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CLINICAL RESEARCH ARTICLE

Risk factors for unfavorable outcome at discharge of newborns with hypoxic-ischemic encephalopathy in the era of hypothermia

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OBJECTIVE: To re-visit short-term outcomes and associated risk factors of newborns with hypoxic-ischemic encephalopathy (HIE) in an era where hypothermia treatment (HT) is widespread.
METHODS: This is a prospective population-based cohort in French neonatal intensive care units (NICU). Neonates born at or after 34 weeks of gestational age with HIE were included; main outcomes were in-hospital death and discharge with abnormal or normal MRI. Associations of early perinatal risk factors, present at birth or at admission to NICU, with these outcomes were studied.
RESULTS: A total of 794 newborns were included and HT was administered to 670 (84.4%); 18.3% died and 28.5% and 53.2% survived with abnormal and normal MRI, respectively. Severe neurological status, Apgar score at 5 mn ≤5, lactate at birth ≥11 mMoles/l, and glycemia ≥100 mg/dL at admission were associated with an increased risk of death (relative risk ratios (aRRR) (95% CI) 19.93 (10.00–39.70), 2.89 (1.22–1.62), 3.06 (1.60–5.83), and 2.55 (1.38–4.71), respectively). Neurological status only was associated with survival with abnormal MRI (aRRR (95% CI) 1.76 (1.15–2.68)).
CONCLUSION: Despite high use of HT in this cohort, 46.8% died or presented brain lesions. Early neurological and biological examinations were associated with unfavorable outcomes and these criteria could be used to target children who warrant further neuroprotective treatment.
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IMPACT:

- In this population-based cohort of newborns with HIE where 84% received hypothermia, 46.8% still had an unfavorable evolution (death or survival with abnormal MRI). Risk factors for death were high lactate, low Apgar score, severe early neurological examination, and high glycaemia.
- While studies have established risk factors for HIE, few have focused on early perinatal factors associated with short-term prognosis. This French population-based cohort updates knowledge about early risk factors for adverse outcomes in the era of widespread cooling.
- In the future, criteria associated with an unfavorable evolution could be used to target children who would benefit from another neuroprotective strategy with hypothermia.

INTRODUCTION

Early accurate diagnosis of neonatal hypoxic-ischemic encephalopathy (HIE) and assessment of its severity is essential for the effective application of neuroprotective strategies, but remains a major challenge.[1] For the diagnosis of HIE, the attribution of an ischemic hypoxic mechanism to neonatal encephalopathy is complex, especially in the very early phase of the disease.[2] Since neurological signs of Sarnat's classification were established, additional criteria were proposed to improve the identification of this cerebral damage.[3,4] Most HT trials defined HIE by the

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association of biological signs of asphyxia with clinical signs of neurological failure,[5] and current guidelines restrict hypothermia (HT) to the most severe combination of these criteria in neonates of 36 weeks gestational age (wGA) and older.[6,7] HT has been clearly demonstrated to improve the prognosis of HIE, but about 45% of treated children in randomized trials still had an unfavorable evolution with death or disability at 18 months.[5,8–10]

Improving knowledge on the early risk factors for poor prognosis may help to identify neonates who would benefit from additional neuroprotective treatments and other emergent therapies.[1] A national prospective population-based cohort of full-term and late preterm newborns with moderate or severe HIE was initiated in France in 2015 to assess their prognosis after the generalization of HT since 2010.[11] The objective of this study was to describe short-term outcomes among neonates with moderate to severe HIE and to identify early perinatal risk factors present at birth or on admission to neonatal intensive care units (NICU) that are associated with in-hospital death and abnormal neuroimaging at hospital discharge.

METHODS

Study design

The study included all live infants born at 34 wGA, or more and admitted to 68 NICU in 22 regions in France between September 2015 and March 2017 who fulfilled study criteria for moderate or severe HIE, as determined by a senior neonatologist in each unit. The study design, participants, and organization of data collection are detailed in a previous publication.[11] The criteria for inclusion (Table 1) were: (1) an early clinical neurological condition estimated as moderate or severe by the neonatologist at inclusion. A list of the neurological examination signs was provided to the neonatologist, but a minimum number of signs was not fixed for inclusion or for establishing severity (Table 1). (2) Biological parameters of severe or moderate asphyxia at birth or during the first hour of life. One additional perinatal event indicative of intrapartum ischemic hypoxia was required in case of moderate acidosis or unavailable biological results.

