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Factors associated with poor neurological outcome in children after abusive head trauma: A multicenter retrospective study

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ABSTRACT

Background: Abusive Head Trauma (AHT) remains the leading cause of brain injury in infants. **Objective:** This study aims to describe a cohort of patients with AHT and identify early risk factors associated with poor neurological outcome.

Participants and setting: Children under one year old admitted to a Pediatric Intensive Care Unit (PICU) with a suspected or confirmed diagnosis of AHT were included. Neurological outcome was assessed by the Pediatric Overall Performance Category score (POPC) at discharge from the hospital and at two years of follow-up.

Methods: A multicentre retrospective study was conducted over 8 years (from January 2012 to December 2020).

Results: A total of 117 patients (mean age 4.3 (+/- 2.5) months, 61 % boys) from three PICUs were included. A total of 99 (85 %) patients completed a 2-year follow-up. Sixty-one (52 %) and 47 (40 %) children with AHT had a POPC (pediatric overall performance category) score ≥ 2 at discharge from ICU and discharge from hospital, respectively (meaning they had at least a moderate disability). Fifty-one (44 %) had a POPC score ≥ 2 at 2-year follow-up, including 19 patients (19 %) with severe disabilities. The main neurological disabilities were neurodevelopmental ($n = 38$, 35 %), hyperactivity disorder ($n = 36$, 33 %) and epilepsy ($n = 34$, 31 %). After analysis according to the hierarchical model, the occurrence of a cardiorespiratory arrest and a low Glasgow Coma Score at admission stand out as factors of poor neurological outcome. **Conclusion:** This study highlights the wide range of neurological disabilities in children with AHT. Early and multidisciplinary follow-up is crucial to limit the impact of neurological disability.

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1. Background

Abusive Head Trauma (AHT) is the leading cause of brain injury in infants, resulting in severe neurological, cognitive and developmental impairments (Mian et al., 2015; Vinchon, 2017). It mainly affects children under six months of age, with a clear predominance of boys (Antonietti et al., 2019; Lind et al., 2016). The diagnosis of AHT is usually based on several clinical and radiological components, such as subdural hematoma (most often multifocal), rupture of the bridging veins on brain imaging, and retinal hemorrhages (Caffey, 1972; Christian, Block, Committee on Child, Neglect, & American Academy of, 2009; Duhaime et al., 1987; Laurent-Vannier et al., 2011). In France, recent diagnostic guidelines, based on the observed lesions and the alleged history, help clinicians to identify and manage patients with AHT (Santé, 2017).

Although subdural hematoma is likely to cause severe neurologic damage, secondary brain insults due to hypoxia, ischemia, and metabolic or inflammatory response, may contribute to poor neurological outcomes (Ichord et al., 2007). Overall, studies published so far report relatively severe outcomes following AHT (Anderson et al., 2013; Jackson et al., 2021; Lind et al., 2016). The rates of severe impairments tend to increase over time, as children grow into their deficits because they do not meet expected developmental milestones, while environmental demands increase (Jackson et al., 2021; Lind et al., 2016). This is particularly true for academic outcome, with 30 % of children receiving special education services because of cognitive, sensory and behavioral deficits (Lind et al., 2016). Factors reported in the literature to be associated with worse outcomes include demographic factors, health insurance coverage and initial severe presentation (Chevignard & Lind, 2014; Lind et al., 2016; Nuno, Pelissier, Varshneya, Adamo, & Drazin, 2015).

In addition to the disabilities related to the brain injury, outcome may be significantly affected by environmental and demographic factors (Anderson et al., 2001; Badger, Waugh, Hancock, Marks, & Oakley, 2020; Billette de Villemeur & Chabrol, 2019; Crowe, Catroppa, Babl, Godfrey, & Anderson, 2021; Lind et al., 2016). Indeed, family dysfunction, low parental social-economic status, and prior quality of child care have been reported to be associated with worse outcomes in this population (Billette de Villemeur & Chabrol, 2019; Lind et al., 2016; Nuno et al., 2015). Thus, follow-up should be carried out in close collaboration with the justice and social services, in order to also ensure the best possible environmental context to limit the impact of disabilities.

