(13)	4	(15)
Missing, n	9		0		11		1	

Table 1. Characteristics and functional outcome of OHCA survivors and participants neuropsychological assessment 3-6 and 24 months after OHCA

Data are presented as n (%) or median (IQR: 25th -75th percentile)

[a] N = 48, 1 patient died at 6 months

[b] Only applicable for children beyond the age of 4. At 3-6 months N $\geq$ 4 yrs = 24, at 24 months N $\geq$ 4 yrs= 32

[c] Motor symptoms: hemiparesis, tetraparesis or ataxia (Gross Motor Function Classification System (GMFCS) varying from I-V).

CPR=cardiopulmonary resuscitation, PCPC=pediatric cerebral performance category scale, SES= socioeconomic status

Neuropsychological outcome[a]	n[b]	3-6 months Z-score Median	p vs norm	n (%) z<=-1[c]	n[b]	24 months Z-score Median	p vs norm	n (%) z<=-1[c]
		3-6 months				**24 months**		
Total IQ (all)	21	-0.3 (-1.0 to 0.4)	.13	6 (29%)	**24**	**-0.4 (-1.5 to 0.2)**	**.008**	**11 (46%)**
Verbal IQ (all)	16	-0.1 (-1.1 to 0.3)	.28	4 (25%)	**13**	**-0.5 (-1.6 to 0.4)**	**.05**	**6 (46%)**
Performance IQ (all)	17	-0.5 (-1.3 to 0.3)	.07	6 (35%)	**13**	**-0.5 (-2.0 to 0.0)**	**.02**	**5 (38%)**
Selective attention (STROOP ≥11y)	8	0.1 (-0.1 to 0.4)	.59	2 (25%)	**10**	**-1.3 (-1.6 to -0.5)**	**.02**	**7 (70%)**
Sustained attention (Bourdon SD ≥6y)	**8**	**-2.9 (-4.8 to -1.4)**	**.01**	**7 (88%)**	**12**	**-4.7 (-7.4 to -2.2)**	**.002**	**10 (83%)**
Processing Speed (≥4y)	**15**	**-0.8 (-1.3 to 0.1)**	**.01**	**7 (47%)**	**19**	**-1.00 (-1.8 to 0.0)**	**.003**	**11 (58%)**
VMI (Beery ≥2y)	12	0.0 (-1.1 to 0.3)	.20	3 (25%)	17	-0.7 (-1.1 to 0.2)	.08	6 (35%)
Verbal Memory (Rey-AVLT, delayed recall ≥6y)	10	-0.6 (-2.3 to 0.8)	.33	5 (10%)	13	0.2 (-1.1 to 1.1)	.82	4 (31%)
Visual Memory (ReyRecog ≥5y)	9	-1.1 (-2.3 to 0.5)	.15	5 (56%)	12	-0.4 (-0.8 to 0.2)	.28	2 (17%)
Cognitive flexibility (TMTB≥8y)	9	-0.7 (-2.0 to 0.2)	.13	4 (44%)	**10**	**-1.2 (-2.0 to -0.1)**	**.04**	**6 (60%)**
BRIEF Total score (≥2y)	9	0.0 (-1.5 to 1.8)	.86	2 (22%)	19	0.0 (-1.0 to 0.4)	.41	5 (26%)

Table 2. Z-scores neuropsychological outcome 3 and 24 months after OHCA
[a] All neuropsychological tests were converted into Z-scores and compared with norm testdata. A higher Z-score means a better outcome
[b] Numbers of patients differ for neuropsychological tests due to different age ranges and diversity of tests when children were tested elsewhere.
[c] Expected % in general population with Z-score <=-1 = 16%
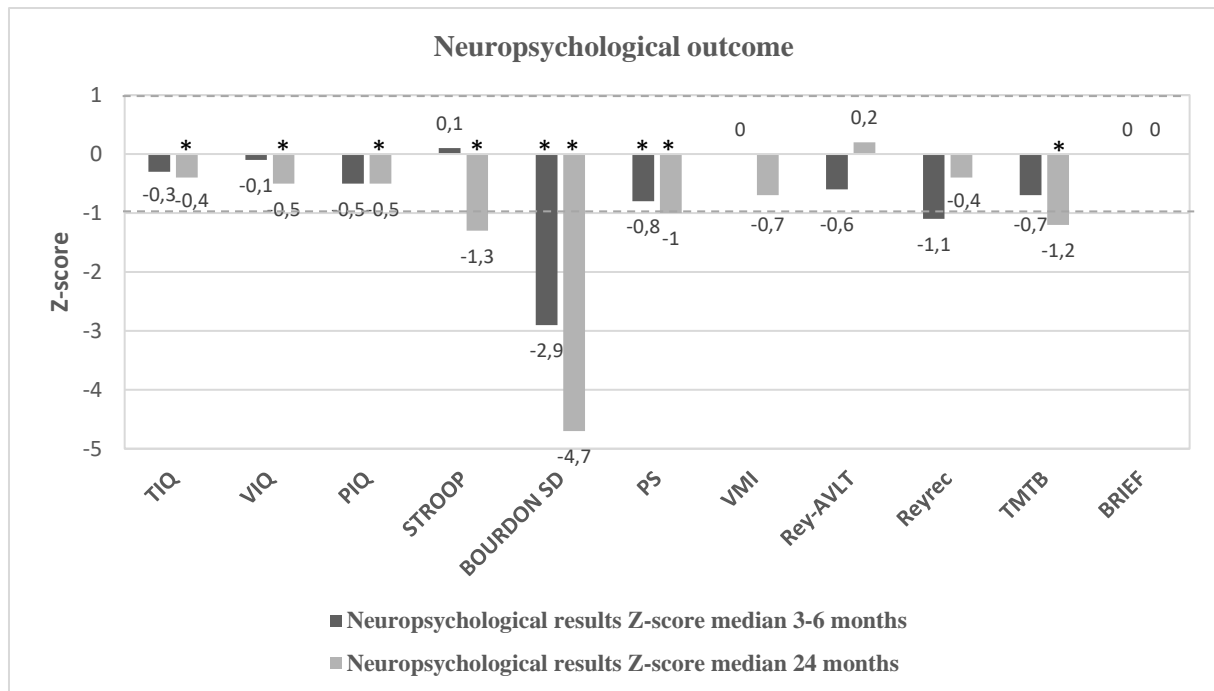
Figure 2. Neuropsychological outcome at 3-6 and 24 months, **median Z-score per domain**
*Median score significantly lower compared to norm testdata.
All neuropsychological tests were converted into Z-scores. A higher Z-score means a better outcome.

BRIEF= Behaviour Rating Inventory of Executive Function questionnaires; Bourdon=Bourdon Vos cancellation test; PIQ=performance intelligence quotient; PS=processing speed; Stroop=Stroop Color Word Test; Rey-AVLT= Rey auditory verbal learning test; Reyrec= Rey-Osterrieth complex figure test Color Word Test; TIQ=total intelligence quotient; TMTB= Trail-Making Test part B; VIQ=verbal intelligence quotient; VMI=Beery Developmental Test of Visual Motor Integration.

Repeated measures 3-6 and 24 months

In 38 of 49 patients, PCPC scores were assessed at both 3-6 and 24 months: in 32 (85%)

PCPC remained good (1-2), in 4 (10%) remained poor (PCPC >2), and in 2 children (5%)

PCPC improved from poor to good.

In 19 patients (39%) with repeated neuropsychological testing, total, verbal and performance

IQ scores and neuropsychological domain scores did not change significantly (supplementary

file 5 and 6, fig. 3).
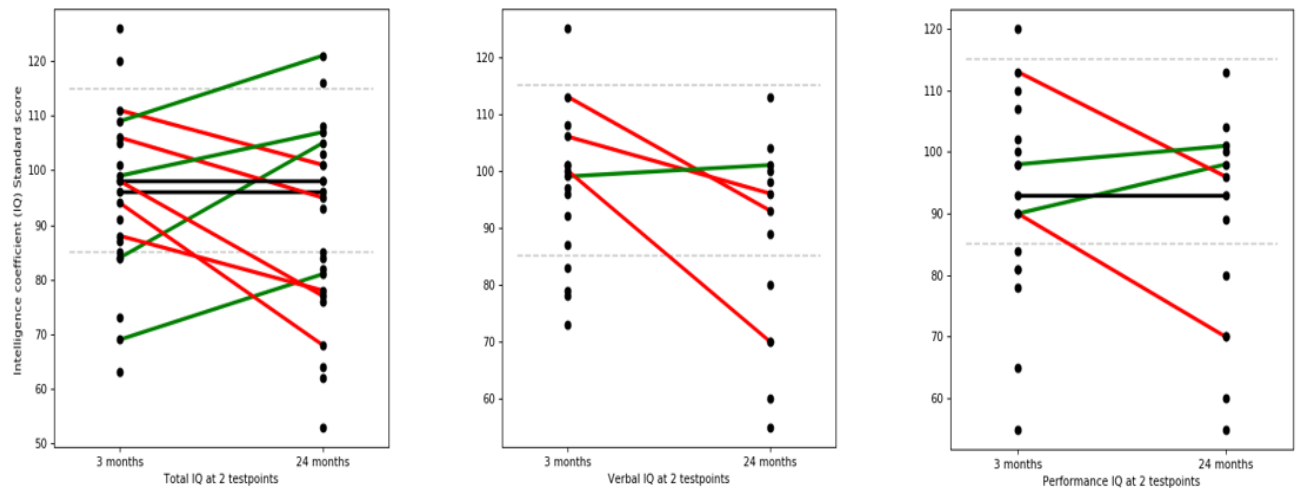
Figure 3. Intelligence tests and its individual course over time
Every dot represents an individual patient. Connected line means repeated measurements for an individual patient, green: improvement over time, red: decline over time, black: no difference over time. Area between the horizontal dotted lines represents the age-appropriate scores (-1SD to +SD).
Standard score: higher is better functioning (mean norm 100, SD15)

Correlation PCPC and intellectual functioning

No correlations were found between PCPC scores and total, verbal, or performance IQ scores on both moments: at 3-6 months, *r* ranged from -0.10 to 0.08; at 24 months, *r* ranged from -0.15 to -0.05, data not shown.

Discussion

To our knowledge, this is the first prospective, longitudinal study on neuropsychological outcomes in paediatric OHCA survivors over a 24 months period.

Among survivors, 3-6 and 24 months post-OHCA respectively 74% and 73% had good outcome expressed in PCPC, defined as score 1-2. Only a minority had motor deficits on neurological exam.

The majority of school-aged children (81%) went back to school without change in school level after 24 months.

Worse scores were found on sustained attention and processing speed compared with norm data at both time-points. Additionally, at 24 months, worse scores were also found on intellectual functioning, selective attention, and cognitive flexibility compared with norm data. In children who underwent neuropsychological testing at both time points no significant changes in neuropsychological outcomes were found over time. Intelligence scores of OHCA children did not correlate with their PCPC scores.

Functional outcomes

The finding that only a minority (around 15%) of our survivors showed motor deficits at neurological exam 3-6 and 24 months post-OHCA seems in contrast with the findings of the THAPCA trial that reported neurological impairments in 55% of children 1 year post-arrest (28). However, in the THAPCA trial these impairments were not only based on motor function but also on language production and comprehension, cognition and behaviour, making comparison with only motor deficits in our cohort difficult.

In our cohort, PCPC scores at hospital discharge (73% 1-2) were in line with those reported by previous research [1, 6, 12]. Silverstein et al. showed that PCPC scores of paediatric OHCA survivors at hospital discharge significantly correlated with PCPC at 3 and 12 months [29]. Our findings at 3-6 and 24 months suggest the same since the percentage of patients with good outcome at discharge remained unchanged over time.

Neuropsychological outcomes

At 3-6 months a selection bias may have occurred because of a trend (p=0.07) towards more favourable PCPC scores in the neuropsychologically tested group compared with the non-tested group. Therefore the finding that OHCA children only scored worse on sustained

attention and processing speed and not on other outcomes at this time-point should be interpreted with caution.

At 24 months follow-up, OHCA children obtained worse intelligence scores compared to norms, which is consistent with outcomes of other paediatric post-CA studies [11, 12, 30]. Additionally, worse scores for attention, cognitive flexibility, and processing speed were detected. This was also found in the THAPCA trial in which CA survivors were tested one year after CA [30]. This is remarkable, since there are differences between the present study and the THAPCA study. The THAPCA trial 1). Included IHCA and OHCA children when they were unresponsive and mechanically ventilated after ROC, creating a population with possibly more severely affected children, 2). Included a fraction of eligible children presenting to the hospital (295/1355, 22%), 3). Had a different study design comparing the efficacy of therapeutic hypothermia with therapeutic normothermia, 4). Had a smaller inclusion period; 2009-2012 in THAPCA versus 2012-2017 in present study, and 5). The follow-up included a cross-sectional assessment moment at 1 year follow-up versus longitudinal follow-up over 2 years in the present study.

Lower intelligence scores were also found at 2 years follow-up in a large heterogeneous cohort of critically ill PICU survivors (n=786), implicating that critical illness itself has negative impact on intelligence [31].

In those children who were assessed repeatedly, no significant changes were found in intelligence scores and neuropsychological outcomes over time. Unfortunately, the sample with repeated measures was small (median n=5 per domain) with a wide age range. This makes it difficult to draw definite conclusions.

Intelligence scores of OHCA children did not correlate with PCPC scores. Silverstein et al. found that PCPC scores were correlated with scores on the Vineland Adaptive Behavior Scales (VABS) (29). However, their inclusion criteria and assessment method (parent-

reported versus objectively tested intellectual functioning) differed from our study, and it is not possible to compare the score of the VABS with tested intellectual functioning.

In conclusion, although the gross outcome during follow-up was favourable in our OHCA children, they do have cognitive deficits, making them cognitively vulnerable during development. What does this mean for the future of these children? Due to several factors, this is difficult to predict from our study: the median age in our cohort was 48 months at arrest, with a wide age range of 3 months up to 18 years. Besides, the longer-term impact and development of these cognitive vulnerabilities throughout their academic career and participation in daily life are still unclear. From follow-up studies in other children with vulnerable brains (e.g. with acquired brain injury after trauma or brain tumor treatment) we know that these children may grow into deficit over time [32-35].