Neonates with congenital malformations and neuromuscular or chromosomal disorders were excluded. In cases of parental refusal to participate, non-French-speaking parents, or imminent life-threatening conditions with very early neonatal death, the neonate was registered in the inventory of non-included eligible neonates with minimal data.[11]

Data collection

The mother's characteristics, circumstances of birth, neonatal clinical biological and cerebral magnetic resonance imaging (MRI) data, treatments, and medical care were extracted from medical records.[8]

Obstetrical events were classified as acute (uterine rupture, cord prolapse or rupture, placental abruption, placenta praevia, Benckiser hemorrhage, head entrapment during vaginal breech delivery or shoulder dystocia, amniotic fluid embolism, maternal shock or sickle cell vaso-occlusive crises), subacute (preeclampsia, chorioamnionitis, metrorrhagia, reduced fetal movements, umbilical cord loop, other protracted labor, other abnormal placentation), and no reported event (none of the events or isolated abnormal fetal heart rate).

The interpretation of MRIs was based on a standardized questionnaire developed by an expert committee of radiologists and completed by a senior radiologist in each center, which identified injured brain regions among basal ganglia and thalami, white matter, cortex, posterior limb internal capsule, corpus callosum, brainstem, and cerebellum. Data used for this study also included the timing of MRI acquisition, type of sequence, and quality of scans (excellent with no artifact, good or poor). Regarding the timing of MRI, 83.8% of children had only one MRI (39.8% before D6, 53.2% between D6 and D12, and 7.0% after D12). Of the 16.2% who had multiple MRIs, 74.5% had their first MRI before D6. T1, T2, and diffusion sequences were performed in 93.7%. The detailed description of the lesions as well as the methods for their classification has been described elsewhere.[12]

Short-term outcome and early perinatal factors

Unfavorable short-term outcomes were defined as in-hospital death and survival to discharge with an abnormal MRI. All circumstances of death were retained, including discontinuation of life-sustaining treatments. MRI was considered abnormal if at least one brain lesion was identified in the seven brain regions.

Risk factors were sought among neonatal characteristics, birth circumstances, neurological and biological examination from birth to admission in NICU, and additional organ failure. Neonatal characteristics and birth circumstances were documented by fetal sex and GA, small for gestational age (SGA)[13] with birthweight centile defined according to French birthweight standards.[13] The mode of delivery, any intrapartum event, and the status inborn/outborn were reported and the outborn status was related to the need for a neonatal transfer to a NICU performing HT. Other factors at admission to the NICU included intrapartum asphyxia (Apgar score ≤5 at 5 mn, cord blood pH ≤7, or lactate ≥11 mmoles/L at birth). The lactate samples analyzed were selected using a hierarchical algorithm: first the cord samples, arterial ($n = 206$), then the venous ($n = 58$), and finally the samples with unspecified vessels ($n = 321$). In the absence of cord sampling, neonatal blood samples were selected, first those taken rapidly in the delivery room ($n = 70$), then those taken during the first hour of life ($n = 5$). The same algorithm was used for the pH values. We also studied the neurological status at admission including the absence of sucking reflexes, mydriasis or clinical seizure, and the presence of additional respiratory disease (FIO2 > 40%), cardiovascular disease (amine treatment and/or volume expansion at admission), or low or high glycaemia (defined as glycaemia <40 and >100 mg/dL, respectively).

Statistical analysis

The characteristics of the overall cohort from birth to early neonatal management in NICU were described. Next, the rates of in-hospital death and survival with an abnormal or normal MRI were presented and compared according to perinatal factors. Then, multinomial logistic regression models were used to estimate adjusted relative risk ratios

Table 1. Neurological and biological inclusion criteria for the LyTONEPAL cohort.