Lack of follow-up and care may exacerbate neurological disability of patients with AHT. The extremely high rates of patients lost to follow-up (that increase with time since injury) in this population in previous reports may significantly impact patient outcome, as timely adequate care may not be provided (Antonietti et al., 2019). Thus, the aims of this study were 1/ to assess neurological outcome and level of disability 2 years after AHT diagnosis in a large multi-center setting, 2/ to determine early injury-related risk factors associated with more severe neurological outcomes. We hypothesized that higher levels of disability would be associated with severe initial clinical presentation (i.e., coma, cardio-respiratory failure, uncontrolled seizures or status epilepticus, extent of brain lesions, especially diffuse anoxic lesions, and degree of atrophy). The early identification of patients at risk of severe neurological impairment could optimize their management and follow-up.

2. Methods

2.1. Study design and population

This is a retrospective, multicenter and observational study conducted in the Auvergne-Rhone-Alpes region in France. The study was approved by the regional research committee (Comité d'Éthique du Centre d'Investigation Clinique de Clermont-Ferrand, France, IRB 5891) and follows the STROBE guidelines (Ghaferi, Schwartz, & Pawlik, 2021). Parents of patients had been informed, and non-opposition had been searched before data collection. Written consent for retrospective data collection in medical files was not necessary according to the French regulation.

Eligible patients were identified on the International Classification of Disease (CIM-10) (codes G00-G99, S00-T98, V01-Y98) database. Data acquired during the study period were extracted from an Intensive Care Unit (ICU) information management system (Centricity™ High Acuity Critical Care, GE Healthcare, Vélizy, France).

Patients younger than one year, who were admitted over 8 years (2012–2020) to one of the three participating Pediatric Intensive Care Units (PICUs), were included. These three PICUs, according to regional care pathways, are designed to centralise care for infants with brain trauma and AHT suspicion (according to the French 2012–2013 recommendations (Santé, 2017)). Children with previously known or diagnosed brain lesions or neurological disease were excluded.

According to the French recommendations, AHT is defined as (in the absence of a history compatible with the observed lesions, and after elimination of differential diagnoses):

- « Confirmed » in case of:

1. plurifocal subdural hematoma associated with blood clot at the convexity indicating the rupture of bridge veins or;
2. plurifocal subdural hematoma associated with retinal hemorrhages or;
3. unifocal subdural hematoma associated with cervical/spinal lesions.

- « Suspected » in case of:

1. plurifocal subdural hematoma without other lesions or;

2. unifocal subdural hematoma with retinal haemorrhage limited to the posterior pole or retinal haemorrhage affecting the periphery and/or several layers of the retina, whether unilateral or bilateral.

2.2. Outcome measures

The primary outcome measure was the Pediatric Overall Performance Category (POPC) scale, designed by Fiser et al. in 2000 (Fiser, 1992) to describe the general functional physical status. The POPC yields 6 categories of outcome, scored from 1 to 6. Scores include 1 for good, 2 for mild disability, 3 for moderate disability, 4 for severe disability, and 5 for vegetative state or coma (6 indicates death) (see Supplementary Material).

In our study, POPC measured at hospital discharge and at 2 years post-injury was retrospectively collected from the patients' medical reports. A POPC score ≥ 2 at hospital discharge and 2 years after trauma defined a poor neurological outcome. A POPC score ≥ 4 determined severe disability.

Demographic and medical data relevant to the study was collected in the medical files and coded when necessary. We collected demographic (age, sex, date of birth, prematurity), clinical (comorbidities, medical history, clinical examination at admission and two years post-injury, Glasgow coma score, cardiopulmonary arrest before or during the stay, need for neurosurgery (excluding intracranial pressure monitoring only) in the first 24 h, need for mechanical ventilation at admission), ICU length of stay, biological (haemoglobin at admission) and radiological data (brain imaging findings from the first magnetic resonance imaging, abnormal electroencephalogram).