Strengths and limitations

Strength of our study is our representative study-population. Characteristics such as age, OHCA cause and distribution of sex are comparable with previous research [2, 6]. Furthermore, our cohort was homogeneous including solely OHCA survivors with a normal functioning pre-arrest with on-site visits at our outpatient clinic at standardised moments, including repeated neuropsychological testing up to 24 months after the OHCA event. Besides general intelligence scores, other more complex neuropsychological domains were assessed using validated, age-appropriate tests.

As to limitations, the relatively high percentage of good PCPC scores may reflect a selection bias due to the high amount of withdrawal of intensive care treatment of children with an expected poor neurological outcome [7].

Our cohort was small (n=49) with a wide age-range. Due to age limitations, most neuropsychological domains were only tested in older children. When children were tested repeatedly, test batteries were not always the same. In our patients SES was significantly

lower than the general Dutch population, which might have influenced the neurocognitive outcome.

When we started the follow-up program, initially the loss to follow-up was high. This improved over time due to a more structured program. Due to these limitations, we were not able to find predictors for neurocognitive outcomes. We also did not include brain imaging as part of our standardised follow-up. Finally, in general OHCA children are offered structured rehabilitation or paramedical programs after discharge. When we started our follow-up program we initially didn't inquire about this routinely. This resulted in many missing data, therefore we did not include this aspect in our description of the study population.

Future directions

Our findings underline the need for a standardised follow-up program (internationally) into adulthood as standard of care in OHCA survivors. In our opinion, this follow-up should include neurological and neuropsychological assessments; it should provide care by an educational psychologist to monitor these children during their development into adulthood and to provide parents a realistic view of the strengths and weakness in their child's intellectual functioning. Neuropsychological assessment should include intelligence scores, attention, processing speed, memory and executive functioning. Moreover, psychosocial functioning, quality of life and participation, may add useful information regarding functioning of OHCA children in daily life.

Furthermore, to improve outcome, it is important to provide OHCA children and their families with resources and education after critical illness and PICU admission [36].

In 2021, a pediatric core outcome set for CA in children (P-COSCA) has been developed, with the purpose to avoid inconsistencies in research regarding outcome after pediatric CA[37]. A core set of 5 outcomes was identified; survival, brain function, cognitive function, physical function, and basic daily life skills at different time points post-CA. Additionally, a scientific

statement has been published recently describing many outcome domains after sudden CA, not only for the individuals themselves, but also for their care providers and community [38]. We recommend that future research on outcome after CA should adhere to these scientific statements.

To answer the" growing into deficit" question, larger cohorts should be assessed into adulthood. One possible way to achieve this is to establish a long-term follow-up program within multicenter international collaborations like the Pediatric Resuscitation Quality Collaborative (PediRES-Q) [39].

Conclusions

Outcome expressed in PCPC was good in the majority of paediatric OHCA survivors at 3-6 months and 24 months post-OHCA. Neuropsychological assessment showed adverse outcome at 3-6 and 24 months, in domains of attention and intelligence, although most children returned to their original school. PCPC scores were not associated with intelligence scores. Due to the relatively young age of our cohort, follow-up should continue over a longer life span in order to fully understand the long-term consequences and impact of OHCA in childhood.

Conflicts of interest

None

Acknowledgements

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Supplementary file 1. PCPC score

Score	Category	Description
1	Normal	Normal; at age-appropriate level
2	Mild disability	Conscious, alert, and able to interact at age-appropriate level; school-age child attending regular school classroom, but grade perhaps not appropriate for age; possibility of mild neurologic deficit
3	Moderate disability	Conscious; sufficient cerebral function for age-appropriate independent activities of daily life; school-age child attending special education classroom and/or learning deficit present.
4	Severe disability	Conscious; dependent on others for daily support because of impaired brain function
5	Coma or vegetative state	Any degree of coma without the presence of all brain death criteria; unaware, even if awake in appearance, without interaction with environment; cerebral unresponsiveness and no evidence of cortex function (not aroused by verbal stimuli); possibility of some reflexive response, spontaneous eye-opening, and sleep-wake cycles
6	Brain death	Apnea, areflexia, and/or electroencephalographic silence

Supplementary file 2. Overview neuropsychological measures

Measurements	Test	Age (yrs.)	Test mean, standard deviation (SD)	Notes
Intellectual functioning	Bayley Scales of Infant Development (BSID-2 or Bayley-3)	0-2.5	Mean 100, SD 15 [1]	Intelligence or developmental quotient standard scores. Higher scores represent better functioning. Due to the small sample size, the outcomes of the different tests are grouped: Total IQ score is based on BSID-cognitive score, WPPSI-III TIQ, WISC-III TIQ, or WAIS-IV TIQ. The Verbal IQ score is based on: WPPSI-III VIQ, WISC-III VIQ, WAIS-IV VC-index. The performance IQ score is based on: WPPSI-III PIQ, WISC-III PIQ, WAIS-IV PO-index
	Wechsler Preschool and Primary Scale of Intelligence (WPPSI-III)	2.6-6	Mean 100, SD 15 [2]	
	Wechsler Intelligence Scale for Children (WISC-III)	7-15	Mean 100, SD 15 [3]	
	Wechsler Adult Intelligence Scale (WAIS-IV)	16-18	Mean 100, SD 15 [4]	
Selective attention	Stroop Color Word Test (Stroop)	≥11	Mean 50 SD10 [5]	T-score; Higher scores represent better functioning
Sustained attention	Bourdon Vos cancellation test	≥6	Mean 0, SD1[6]	Z-score compared with age appropriate scores; Higher scores represent better functioning

Processing speed	Age-appropriate versions of the Wechsler Scales (WPPSI-III, WISC-III, WAIS-IV)	≥4	Mean 100, SD 15 [2-4]	Standard norm score: Higher scores represent better functioning
Visual-Motor Integration	Beery Developmental Test of Visual Motor Integration (Beery-VMI)	≥2	Mean 100, SD 15 [7]	Standard norm score: Higher scores represent better functioning
Verbal memory: delayed recall	Rey auditory verbal learning test (Rey-AVLT)	≥6	Mean 0, SD1[8, 9]	Z-score compared with age appropriate scores: Higher scores represent better functioning
Visual memory: recognition	Rey-Osterrieth Complex Figure test (Rey CFT)	≥6	Mean 50, SD 10 [10]	T-score: Higher scores represent better functioning

Executive functions: flexibility	Trail Making Test part B (TMT-B)	≥8	Mean 0, SD1[11]	Z-score compared with age appropriate scores: Higher scores represent better functioning
Parent-reported executive function questionnaire	Behaviour Rating Inventory of Executive Function questionnaires (BRIEF-P and BRIEF)	≥2	Mean 50, SD 10 [12]	T-score; A higher score means worse functioning (more reported problems)

Supplementary file 3. Causes of OHCA
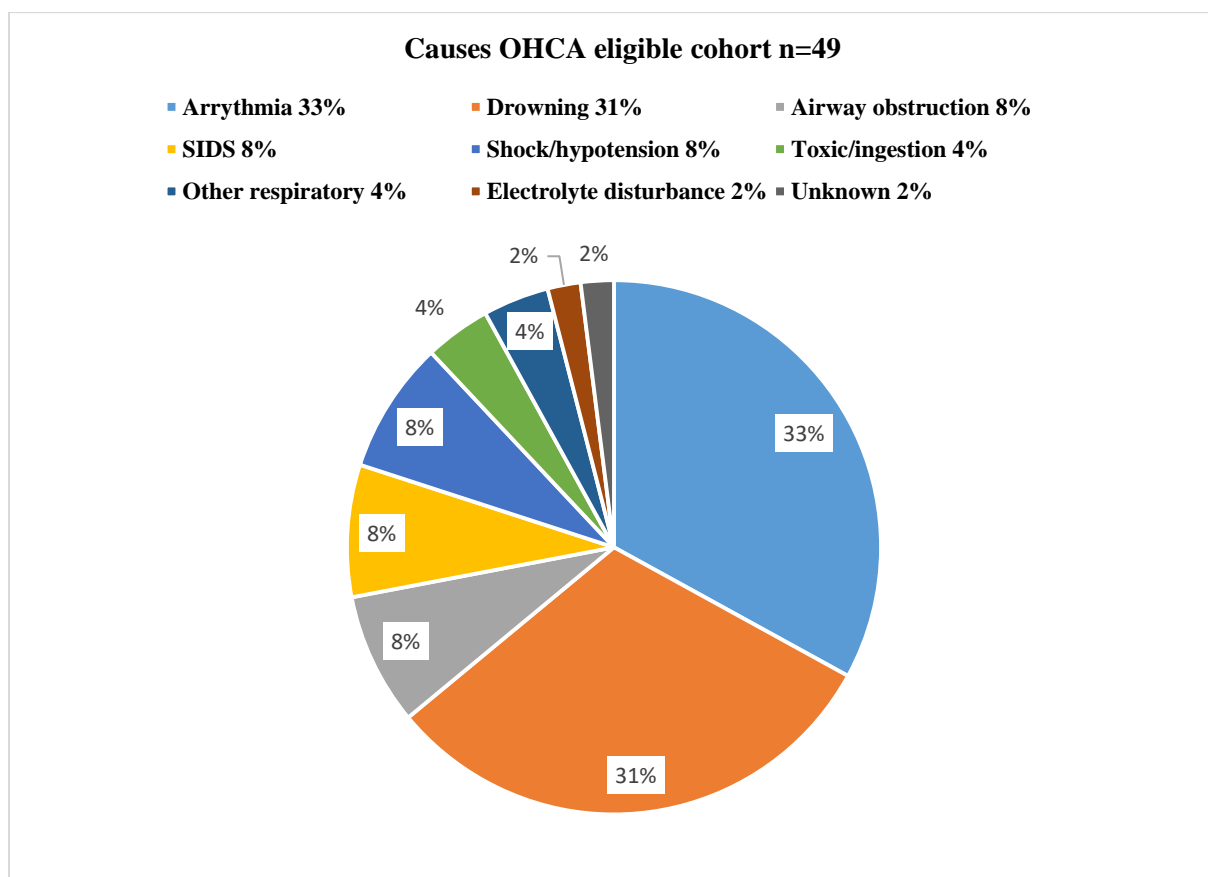
Supplementary file 4. Characteristics and functional outcome of participants and non-participants neuropsychological assessment 3-6 and 24 months after OHCA

	Tested 3-6 months n=26		Non-tested 3-6 months n=23		*p*-value	Tested 24 months n=27[a]		Non-tested 24 months n=21[a]		*p*-value
Characteristics										
Age at admission (months)	90	(31-177)	28	(5-120)	P 0.03	88	(32-164)	22	(4.5-173)	P 0.09
Gender male	19	(73)	14	(61)	P 0.54	18	(67)	15	(68)	P 0.76
Bystander CPR	22	(85)	17	(74)	P 0.48	22	(73)	16	(85)	P 0.48
Initial rythm shockable	12/19	(63)	5/15	(33)	P 0.17	12/21	(57)	5/13	(42)	P 0.48
Duration CPR (min) Missing, n	10 5	(3.5-20)	15 6	(3-25)	P 0.77	8 6	(3-44)	15 5	(4-20)	P 0.84
First lactate Missing, n	6.0 1	(4.5-13.4)	6.5 2	(4.4-11.2)	P 0.80	5.6 3	(4.4-13.3)	6.5 0	(4.4-13)	P 0.96
First pH Missing, n	7.2 1	(7.0-7.3)	7.1 3	(6.9-7.2)	P 0.79	7.2 4	(7.1-7.3)	7.1 0	(6.9-7.3)	P 0.07
Etiology arrest **Cardiac**	12	(46)	8	(35)	P 0.67	10	(37)	10	(48)	P 0.77
Respiratory	11	(42)	10	(43)		13	(48)	7	(33)	
Other	3	(12)	5	(22)		4	(15)	4	(19)	
PCPC discharge	2	(1-2)	2	(1-4)	P 0.43	2	(1-3)	1	(1-3)	P 0.16
SES **low**	6	(23)	4	(18)	P 0.90	8	(30)	2	(10)	P 0.07
middle	16	(62)	14	(64)		17	(63)	12	(60)	
high	4	(15)	4	(18)		2	(7)	6	(30)	
Functional outcome										
PCPC **Poor**	2	(8)	5	(29)	P 0.07	2	(8)	2	(15)	P 0.41
Good	24	(92)	12	(71)		24	(92)	11	(85)	

Return to school[b]	14 (88)	6	(75)	22	(96)	4	(44)
Missing, n	0	2		1		5	

Data are presented as n (%) or median (IQR: 25th -75th percentile)

[a] N = 48, 1 patient died after 6 months

[b] Only applicable for children beyond the age of 4. At 3-6 months N ≥ 4 yrs = 24, at 24 months N ≥ 4 yrs= 32. P value not reported due to small sample size and high number of missings.

CPR=cardiopulmonary resuscitation, PCPC=pediatric cerebral performance category scale, SES= socioeconomic status

Supplementary file 5. Results repeated neuropsychological testing at 3-6 and 24 months after OHCA

Repeated measurements 3-6 and 24 months[a] (n=19)	n	*Z*-score median 3-6 months	Z-score median 24 months	*p* vs norm
Total IQ (all)	11	-0.1 (-0.8 to 0.4)	-0.3 (-1.5 to 0.3)	.72
Verbal IQ (all)	4	0.2 (-0.1 to 0.8)	0.0 (-1.3 to 0.7)	.11
Performance IQ (all)	5	-0.5 (-0.7 to 0.4)	-0.3 (-1.2 to 0.0)	.47
Selective attention (STROOP ≥11y)	5	0.2 (-0.7 to 0.7)	-0.5 (-1.4 to 0.7)	.50
Sustained attention (Bourdon SD ≥6y)	5	-2.7 (-3.2 to -1.6)	-2.4 (-6.9 to -1.0)	.50
Processing Speed (≥4y)	9	-0.8 (-1.2 to 0.1)	-0.7 (-1.4 to 0.5)	.92
VMI (Beery ≥2y)	7	0.1 (-0.1 to 0.3)	0.2 (-0.7 to 0.5)	.60
Verbal Memory (Rey-AVLT, delayed recall ≥6y)	7	0.1 (-2.3 to 1.4)	-0.1 (-1.0 to 1.0)	.74
Visual Memory (ReyRecog ≥5y)	5	-1.1 (-2.1 to 0.5)	-0.3 (-1.8 to 0.7)	.47
Cognitive flexibility (TMTB≥8y)	5	0.0 (-1.2 to 0.9)	-0.3 (-2.0 to 0.1)	.79
BRIEF Total score (≥2y)	7	-0.2 (-2.2 to 1.2)	0.3 (-0.2 to 1.2)	.46

Data are presented as median (IQR: 25th -75th percentile)
[a]All neuropsychological tests were converted into Z-scores and compared with norm data. A higher Z-score means a better outcome.

