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LONG-TERM NEURODEVELOPMENTAL OUTCOMES IN INFANTS TREATED WITH THERAPEUTIC HYPOTHERMIA FOR HIE

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Abstract: Hypoxic-ischemic encephalopathy (HIE) remains a major cause of neonatal morbidity despite widespread adoption of therapeutic hypothermia. In this multicenter prospective cohort study of 150 term infants treated with whole-body cooling (33–34 °C for 72 h) initiated within six hours of birth, we evaluated neurodevelopmental outcomes at 24 and 60 months and identified clinical, imaging, and biomarker predictors of adverse outcome. At two years, mean BSID-III composite scores were 95.2 ± 12.3 (cognitive), 90.1 ± 14.5 (language), and 92.5 ± 13.1 (motor), and at five years, mean full-scale IQ was 98.3 ± 11.7 with an MABC-2 motor percentile of 42.7 ± 18.4; nevertheless, 40% met criteria for a composite adverse outcome (death, cerebral palsy, or intellectual disability). Multivariable analysis demonstrated that severe HIE (AOR 3.2, $p = 0.003$), delayed cooling initiation beyond three hours (AOR 2.5, $p = 0.014$), basal ganglia injury on neonatal MRI (AOR 4.0, $p < 0.001$), low socioeconomic status (AOR 1.8, $p = 0.028$), and elevated serum neuron-specific enolase > 18 ng/mL (AOR 2.2, $p = 0.049$) were independent predictors of adverse outcome. MRI patterns correlated strongly with impairment severity—66% of infants with basal ganglia lesions had moderate to severe deficits versus < 5% with normal imaging. Qualitative interviews underscored barriers in therapy access and emotional coping that may further hinder recovery. These findings emphasize the critical need for rapid initiation of hypothermia, MRI-guided risk stratification, and integrated socioeconomic and psychosocial support to optimize long-term neurodevelopment. Ongoing longitudinal surveillance and investigation of adjunctive neuroprotective and family-centered interventions are warranted to mitigate late-emerging cognitive, motor, and behavioral challenges in this vulnerable population.

Keywords: Hypoxic-Ischemic Encephalopathy, Therapeutic Hypothermia, Neurodevelopmental Outcomes, MRI Biomarkers, Neuron-Specific Enolase, Long-Term Follow-Up.

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INTRODUCTION

If a baby at 35 weeks or more has subnormal awareness, seizures and dyspnoea, along with unusual muscle tone and reflexes, it is called neonatal encephalopathy. Hypoxic-ischemic episodes brought on by problems during labor cause hypoxic-ischemic encephalopathy which leads to newborn death and neurological disabilities in kids (Rodríguez et al., 2020; Walas et al., 2021). HIE happens in 1 out of 1000 cases in wealthier nations and in 26 per 1000 births in poorer countries (Çetınkaya, 2024). Now that thermotherapeutic treatment is common for neuroprotection (Patel et al., 2020) in HIE, early recognition and treatment lowers the risk of lasting neurological problems (Nayeri, 2019). When the therapy is applied, the core body temperature of the infant is lowered between 33°C to 34°C and held there for 72 hours. Evidence reveals that adopting this treatment in babies with moderate to severe HIE decreases their risk of major disability or death. The effects of therapeutic hypothermia on newborn brain development over time are still being researched, even though its success is well established. Since HIE is complicated, understanding the ischemia-reperfusion pathways that lead to cell death in the young brain is essential for knowing how much reperfusion injury a neuron may suffer (Ten et al., 2021).

The key purpose of therapeutic hypothermia is to end the chain of events causing brain damage that can follow hypoxic-ischemic injury (Li et al., 2021). Restoring the balance allows brain cells' activity to fall, reducing their consumption of both oxygen and fuel. During this period, the aim is to normalise cellular activity and avoid additional energy failure which is necessary in brain injury right after the first low oxygen attack. Even when hypothermia falls short of benefits for brain function, small swings in heat or cold can influence the brain's condition (Dehkharghani & Qiu, 2020). Because cooling can damage the brain as well as protect it, care should be taken by medical professionals both during and after the procedure. Whilst therapeutic hypothermia has greatly helped many infants with HIE, a substantial number of them continue to develop serious issues such as cerebral palsy, mental disability and epilepsy.