Hemodynamic failure was defined by an arterial hypotension (< 2 standard deviations for age) and/or by the need for inotropic/vasopressor. The type of neurological injuries and the diagnosis of cerebral edema and ischemic lesions were based on the results of the first magnetic resonance imaging. We considered increased head circumference when we observed an increase of two standard

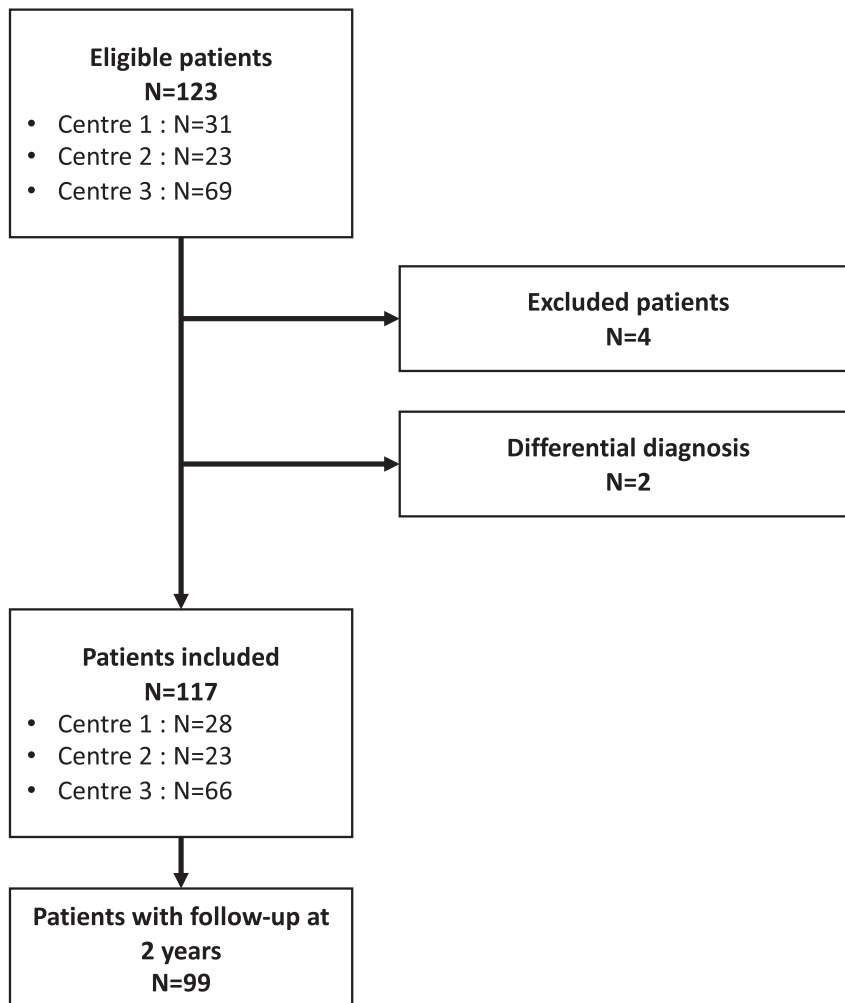


Fig. 1. Flowchart of the study.

deviations in head circumference from the theoretical value for age and sex. An abnormal electroencephalogram was defined by the presence of paroxysmal epileptic elements such as spikes, spike-waves, poly-spikes that could be focal or generalized.

The 2-year follow-up time point was collected from reports of a medical clinic by either by a neuro pediatrician, a pediatric rehabilitation physician or a neurosurgeon performed at 2 years \pm 3 months post-injury.

Psychomotor development was retrospectively assessed based on the medical records. Psychomotor development retardation was defined by a significant delay in at least two areas of development relative to the age norm (motor, fine motor, vision, speech, language, adaptive skills). Presence of behavioral disorders was defined as the mention of significant mood and emotion regulation disorders, hyperactivity, stereotyped behaviors, and autism spectrum disorders reported by a parent/caregiver in the chart. Blindness was defined as visual acuity of $<1/20$ in the better eye after correction.