Supplemental file 6. Neuropsychological outcome per individual patient

Visual-Motor Integration

Rey-AVLT

Rey-Osterrieth Complex Figure test
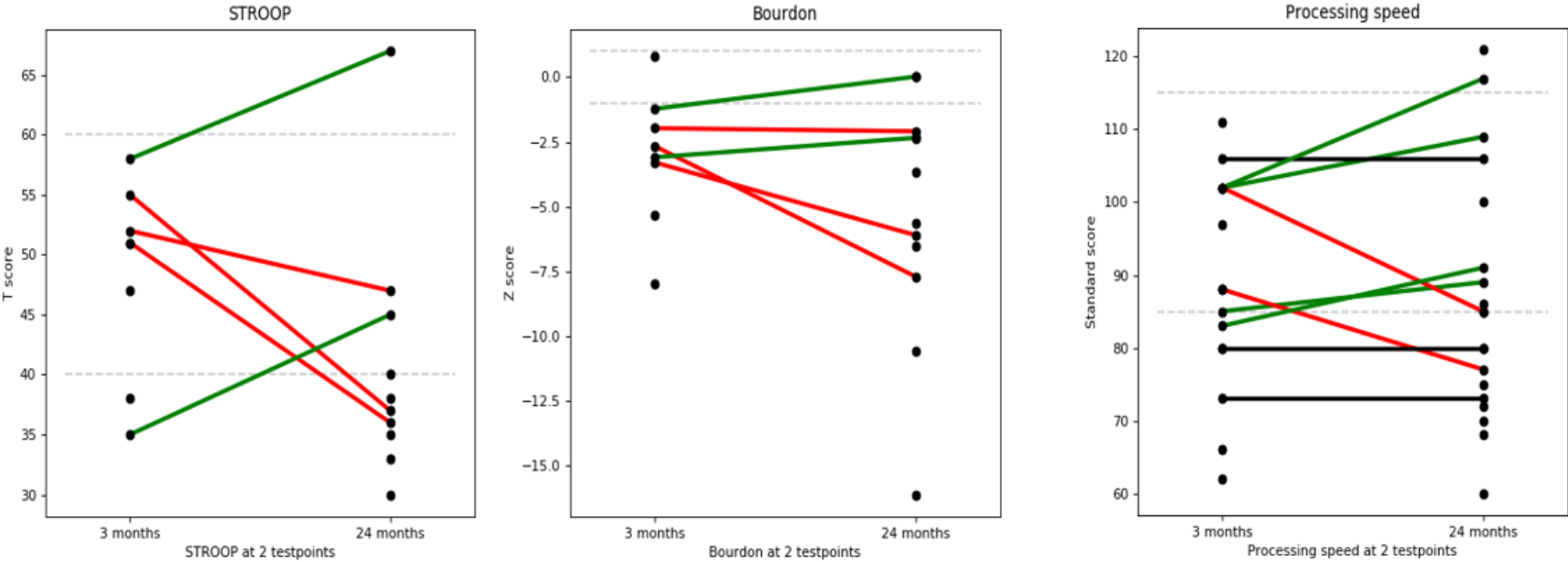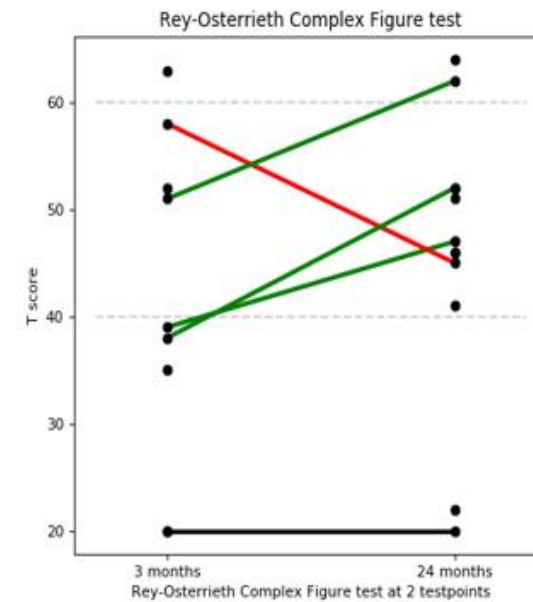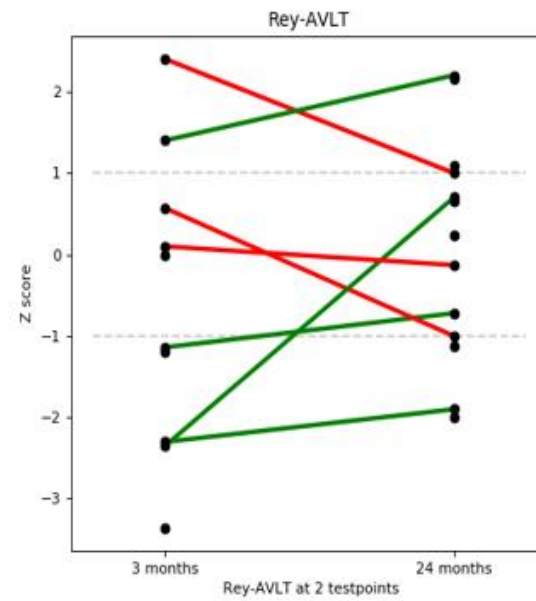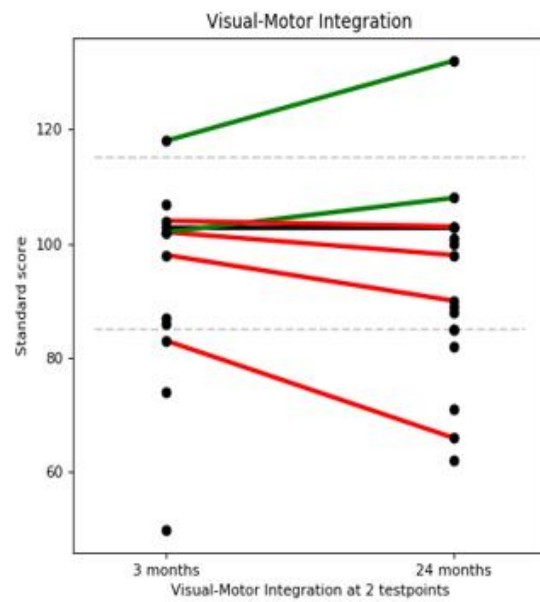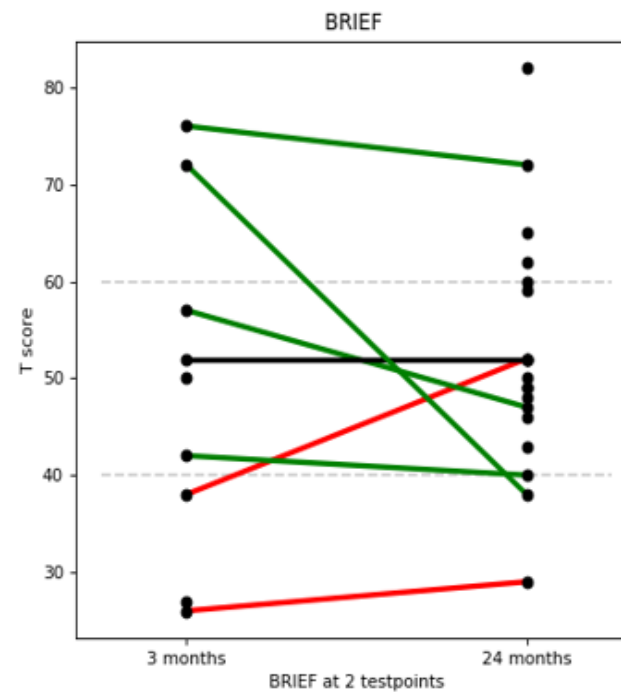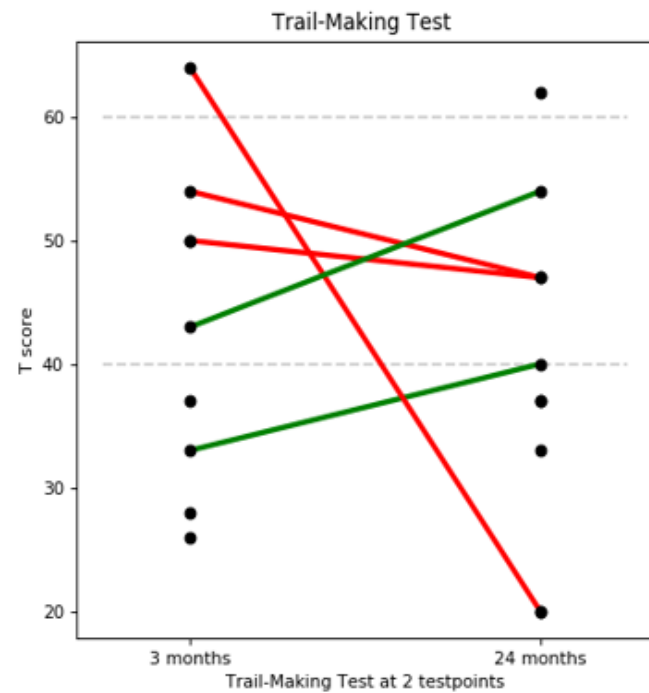
All neuropsychological tests and its individual course over time. Every dot represents an individual patient. Connected horizontal line means repeated measure for individual patient, green: improvement over time, red: decline over time, black: no difference over time. Area between the dotted lines represent the mean scores (-1SD to +SD).

Z-score: higher is better functioning (mean norm 0, SD1)
T-score: higher is better functioning (mean norm 50, SD10), standard score: higher is better functioning (mean norm 100, SD15)

Chapter 8.

General discussion

Thesis at a glance

The research in this thesis describes various aspects of outcome in children with out-of-hospital cardiac arrest (OHCA). In the first part, neuromonitoring method studies were reviewed regarding the specificity and sensitivity of monitoring modalities to predict outcome in children admitted to the Pediatric Intensive Care Unit (PICU) post-cardiac arrest (CA). Furthermore, the current practice of neuro-prognostication for comatose CA survivors among European pediatric intensivists and neurologists was explored. These evaluations were followed by an analysis of survival and causes of death in children admitted to the PICU in the Erasmus MC-Sophia Children's hospital after OHCA and return of circulation (ROC). The prognostic value of early magnetic resonance imaging-diffusion weighted imaging (MRI-DWI) in predicting long-term outcome after pediatric OHCA was examined. Next, the association was explored between shockable rhythms and long-term outcome after pediatric OHCA in Rotterdam, over an 18-year period.

Lastly, the neuropsychological outcomes of OHCA survivors 3-6 and 24 months after pediatric OHCA were investigated, with its longitudinal course. The results and future perspectives were described in the general discussion part of the thesis.

Part 1. Neuromonitoring methods

Chapter 2 presents an overview of neuromonitoring methods and their potential roles in neuro-prognostication in post-CA children, in particular those who remain comatose after achieving ROC. Methods included neurological exam, routine electroencephalography (EEG) and continuous EEG (cEEG), transcranial Doppler (TCD), brain MRI and computed tomography (CT), plasma biomarkers, somatosensory evoked potentials (SSEP), and brainstem auditory evoked potentials (BAEP). We concluded that due to a lack of evidence

from the currently available literature, these neuromonitoring methods must be interpreted with extreme caution in the context of the patient's individual clinical neurological status. The appropriate application in time following the event and the precise interpretation of available modalities still need to be determined in relation to the individual patient. Most promising at this moment is cEEG monitoring, which was addressed in 10 out of 26 studies reviewed. The following EEG patterns were found associated with a poor outcome, including death, within 24 hours post-CA: discontinuous, burst-suppression or flat. Furthermore, a non-reactive pattern EEG and the presence of electrographic status epilepticus are associated with a poor outcome and death(1-5). In contrast, a reactive EEG pattern and a continuous background pattern at 12 hours post-CA are associated with a good outcome (2, 6). These EEG studies, however, are limited in several aspects.

First, all were single-center studies; and most of them were retrospective studies with small sample sizes (median $n = 34$; IQR 28–56). Second, clinicians were not blinded for the EEG results; this knowledge may have influenced their decisions to withdraw treatment if EEG patterns were abnormal. Third, mainly short-term outcomes were presented, established with crude outcome measures such as Pediatric Cerebral Performance Category (PCPC) and Glasgow Outcome Scale (GOS). Many studies did not specify causes of death. For example, it whether the cause was refractory circulatory failure withdrawal of life-sustaining therapies (WLST) based on a poor neurological prognosis. Fourth, the studies used different EEG classifications – and, therefore, are hard to compare. Fifth, the timing of the EEG was not always specified. This should be taken into account, as studies in adults after CA suggest that EEG patterns at 12 hours after ROC have the best predictive value for good outcome, while patterns at 24 hours post-ROC have the best predictive value for poor outcome. Of note, although a normal EEG is associated with a good outcome, some studies described children with a normal EEG and poor outcome and vice versa (1, 3).

The above-described review gave insight into the challenges of outcome studies after pediatric CA.

Most importantly, a child's brain – and thus the EEG patterns - are continuously developing and changing, especially at early age (7). The wide age range in pediatrics (1 month to 17 years) hampers meaningful outcome comparison. In children with brain damage, growing into deficit can occur later in life.

Second, additional investigations (e.g. EEG, MRI) were often only done when clinically indicated, and clinicians were unblinded to the results. This could gave led to selection bias and self-fulfilling prophecies in relation to patient outcome (e.g. decision-making regarding WLST).