Neurological signs	• Moderate: lethargy, hyper-reflexia, myosis, bradycardia, seizures, hypotonia with weak suck and poor Moro reflex
	• Severe: stupor, flaccidity, small to mid-position pupils that react poorly to light, decreased stretch reflexes, hypothermia, or absent Moro reflex
Biological criteria[a]	• Severe biological signs: pH ≤7.0 or less or a base deficit ≥16 mmol/L or lactate ≥11 mmol/L
	• Moderate/absent biological signs with additional perinatal events:
	– 7.0 < pH ≤ 7.15, or 10 ≤ base deficit < 16 mmol per liter, or 8 ≤ lactate < 11 mmol/L, or blood gas measurement unavailable with:
	– an acute perinatal event (e.g., late or variable decelerations, cord prolapse, cord rupture, uterine rupture, maternal trauma, hemorrhage, or cardiorespiratory arrest)
	– or an abrupt change in fetal heart rate (FHR), defined as a persistent abnormal FHR after a period of normal tracing: bradycardia or prolonged deceleration, persistent variable decelerations, persistent late decelerations, and reduced heart variability
	– or either a 10-min Apgar score of 5 or less or assisted ventilation initiated at birth and continued for at least 10 min.

[a]Biological criteria indicating asphyxia were provided by umbilical cord blood or any other blood sampled during the first hour after birth.

(aRRR) and 95% CI for these risk factors, selected for their clinical relevance and availability at NICU admission. Model 1 examined only newborn characteristics, Model 2 included outborn status, perinatal event, lactate, Apgar score at 5 min, and neurological conditions while Model 3 included additional disorders (respiratory, cardiovascular, or metabolic).

Missing data

MRI was performed but unavailable for 32 (4.9%) neonates and not performed (no MRI) for 36 (5.5%). The comparison of these groups with the 581 survivors with MRI data showed that children with unavailable MRI had similar characteristics, but those with no MRI were less severe cases (Supplementary Table 1). To correct for bias in the analysis, missing outcomes were therefore imputed by multiple imputation using chained equations. Variables used as predictors were GA, birthweight, sex, resuscitation in the delivery room, severity of neurological condition and sucking reflex at admission, Sarnat grade, HT, and length of hospital stay. We generated 20 independent imputed datasets with 10 iterations each and estimates were pooled according to Rubin's rule.[14] A sensitivity analysis comparing risk factors associated with neonatal outcomes was undertaken using the complete case sample.

P values less than 0.05 were considered to be statistically significant. The statistical analysis was conducted using STATA IC (Version 13, Stata Corporation, College Station, TX).

Ethics and regulatory considerations

The study protocol was approved by a national advisory committee, the CCTIRS (November 20, 2014; n°14.724), and authorized by the National Data Protection Authority (March 27, 2015; DR-2015-136), and from the French South-East Regional Ethics Committee (July 18, 2014; IRB n°5891).

RESULTS

Population

Between 28 September 2015 and 31 March 2017, 869 neonates were screened, 844 were considered eligible, and 794 were included (Fig. 1). A minimal dataset was available for the 50 infants who were not included. Moderate and severe early neurological examination was reported for 18 (36%) and 32 (64%) neonates, respectively (data not shown) and 32 died very soon after admission. Over the same period, 1,157,846 live births were identified in the national hospital discharge database, leading to an HIE prevalence estimate of 0.73 per 1000 live births.

At NICU admission, coma, absence of motor activity or of sucking reflex, mydriasis, and clinical seizure were observed in 172/660 (26.1%), 182/671 (27.1%), 305/641 (47.6%), 66/498 (13.2%), and 86/675 (12.7%), respectively. The neurological examination was judged to be as severe for 43.5% of neonates, and a Sarnat grade III was observed for 35.6% of the cohort (Table 2). Severe asphyxia was observed for 61.5 and 59.7%, respectively, to pH and lactate. An acute event was reported for 32.0% of the infants. HT was performed for 84.4% of HIE and early discontinuation of HT before the full 72 h was observed for 69/670 (10.4%). A small proportion of the infants (3.5%) received magnesium sulfate therapy as an additional neuroprotective strategy. No other intervention, e.g., erythropoietin treatment, was performed.