2.3. Statistical analysis

Analyses were performed using the Jamovi© (Version 1.6.8.0) and RStudio (Version 1.3.959, © 2009–2020 RStudio, PBC) statistical softwares. Descriptive data were presented as numbers/percentages for categorical data and mean values (standard deviation) for normally distributed continuous data. Differences in categorical variables were tested using the Chi-square or Fisher's exact test. Differences in continuous variables were assessed by Mann–Whitney test or a Student *t*-test after verifying the eligibility conditions. Regarding the primary endpoint, a multidimensional analysis of the principal component analysis focused on the POPC score, including all the clinical, biological, and radiological characteristics of children. The univariate analysis was supplemented by a multivariate analysis via a linear regression model with adjustment for the confounding factors (described below). The threshold of statistical significance was set at 5 % for all the analyses carried out according to the hierarchical model and the following sequential diagram to limit the inflation of the alpha risk due to the multiplicity of statistical tests. The factors at admission included in the analysis were: Glasgow coma score (GCS), cardiopulmonary arrest (CPA) before or during the stay, intracranial hypertension, need for neurosurgery in the first 24 h, need for mechanical ventilation, cerebral atrophy, cerebral edema, ischemic lesions on first brain imaging, retinal hemorrhages, ICU length of stay, abnormal transcranial Doppler values, seizures, hemodynamic failure, pupil's asymmetry, age, cranial perimeter, associated bone lesions, prematurity.

No replacement of missing data was made. *P* values of <0.05 were considered significant.

Table 1
Characteristics of the study population.

	Total N = 117
Demographic data	
Male gender, n (%)	71 (61)
Age (months) at admission, mean (SD)	4.3 (2.5)
Premature, n (%)	19 (16)
Clinical data at admission	
Cardiac arrest before or at admission, n (%)	12 (10)
Hemodynamic failure, n (%)	48 (41)
Glasgow coma score, mean (SD)	11 (4)
Seizures, n (%)	61 (52)
Focal deficit, n (%)	9 (8)
Pupils asymmetry, n (%)	37 (32)
Increased head circumference, n (%)	64 (55)
Retinal haemorrhage, n (%)	92 (79)
Management	
Invasive ventilation at admission, n (%)	70 (60)
Need for neurosurgery within the first 24 h after admission, n (%)	90 (77)
Biological, physiological, and radiological findings	
Haemoglobin <10 g/L at admission, n (%)	86 (74)
Abnormal electroencephalogram during stay, n (%)	95 (84)
Associated bone lesions (excluding skull), n (%)	37 (32)
Subdural hematoma, n (%)	112 (96)
Extradural hematoma, n (%)	3 (3)
Subarachnoid haemorrhage, n (%)	68 (58)
Skull fracture, n (%)	13 (11)
Rupture of bridge veins, n (%)	80 (68)
Outcome	
ICU length of stay (days), median (IQR)	8 [5–13]
Hospital length of stay (days), median (IQR)	21 [13–28]
Death, n (%)	9 (8 %)

N indicates the number of data available. Categorical variables are described by numbers and percentages. Quantitative variables are described by means and standard deviations.

3. Results

3.1. Study sample

Over the study period, 117 children were included (28, 23, and 66 respectively in centres 1, 2 and 3,) (Fig. 1). The mean age at admission was 4.3 months (+/- 2.5), and 71 (61 %) were males. The cohort is described in Table 1.

Six patients were excluded: four for previous neurological disease or developmental delay (including one with Di George syndrome, one with congenital hydrocephalus, one with chromosome 13 deletion and one with anoxic-ischemic encephalopathy), and two for differential diagnosis (one with glutaric aciduria type 1 and one with osteogenesis imperfecta).

A total of 99 (85 %) patients completed a 2-year follow-up. As shown in Figs. 2, 61 (52 %) and 47 (40 %) children with AHT had a POPC score ≥ 2 at PICU discharge and at hospital discharge, respectively. Fifty-one (44 %) had a POPC score ≥ 2 at 2-year follow-up. Overall, 19 children (19 %) presented with severe disability two years post-injury. The types of disabilities at 2-year follow-up are detailed in Table 2.