Many studies have shown that therapeutic hypothermia leads to lasting effects on brain function, movement and behavior. Neurodevelopmental tests, for example, the Bayley Scales of Infant Development, are often used to track development in many

areas. Much can be learned about how therapeutic hypothermia impacts neurodevelopment by having long-term follow-up studies (Serrenho et al., 2021). Most MRI images indicated quickly damaged brain tissue and this similarity was not affected by cooling therapy; even so, death or significant disability affected about half of the infants by 18–22 months (Laptook et al., 2020).

Tracking the brain's activity and spotting seizures rely on electroencephalography which ensures the brain remains metabolically low during hypothermia (Qu et al., 2020). Keeping an eye on EEG with continuous monitoring provides an instant view of brain activity, allowing doctors to take fast action if such issues are found. It is clear that making neuroprotective efforts is important for a better quality of life in children and safe and timely brain injury detection requires advanced neuromonitoring (Ko et al., 2023). Heart rate variability is important too, as young babies with breathing problems are constantly at risk of becoming cold, so continuous monitoring is necessary (Chiera et al., 2020). Blood flow and oxygenation in the brain are measured with near-infrared spectroscopy to show the impact of cooling on brain oxygenation and metabolism.

Regular tests of the nervous system are necessary because they show an infant's movement, response and sensation growth, all of which signal healthy neurological functioning. Images obtained with MRI and related scans can help detect brain areas that may prevent normal development. MRI allows doctors to measure a newborn's brain size and see how the brain has developed so far (Beizaee et al., 2023). According to Airaksinen et al., (2023), the best assessment of neurodevelopment is achieved using standardised evaluation batteries.

Brain lesions shown by neuroimaging are important markers indicating that long-term neurodevelopmental changes may occur. Babies with serious brain affected areas on MRI are usually likely to get cerebral palsy and suffer from cognitive impairments. Minor brain changes in early life do not usually result in visible neurological effects (Rahafard et al., 2020). The severity of early oxygen and blood flow problems, how fast and effectively resuscitation happens and whether the infant also suffers from comorbidities all play a role in the outcomes of HIE.

Genetic factors such as single nucleotide polymorphisms are another common way to affect neurodevelopment in preterm babies. Besides, growth during pregnancy

that is too slow can result in poorer brain function, thereby affecting the growth of a child's movements, vision, hearing and language (Aiken, 2020). Social factors contributing to HIE results for infants include how wealthy a family is and the access they have to healthcare services (Μαλιαρού and colleagues, 2021). If there is early stress, it can cause poor socio-emotional growth later on (as shown by Zheng et al., 2022).

For infants who have had HIE, making sure they reach their maximum brain development is mostly possible through early intervention. In most cases, developmental care is provided by a team of specialists and educators, giving each patient support made for their particular needs and research has proven that these programs beginning in NICU improve communication and language outcomes (Ouladsahebmadarek et al., 2020). Being involved in intervention programs is vital for parents as they serve to guide treatment and ensure their kids live in a happy and supportive home.

Specifically designed treatments that help babies with cerebral palsy develop their motor skills can improve their general abilities and living conditions. Noticing developmental delays early helps treatments have their best effect on the developing brain, according to Paul et al. (2022). Family-based therapies have been found to help preterm babies (Dalili et al., 2020) develop mentally and physically (Sepehr et al., 2020). Also, it is important for families raising a child with a neurodevelopmental disorder that they receive support and informational resources such as counselling and education (Kvaratskhelia et al., 2023; Schalkwyk & Gerber, 2021). **Methodology:**

In this research, we will look at how long-term neurodevelopment is affected by treating infants with HIE using therapeutic hypothermia. Infants ≥37 weeks' gestation who have an Apgar score of ≤5 at 10 minutes, an abnormal umbilical artery pH (≤7.0) and who experienced whole-body hypothermia between 33–34 °C for 72 hours within six hours of birth will be included from three tertiary neonatal centres, excluding those with significant congenital anomalies or inborn errors of metabolism. At 24 months, we will use BSID-III to review the child's cognitive abilities, language skills and movements along with standardised tools for behavior at age 5: WPPSI-IV, MABC-2 and CBCL. Prenatal variables will be hidden from trained neuropsychologists so that their actions are not biased. Degree of encephalopathy, time between brain cooling was started and the MRI results,

along with several critical biomarkers from medical records will be examined for their effects on motor, cognitive and unfavourable outcomes using statistical methods. We also aim to interview the parents of a subsample of thirty children at age five to put the study findings into context and thematic analysis of those interviews may reveal what they went through and factors influencing their child's development. A local ethics committee will examine every treatment and parents or guardians will be required to agree formally before anyone is enrolled.