Neonatal outcomes

Eighteen percent of the infant died, while 28.5% and 53.2% survived with and without brain lesions (Table 3). Rates of death were significantly higher among neonates with Apgar score ≤5 at 5 min (24.6%), lactate ≥11 mmol/L (21.6%), with a severe neurological condition (37.4%), clinical seizure (33.7%), Sarnat grade III (50.7%), additional respiratory or cardiovascular disease (28.9 and 31.6%) and glycaemia <40 or >100 mg/dL (18.8 and 20.8%, respectively). Among these factors, increased risk of survival with abnormal MRI was only observed following clinical seizure (38.4%). No significant differences for death or survival with abnormal MRI were observed according to neonatal characteristics or acute and subacute obstetrical events. The most common acute events were placental abruption (90), uterine rupture (47), cord prolapse or rupture (27), or Benckiser

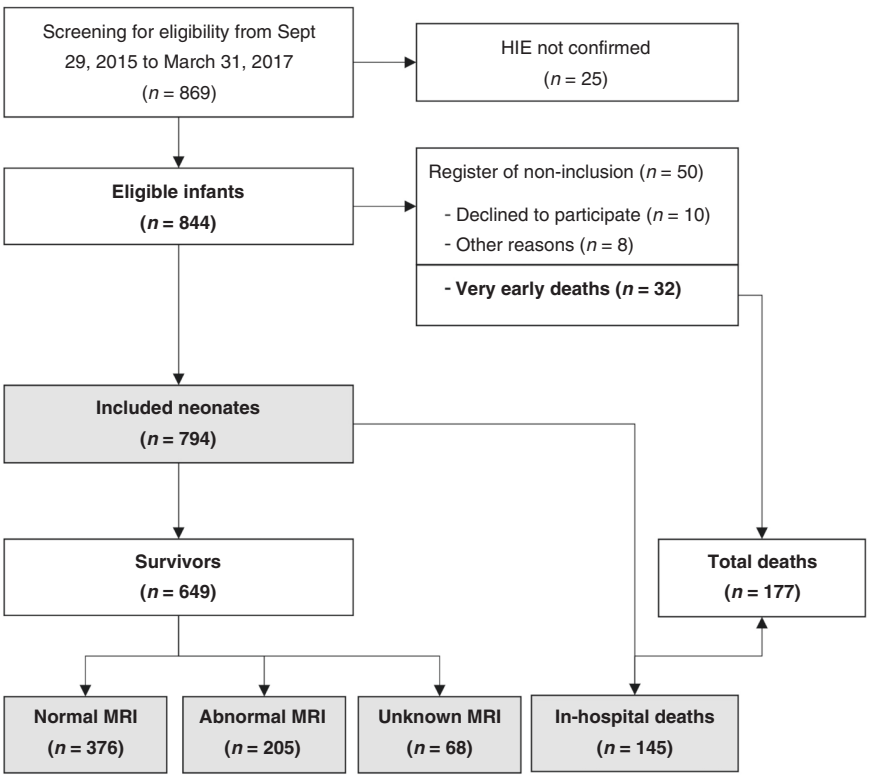

Fig. 1 Flowchart of the LyTONEPAL cohort. HIE hypoxic-ischemic encephalopathy, MRI magnetic resonance imaging.

Table 2. Clinical and biological characteristics of newborns included in the LyTONEPAL cohort at admission to NICU ($N = 794$).