3.2. Prognostic factor analysis

The factors associated with poor neurological outcome at discharge and at 2-year follow-up are represented in Table 3 and Fig. 3. After adjustment for confounding factors, the occurrence of a cardiopulmonary arrest before or at admission ($p < 0.001$), a low GCS at admission ($p < 0.001$), the presence of cerebral ischemia or atrophy on the first brain magnetic resonance imaging ($p < 0.001$) and the need for mechanical ventilation at admission ($p = 0.027$) were associated with poor neurological outcome at hospital discharge. At 2-year follow-up, only a low GCS at admission ($p = 0.004$), the need for neurosurgery in the first 24 h ($p = 0.005$) and the presence of cerebral ischemia ($p < 0.001$) or atrophy ($p = 0.020$) on the first brain magnetic resonance imaging were considered as significant factors associated with poor neurological outcome.

After analysis according to the hierarchical model, only the occurrence of a cardiorespiratory arrest and a low GCS stand out as factors of poor neurological outcome on both time points.

4. Discussion

In this large multicentre retrospective cohort, we found that a high proportion of patients with AHT had a poor neurological outcome and a wide range of neurological disabilities, after a follow-up of only 2 years. We also identified initial factors of injury severity associated with poor outcome at discharge and 2 years later.

Published studies on long-term outcome of patients with AHT are scarce, and most have included a limited number of patients with a short duration of follow-up (Antonietti et al., 2019; Badger et al., 2020; Chevignard & Lind, 2014; Lind et al., 2016) and high attrition rates. Indeed, loss to follow-up has been shown to be highly expected in this population (Antonietti et al., 2019; Badger et al., 2020; Catroppa, Godfrey, Rosenfeld, Hearps, & Anderson, 2012; Chevignard & Lind, 2014; Lind et al., 2016). Overall, the level of disability was high, with a fifth of cases suffering severe disability, and only 13 % rated as having "good outcome". Patients with good outcome represent only 15 % of patients with AHT according to the literature (Barlow, Thomson, Johnson, & Minns, 2005; Lind et al., 2016; Makaroff & Putnam, 2003). Overall, the prevalence of neurologic and ophthalmologic disabilities and their types were similar compared to previously published studies (Antonietti et al., 2019; Badger et al., 2020; Caffey, 1972; Chevignard & Lind, 2014; Jayawant & Parr, 2007; Keenan, Hooper, Wetherington, Nocera, & Runyan, 2007; Lind et al., 2016). Developmental delay and behavioral disorders, as well as a visual deficit, seem to be the most common disabilities (Adamsbaum, Grabar, Mejean, & Rey-Salmon, 2010; Antonietti et al., 2019; Badger et al., 2020; Bonnier, Nassogne, & Evrard, 1995; Caffey, 1972; Catroppa et al., 2012; Chevignard

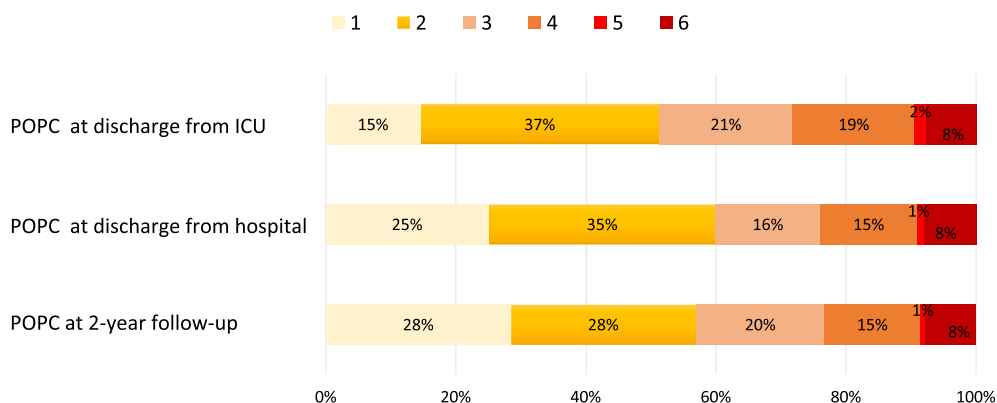


Fig. 2. Distribution of POPC scores in patients with AHT. Scores include 1 for good, 2 for mild disability, 3 for moderate disability, 4 for severe disability, and 5 for vegetative state or coma (6 indicates death).