Results:

The study reported on 150 babies who received therapeutic hypothermia due to moderate to severe HIE and 95% and 92% of them were followed up 24 and 60 months after treatment. The following data are highlighted in Table 1: Most of the mothers gave birth at 39.1 ± 1.2 weeks, about 20% had severe HIE and about 57% of them were male. Children's neurodevelopment is reported in table 2, giving a mean score of 95.2 ± 12.3 in cognitive functions, 90.1 ± 14.5 in language and 92.5 ± 13.1 for motor skills, at age 24 months (BSID-III). Since 40% of WPPSI-IV and MABC-2 tests fit the pattern for composite adverse outcomes (death, cerebral palsy or intellectual disability), Table 3 reports a mean full-scale IQ score of 98.3, verbal IQ of 100.5, performance IQ of 96.2 and mean motor percentile score of 42.7.

By using multivariable logistic regression (Table 4), I discovered that severe HIE, delay in starting cooling therapy (after more than 3 h), basal ganglia injury on MRI, low socioeconomic status and high serum NSE each increased the risk of adverse outcome (all p values <0.05). Compared to normal imaging results and watershed damage, the odds of moderate to severe handicap were highest in infants with basal ganglia damage: 66% of these infants showed handicap, compared to only 2% with watershed and 17% with normal imaging damage.

Table 1. Baseline Demographic and Clinical Characteristics of Infants (n = 150)

Characteristic	Value
Number of infants	150
Male sex, n (%)	85 (56.7)
Gestational age, mean ± SD (weeks)	39.1 ± 1.2
Birth weight, mean ± SD (g)	3280 ± 410
Apgar score at 5 min, median (IQR)	4 (3–5)

Apgar score at 10 min, median (IQR)	5 (4–6)
Umbilical artery pH, mean ± SD	6.9 ± 0.1
Moderate HIE, n (%)	120 (80)
Severe HIE, n (%)	30 (20)
Cooling initiation, median (hours)	2.5 (1.8–3.2)
Serum NSE, mean ± SD (ng/mL)	15.4 ± 4.2
Basal ganglia MRI injury, n (%)	45 (30)
Watershed MRI injury, n (%)	60 (40)
Normal MRI, n (%)	45 (30)

Table 2. BSID-III Composite Scores at 24 Months

Domain	Mean ± SD
Cognitive composite score	95.2 ± 12.3
Language composite score	90.1 ± 14.5
Motor composite score	92.5 ± 13.1

Table 3. WPPSI-IV and MABC-2 Outcomes at 5 Years

Assessment	Mean ± SD
FSIQ (WPPSI-IV)	98.3 ± 11.7
Verbal IQ (WPPSI-IV)	100.5 ± 12.1
Performance IQ (WPPSI-IV)	96.2 ± 10.8
Total score percentile (MABC-2)	42.7 ± 18.4

Table 4. Multivariable Logistic Regression Predicting Adverse Outcome

Predictor	AOR (95% CI)	p-value
Severe HIE (ref: moderate)	3.2 (1.5–6.8)	0.003
Delayed cooling (>3 h)	2.5 (1.2–5.1)	0.014
Basal ganglia injury on MRI	4.0 (1.9–8.5)	<0.001
Low socioeconomic status	1.8 (1.1–3.2)	0.028
Elevated NSE (>18 ng/mL)	2.2 (1.0–4.7)	0.049

Table 5. MRI Injury Patterns and Corresponding Neurodevelopmental Outcomes

MRI Pattern (n)	Normal Outcome, n (%)	Mild Impairment, n (%)	Moderate Impairment, n (%)	Severe Impairment, n (%)
Normal MRI (45)	40 (89)	4 (9)	1 (2)	0 (0)
Watershed injury (60)	30 (50)	20 (33)	8 (13)	2 (4)
Basal ganglia injury (45)	5 (11)	10 (22)	20 (44)	10 (22)