Third, the majority of neuromonitoring studies included both in-hospital cardiac arrest (IHCA) and OHCA with different etiologies, resulting in heterogeneous patient groups. Finally, in the majority of studies, outcome was measured using gross outcome scales (e.g. PCPC, GOS).

In **chapter 5.** we have shown that a normal brain MRI (without post-hypoxic injury) on T1/T2 and diffusion weighted imaging (DWI) within 1 week after pediatric OHCA is 100% predictive for a good neurological outcome at 2 years post-OHCA. Conversely, the presence of extensive injury injury (≥50% of the cortex/white matter or in 4 or more defined brain regions (with or without involvement of deep grey matter)) on T1/T2 and DWI/apparent diffusion coefficient (ADC) is 100% predictive for a poor neurological outcome (both including and excluding death) or death at hospital discharge and 2 years post-OHCA. However, solely based on MRI with focal injury (<50% of the brain), it is impossible to predict neurological outcome accurately at hospital discharge or 2 years post-OHCA.

In this study, we have attempted to predict neurological outcome without using other OHCA variables. However, due to a small sample size and the use of a crude outcome scale (PCPC), we think that predicting outcome solely based on a normal MRI or MRI with extensive injury, is inappropriate. Besides, MRIs were only performed at the discretion of the treating clinician and not as part of standard care. The children who didn't receive MRI were more severely affected, creating a selection bias.

In 2019, a scientific statement on pediatric post-CA care from the American Heart Association was published (8). The authors also concluded that no single test (neurological exam, EEG, neuro-imaging, SSEP, biomarkers) is sufficiently accurate and reliable for prognostication after pediatric CA. Multiple factors and ancillary tests should be considered when predicting outcome in children who achieve ROC after CA.

UNRESOLVED PROBLEMS 1.

The precise value of the various available neuromonitoring methods (including neurological exam, routine EEG and continuous EEG, transcranial Doppler, brain MRI and CT, plasma biomarkers, SSEP, and BAEP) to predict outcome of the individual child post-CA is not known.

An evidence-based statement on which neuromonitoring method should preferably implemented first is not available.

Unresolved problem 1.

Potential solution 1a. International collaboration

National, but even more importantly, international collaboration is warranted to learn how to implement and interpret available neuromonitoring modalities with regard to neuro-prognostication. Within the Netherlands, this can be achieved through cooperation between all

seven PICUs. International collaboration can be accomplished by establishing a pediatric CA consortium with members of the European Society of Paediatric Neonatal Intensive Care (ESPNIC), the European Paediatric Neurology Society (EPNS) with a special interest in this topic and/or the pediatric section of the Intensive Care working group of the European Academy of Neurology (EAN). Besides, outside Europe, collaboration with existing consortia, such as the Pediatric Resuscitation Quality Collaborative (PediRES-Q), is desirable. We are aware that it is difficult to set up randomized controlled trials, due to small patient numbers, different age categories with different neurodevelopmental stages of the central nervous system, and the fact that withdrawal of treatment is unavoidable in a subgroup of patients against the background of differences in ethical and cultural points of view internationally. In order to interpret the precise value of the various neuromonitoring modalities, we need to develop standardized care including the use and interpretation of the results of these modalities and outcome measurements for children post-CA (national and international), in particular for children who remain comatose after CA.

This international approach to guarantee standardized care should at least include: 1) the collection of individual patient information; 2) post-CA care such as temperature management, RR, Co2, O2 levels; 3) standardized intervals at which neurological exam should be performed; and 4.) a minimum set of ancillary tests post-CA (preferably cEEG, starting as soon as possible after the arrest, and brain MRI within 1 week post-CA).

All standardly collected patient data– medical history, etiology of CA, CPR variables such as duration, witnessed arrest, bystander CPR, clinical exam, neurological exam, post arrest-care, neurological ancillary tests and outcome – should be stored in an electronic database, taking into account the FAIR principles (principles to improve Findability, Accessibility, Interoperability and Reusability) (9). Analysis of the data of a large patient sample could eventually enable us to design evidence-based guidelines for the management of the

individual patient. This operation is a tremendous challenge in view of the current lack of

financial resources and differences in expertise between countries and even between hospitals

in Europe. Self-fulfilling prophecy will remain an issue because clinicians will potentially use

the information collected in this setting for decision making in favor of prematurely

withdrawing technological support, thus leading to a bias of unfavorable neurological

outcome.

Potential solution 1b. Quantitative EEG

As mentioned earlier, EEG monitoring seems promising in predicting outcome in comatose

children post-arrest. Current (international) practice is that experienced physicians, mostly

clinical neurophysiologists, interpret an EEG by visual assessment. However, the assessment

of specific EEG patterns in children of different ages requires special expertise, as

background patterns evolve as children age and their brain matures (10). Furthermore, the

interpretation of (c)EEGs is very time consuming, and various degrees of interrater agreement

has been reported for the interpretation of EEGs (11-13).

A possible solution to do away with the above-mentioned issues is to combine the visual

assessment of the EEG with computer-assisted interpretation, also known as quantitative EEG

(QEEG). QEEG analyses use computationally derived features that highlight specific

components of the EEG with numerical values (14). In adults, QEEG features are associated

with outcome after CA (15-17). Extrapolating adult findings to children is inappropriate, since

children have age-dependent anatomy and physiology and responses relevant to injury of

central nervous system (18). Thus far, only one study has reported the ability QEEG features

to predict neurological outcomes in 87 children after CA (19). Their model that best predicted

unfavorable neurological outcome had a specificity of 0.75 and positive predictive value

(PPV) of 0.79, which illustrates that at this stage it should not be used solely in neuroprognostication.

Recently a collaboration has been set up between our PICU, our neurology/neurophysiology department and Delft University of Technology, with the purpose of integrating machine learning with clinical patient data. One of the next steps is designing a machine-learning algorithm for cEEGs in children of different age groups after OHCA. The primary goal of this project is to investigate the role of QEEG in neuroprognostication after OHCA.

Potential solution 1c. Qualitative and quantitative MRI

In analogy to potential solution 1a, a scoring system should be designed to report brain MRIs. Preferably, brain MRIs must be performed using to the same acquisition parameters, scan quality (preferably on the same scanner), and timing.

The use of quantitative MRI, such as brain diffusion tensor imaging (DTI), might be another prognostic tool for pediatric comatose OHCA survivors. DTI enables to calculate the fractional anisotropy, which indicates the quantification of white matter injuries that occur during and around global anoxia (20, 21).

In a prospective multicenter cohort of adult patients who had been comatose for 7 days after CA, whole brain white matter fractional anisotropy could accurately predict neurological outcome at 6 months post-CA (22). Another DTI technique is white matter tractography, which studies the organization of structural connectivity (23). In children with moderate and severe traumatic brain injury (TBI), tractography has revealed abnormal organization of the structural connectome (i.e., the comprehensive map of neural connections in the brain), which was associated with impaired neurocognitive function (24). Up to now, age-dependent normal values of DTI for children are lacking. The Generation R study, a large prospective cohort

study in healthy children in Rotterdam from fetal life until young adulthood, might generate these normal values. In this cohort, MRIs are made at the ages of 9 and 13 years (25).

Part 2. Neuro-prognostication guidelines

Survey

Predicting the long-term outcome in children after ROC is challenging, especially in children who remain comatose after the arrest. International guidelines for neuro-prognostication are available for adults, but not for children due to lack of evidence of the predictive value of neuromonitoring modalities (26). To fill in this knowledge gap, we surveyed members of ESPNIC and EPNS **(chapter 3)** on current practices regarding neuro-prognostication for comatose children post-CA. Not surprisingly, we learned that practices differ between and within European PICUs.

The respondents represented 23 European countries and 45 different PICUs. Only Ukraine has a national guideline for neuro-prognostication after pediatric CA, and eight PICUs (20%) have a local guideline.

Regarding methods to assess neurological outcome in comatose children post-CA, neurological exam (Glasgow Coma Score (GCS) and brainstem reflexes), MRI and EEG were considered most useful, but the actual use and timing of these tests differed.

The aftermath of a futile prognosis (established from <48 hours up to > 14 days) differed between respondents and countries. The majority of respondents (mainly from Western and Northern Europe) mentioned WLST, but continuation of intensive care treatment with or without restrictions was also opted for (mainly respondents from Eastern and Southern Europe). Some respondents noted that the decision whether or not to continue intensive care treatment depended on the parents' point of view. The above findings are in line with a previous study showing that physicians from northern European countries more often decided

on WLST than physicians from southern countries (27). Personal beliefs and experiences, cultural and religious aspects and local policies may play a role in these interregional European differences.

Definition of a poor outcome differed among the responders. The majority considered a PCPC ≥ 4 as a poor outcome, whereas others mentioned a PCPC ≥3 or ≥5, or a difference in PCPC pre- and post-arrest of 1 or 2. This is in line with literature; in some studies a PCPC score of 1-2 is considered a good outcome, in other studies 1-3, or a difference in PCPC pre- and post-arrest < 1 or 2 (28). In our survey, we used PCPC at hospital discharge as outcome measure, because this is frequently used in studies describing outcome post-CA. It should be noted, however, that this is a very gross tool with only 6 items (see Table 1, Introduction), which does not precisely evaluate the quality of life and participation of these children.

Other validated scales of neurological function after pediatric CA used in literature include the GOS (29), the King's Outcome Scale for Childhood (Koschi) (30), the pediatric Stroke Outcome Measure (PSOM)(31), and the Functional System Score (FSS) (32). However, the scores on these scales do not precisely reflect the patient's clinical condition.

Timing and cause of death

The study presented in **chapter 4** explored the timing and cause of death in 113 children admitted to our PICU following ROC after OHCA between 2012 and 2017. The causes of OHCA were diverse; the most common causes were drowning (21%) and arrhythmia (17%). We found that 56% of the children who achieved ROC had died prior to hospital discharge. These children's most common cause of death was WLST based on poor neurological prognosis (WLST-Neuro; 67%), whether or not combined with WLST due to refractory circulatory and/or respiratory failure or recurrent CA. In in most cases, the decision had been made within 72 hours after the CPR event and, in half of the cases even within 24 hours.

Other causes of death were brain death (BD, 29%), recurrent CA (2%) or refractory circulatory and/or respiratory failure (2%).

Only one other study, from the USA, described the causes and timing of death of children admitted to the PICU after OHCA (33). In this cohort, BD was the most common cause of death (47%), while WLST based on poor neurological prognosis was less common (34% vs 67% in our study). The following reasons might explain this discrepancy: First, the definition of BD differed between studies, because the BD criteria differed between the Netherlands and the USA. For that matter, up to now, there are no worldwide consensus criteria for BD. Second, the children in our study may initially have been in a better condition after ROC. If so, this could be due to the setting in the Netherlands: a higher occurrence of automatic external defibrillator (AED) use and bystander CPR, the availability of helicopter emergency medical service, and thus short transfer time from the incident scene to the hospital (34-37). Nevertheless, this assumption is purely speculative, because documentation of these variables is lacking in both studies.

Although in our study the survivors were discharged from the PICU with relatively good outcome (median PCPC = 2; IQR, 1–3), we did not focus on long-term outcomes in domains such as neuropsychological assessments and quality of life (QoL). The question remains whether in view of the lower percentage of WLST in the USA study, the survivors will have developed more severe long-term neurological deficits.

In our study, we defined BD as clinically BD; i.e., a GCS score of 3 without brainstem reflexes for more than 24 hours after CPR, no sedation for at least 24 hours, possible effects of neuromuscular blockade administration at the time of neurological exam, and a temperature of at least 32°C. For various reasons, our study might have given an underestimation of the total number of BD patients.

First, in 2016, the Dutch guideline for BD diagnosis was changed to the effect that BD was not to be determined until 12–24 hours after the CPR event, which was a new requirement (38). This implies that children admitted before 2016 may have been declared BD without fulfilling the BD criteria of the present study (wait for at least 12–24 hours with neurological exam). Second, forty percent of the children in the WLST-Neuro group had received a sedative or opioid infusion during the neurological exam, or had been administered the last dosage within 24 hours at time of neurological exam. The possible influence of sedatives/analgesics and hypothermia on neurological exam and EEG blurs the exact differences between the BD and WLST-Neuro groups, with presumably an overlap. It could well be that if the clinicians had postponed WLST in the WLST-Neuro group (to exclude the possible influence of sedatives/analgesics, potentially also taken into account the plasma levels of analgosedative agents, and to wait until the patient had normal body temperature), more children would have declared BD.

Was the decision to WLST made too early in some cases? Due to the retrospective design of our study, this is difficult to answer. As mentioned before, international evidence-based neuro-prognostication guidelines are available for adults, but not for children. Nevertheless, the fact that no differences were found in basic CPR event and post-ROC characteristics between the WLST-Neuro and BD groups is quite reassuring and suggests that the WLST decisions were justified. There is still some reason for caution, however, because 40% of the children in the WLST-Neuro group had received a sedative or opioid infusion. Although the dosages of these sedatives or opioids were within normal ranges, we cannot exclude that they have had an effect on the neurological exam, also given the children's slower metabolism due to organ failure (for example acute kidney injury, which affects the pharmacokinetics of these drugs) and cooling. Reasons for administering sedative drugs were to prevent shivering, facilitate mechanical ventilation, and treat seizures. Clinicians should, if the patient's

condition allows it, avoid as much as possible the administration of sedatives, or otherwise regularly quantify the plasma levels.

Unresolved problem 2.

Potential solutions 2. Neuro-prognostication guideline

The answer to the lack of neuro-prognostication guidelines overlaps with the possible solution of problem 1. There is an urgent need for national and international collaboration.

The first step is standardization of care within PICUs across Europe, and preferably worldwide. This generates useful data that can answer relevant research questions. The ultimate aim is to establish an international, evidence-based neuro-prognostication guideline. However, even if this would become true, the question arises whether this guideline would be adhered to worldwide. Lack of financial resources and sufficient expertise to perform and interpret ancillary tests (such as neuroimaging and electrophysiology) could stand in the way. Furthermore, the consequences of a poor outcome in the individual patient – whether or not to continue intensive care treatment and whether or not to include the parent's whishes in this decision – will remain different among countries and even between clinicians. Regarding the situation in Europe, the European Brain Council (EBC) could play a facilitating role. The EBC is a network of key players in the 'brain area', with a membership encompassing scientific societies, patient organizations, professional societies and industry partners. It would be very interesting, though challenging, to study the long-term outcome of pediatric comatose CA survivors in countries where WLST is uncommon. Do these countries (i.e.,

Eastern and Southern Europe, central Asia) have data on the long-term outcome? How do these children function, and are there any data on mortality after PICU admission?