Table 2
Outcome of patients at 2-year follow up.

	N	Total
Severe disabilities, n (%)	99	19 (19)
Neuropediatric follow-up 2 years after the trauma, n (%)	99	88 (88)
Type of neurological impairment		
Focal deficit, n (%)	99	26 (26)
Epilepsy, n (%)	99	31 (31)
Psychomotor development retardation, n (%)	99	35 (35)
Behavioral disorder, n (%)	99	33 (33)
Age of walking acquisition (months), mean (SD)	41	17.3 (5.8)
Visual impairment, n (%)	99	37 (37)
Blindness, n (%)	99	2 (2)
Amblyopia, n (%)	99	14 (15)
Strabismus, n (%)	99	21 (21)

N indicates the number of data available. Categorical variables are described by numbers and percentages. Quantitative variables are described by means and standard deviations.

Table 3
Factors associated with poor neurological outcome (as defined by a POPC score > 2) at discharge and at 2-year follow-up.

Variables	At hospital discharge			At 2-year follow-up		
	Mean POPC score (SD)	P-value univariate	P-value multivariate	Mean POPC score (SD)	P-value univariate	P-value multivariate
Demographic						
Prematurity	2.7 (1.4)	0.67	0.72	2.6 (1.4)	0.45	0.68
Age in months		0.78			0.67	
Clinical factors at admission						
Cardiorespiratory arrest before or at admission	4.7 (1.8)	<0.001	<0.001	4.5 (2.1)	<0.001	0.19
Hemodynamic failure	3.4 (1.6)	<0.001	0.82	3.1 (1.6)	<0.001	0.38
Glasgow coma score at admission		<0.001	<0.001		<0.001	0.004
Seizures	2.7 (1.2)	0.36	0.77	2.4 (1.1)	0.46	0.78
Focal deficit	3.0 (1.2)	0.33	0.17	2.4 (1.2)		0.79
Pupils asymmetry	3.5 (1.7)	<0.001	0.25	3.4 (1.7)	<0.001	0.18
Retinal haemorrhage at admission	2.7 (1.5)	0.041	0.32	2.5 (1.5)	0.08	0.43
Radiological factors						
Associated bone lesion	2.8 (1.4)	0.15	0.21	2.6 (1.4)		0.39
Cerebral oedema on first MRI	3.1 (1.7)	<0.001	0.21	2.9 (1.7)	0.003	0.33
Ischemic lesion on first MRI	3.7 (1.4)	<0.001	<0.001	3.3 (1.4)	<0.001	<0.001
Management						
Need for neurosurgery within the first 24 h	2.6 (1.2)	0.39	0.21	2.4 (1.2)	0.75	0.005
Need for mechanical ventilation at admission	3.2 (1.5)	<0.001	0.027	2.9 (1.5)	<0.001	0.17
Outcome						
Hospital length of stay		0.08			0.39	

MRI: Magnetic resonance imaging.

POPC: Pediatric overall performance category.

p value is significant if in bold

& Lind, 2014; Duhaime et al., 1987; Ichord et al., 2007; Jayawant & Parr, 2007; Keenan et al., 2007; Lind et al., 2016; Talvik et al., 2007).

Given the young age of the patients at this stage, one can fear that the disability levels will increase over time (Badger et al., 2020; Bonnier et al., 1995; Manfield, Oakley, Macey, & Waugh, 2021). For example, in a similar retrospective cohort study, Badger et al. assessed 85 infants who had received rehabilitation following AHT and assessed them 2 years post-injury: 42 % were rated as “good outcome”. The same team performed subsequent follow-up of the cohort 5 years post-injury (Manfield et al., 2021), and reported that only 18 % of cases still displayed “good outcome”, while the large majority now displayed moderate to severe disability. This finding has been confirmed in a very large study (Nuno et al., 2015).