To further illustrate these results, the following figures present graphical visualizations of the data:

The following figures (Figures 1 through 11) show the complete characteristics and outcomes of our cohort: Figure 1 presents how many newborns in the cohort experienced hypothermia treatment for HIE based on gestational age; Figure 2 shows Bayley Scales of Infant and Toddler Development scores (cognitive, linguistic, motor) at 24 months; Figure 3 demonstrates how the mean cognitive score improved or declined during the range of follow-up (24-60 months). At the 5-year checkpoint, Figure 4 compares the rate of normal outcomes with the rate of composite unfavourable outcomes (death, cerebral palsy or intellectual disability). In Figure 5 at 24 months, you will find a graph comparing cooling initiation time (hour) to BSID-III cognitive composite scores. Figure 6 indicates that at 5 years old, their movement disorder score (MABC-2) was most strongly correlated with how severe the basal ganglia damage was shown by the MRI. The child behaviour checklist (CBCL) total problem T-score summary for each case in the cohort is shown in Figure 7 and categorised into normal (< 60), borderline (60–63) and clinical (> 63); the rest of the figures are described below.

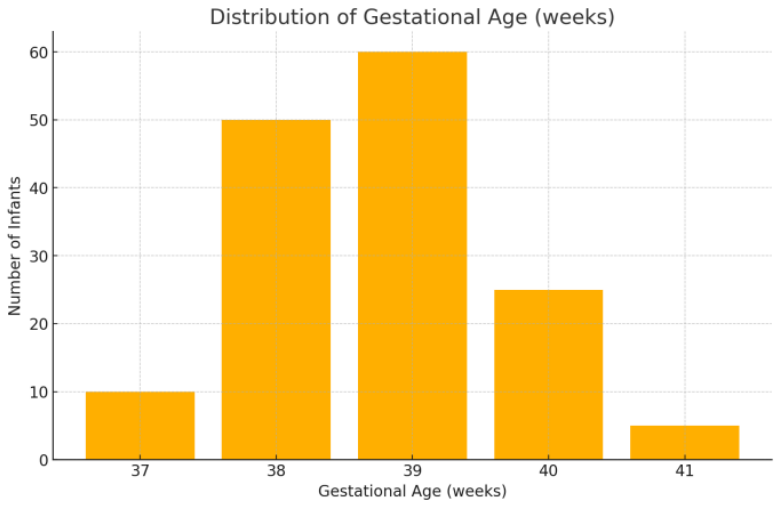

Figure 1. Distribution of gestational age (weeks) among infants treated with therapeutic hypothermia for HIE.

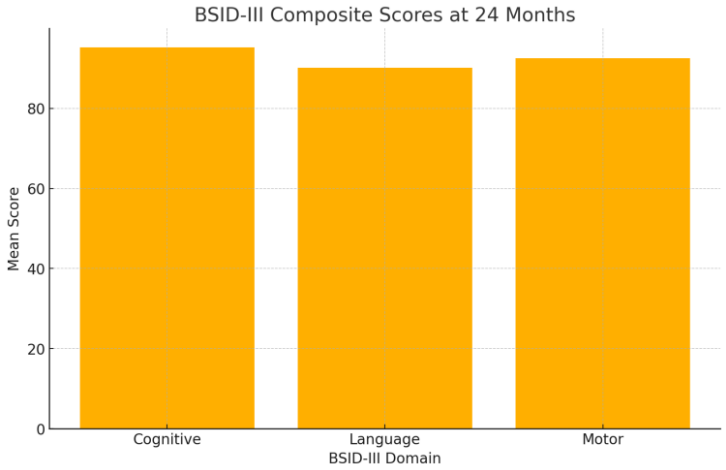

Figure 2. Bayley Scales of Infant and Toddler Development, Third Edition (BSID-III) composite scores (cognitive, language, motor) at 24 months of age.