Unresolved problem 3.

Potential solution 3. Brain Death

An unambiguous definition of BD worldwide would facilitate accurate decision-making. Worldwide, perceptions and criteria of BD definition differ, for both adults and children (39-41). Examples of differences in perceptions include: acceptance of BD as death, religious beliefs and cultural norms about death, and legal standards of determination of BD and death. Regarding the practices, there is a great diversity in the availability of national and or institutional BD protocols and in the criteria to determine BD. For instance, requirements for physicians' expertise to be allowed to determine BD (pediatric neurologists, pediatric neurosurgeons or pediatric intensivists, consultants or residents etc.) may differ, as well as the required minimum number of physicians involved in the decision. Issues such as the timing and necessity of repeated neurological exams, and the choice and timing of ancillary tests may also vary between countries.

In the Netherlands, a neurological exam AND confirmatory tests (EEG, TCD, or CT-angiography) and finally the apnea test are required to determine 'whole' BD (for the purpose of possible organ donation) in both adults and children. Ancillary tests are only done when neurological exam and apnea testing can be performed reliably and completely (38).

In children younger than 1 year, the whole procedure must be repeated after a certain age-dependent waiting time.

In the United States and the United Kingdom, however, only a neurological exam with apnea testing will suffice for the determination of pediatric BD. Ancillary tests can be used when parts of the neurological exam or apnea testing cannot be completed safely or adequately.

Consensus among leading experts in the field is desirable. Future efforts will need to involve physicians with neurological and critical care expertise, representatives of national and international major medical organizations (such as the World Health Organization or World Federation of Neurology), and scientific and medical advisors of government agencies (39). However, due to the enormous variation in perception and practices among countries, the question arises whether agreement on international standards and practices of BD is an achievable goal.

Part 3. Long-term outcome after out of hospital cardiac arrest
Follow-up program

As part of standard care, pediatric OHCA survivors are invited to participate in our multidisciplinary follow-up program at the outpatient clinic 3-6, 12 and 24 months after OHCA and subsequently, dependent on the age at time of arrest, at the ages of 5, 8, 12 and 17 years. During on-site visits, a semi-structured interview with the children and their caregivers takes place, and both a physical and neurological exam are performed as well as neuropsychological assessments by psychologists. This program started in 2012 with the primary goal to provide good care to patients and their caregivers, and boasts a high response rate with few refusals.

In **chapter 7,** the functional and neuropsychological outcomes at 3-6 and 24 months post-OHCA (between 2012-2017) were presented.

Of the 49 survivors, respectively 74% and 73% had a good outcome at 3-6 and 24 months post-OHCA, as reflected by a PCPC score 1-2. Only a minority had motor deficits on neurological exam. The majority of school-aged children (81%) went back to school without a change in school level after 24 months. The question arises whether the relatively high

percentage of good PCPC scores in our cohort is associated with the high amount of WLST of children due to expected poor neurologic outcome. If so, this may have caused a selection bias. On the other hand, good PCPC scores at hospital discharge are in line with those reported by previous studies (42-44).

Worse scores were found on sustained attention and processing speed compared with norm data at both time points. Additionally, at 24 months, worse scores were also found on intellectual functioning, selective attention, and cognitive flexibility compared with norm data. The neuropsychological outcomes of children who underwent neuropsychological testing at both time points had not significant changed over time.

Only few studies have been published regarding the long-term neuropsychological outcome in children after OHCA (see introduction of this thesis).

Slomine et al. described the neuropsychological outcomes of 160 children after CA (45), and likewise found worse intelligence scores and worse scores on attention, cognitive flexibility and processing speed (all compared with normative data). This is remarkable, since our study differed in some aspects from the study of Slomine and colleagues:

 1. Slomine and colleagues retrieved outcomes from the THAPCA trial – a randomized trial comparing the efficacy of therapeutic hypothermia with that of normothermia on survival.

2. In the THAPCA trial, children were included after both IHCA and OHCA and when they were unresponsive and mechanically ventilated after ROC, creating a population with possibly more severely affected children.

3. Moreover, the follow-up interval in the THAPCA trial was cross sectional at 1 year versus longitudinal (with repeated onsite visits with repeated measures) up to 2 years in our study.

The pathophysiological mechanisms underlying the neuropsychological deficits in children post-CA are not completely understood. The question is whether neuropsychological deficits are fully explained by the areas of the brain that have been damaged due to ischemia. During CA the brain is injured directly as a result of loss of blood flow (no-flow time) and the suboptimal flow that depends on the quality of CPR. Secondary neurological injury in which hyperoxia is a common feature, has also been described due to reperfusion after successful resuscitation. The neuronal injury cascade leading to cell death is a complex process, including excitotoxicity, disrupted calcium homeostasis, free radical formation, pathological protease cascades, and activation of cell death signaling pathways (46, 47). The areas which are most vulnerable to ischemia are the cerebral cortex, watershed areas, subcortical white matter, vascular end zones, hippocampus, cerebellar Purkinje cells and basal ganglia (46, 48-52).

In our cohort, intelligence scores 2 years post-OHCA were lower than normative data. Previous studies have shown that intellectual outcome is dependent on the age at which brain injury was acquired. In young children, acquired brain injury causes diffuse deficits, whereas in older children more specific deficits are found (53, 54). The median age of our OHCA cohort was relatively low at 48 months. Young children with brain injury have to learn new skills with impaired basal functions, causing a more negative effect on intelligence at long-term (55, 56). White matter injury is often seen after prolonged ischemia (46). The integrity of the white matter is correlated with full scale IQ and performance IQ (57). There is a parallel with children with TBI, in which white matter is also implicated; Tractography on DTI has revealed abnormal organization of the structural connectome in children with moderate and children with severe TBI. This abnormal organization was associated with lower intelligence (24) .

Executive functions such as attention and cognitive flexibility were also affected in our cohort. These are functions that are controlled by the frontal lobes of the brain, which are often injured after hypoperfusion and hypoxia (58). Besides, damage to other brain areas connected to the frontal lobes can also impair executive functions.

The hippocampus is another brain structure sensitive for hypoxia, and this sensitivity might also explain attention deficits (51). Unfortunately, we could not correlate neuropsychological findings with MRI results, because only few children had received both MRI during PICU admission and neuropsychological assessment during follow-up. Standard brain MRI at follow-up is not included in our clinical follow-up protocol. Because there is rarely a clinical indication for follow-up brain MRI, relating neuropsychological findings with MRI results is feasible only in the context of a research project beyond routine clinical care.

The current literature does not yet contain studies on the association of MRI findings and neuropsychological functioning.

Obviously, other factors also contribute to neurocognitive outcome: 1) underlying disease and genetic factors (59); 2) socioeconomic status (SES) of the patient and parents (in our patients, SES was significantly lower than that of the general Dutch population, which may have influenced neurocognitive outcome) (60); and 3) treatment post-OHCA (administration of sedatives, inadequate analgesia, number of invasive procedures, temperature management and the occurrence of hyperoxia or hypotension) (8, 61-63). All these factors make it a complex interplay and makes comparison of our study with the THAPCA trial difficult.

Regarding the neuropsychological outcomes 3-6 months after OHCA, a selection bias may have occurred because we found a trend (p=0.07) towards more favorable PCPC scores in the neuropsychologically tested group compared with the non-tested group. Therefore the finding that OHCA children scored worse on sustained attention and processing speed and not on other outcomes at this time point should be interpreted with caution. Consequently, a

neuropsychological assessment at 3-6 months post-arrest may be not yet fully reliable or possible, because children are then still recovering from their OHCA. However, from a care point of view it can be very useful to detect a child strengths and deficits at this time point, because these provide an indication for need of a patient-targeted rehabilitation treatment. Although the gross outcome during follow-up was good in our OHCA cohort, children generally did have deficits at 24 months post-arrest, making them cognitively vulnerable during development. What does this mean for the future of these children? This is difficult to predict from our study, for one thing because the median age in our small cohort was 48 months at the time of arrest, with a wide range of 3 months up to 18 years. Besides, the long-term impact on their academic career and participation in daily life is still unclear. From follow-up studies in other children with acquired brain injury (e.g. TBI or brain tumor), we know that these children may grow into deficit over time (64-67). This means that follow-up over a longer time span is needed to gain more insight in these aspects.

An international standardized follow-up program is lacking, and so are follow-up studies examining long-term outcome after OHCA in adulthood.

What is 'good' outcome?

In our cohort, almost three quarters of survivors had a PCPC score of 1 or 2 years post-arrest, which is considered a 'good' outcome. Still, we believe that the definition of a good outcome is more than only a crude functional measure such as a PCPC. A PCPC score does not reflect QoL or participation of patients and their parents and families.

The prediction of long-term neurological outcome in children with severe acute brain injury is one of the most difficult tasks pediatric neurologists and intensivists encounter. They are challenged to provide parents with the most accurate prognosis possible. A too optimistic prediction can unexpectedly result in survival of a child with severe, devastating neurological

deficits. On the other hand, a too pessimistic prediction may lead to unnecessary WLST in a child with a potential good outcome. Clinicians aim to predict outcome after OHCA in an early stage, but why? Knowing in an early stage that the outcome on the short and long-term is 'good', takes away the parents'/caregivers' tremendous anxiety and stress. Nevertheless, it also comforts the chain of caregivers: from firemen who were at the scene, to nurses and doctors. It makes them feel good and motivates them to keep doing their sometimes-challenging jobs.

However, when the prognosis is futile or uncertain, it becomes more difficult. The questions that arise in the medical team are: to what extent do we need to treat the child? Is an expensive intensive care treatment with possible suffering always justified? For the parents this is an even more very strained and demanding period. They live with fear, not knowing where the intense and painful treatment will lead. Will their child survive? And if he or she survives, what will the future be like: with or without neurological sequelae, both at the short and long term? Will their child be able to enjoy life, communicate, live independently, participate in society?

The definition of a good outcome after OHCA will vary across families, but also between individual caregivers, and even within a medical team. Different components are at play here, such as gender, cultural and religious beliefs, ethnicity, and personal experiences. For some families, a child's physical presence is worthwhile, even if the child is vegetative, or wheelchair-bound and not able to communicate, whereas others feel that any degree of neurological deficit is unacceptable and therefore want to discontinue life-sustaining therapies. Parents and clinicians often differ in the assessment of what is in a child's best interest (68). This often leads to discussion within the medical team, but also in the conversations of professionals with parents. We should not forget that older children themselves also might have an opinion about their outcome and their QoL, which might differ

from their parent's view. Van Zellem et al. investigated self-reported QoL of pediatric IHCA and OHCA survivors. Health-related QoL was significantly worse than that of the norm population on various domains (69). In contrast, previous research showed that self-reported QoL of neurologically impaired children and adolescents with brain or neuromuscular disorders such as epilepsy, cerebral palsy, brain tumors and Duchenne muscular dystrophy was equal or even better than that of the general population. In these often neurologically very limiting conditions, parents tend to rate their child's QoL lower than the child itself does (70-73).

From a societal perspective, children with severe neurological deficits are a financial burden on our society. They need extensive and expensive medical and supportive care for a prolonged period, or even their entire life span. They will not be able to participate in society in adulthood, not be able to participate in payed labor, not be able to pay taxes, etc. Up to now, this issue is underexposed, and is not well taken into account in clinical situations. Nevertheless, health economists have tools available to calculate both direct and indirect costs. In the future thinking about value based care, also Patient Recorded Outcome Measures (PROMs) and Patient Reported Experience Measures (PREMs) could be used within this context.

UNRESOLVED PROBLEMS 4.

What is 'a good' outcome?

UNRESOLVED PROBLEMS 5.

It is unknown how children function on different outcome domains in adulthood after undergoing OHCA at childhood

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Unresolved problem 4.

Potential solution 4. Outcome

4a.Outcome of child

For research purposes, it would be desirable to define a poor or good outcome not only based on PCPC, but take into account other domains of outcome as well.

The International Classification of Functioning, Disability and Health for Children and Youth (ICF-CY) of the World Health Organization is widely used in outcome research as a structured framework to describe the complex interaction between the health problem and its consequences (74) (Figure 1). This classification could be used in future studies on outcome in pediatric OHCA survivors.