	N (%) median [IQR]	
Neonatal characteristics and birth circumstances		
Male sex ($n = 794$)	427	(53.8)
Gestational age in weeks ($n = 794$)	39	[37–40]
Gestational age in weeks 34–36	123	(15.5)
37–38	194	(24.4)
39–40	337	(42.5)
41–42	140	(17.6)
Birthweight in g ($n = 788$)	3080	[2725–3492]
Birthweight centile[a] <10th	130	(16.5)
>90th	79	(10.0)
Head circumference in cm ($n = 656$)	31	[33–35]
Twins newborns ($n = 783$)	26	(3.3)
Fetal presentation ($n = 768$)		
Cephalic	683	(88.9)
Breech	60	(7.8)
Mode of delivery ($n = 780$)		
Instrumental delivery	152	(19.5)
Cesarean before onset of labor	206	(26.4)
Cesarean during labor	292	(37.4)
Level of care of birth center ($n = 782$)		
III	250	(31.8)
II	356	(45.3)
I	172	(21.9)
Outborn status[b] ($n = 794$)	561	(70.7)
Admission to NICU within 6 h of life ($n = 756$)	673	(89.0)
Delay for admission in NICU in min ($n = 756$)	169	[80.5–258]
Clinical entry criteria in the cohort		
Severe neurological signs[c] ($n = 790$)	344	(43.5)
Biological signs of severe asphyxia[d] ($n = 712$)	544	(76.4)
pH ($n = 710$)	6.96	[6.82–7.09]
pH ≤7.0	437	(61.5)
Lactate in mmol/L ($n = 660$)	12	[9–15]
Lactate ≥11 mmol/L	394	(59.7)
Base deficit in mmol/L ($n = 605$)	10.6	[6.2–17]
Base deficit ≥16 mmol/L	125	(20.7)
Intrapartum abrupt change in fetal heart ($n = 766$)	649	(84.7)
Obstetrical event ($n = 790$)[e]		
Acute	253	(32.0)
Subacute	247	(31.3)
No event	290	(36.7)
Apgar score at 5 min ($n = 737$)	4	[2–6]
Apgar score ≤5 at 5 min	513	(69.6)
Intubation in delivery room ($n = 789$)	581	(73.6)
Early management and clinical examination at admission in NICU		
Sarnat grade ($n = 758$)		
Grade I	77	(10.2)
Grade II	411	(54.2)
Grade III	270	(35.6)
Hypothermia treatment ($n = 794$)	670	(84.4)
Anticonvulsant treatment initiated before admission ($n = 542$)	69	(12.7)
Respiratory distress defined by a FIO2 >40% ($n = 754$)	156	(20.7)
Inhaled nitric oxide treatment ($n = 767$)	53	(6.9)
Cardiovascular disease with amine and/or volume expansion ($n = 764$)	172	(22.5)
Exteriorized bleeding ($n = 765$)	13	(1.7)
Glycemia ≥100 mg/dL ($n = 648$)	351	(54.2)

[a]Birthweight centile was assessed according to French birthweight standards.[13]
[b]Outborn status was related to the need for a neonatal transfer to a NICU performing HT.
[c]Severe neurologic signs were defined by at least one of the following signs: stupor, flaccidity, small to mid-position pupils that react poorly to light, decreased stretch reflexes, hypothermia, or absent Moro reflex.
[d]Severe biological signs were defined by pH ≤7.0 or less or a base deficit ≥16 mmol/L or lactate ≥11 mmol/L.
[e]Obstetrical events were classified as acute (uterine rupture, cord prolapse or rupture, placental abruption, placenta praevia, Benckiser hemorrhage, head entrapment during vaginal breech delivery or shoulder dystocia, amniotic fluid embolism, maternal shock or sickle cell vaso-occlusive crises), subacute (preeclampsia, chorioamnionitis, metrorrhagia, reduced fetal movements, umbilical cord loop, other protracted labor, other abnormal placentation), and no reported event (none of the events or isolated abnormal fetal heart rate).

hemorrhage (27). A full list with their short-term outcomes is detailed in Supplementary Table 2.

Adjusted models confirmed descriptive findings (Table 4). In the final model, the only factors associated with in-hospital death were severe neurological status at NICU admission (aRRR (95% CI) 19.93 (10.00–39.70), Apgar score at 5 mn ≤5 (aRRR 2.89 (1.22–6.82)), lactate at birth ≥11 mMoles/L (aRRR 3.06 (1.60–5.83)), and glycemia <40 or >100 mg/dL at admission (aRRR 4.27 (1.42–12.77) and 2.55 (1.38–4.71, respectively)). Severe neurological status was the only factor associated with survival with abnormal MRI (aRRR (95% CI) 1.76 (1.15–2.68)).

Finally, the sensitivity analysis using complete cases yielded similar results, although the association between severe neurological signs and survival with abnormal MRI, was at the limit of significance (aRRR = 1.54 (0.94–2.50)) (Supplementary Table 3).

DISCUSSION

Main findings

In this French population-based cohort of term and late preterm neonates with HIE, 84.4% of infants received HT, 18.3% died before discharge and 28.5% survived with abnormal neuroimaging. Lactate ≥11 mmol/L in early blood samples and low Apgar at 5 min were related to a two-to-three-fold increase in the risk of in-hospital death. Our results also suggest increased risks associated with hyperglycemia. Severe neurological disorder at admission was strongly related to in-hospital death (aRRR (95% CI) 19.93 (10.00–39.70)), and to a lesser degree to survival with brain lesions (aRRR (95% CI) 1.76 (1.15–2.68)). Other common risk factors for neonatal morbidity, such as preterm birth or SGA, were not associated with short-term outcomes.