Thus, appropriate specialised follow-up of these patients is crucial to detect as soon as possible the potential consequences of AHT and to limit the clinical, social and psychological impact of disabilities. Follow-up should be multidisciplinary, including pediatric neurologist, neuropsychologist, psychologist, audiologist, rehabilitation physician and ophthalmologist. It should be pursued until the end of the brain development period, i.e. until transition to adulthood, in order to diagnose new emerging deficits, and implement adequate tailored interventions, including rehabilitation and environmental interventions, such as adaptations at school, or special education if needed.

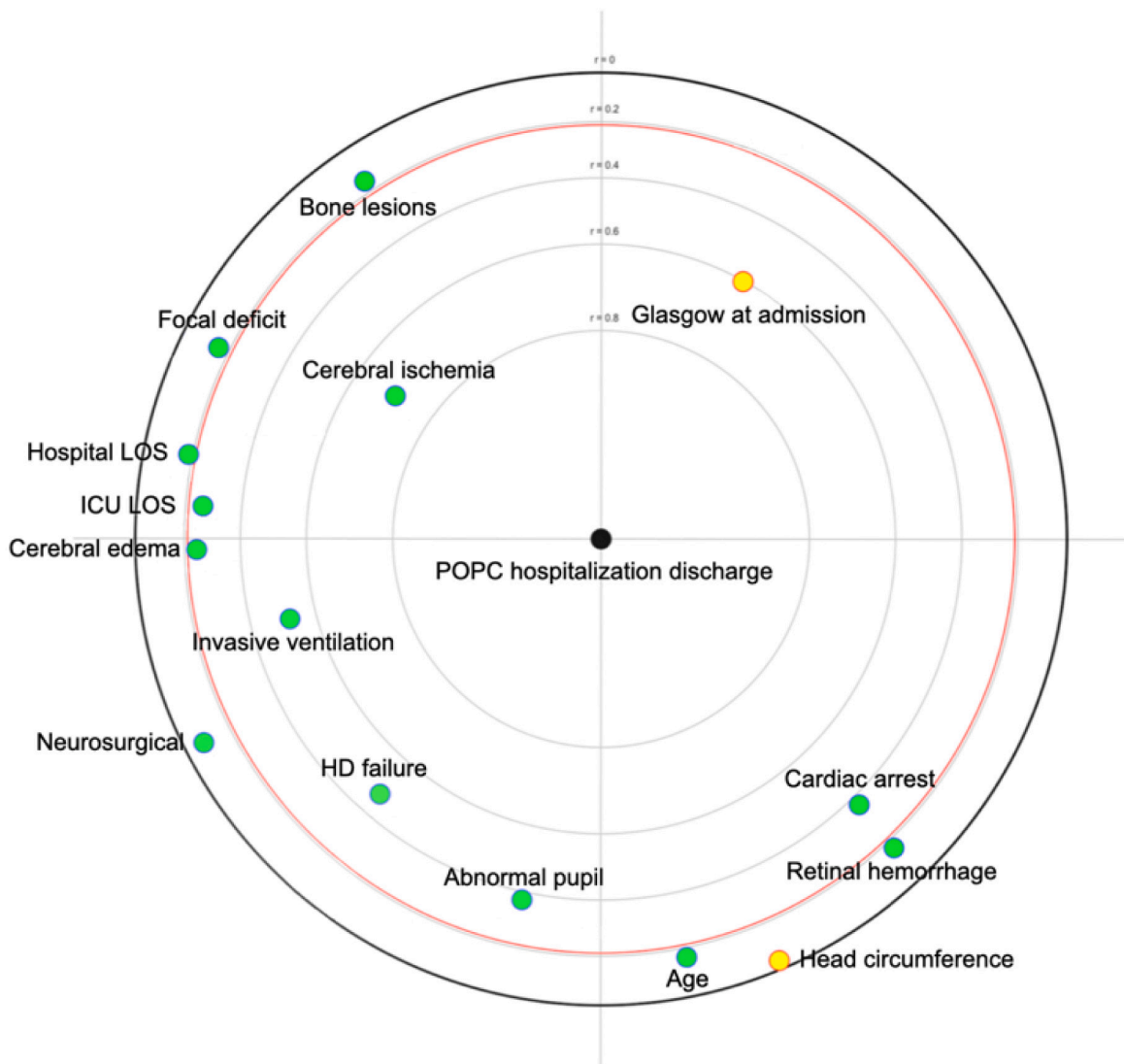


Fig. 3. Focused principal component analysis: initial clinical and paraclinical risk factors associated with a poor neurological outcome as defined by POPC score > 2 at hospital discharge. The red circle represents the significance limit ($r = 0.2$). The closer to the circle a variable stands the greater the correlation with POPC is. The variables in green evolve in the same direction as the POPC, variables in yellow in the opposite direction. HD: hemodynamic; ICU: Intensive Care Unit; LOS: Length of stay. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

In this study, we focused on factors of initial injury severity because knowledge of these potential predictive factors of poor neurological outcome may help clinicians identify early those children requiring closer monitoring (Chevignard & Lind, 2014). As Lind et al. reported, we found that a low GCS at admission was associated with a poor neurological outcome both at hospital discharge and at 2-year follow-up (Lind et al., 2016). Unsurprisingly, we found that the occurrence of cardiac arrest before or at admission was a significant factor of poor neurological outcomes. Indeed, the neurological consequences of cerebral anoxic lesions are now well-known (Antonietti et al., 2019; Chevignard & Lind, 2014; Nuno et al., 2015). Further, in children with AHT, cardiac arrest may be related to more severe shaking with lesions of the bulbous protuberance and the cervical medulla (Anderson et al., 2001; Crowe et al., 2021). However, multivariate analyses did not yield any other significant factor associated with a poor neurological outcome, as reported mainly in previous studies (Fiser, 1992; Nuno et al., 2015). This is probably due to the strong inter-relationships between the injury severity related factors explored (e.g., cardiac arrest, lower GCS, necessity for intubation and monitoring, length of stay in ICU).