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                    ┌─────────────────────┐
                    │  Health condition   │
                    │      (OHCA)         │
                    └─────────────────────┘
```

Health condition
(OHCA)

Body functions and structures
(physical and mental/cognitive functions)

Activities
(Execution of tasks or actions by the child)

Participation
(Child's involvement in meaningful life situations)

Environmental factors
(Family situation, socioeconomic status)

Personal factors
(Age, sex, ethnicity)
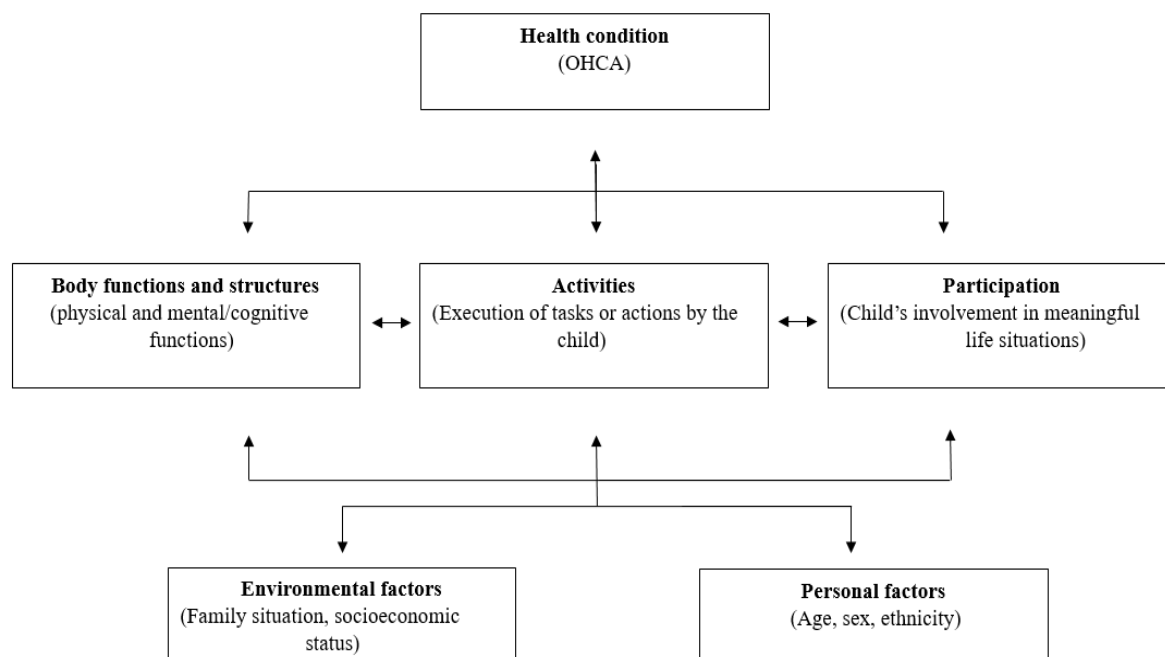
Figure 1. The International Classification of Functioning, Disability and Health for Children and Youth applied to pediatric OHCA survivors

OHCA= Out-of-hospital cardiac arrest

In 2021, a pediatric core outcome set for CA in children (P-COSCA) was developed by international multidisciplinary health care providers and parents/caregivers, with the purpose to avoid inconsistencies in outcome research (75). A core set of five outcomes was identified: survival, brain function, cognitive function, physical function, and basic daily life skills at different time points post-CA (table 1). The P-COSCA does not fully cover the ICF-CY.

Outcome (domains)	Measure	Time point	Methods
Survival		Hospital discharge and/or 3 mos after arrest Between 6-12 mos after arrest	Caregiver report Medical records Death registry
Brain function	PCPC	Baseline Hospital discharge and/or 3 mos after arrest Between 6-12 mos after arrest	Caregiver report Medical records
Cognitive function	PedsQL Scales	Between 6-12 mos after arrest	Caregiver report
Physical function	PedsQL Scales		
Basic daily life skills	PedsQL Scales Daily Activities Scale		

Table 1. P-COSCA

PedsQL= Pediatric Quality of Life Inventory; PCPC= Pediatric Cerebral Performance Category Scale

It should be possible to develop a scorings system which at least for the long-term outcome dichotomizes the outcome into 'good' or 'poor', based on the outcome set of P-COSCA, combined with domains of ICF-CY, such as participation and activities.

However, it is unlikely that a scoring system is helpful in the clinical setting directly following CA for the individual parent/caregiver, patient, or clinician due to different values and norms about the meaning and consequences of an outcome. We have to accept this and we cannot change this. However, it is still our duty to inform parents as accurately as possible about their child's expected prognosis, taking into account that percentages of good/poor outcome reflect a group and not an individual. It is inevitable that situations arise where clinicians and parents have diverging views regarding the acceptance of an expected poor clinical outcome with little to no functional recovery, possibly leading to parents' distrust of the medical team.

To avoid this situation, it is very important that clinicians should timely confer an accurate diagnosis and determine a prognosis. Furthermore, by implementing family-centered care, clinicians are able to explore the parent's wishes for their child, and parents are better involved in the treatment of their child (76). This way, shared decision making can be achieved together with parents, and treatment goals and options can be determined (77). If disagreement persists, an ethicist, a religious consultant or social worker can be consulted. Sometimes a second opinion is required to reach consensus with parents.

4b.Outcome of family

It is urgently necessary not only to assess the child's outcome, but also that of parents and other family members. How do they appreciate life after such a major life event with many uncertainties and strains? Many family members suffer from psychosocial and social sequelae

after hospital discharge, also known as 'post-intensive-care syndrome-pediatric' (PICS-p) (78). They will have to cope with their grieves and the trauma caused by the child's hospital admission and the sorrow that their previously healthy child will not the same person anymore. The future perspective of their child or sibling can be completely different. Additionally, families end up in a new situation where their child or sibling has neurological sequelae with a big impact on every family member. The child may not be independent anymore and may need help in every daily activity. Relations within a family may change, which can for example result in disintegration due to divorce. Parents may not be able to return to their jobs and sometimes they even lose their jobs with all the financial consequences that this entails.

On the other end of the spectrum, a life-threatening situation such as a pediatric OHCA can also bring more cohesion in the family. Parents are grateful that their child is still alive after this nerve-racking period (69).

Family functioning and well-being are important factors that have been demonstrated to have a positive effect on the child's outcome (79). There is an urgent need of structural support of parents and siblings by a professional team of social workers and psychologists– not only during the child's hospitalization but also afterwards. A support program needs to be developed, probably first in the context of research with the ultimate goal of implementing it as a standard of care. Within this program, parents and siblings must be provided with information and education and support. This is called a 'parent or family empowerment program'.

The first step in the development process, is implementing various questionnaires for parents and siblings that covers different aspects:

1. The experiences of parents and siblings around the CA-event and during hospitalization of their child or sibling. What were their needs during this very tense period, did they miss support of professionals? The surveying can be done both retrospectively and prospectively.

2. The health status, QoL, psychosocial functioning and participation of parents and siblings during hospitalization of their child or sibling and at different time points after hospital discharge, to be surveyed prospectively. This will gain good insight of how parents and siblings are doing and what their needs are.

The next step is setting up a focus group with people who are involved in the patient journey. Input is needed from physicians, nurses, social workers and psychologists with knowledge of critical illness (especially CA) and or involvement with follow-up. Moreover, input is needed from parents and siblings themselves. The aim of this focus group is the development of a support program.

Unresolved problems 5. and 6.

Potential solutions 5. and 6. Standardized follow-up program

5-6a. Adult extension to the Erasmus MC pediatric follow-up program

To find an answer to the unresolved problem of how children after OHCA will function on different domains in adulthood, our follow-up program needs to be extended into adulthood by designing a transition research protocol. As a start, we will design a cross-sectional study in which young adults aged 23-30 years are invited to the outpatient clinic for the assessment of cognitive functioning and academic achievements, physical functioning, health status, QoL and participation. An example of a design for this follow-up program is presented in Table 2. However, to develop this follow-up program more input is needed. Again, a focus group is warranted, including individuals who are/were involved in the patient journey of OHCA survivors (physicians, nurses, psychologists, social workers, patients, parents). From the

different point of views of the various stakeholders, it should be possible to determine the outcome domains that matter.

Domains	Tests	Performed by
Health status and physical functioning	Interviews physical and neurological exam Questionnaires regarding general health status and health perception	Pediatric intensivist Pediatric neurologist Patient and parents/caregivers
Neurocognitive functioning	Neuropsychological assessments Questionnaires regarding executive functioning	Psychologist Patient and parents/caregivers
Motor functioning	Motor function testing	Physical therapist
Quality of life	Questionnaires regarding QoL and health-related QoL	Patient and parents/caregivers
Mental health	Questionnaires regarding mental health, behavior, social-emotional functioning	Patient and parents/caregivers
Participation	Questionnaires regarding participation in home, community, society, jobs, relationships	Patient and parents/caregivers

Table 2. An example of design of adult follow-up program from the physician's point of view.

QoL= Quality of life

5-6b. Future perspectives follow-up program

We should not only extend the current follow-up program with follow-up into adulthood; the findings of the present PhD thesis offer an excellent opportunity to revise our existing follow-up program:

1. The study presented in **chapter 7,** focused on functional and neuropsychological outcomes in children after OHCA (for 2012-2017), but we did not describe the QoL and participation of these children. Parents and children were asked to fill in questionnaires in advance to the outpatient clinic visits 3-6 and 24 months after the arrest, but unfortunately the response rate was very low (<50%). The response rate might be improved by gently reminding parents to fill in the questionnaires, by explaining the aims of the questionnaires, and giving them the opportunity to fill out the questionnaires online during the visit. Moreover, striking information from the questionnaires should be discussed with parents and patients. When needed, parents and children should be offered support. For example, if parents have symptoms of post-traumatic stress disorder, we should refer them to an appropriate therapist. In our current follow-up program, all children are planned for neuropsychological assessment 3-6 and 24 months post-CA. Yet, we may wonder whether all children need to undergo the time-consuming neuropsychological testing. It may be more efficient to use stepped care: First, children, parents and teachers are asked to complete validated neuropsychological questionnaires with the purpose of screening for neuropsychological deficits. Second, when problems are reported, full neuropsychological assessment takes place.

2. When our follow-up program started in 2012, children and their parents were invited to the outpatient clinic 3-6, 12 and 24 months after OHCA. Recently we extended the program with visits at the child's ages of 5, 8 12 and 17 years. It is essential to evaluate outcome at these ages.

3. As already mentioned, there is an urgent need of a 'parent or family-empowerment program' supported by motivated parents/family members who went through this experience.

5-6c. Standardized national and international follow-up program

Our findings underline the need for a standardized follow-up program into adulthood as standard of care in OHCA survivors.

In 2017, a Dutch national guideline was developed regarding follow-up after critical illness and PICU admission, but not specifically for OHCA children (80). This guideline recommends outpatient clinic visits 3 to 6 months after PICU admission, and in case of problems, 12 months post PICU admission. During these visits, parents and children are asked to fill in validated psychological and neuropsychological questionnaires. Standardized interviews are held, and the child undergoes a physical exam and a neurological exam. Neuropsychological assessments as well as ancillary tests are performed on indication. Thereafter, the guideline recommends screening for problems at the ages of 5-6, 11-12 and 15-17 years, using validated psychological and neuropsychological questionnaires.

The Netherlands is a relatively small country with a good infrastructure, and medical care paid for by health insurance companies, which means that follow-up care with on-site visits is easily realized. By providing structured follow-up, problems can be detected in an early stage and targeted therapeutic interventions can be offered to improve outcomes and reduce costs, both direct and indirect costs.

Besides a national guideline, there is a need for an international guideline.

The above-describe P-COSCA (75) was designed for research purposes and not for primary care, and does not address follow-up into adulthood.

In our opinion, a standardized international follow-up program should include follow-up moments at fixed time points with physical, neurological and neuropsychological

assessments; it should also include monitoring by an educational psychologist of these children's development into adulthood, which may provide parents a realistic view of the strengths and weakness in their child's intellectual functioning. Neuropsychological assessment should at least include intelligence scores, attention, processing speed, memory and executive functioning. Moreover, psychosocial functioning, QoL and participation, may add useful information regarding the functioning of OHCA children in daily life.

One possible way to achieve international guidelines is to establish a long-term follow-up program within multicenter international collaborations such as the Pediatric Resuscitation PediRES-Q, in which our PICU department participates. In this collaborative (PI: Vinay Nadkarni, The Children's Hospital of Philadelphia), many pre-arrest, arrest and post-arrest data are collected in a web-based database. Another possibility is collaboration of members of the EPNS/ESPNIC. The P-COSCA paper might be used as a starting point and can be further elaborated. This will be a great challenge: In many countries the distance to a hospital is too great, which hampers on-site visits of patients and their caregivers. Moreover, many hospitals outside the Netherlands do not receive financial compensation for this follow-up program. Furthermore, there is little interest from PICUs in organizing a follow-up program.

National and international guidelines not only provide insight into the long-term outcome of children after OHCA in large groups and per age category, but have more advantages: In the study presented in **chapter 7,** we explored the association between PCPC and neuropsychological outcome, but found it hard to draw a solid conclusion because of the small sample size. Implementing a follow-up guideline widely generates many outcome data, providing the opportunity to examine the association between PCPC and neuropsychological outcome on a large scale. In addition, it will create opportunities to develop interventions to improve outcome.

In children with neurological injury caused by for example TBI, brain tumors or critical illness, there is growing evidence that cognitive rehabilitation and pharmacological interventions might influence outcome in a positive way. Pediatric brain tumor survivors might benefit from stimulant medications, which have been shown related to improvements in performance-based attention as well as improvements in academic competence (81, 82). In adolescents with severe TBI and prolonged disorders of consciousness, amantadine may promote functional recovery, although the drug's mechanism of action is unclear (83).

In addition, CogMed, a computerized intervention program targeting working memory, has been associated with improvements in visual working memory in survivors of pediatric cancer (84). Positive effects were also seen in children after neonatal extracorporeal membrane oxygenation (ECMO) therapy and/or survivors of congenital diaphragmatic hernia (at the age of 8-12 years), although this effect was temporary (85).

There is some evidence that physical exercise programs have an effect on the brain structure, including increased white matter and hippocampal volume and increased cortical thickness in multiple brain regions in pediatric brain tumor survivors (86, 87). In children with mild TBI, reduction of post-concussive symptoms and faster reaction times after moderate exercise have been reported (88).