Interpretation

The mortality rate of 18.3% in the LyTONEPAL cohort was in line with those previously reported in population-based studies, ranging from 9 to 27%,[7,15–17] but contrasted with a rate of only

Table 3. Neonatal short-term outcome according to perinatal risk factors expressed as numbers and imputed percentages.

		Short-term outcome (%)			*p* value
	N	**Survival with normal MRI**	**Survival with abnormal MRI**	**In-hospital death**	
Total sample		53.2	28.5	18.3	
Neonatal characteristics					
Gestational age at delivery in weeks					
34–36	123	46.5	33.2	20.3	0.61
37–38	194	52.3	26.6	21.1	
39–40	337	55.0	28.1	16.9	
41–42	140	56.2	28.1	15.7	
Neonatal gender					
Female	367	54.5	28.3	17.2	0.72
Male	427	52.1	28.7	19.2	
Birthweight centile[a]					
<10th	130	59.4	28.3	12.3	0.22
10–90th	579	53.0	28.6	18.5	
>90th	79	48.0	26.7	25.3	
Birth circumstances and biological or clinical examination					
Obstetrical event[b]					
Acute	235	52.1	29.4	18.6	0.58
Subacute	247	49/9	31.4	18.6	
No event	290	56.6	25.5	17.9	
Outborn status[b]					
Inborn	233	49.3	33.6	17.2	0.14
Outborn	561	54.9	26.4	18.7	
pH					
>7.0	273	57.4	28.7	13.9	0.10
≤7.0	437	50.6	29.5	19.9	
Lactate in mmol/L					
<11	266	61.3	28.2	10.5	0.001
≥11	394	48.5	29.9	21.6	
Apgar score at 5 min					
>5	240	63.1	32.4	4.5	<0.001
≤5	543	47.5	27.9	24.6	
Clinical data of the newborn at admission					
Neurological signs[c]					
No severe	448	66.4	30.3	3.3	<0.001
Severe	345	36.3	26.3	37.4	
Clinical seizure					
Yes	86	27.9	38.4	33.7	<0.001
No	593	56.0	28.0	16.0	
Sarnat grade					
Grade I	81	69.9	27.6	2.5	<0.001
Grade II	435	71.3	28.2	0.5	
Grade III	278	20.0	29.3	50.7	
Respiratory distress[d]					
Yes	163	42.8	28.2	28.9	<0.001
No	626	56.3	28.8	14.8	
Cardiovascular disease with amine and/or volume expansion					
Yes	177	39.7	28.8	31.6	<0.001
No	615	57.3	28.5	14.2	

Table 3. continued

	N	Short-term outcome (%)			p value
		Survival with normal MRI	Survival with abnormal MRI	In-hospital death	
Glycemia					
Hyperglycemia <40 mg/dL	64	45.4	35.8	18.8	0.01
Normoglycemia	299	58.3	31.7	10.0	
Hypoglycemia >100 mg/dL	414	53	26.3	20.8	

[a]Birthweight centile was assessed according to French birthweight standards.[12]
[b]See Methods for definition.
[c]See Table 1 for definition.
[d]Respiratory distress was defined by an FIO2 >40%.

Table 4. Risk factors of survival with abnormal neuroimaging or death at the end of neonatal hospitalization: multinomial logistic regression models with multiple imputation.