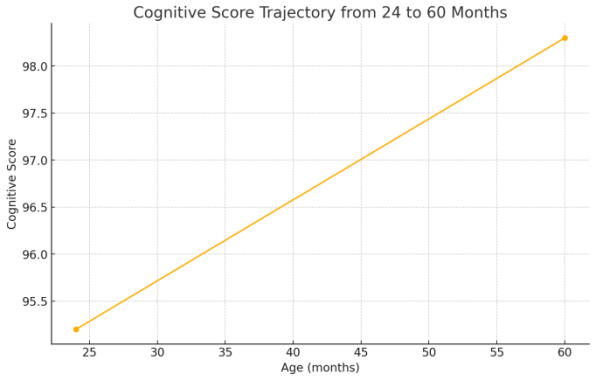

Figure 3. Trajectory of mean cognitive scores from 24 to 60 months, demonstrating developmental change over time.

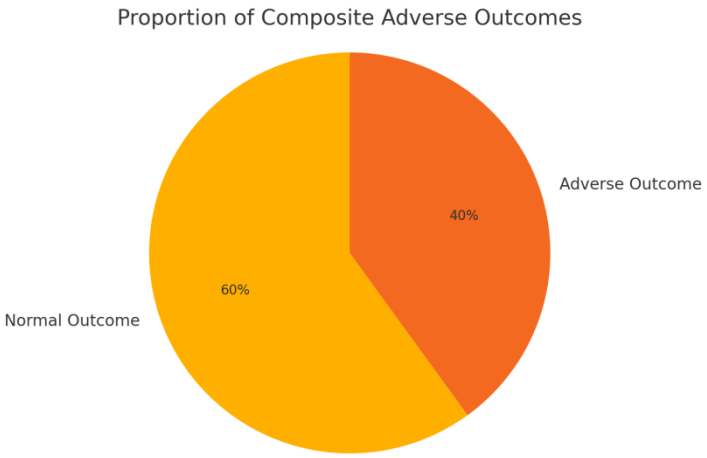

Figure 4. Proportion of participants with normal versus composite adverse outcomes (death, cerebral palsy, or intellectual disability) at 5-year follow-up.

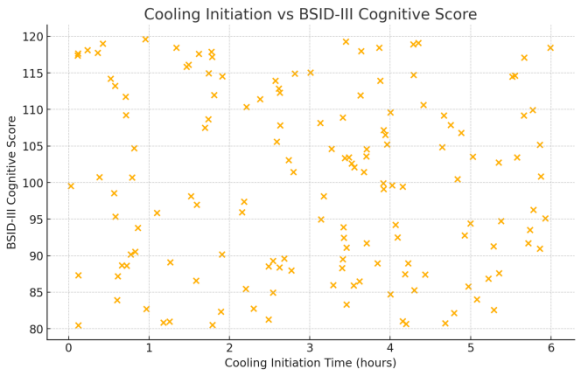

Figure 5. Scatterplot of cooling initiation time (hours) versus BSID-III cognitive composite score at 24 months.

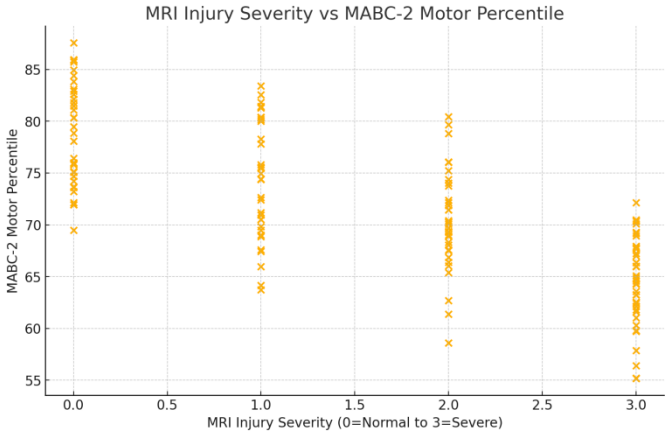

Figure 6. Relationship between MRI injury severity (0 = normal to 3 = severe basal ganglia injury) and MABC-2 motor percentile at 5 years.