Another promising technique to improve motor and cognitive functions is the use of virtual reality (VR) in neurorehabilitation. The therapy is provided through a computer-simulated environment where children interact with real-world-like objects and events through sight, sound, smell and touch (89). Recently, much attention has been paid to high-tech augmentative and alternative communication (AAC) systems, developed for patients with complex communication needs. AAC has been proven to improve communication in patients with communication impairments (90, 91). This includes unaided and aided communication systems. Examples of unaided systems are body signs and gestures. Aided communication

systems involve external equipment. Picture boards are examples of low-tech AAC, while electronically powered devices include voice output and allow users to store and retrieve messages are examples of high-tech AAC. The use of high-tech AAC has significantly increased in recent years, primarily due to the accessibility through mobile phones and tablet touch-screen devices (92). For children with neurological deficits after OHCA the effect of such interventions has yet to be investigated.

Collaboration between our institution with Delft University of Technology and Rijndam Rehabilitation Center would create a great opportunity to investigate intervention methods at the short term, such as AAC strategies, and at the long term, such as VR and computer-based intervention programs. It is preferable to start with AAC interventions during PICU admission, with involvement of the parents, because improvement of communication reduces patients' anxiety.

Part 4. Prediction

One of the goals of this PhD research was to develop an outcome prediction model in children after OHCA, especially for those who remain comatose after CA. The question was: Are we able to predict a long-term outcome within a few days after CA based on factors such as the duration of CPR, first lactate after ROC, results of neurological exam and additional tests, etc.?

In the study presented in **chapter 6** we showed that children with a shockable pediatric OHCA had an almost nine times higher odds of long-term good neurologic survival compared to children with a non-shockable rhythm, adjusted for confounders. The study of Meert et al., a secondary analysis of THAPCA-OH trial also showed that shockable rhythm was associated with greater 12-month survival with favorable neurobehavioral functioning, assessed with the Vineland Adaptive Behavior Scales (93). Our results might implicate that the efforts for

improving outcome of pediatric OHCA should focus on early recognition and treatment of shockable OHCA at scene, and the importance of improvements in the chain of survival (e.g., bystander basic life support (BLS), public access to and use of AED and adequate emergency medical service response)(94).

To proceed towards the ultimate goal of a prognostic model we need to take into account the following factors:

First, outcome is determined by many factors, such pre-CA variables (SES, medical history), CA variables (witnessed CA, rhythm, bystanders BLS, quality BLS, duration of CA), and post-CA variables (post-CA care at PICU, results of ancillary tests, intensity of rehabilitation etc.). It is likely that we are not yet aware of other variables associated with a good or poor outcome, or which have not been studied in detail yet (see introduction). We do know that all these variables do influence outcome, but unfortunately evidence is often lacking and it is unknown what each variable's predictive value is for the prognosis for each individual patient. Second, all observational research presented in this thesis was single center. Because OHCA in children is uncommon and the mortality is high (60% in our cohort), our patient samples were small. Third, in the attempt to develop a prediction model for critically ill children, one is always faced with the problem of self-fulfilling prophecy. It is unavoidable that results of tests and examinations are taken into account in the decision whether or not to continue treatment.

UNRESOLVED PROBLEMS 7.

Prediction models with the purpose to predict outcome in children after OHCA do not exist so far

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Unresolved problem 7.

Potential solution 7. International collaboration

The potential solution of this unsolved problem overlaps to some extent with the potential solution of problem 1.

By creating national and international collaboration, standardized care can be developed, preferably with a high level of evidence by using the Delphi technique – not only with medical experts, but also with involvement of parents (95). All patient data (pre-OHCA, OHCA and post-OHCA data) can be collected in an electronic database and analyzed. This way guidelines and prediction models can be developed.

An existing international collaboration, which offers opportunities to develop a prediction model, is PediRES-Q, in which our PICU department participates. Various international observational CA studies are generated from the PediRES-Q with large sample sizes. Even if a prediction model can be developed, we must keep in mind that it should never be at the expense of individualized patient care.

Future research plans (Erasmus MC)
Investigate psychosocial functioning, QoL and participation in pediatric OHCA survivors and their parents
Investigate outcome of pediatric OHCA survivors at the ages of 5,8,12 and 17 years
Investigate long-term outcome of pediatric OHCA survivors at the age of 23-30 years
Development and implementation of a support program for parents and siblings of pediatric OHCA survivors
Investigate the potential predictive role of quantitative MRI (DTI) in children after OHCA
Investigate the role of QEEG in the prediction of outcome after OHCA by designing a machine learning algorithm for cEEGs in children admitted at our PICU after OHCA (together with Delft University of Technology)

Investigate intervention methods at the short term, such as AAC strategies, and at the long term, VR and computer-based intervention programs, together with Delft University of Technology and Rijndam Rehabilitation Center with the aim to improve outcome of pediatric OHCA survivors.

Table 3. Summary of future research plans Erasmus MC

AAC= augmentative and alternative communication; cEEG= continuous electroencephalography; DTI= diffusion tensor imaging; MRI= Magnetic resonance imaging; OHCA= Out-of-hospital cardiac arrest; PICU= Pediatric Intensive Care Unit; QEEG= Qualitative electroencephalography; QoL= Quality of life; VR= Virtual reality

International research agenda

Establish an international pediatric CA consortium with members of EPNS/ESPNIC and PediRES-Q with special interest in outcome.

Aims:

1. The development of neuro-prognostication guidelines and prediction model by

-Developing standardized care for children after CA, followed by

-Collecting data in an international database, followed by

-Evaluating all collected data

2. The development of a standardized follow-up program for pediatric OHCA

   survivors

Development of a definition of a 'good' or 'poor' outcome by Steering committee from P-COSCA paper.

Table 4. Summary of international research agenda

CA= Cardiac arrest; EPNS= European Paediatric Neurology Society; ESPNIC= European Society of Paediatric and Neonatal Intensive Care; OHCA= Out-of-hospital cardiac arrest; P-COSCA= Pediatric core outcome set for CA in children; PediRes-Q= Pediatric Resuscitation Quality Collaborative

Conclusion

Pediatric OHCA is rare, and associated with high mortality. Although most survivors have a good outcome reflected by the PCPC score 2 years post-OHCA, they may have cognitive deficits in domains of attention and intelligence and executive function at 2 years. Predicting outcome in children after OHCA, in particular when they are comatose, is a challenging for physicians. In Europe, neuro-prognostication practices differ between countries and hospitals. International prognostication guidelines and prediction models are non-existent so far.

There is an urgent need of developing an international neuro-prognostication guideline with a prediction model and an international standardized follow-up program. This program should continue into adulthood with longitudinal data acquisition in order to fully understand the long-term consequences and impact of OHCA in childhood (see tables 3 and 4). This can only be achieved through national and international collaboration.

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Chapter 9.

Summary

Samenvatting

Summary

The aim of this thesis was to investigate the current practice regarding neuro-prognostication and decision making in children after cardiac arrest (CA). Furthermore, we aimed to study the short- and long-term neurocognitive outcome in a homogeneous cohort of children after out-of-hospital cardiac arrest (OHCA), admitted to the pediatric intensive care unit (PICU) of the Erasmus MC Sophia Children's Hospital in Rotterdam, the Netherlands, in a prospective longitudinal way, using repeated and validated measures.

Chapter 2 gave an overview of the literature from the last 20 years on neuromonitoring modalities in comatose children after CA. Their potential prognostic value in predicting neurological outcome at an early stage was evaluated.

Methods included neurological exam, routine electroencephalography (EEG) and continuous EEG (cEEG), transcranial Doppler (TCD), brain Magnetic Resonance Imaging (MRI) and computed tomography (CT), plasma biomarkers, somatosensory evoked potentials (SSEP), and brainstem auditory evoked potentials (BAEP). Twenty-seven neuromonitoring studies met the inclusion criteria and were reviewed. We concluded that the precise role of neuromonitoring methods is still unclear, because no single test is 100% accurate yet. Thus, these neuromonitoring methods must be interpreted with extreme caution in the context of the patient's individual clinical neurological status.

In **Chapter 3** the results of an international survey were presented. The aim of this survey was to describe current practices in European PICUs regarding neuro-prognostication in comatose children after CA and, in particular the methods used, their timing, and end-of-life decision making. The survey was sent to European Paediatric Neurology Society (EPNS) and European Society of Paediatric and Neonatal Intensive Care (ESPNIC) members. One-

hundred-eight respondents, mainly pediatric intensivist and neurologists, representing 23 countries and 45 PICUs, (partly) completed the survey. Only one nation had a national guideline for neuro-prognostication after pediatric CA. Regarding methods to assess neurological outcome in comatose children post-CA, neurological exam (Glasgow Coma Score (GCS) and brainstem reflexes), MRI and EEG were considered most useful, but the actual use and timing of these tests differed. Definition of a poor outcome varied among the respondents. The aftermath of a futile prognosis (established from <48 hours up to > 14 days after CA) differed between respondents and countries, varying from withdrawal of life sustaining therapies (WLST) to continuation of intensive care treatment with or without restrictions.

The study presented in **chapter 4** explored the timing and cause of death in 113 children admitted to our PICU following return of circulation (ROC) after OHCA between 2012 and 2017. Fifty-one children survived to hospital discharge. Of the 62 non-survivors, causes of death were: brain death (BD) (18/62), WLST due to poor neurologic prognosis (WLST-neuro) (42/62), WLST due to refractory circulatory and/or respiratory failure (1/62) and recurrent CA (1/62). Compared with non-survivors, survivors had more witnessed arrest, more initial shockable rhythm, shorter cardiopulmonary resuscitation (CPR) duration and more favorable clinical neurological exam within 24h after PICU admission. Basic, CPR-event and post-ROC (except for number of Extracorporeal membrane oxygenation (ECMO)) characteristics did not significantly differ between WLST-Neuro and BD patients. Timing of decision making to WLST due to poor neurological prognosis ranged from 0 to 18 days (median 0 days). The decision to WLST was based on neurologic exam (100%), electroencephalography (44%) and/or brain imaging (35%).

The purpose of the study in **chapter 5** was to examine whether early brain MRI including diffusion weighted imaging (DWI) predicts neurological outcome at hospital discharge and two years post-OHCA in children. Forty children, admitted to our PICU after OHCA between 2012-2017, who received MRI within 1 week post-OHCA were included in the study. We showed that a normal brain MRI (without post-hypoxic injury) on T1/T2 weighted images and DWI within 1 week after pediatric OHCA was 100% predictive for a good neurological outcome at 2 years post-OHCA. Conversely, the presence of extensive injury (≥50% of the cortex/white matter or in 4 or more defined brain regions (with or without involvement of deep grey matter)) on T1/T2 and DWI was 100% predictive for a poor neurological outcome or death at hospital discharge and 2 years post-OHCA. However, solely based on MRI with focal injury (<50% of the brain), it was impossible to predict neurological outcome accurately at hospital discharge or 2 years post-OHCA.

In **Chapter 6** we investigated the association between first documented rhythm and long-term outcomes in a pediatric OHCA cohort over 18 years. Three-hundred-sixty children who experienced OHCA between 2002-2019 and subsequently admitted to our emergency department or PICU were included. Fourteen percent of the total cohort had a shockable rhythm, in adolescents (aged 12-18 years) this was 39%. Thirty-nine percent survived to hospital discharge. On median follow-up interval of 25 months, 81% of hospital survivors had a favorable neurologic outcome. Shockable rhythm had significantly higher odds of survival with long-term favorable neurologic outcome compared to non-shockable rhythm.

In **chapter 7** longitudinal functional and neuropsychological outcomes 3-6 and 24 months post-OHCA were investigated. Further, the association between pediatric cerebral performance category (PCPC) score and intelligence scores was explored. The total eligible

cohort consisted of 49 OHCA survivors admitted to our PICU between 2012 and 2017. At 3-6 and 24 months post-OHCA, respectively 74 and 73% had a good PCPC score. Compared with normative data, OHCA children obtained worse sustained attention and processing speed scores 3-6 and 24 months post-OHCA. At 24 months, they also obtained worse intelligence, selective attention and cognitive flexibility scores. In children tested at both time-points, no significant changes in neuropsychological outcomes were found over time. Intelligence scores did not correlate with PCPC.

In **chapter 8** we discussed the findings presented in this thesis, with their strengths, weaknesses. We proposed recommendations for future studies.

Samenvatting

Een doel van dit proefschrift was het onderzoeken van de huidige gang van zaken omtrent het stellen van een neurologische prognose na het doormaken van een hartstilstand op de kinderleeftijd. Een ander doel was de korte en lange termijn uitkomsten op neurologisch en cognitief vlak onderzoeken bij kinderen die een hartstilstand hebben gehad buiten het ziekenhuis en hierna opgenomen zijn op de Intensive Care voor Kinderen (ICK) in het Erasmus MC Sophia kinderziekenhuis in Rotterdam. Dit is prospectief en longitudinaal uitgevoerd, met herhaalde en gevalideerde meetinstrumenten.