	Short-term outcome (Relative risk ratio (95% CI))	
	Survival with abnormal MRI	Death
Model 1: neonatal characteristics ($n = 788$)		
Gestational age in weeks	0.95 (0.87–1.04)	0.93 (0.85–1.03)
Male fetus (Ref female)	1.04 (0.74–1.45)	1.13 (0.77–1.66)
Small for GA[a] (Ref AGA)	0.90 (0.57–1.42)	0.61 (0.34–1.09)
Large for GA[a] (Ref AGA)	1.02 (0.57–1.84)	1.50 (0.83–2.70)
Model 2: neonatal characteristics, birth circumstances, and biological and clinical examination ($n = 687$)		
Gestational age in weeks	0.94 (0.85–1.04)	1.00 (0.88–1.14)
Male fetus (Ref female)	0.96 (0.66–1.39)	1.03 (0.63–1.70)
Small for GA[a] (Ref AGA)	0.98 (0.60–1.61)	0.64 (0.29–1.38)
Large for GA[a] (Ref AGA)	1.22 (0.65–2.28)	1.64 (0.75–3.58)
Outborn status[b] (Ref inborn)	0.75 (0.50–1.12)	1.12 (0.65–1.91)
Subacute obstetrical event[b] (Ref no event)	1.46 (0.92–2.33)	1.05 (0.57–1.93)
Acute obstetrical event[b] (Ref no event)	1.25 (0.79–1.98)	0.83 (0.46–1.49)
Lactate ≥11 mmol/L[c] (Ref <11 mmol/L)	1.42 (0.93–2.16)	2.69 (1.48–4.90)
Apgar at 5 min ≤5 (Ref >5)	1.02 (0.66–1.60)	3.04 (1.37–6.75)
Severe neurological signs[d] (Ref moderate)	1.80 (1.19–2.73)	20.12 (10.71–37.79)
Model 3: neonatal characteristics, birth circumstances, biological and clinical examination, and additional organ failure ($n = 672$)		
Gestational age in weeks	0.95 (0.86–1.05)	0.97 (0.84–1.12)
Male fetus (Ref female)	0.95 (0.66–1.38)	1.13 (0.67–1.93)
Small for GA[a] (Ref AGA)	1.00 (0.61–1.66)	0.64 (0.28–1.45)
Large for GA[a] (Ref AGA)	1.20 (0.64–2.28)	1.84 (0.79–4.24)
Outborn status[b] (Ref inborn)	0.77 (0.51–1.16)	1.14 (0.64–2.03)
Subacute obstetrical event[b] (Ref no event)	1.38 (0.85–2.22)	0.92 (0.47–1.77)
Acute obstetrical event[b] (Ref no event)	1.23 (0.77–1.97)	0.64 (0.34–1.21)
Lactate ≥11 mmol/L[c] (Ref <11mmol/L)	1.44 (0.94–2.19)	3.06 (1.60–5.83)
Apgar at 5 min ≤5 (Ref >5)	1.05 (0.67–1.65)	2.89 (1.22–6.82)
Severe neurological signs[d] (Ref moderate)	1.76 (1.15–2.68)	19.93 (10.00–39.70)
Respiratory distress with FIO2 >40% (Ref no)	1.14 (0.68–1.91)	1.26 (0.68–2.37)
Cardiac failure indicating treatment[e] (Ref no)	1.37 (0.85–2.22)	1.59 (0.88–2.88)
Hypoglycemia <40 mg/dL (Ref normal)	1.72 (0.77–3.83)	4.27 (1.42–12.77)
Hyperglycemia >100 mg/dL (Ref normal)	0.99 (0.64–1.52)	2.55 (1.38–4.71)

[a]Small, appropriate and large for gestational age (SGA, AGA, and LGA) are defined as newborns with a birthweight <10th, between the 10th and the 90th centile, and >90th centile of French birthweight standards.[12]
[b]See Methods for definition.
[c]To handle with missing values in the regression models, we created a specific modality for which the RRR is not resented.
[d]See Table 1 for definition.
[e]Indicated treatment was amines and/or volume expansion.

2.7% in a Japanese registry.[18] Our finding that 47.4% of infants survived with a normal MRI is encouraging and is comparable with other studies conducted after the widespread adoption of HT.[19–22] However, comparisons between studies should be made with caution because of different proportions of moderate and severe HIE, varying indications for HT, and ethical considerations about withholding or withdrawing life support.

The only early factor which distinguished between surviving neonates with or without brain lesions at hospital discharge was the prevalence of neurological signs at NICU admission, and this factor was also the major factor associated with in-hospital death. This finding is consistent with previous studies, in which the Thompson score based mostly on neurological signs, was found to be predictive of death.[19,23] More recently, a secondary analysis from a randomized trial showed that the early neurological examination, before 6 h of life, was one of most the relevant tools for predicting death and moderate or severe disability at 18–22 months.[20]