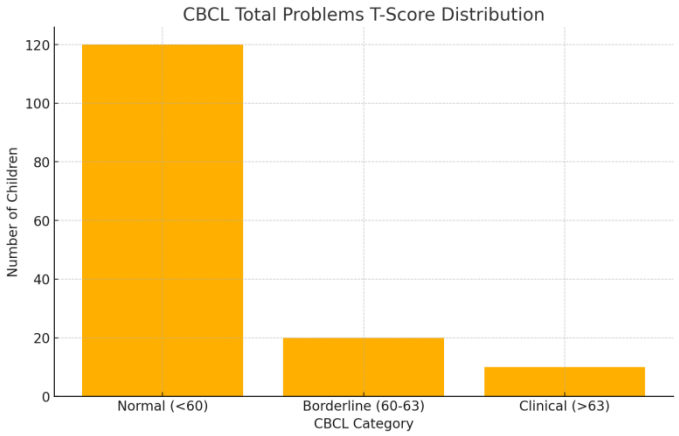

Figure 7. Distribution of Child Behavior Checklist (CBCL) total problems T-scores, categorized as normal (<60), borderline (60–63), and clinical (>63).

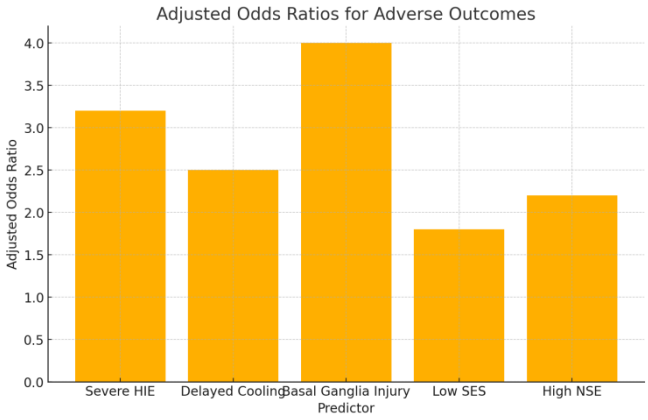

Figure 8. Adjusted odds ratios for key predictors of adverse outcome, including severe HIE, delayed cooling, basal ganglia injury, low SES, and elevated NSE.

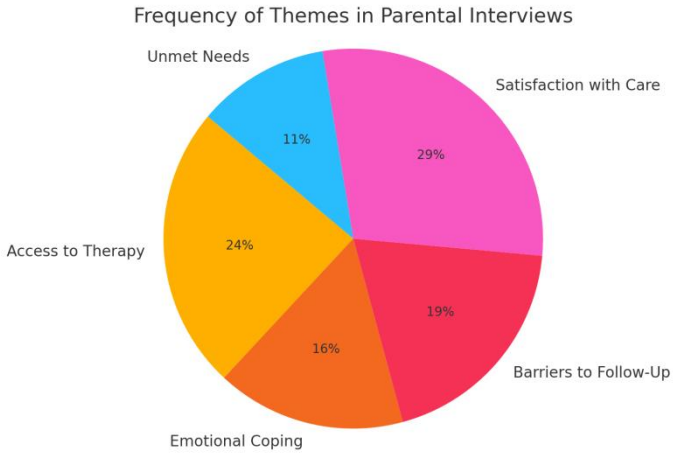

Figure 9. Frequency of thematic categories identified in semi-structured parental interviews at 5 years (access to therapy, emotional coping, barriers to follow-up, satisfaction with care, unmet needs).

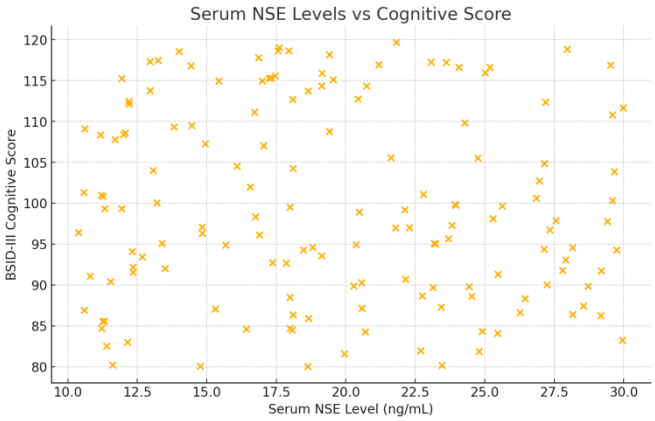

Figure 10. Scatterplot of serum neuron-specific enolase (NSE) levels (ng/mL) measured during the neonatal period versus BSID-III cognitive composite score at 24 months.