This study has several limitations that should be highlighted. First, this is a retrospective study, and consequently, some data were missing. However, these data were available for >100 cases, which provides unique information, in addition to the medical data. It is true that we only included patients admitted to PICUs (i.e. the most severe patients), which may constitute a selection bias. Nevertheless, in our experience, the vast majority of patients with AHT are admitted to a critical care unit at some point in their course. Secondly, the POPC score did not provide details regarding neurological disabilities but provided an overall assessment and was

collected retrospectively. However, the same assessment was performed for the whole cohort with very little attrition and results are very similar to those reported in the literature in the field. Third, given the multicentre design, the management of patients with AHT may be heterogeneous despite guidelines. Finally, the duration of follow-up was indeed shorter in our study compared to previously published studies (Antonietti et al., 2019; Lind et al., 2016), whereas some impairment, e.g. cognitive sequelae, may be diagnosed from 4 to 5 years of age, and the full extent of disability and academic potential is only fully known when those patients reach adulthood.

5. Conclusion

In this retrospective multicentre study, we found that a large proportion of patients with AHT had a severe disability, already evident only two years post-injury. Cardiopulmonary arrest and a low Glasgow score at admission were strongly associated with poor neurological outcome. Future studies with a longitudinal design and using standardized tools should be conducted to assess comprehensive outcomes several years post-injury, especially learning potential and academic outcome, and to evaluate the role of family and environmental factors on overall outcome.

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.chiabu.2022.105779>.

Institution

The work was performed at CHU de Grenoble-Alpes, La Tronche, France.

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CRediT authorship contribution statement

FG, MC and AM wrote the manuscript, which was reviewed, edited, and approved by AB, IW, HP, EJ and GM. AB performed the statistical analysis.

Declaration of competing interest

The authors have no conflict of interest to declare.

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