In **hoofdstuk 2** is de literatuur van de afgelopen 20 jaar samengevat over de voorspellende waarde van neuromonitoring modaliteiten bij comateuze kinderen, kort na een hartstilstand. Er is gekeken naar neurologisch onderzoek, routine elektro-encefalogram (EEG), continu EEG (cEEG), transcraniële doppler (TCD), Magnetic Resonance Imaging (MRI) en computer tomografie (CT) hersenen, plasma biomarkers, Somato Sensory Evoked Potential (SSEP) en brainstem auditory evoked potentials (BAEP). Zeven en twintig studies voldeden aan de inclusiecriteria en zijn beoordeeld. Wij concludeerden dat de precieze rol van neuromonitoring modaliteiten onduidelijk is, omdat tot op heden geen enkele test 100% betrouwbaar is.
Dit betekent dat de neuromonitoring modaliteiten met extreme voorzichtigheid geïnterpreteerd dienen te worden binnen de context van de klinische neurologische status van de individuele patiënt.

In **hoofdstuk 3** worden de resultaten gepresenteerd van een internationale enquête. Het doel van deze enquête was de huidige gang van zaken te beschrijven binnen Europese afdelingen Intensive Care Kinderen (ICKs) ten aanzien van de neurologische prognose stelling in comateuze kinderen na een hartstilstand. Er werd in het bijzonder gekeken naar de methodes

en testen die gebruikt werden, op welk tijdstip na de hartstilstand, en naar beslissingen rondom het al dan niet staken van een behandeling.

De enquête werd verzonden naar leden van de European Paediatric Neurology Society (EPNS) en de European Society of Paediatric and Neonatal Intensive Care (ESPNIC).

Honderd acht respondenten, met name kinderintensivisten en kinderneurologen, afkomstig uit 23 landen en 45 ICKs, hebben de enquête (deels) ingevuld.

Slechts 1 land bleek een nationale richtlijn te hebben betreffende neurologische prognose stelling na hartstilstand bij kinderen.

Neurologisch onderzoek (Glasgow Coma Score (GCS) en hersenstamreflexen), MRI en EEG werden als meest nuttig beschouwd om de neurologische uitkomst vast te stellen, maar de daadwerkelijke toepassing en timing hiervan waren wisselend.

De definitie van een slechte uitkomst verschilde tussen de respondenten.

Wanneer een infauste prognose vastgesteld werd (tijdsinterval varieerde van < 48 uur tot >14 dagen), dan waren de consequenties verschillend tussen respondenten en landen. Dit varieerde van het staken van de intensive care behandeling tot continueren van de behandeling op de ICK, met of zonder restricties.

De studie gepresenteerd in **hoofdstuk 4** onderzocht de timing en doodsoorzaak bij 113 kinderen die tussen 2012-2017 werden opgenomen op de ICK van ons ziekenhuis na een hartstilstand buiten het ziekenhuis en waarbij de circulatie weer hersteld was.

Een en vijftig kinderen hebben het ziekenhuis levend verlaten. De doodsoorzaken van de 62 overleden kinderen waren als volgt: hersendood (18/62), staken van de behandeling vanwege sombere neurologische prognose (42/62), staken van de behandeling vanwege therapie resistent cardiaal en of circulatoir falen (1/62) of opnieuw een hartstilstand (1/62).

De overlevenden hadden, vergeleken met overleden kinderen, vaker een hartstilstand in bijzijn van een ander, vaker een schokbaar ritme, de duur van de reanimatie was korter en het neurologisch onderzoek binnen 24 uur na opname was gunstiger.

Er waren geen verschillen in basis-, reanimatie- en post-reanimatie variabelen (behoudens het aantal Extra Corporele Membraan Oxygenatie (ECMO) behandelingen) tussen de groep kinderen waarbij de behandeling gestaakt was vanwege een sombere neurologische prognose en tussen de groep kinderen die hersendood waren. De tijd die nodig was om tot de beslissing te komen om de behandeling te staken vanwege een sombere neurologische prognose varieerde van 0 tot 18 dagen (mediaan 0 dagen). Deze beslissing was gebaseerd op neurologisch onderzoek (100%), EEG (44%) en beeldvorming van de hersenen (35%).

Het doel van **hoofdstuk 5** was om te onderzoeken of een vroege MRI hersenen met diffusion weighted imaging (DWI) bij een kind na hartstilstand buiten het ziekenhuis de neurologische uitkomst kan voorspellen op het moment van ontslag uit het ziekenhuis en 2 jaar later. Er werden 40 kinderen geïncludeerd, die opgenomen waren op de ICK van ons ziekenhuis tussen 2012-2017 en vervolgens een MRI hersenen hebben gekregen binnen 1 week na de hartstilstand.

We hebben aangetoond dat een MRI hersenen zonder tekens van hypoxische schade op T1 en T2 gewogen opnames en op DWI, 100% voorspellend was voor een goede uitkomst 2 jaar na de hartstilstand. Daarentegen was een MRI met tekens van uitgebreide schade (≥50% van de grijze of witte stof of in 4 of meer gedefinieerde hersengebieden (al dan niet met betrokkenheid van de diepe grijze stof)) op T1 en T2 gewogen opnames en op DWI 100% voorspellend voor een slechte neurologische uitkomst of overlijden op het moment van ziekenhuis ontslag of 2 jaar na de hartstilstand. Indien er sprake was van focale schade (<50% van de hersenen), dan was het niet mogelijk om alleen op basis van de vroege MRI een

neurologische uitkomst te voorspellen voor zowel ontslag ziekenhuis als 2 jaar na de hartstilstand.

In **hoofdstuk 6** onderzochten we de associatie tussen het eerst gedocumenteerde hartritme en de lange termijn uitkomsten van een cohort met kinderen met een hartstilstand buiten het ziekenhuis over een periode van 18 jaar.

Drie honderd zestig kinderen werden geïncludeerd, die tussen 2002 en 2019 een hartstilstand hebben gehad buiten het ziekenhuis, waarna ze opgenomen zijn op de spoedeisende hulp of ICK van ons ziekenhuis.

Veertien procent van het totale cohort had een schokbaar hartritme, bij de adolescenten (12 tot 18 jaar) was dit 39%.

Negen en dertig procent heeft het ziekenhuis levend verlaten. Bij een mediane follow-up van 25 maanden had 81% van de overlevenden een goede neurologische uitkomt.

De kans op een goede lange termijn uitkomst (overleven met een goede neurologische uitkomst) was negen keer zo hoog in het geval van een schokbaar hartritme, vergeleken met een niet-schokbaar hartritme, zelfs na correctie van confounders.

In **hoofdstuk 7** zijn de functionele en neuropsychologische uitkomsten bij kinderen onderzocht, 3-6 en 24 maanden na hartstilstand buiten het ziekenhuis. Daarnaast werd de associatie tussen de pediatric cerebral performance category (PCPC) score en intelligentie scores geëxploreerd.

Het totale cohort bestond uit 49 kinderen (overlevenden) die opgenomen zijn geweest op onze PICU na een hartstilstand buiten het ziekenhuis tussen 2012 en 2017.

Drie tot zes en vier en twintig maanden na de hartstilstand had respectievelijk 74% en 73% een goede uitkomst, uitgedrukt in PCPC score.

Drie tot zes en vier en twintig maanden na de hartstilstand scoorden de kinderen lager op het gebied van vastgehouden aandacht en verwerkingssnelheid in vergelijking met de norm. Daarnaast scoorden ze 24 maanden na de hartstilstand ook lager op intelligentie, selectieve aandacht en cognitieve flexibiliteit. Bij de kinderen die op beide tijdstippen neuropsychologisch werden getest, werden in de loop van de tijd geen significante veranderingen in neuropsychologische uitkomsten gevonden.

Intelligentie scores correleerden niet met de PCPC scores.

In **hoofdstuk 8** bespraken we de bevindingen van dit proefschrift met de sterke en zwakke punten en de beperkingen. Tevens hebben we aanbevelingen gedaan voor toekomstige studies.

Chapter 10.

List of abbreviations

Curriculum Vitae

List of publications

PhD portfolio

Dankwoord

List of abbreviations

AAC = Augmentative and alternative communication

ADC = Apparent diffusion coefficient

AED = Automated external *defibrillator*

AHA = American Heart Association

APLS = Advanced pediatric life support

BAEP = Brainstem auditory evoked potentials

BD = Brain death

BLS = Basic life support

Bourdon = Bourdon Vos cancellation test

BRIEF = Behaviour Rating Inventory of Executive Function

BS = Burst suppression

CA = Cardiac arrest

cEEG = Continuous electroencephalography

COSCA = Core outcome set for cardiac arrest

CP = Cerebral palsy

CPR = Cardiopulmonary resuscitation

CT = Computed tomography

DTI = Diffusion tensor imaging

DWI = Diffusion weighted imaging

EAN = European Academy of Neurology

EBC = European Brain Council

ECMO = Extracorporeal membrane oxygenation

ECPR = Extracorporeal cardiopulmonary resuscitation

EEG = Electroencephalography

ED = Emergency department

EMS = Emergency Medical Service

EPNS = European Paediatric Neurology Society

ESPNIC = European Society of Paediatric and Neonatal Intensive Care

FLAIR = Fluid attenuated inversion recovery

FSS = Functional Status Scale Score

GCS = Glasgow Coma Scale

GMFCS = Gross Motor Function Classification System

GOS = Glasgow Outcome Scale

GWM = Gray-white matter

HEMS = Helicopter Emergency Medical Service

HIE = Hypoxic ischaemic encephalopathy

HUI:1 = Health Utilities Index Mark 1

ICF-CY = The International Classification of Functioning, Disability and Health for Children and Youth

IHCA = In-hospital cardiac arrest

IQ = Intelligence quotient

IQR = Interquartile range

Koschi = King's Outcome Scale for Childhood

MCA = Middle cerebral artery

MRI = Magnetic resonance imaging

MRI DWI = Magnetic resonance imaging diffusion weighted imaging

NIRS = Near infrared spectroscopy

NPV = Negative predictive value

NSE = Neuron-specific enolase

OHCA = Out-of-hospital cardiac arrest

OR = Odds ratio

PCPC = Pediatric Cerebral Performance Category Scale

P-COSCA = Pediatric core outcome set for CA in children

PediRes-Q = Pediatric Resuscitation Quality Collaborative

PedsQL= Pediatric Quality of Life Inventory

PI = Pulsatility index

PICS-p = Post-intensive-care syndrome- pediatric

PICU = Pediatric Intensive Care Unit

PIQ = Performance intelligence quotient

PREMs = Patient Reported Experience Measures

PROMs = Patient Recorded Outcome Measures

PPV = Positive predictive value

PS = Processing speed

PSOM = Pediatric Stroke Outcome Measure

QEEG = Qualitative electroencephalography

QoL = Quality of life

pOHCA = Pediatric out-of-hospital cardiac arrest

Rey-AVLT= Rey auditory verbal learning test

Reyrec = Rey-Osterrieth complex figure test Color Word Test

ROC = Return of circulation

ROSC = Return of spontaneous circulation

S100b = S100 calcium-binding protein B

SD = Standard deviation

SES = Socioeconomic status

SHD = Survival to hospital discharge

SIDS = Sudden Infant Death Syndrome

SSEP = Somatosensory evoked potentials

Stroop = Stroop Color Word Test

TBI = Traumatic brain injury

TCD = Transcranial Doppler

TH = Therapeutic hypothermia

THAPCA = Therapeutic Hypothermia after Pediatric Cardiac Arrest

THAPCA-OH = Therapeutic Hypothermia after Pediatric Cardiac Arrest Out-of-Hospital

TIQ = Total intelligence quotient

TMTB = Trail-Making Test part B

TOF = Train of Four

TTM = Targeted temperature management

VABS II = Vineland adaptive behavior scales-second edition

VIQ = Verbal intelligence quotient

VMI = Beery Developmental Test of Visual Motor Integration

VR = Virtual reality

WHO = World Health Organization

WLST = Withdrawal of life sustaining therapies

WLST-Cardiopulmonary = Withdrawal of life sustaining therapies due to refractory circulatory and/or respiratory failure

WLST-neuro = Withdrawal of life sustaining therapies due to poor neurological prognosis

Curriculum Vitae

Maayke Hunfeld was born on September 12[th] 1980 in Waalwijk. She grew up in Kaatsheuvel and received her Atheneum degree at the Doctor Mollercollege in Waalwijk in 1998.

She started her medical training in 1998 at Leiden University and obtained her medical degree in 2005.

She worked as a resident (ANIOS) at the Department of Neurology in Haga Teaching Hospital in The Hague in 2005. In 2006 she started her neurology training in Haga Teaching Hospital.

She interrupted her training for a year in 2011 for a neurology research project (an epilepsy model in rats) at Flinders Medical Center in Adelaide, Australia.

She completed a pediatric neurology fellowship at the Wilhelmina Children's Hospital in Utrecht in 2012.

After completing her neurology training in December 2012, she followed a training in Pediatrics and Neonatology from January 2013 until April 2014 at the Juliana Children's Hospital in The Hague and the Wilhelmina Children's Hospital in Utrecht. She completed her training in pediatric neurology in 2014.

From May 2014 until August 2014 she worked in Kempenhaeghe, Academic Center for epilepsy.

Since September 2014 she has been working as a pediatric neurologist at the Department of Pediatric Neurology and Intensive Care and Department of Pediatric Surgery at the Erasmus MC Sophia Children's Hospital.

In 2016 she commenced her PhD project on pediatric out-of-hospital cardiac arrest under supervision of prof. dr D. Tibboel, dr C.M.P. Buysse and dr C.E. Catsman-Berrevoets.

Maayke lives in Rotterdam together with Joost and their children Boris and Okke.

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PhD Portfolio

Name of PhD Student   Maayke Hunfeld
Erasmus MC Department   Intensive Care and Department of Pediatric
                                     Surgery
                                     Department of Pediatric Neurology
PhD period   Jan 2017-July 2021
Promotors   Prof. dr. D. Tibboel
Copromotors   Dr. C.M.P. Buysse
                                     Dr. C.E. Catsman-Berrevoets

	Year	Workload (ECTS)
1. PhD training		
General courses		
Erasmus MC - BROK®	2014	1.5
Erasmus MC - Basic Introduction Course on SPSS	2017	1.0
Erasmus MC – BROK® renewal	2018	1.5
EGSL - Academic Integrity	2020	1.0
National presentations		
Hersenletsel congres	2017	0.5
ICK refereeravond	2019	0.5
Nederlandse reanimatie raad	2019	0.5
ICK refereeravond	2020	0.5
Neurologie refereeravond	2020	0.5
Meetings		
Biemond neurology course	2016	1.0
Biemond neurology course	2017	1.0
Biemond neurology course	2018	1.0
Biemond neurology course	2019	1.0
Biemond neurology course	2020	1.0
PICU research meeting	2018 - present	1.0
International conferences and presentations		
EPNS congress Vienna	2015	1.5
ICNA congress Amsterdam	2016	2.0
Masterclass EPNS Cambridge	2017	1.5
EAPS congress Paris	2017	1.5
Masterclass EPNS Cambridge	2018	1.5
PREM congress Brussel	2019	1.0
ESPNIC congress Salzburg	2019	2.0
Neoheart conference virtual	2020	0.5
ESPNIC congress virtual	2021	1.0
2. Teaching		
Neurology teaching residents pediatrics	2016	0.5
Neurology-neuro critical care teaching fellow intensivists	2016	0.5
Neurology-neuro critical care teaching fellow intensivists	2019	0.5
Teach-the-teacher III	2019	0.5
Course communication organ donation	2021	0.2
PICU/Neurology teaching (nursing staff and residents PICU/neurology)	2017 - present	1.0

3. Other		
Member dutch guideline: Radiologische diagnostiek bij de acute trauma-opvang van kinderen	2020 - present	1.0
Member dutch guideline: Advies expertise centra wet langdurige zorg	2020	1.0

ECTS = European Credit Transfer and Accumulation System; 1 ECTS credit represents 28 hours

Dankwoord

'Research is what I am doing when I don't know what I am doing.' Toen ik eind 2014 begon als kinderneuroloog op de Intensive Care Kinderen besefte ik mij nog niet dat prognosestelling bij kinderen met een potentieel beschadigd brein zo'n essentieel onderdeel zou zijn van mijn werkzaamheden en dat dit uitermate lastig en precair kan zijn. In het bijzonder voor kinderen die niet wakker worden na een reanimatie.

Richtlijnen omtrent prognose stellen ontbreken en collega kinderneurologen en intensivisten zitten regelmatig niet op één lijn als het gaat om het voorspellen van een lange termijn uitkomst. Dit zijn voor mij de belangrijkste redenen geweest om hier onderzoek naar te gaan doen. Het is hard werken geweest, maar ik heb het met heel veel plezier gedaan, het onderwerp fascineert me enorm en ik heb fijne en kundige mensen om me heen gehad die me enorm geholpen en gemotiveerd hebben. Ik ben trots op het eindresultaat en ik durf te zeggen dat we echt een stapje verder gekomen zijn.

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