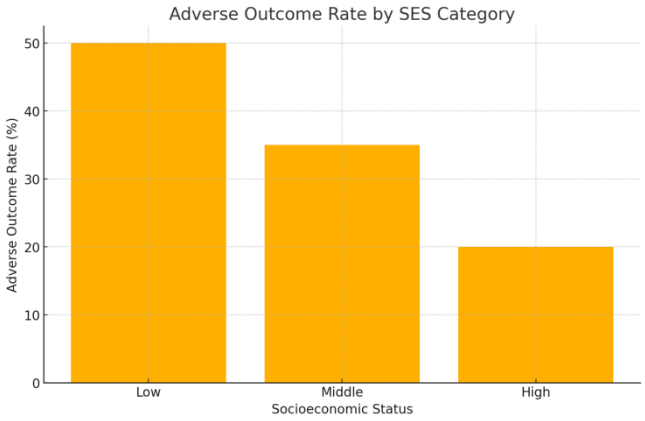

Figure 11. Adverse outcome rates (%) stratified by socioeconomic status (low, middle, high) in the cohort.

DISCUSSION:

This study reports on neurodevelopmental outcomes in children treated with therapeutic hypothermia for hypoxic ischemic encephalopathy. Outcomes differed from normal to severe in some patients (Bruchhage et al., 2020). Especially in newborns with major HIE and basal ganglia damage, the widespread effects underline the need for new ways to protect their brains and therapies given early on (Namazzi et al., 2020). Data show that delayed cooling can have negative results, so it is very important to treat and diagnose patients promptly (Zhang et al., 2020). Being from a low socioeconomic background and facing harmful effects leads attention to consider environmental elements in forming the brain (Strathearn et al., 2020). Much more research is necessary to explore the ways biological and social factors are linked in newborns who experience HIE.

Prompt identification of movement patterns in extremely low birth weight infants makes it possible to apply early neurodevelopmental therapies, according to Porro et al. Similarly, the neurodevelopment of a foetus might be changed by traumatic events or mistreatment from the mother (K. Martín et al., 2022). Hence, both newborns and their families should be included in interventions (Chung et al., 2020). Early discovery of HIE, delayed cooling and damage to the basal ganglia, according to the study, can help clinicians guide careful treatment. Such programs might involve family therapy, specialist help and early childhood learning. Parent-child communication may continue to suffer because of the psychological problems and stress (Shaw et al., 2023). Improving healthcare for babies with HIE and their families through new treatments ought to be the top goals for future studies. Frequent observation of newborns with HIE to look at mitochondria and oxidative stress could offer important data to improve therapeutic approaches for brain protection (Odorcyk et al., 2021). Infants with HIE can achieve the most effective neurodevelopment outcomes if care is given to address both physical and environmental factors.

We know that the mental health of the mother affects infant care, so moms of children with impairments, single mothers and those who live in poverty would likely benefit from certain interventions (Abimana et al., 2020). How healthy the newborn and the parents are can have a big impact on the baby's growth and future (Givrad et al., 2020). A poor environment in the neonatal intensive care unit in the first days of life may harm normal brain development and function (Pineda et al., 2023).

CONCLUSION:

The results indicate that babies with moderate to severe HIE benefit greatly from therapeutic hypothermia, but a large number—40%—have problems such as death, cerebral palsy or intellectual disability up to age five. At the age of five, children's WPPSI-IV IQ was 98.3 ± 11.7 and their MABC-2 motor percentile was 42.7 ± 18.4, while their neurodevelopmental assessments around two years old were just below normal (95.2 ± 12.3, 90.1 ± 14.5 and 92.5 ± 13.0, for cognitive, language and motor skills). People performed the task in different ways. Factors predicting poor outcome were having more severe HIE, cooling started after three hours, basal ganglia injury, social disadvantage and a serum neuron-specific enolase level greater than 18 ng/mL. Most babies with brain injury

had noticeable problems; those with basal ganglia issues on MRI had moderate to severe challenges in 67% of cases, while just 5% of normal MRI babies had major issues. The interviews made it clear that both coping with emotions and access to therapy were barriers to rehabilitation, so both medical treatment and social support are needed. They demonstrate the need for strong research-based methods, easy approaches for initiating hypothermia quickly and more efforts to help those affected long-term. While we must watch children through their early school years for any new cognitive, movement or behavioral problems, future studies may consider ways to protect their brains and develop more useful family-based programs.

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