Our cohort confirms the importance of lactate in identifying children at risk of death. Lactates were previously reported as a predictor of HIE and recently in a metabolomic study that tested 27 biologic candidates.[21,22] However, only one study showed that lactate could discriminate between moderate to severe HIE and mild or no HIE after asphyxia.[24] Lactates were also reported as predictors of unfavorable long-term outcomes at 12 or 24 months.[21,25] In contrast, we found no significant impact of pH on poor outcome, which supports the hypothesis that the interpretation of a low pH might be not relevant without an analysis of capnia.[26]

An interesting preliminary finding was the significant association between blood glucose level >100 mg/dL on NICU admission and the risk of death. The role of glycaemic control during the early phase of HIE is controversial. While some smaller studies have found an increase in the risk of adverse outcome, the results of the Cool Cap study showed that a hyperglycaemic profile in the early period of the disease could be somewhat protective.[27–30] Conversely, while multi-organ failure was previously described as a factor determining the severity of HIE and could be expected to impact short-term prognosis, it was not a risk factor in our study.[31,32]

Interestingly, the usual antenatal or intrapartum risk factors for perinatal morbidity do not seem to have an influence on short-term HIE outcomes. Infants born late preterm or SGA, representing 15.5% and 16.5% of the cohort, were not more susceptible to either adverse outcome. We did not find an association between acute or subacute obstetrical events and outcomes. Previous studies reported a relationship between sentinel events and the occurrence of HIE, but did not investigate their role in its severity or its short-term consequences.[33–37] Our finding might be explained by the difficulty of early identification of less acute situations, leading to a longer exposition to fetal hypoxia before instrumental delivery or cesarean section. Finally, no event or only an isolated abnormal fetal heart rate was reported for 290 (36.7%) neonates, and this context is widely described in the literature.[38–40]

Strengths and limitations of this study

The strengths of the LyTONEPAL study include its population-based design and the prospective enrollment of infants from regions in France with over one million births during an uninterrupted 18-month period. This cohort collected detailed clinical information from the antenatal period to hospital discharge, and enabled us to track the "real world" dissemination of HT and to document the course and outcomes of this uncommon disorder. It also provides valuable population-based benchmarks for comparisons of outcomes with other contemporary cohorts of neonates with HIE.

We did not include children who died very soon after admission to the NICU because of a severe condition, such as children who died during transport or in the delivery room because of the study's focus on postnatal factors. The inclusion of these children may have affected the results regarding the association between obstetric factors and death. This potential selection bias was anticipated in the study design and addressed through the maintenance of a non-inclusion register with a minimal dataset. Another limitation is that some important information, particularly neuroimaging at hospital discharge, was incomplete. This limitation is inherent to the observational and nationwide nature of this large cohort. Nevertheless, the cases with missing MRI data (unavailable or no MRI performed) were reasonable (10.4% of survivors) and multiple imputation was carried out to limit bias resulting from these cases. The bias would be mainly due to children without an MRI performed, who have a less severe HIE than all others. Brain damage was defined by the existence of at least one lesion among 7, whatever the extent and the total number of lesions, although the associated later sequelae are likely to vary according to these criteria. We did not present the MRIs of deceased children, which were not always performed, considering that death was a sufficient determinant of severity.

CONCLUSION

This large population-based cohort of neonates with moderate and severe HIE, who benefited from the generalization of HT treatment, showed that death still occurred for 18.3% of neonates and that 28.5% survived with abnormal MRI. Several early risk factors for death were identified, justifying the importance of biological signs of asphyxia and clinical signs from early neurological examinations. These results can help guide clinicians in identifying neonates most at risk of poor prognosis and encourage the development of other neuroprotective strategies to be associated with HT for children at the highest risk. These short-term results need to be considered alongside the analysis of risk factors of unfavorable long-term follow-up.

DATA AVAILABILITY

Data cannot be shared publicly but will be available from the Grenoble University Hospital on request for researchers who meet the criteria for access to confidential data.

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AUTHOR CONTRIBUTIONS

T.D., N.B., and A.E. conceptualized and designed the study, wrote the grant proposal, supervised data collection, drafted the manuscript and reviewed and revised it. L.S., G.K., O.B., P.Y.A., and I.G. helped design the study and critically reviewed and revised the manuscript. J.Z., M.C., and V.P. critically reviewed the manuscript for important intellectual content. A.V. carried out the statistical analysis and reviewed the manuscript.

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COMPETING INTERESTS

The authors declare no competing interests.

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