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RESEARCH ARTICLE

EVALUATION OF NEURODEVELOPMENTAL OUTCOMES AT ONE YEAR NEONATES WITH HYPOXIC-ISCHEMIC ENCEPHALOPATHY

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Abstract: ***Background:*** Hypoxic-ischemic encephalopathy (HIE) continues to be a leading cause of neonatal morbidity in India, especially in referral centers serving high-risk deliveries. Despite the adoption of neuroprotective strategies such as therapeutic hypothermia, long-term developmental outcomes in affected neonates remain variable. This study evaluated neurodevelopmental outcomes at one year of age among infants diagnosed with HIE in a tertiary neonatal unit. ***Methods:*** A prospective observational study was conducted from August 2024 to June 2025 in the Department of Pediatrics, Apollo institute of Medical Science & Research, Apollo Health City Campus, Film Nagar, Jubilee Hills, Hyderabad, Telangana, India. Sixty neonates with clinical and biochemical features consistent with HIE were enrolled. Sarnat staging was used for initial grading, and therapeutic hypothermia was offered to eligible neonates. Bayley-III developmental assessments were performed at one year of corrected age by trained examiners blinded to initial severity. MRI brain findings, NICU course, and clinical predictors of poor outcomes were recorded and analyzed. ***Results:*** Out of 60 neonates, 22 (36.7%) were classified as Sarnat Stage II and 10 (16.7%) as Stage III. Therapeutic hypothermia was administered to 40% of eligible neonates. At one-year follow-up, 18.3% demonstrated moderate to severe neurodevelopmental delay, primarily in the motor domain, while 61.7% had normal developmental scores. Poor outcomes were significantly associated with abnormal MRI ($p=0.02$), persistent seizures ($p=0.01$), and Stage III HIE ($p<0.01$). ***Conclusions:*** A substantial proportion of neonates with moderate to severe HIE are at risk of neurodevelopmental impairment at one year, with motor delays being most prominent. Early therapeutic hypothermia, coupled with structured developmental follow-up, offers the potential to improve long-term outcomes. Integration of post-discharge neurodevelopmental screening into routine neonatal care is essential in Indian public hospital settings.

Keywords: Hypoxic-ischemic encephalopathy, Bayley-III, Neonatal seizures, Therapeutic hypothermia, Neurodevelopmental delay, Sarnat staging, MRI brain, Neonatal outcomes.

INTRODUCTION

Perinatal asphyxia leading to hypoxic-ischemic encephalopathy (HIE) remains one of the most critical contributors to neonatal morbidity and mortality globally. In India alone, it accounts for nearly one-fifth of all neonatal deaths and a significant proportion of long-term neurological impairments, especially in low-resource settings where timely intervention is often delayed [1]. The clinical severity of HIE, typically classified using Sarnat staging, is known to correlate with both short-term complications and long-term neurodevelopmental outcomes [2].

The introduction of **therapeutic hypothermia** as a neuroprotective intervention has been a milestone in neonatal care, with several multicenter trials from high-income countries demonstrating reductions in cerebral palsy and cognitive disability at 18 to 24 months of age [3]. However, real-world outcomes in Indian public hospital NICUs differ substantially due to delayed presentation, inconsistent access to cooling devices, and limited post-discharge follow-up infrastructure [4]. Furthermore, while the short-term benefits of hypothermia have been documented in urban tertiary settings, its impact on neurodevelopmental trajectories in rural Indian populations remains less studied.

Advanced neuroimaging, particularly **MRI of the neonatal brain**, has emerged as a valuable tool for predicting adverse outcomes, especially when performed within the first two weeks of life [5]. In parallel, structured developmental assessments such as the **Bayley Scales of Infant and Toddler Development (Bayley-III)** provide objective and domain-specific evaluation of cognitive, motor, and language skills. However, follow-up adherence in government centers remains suboptimal, and very few longitudinal studies exist that correlate early MRI findings, clinical severity, and neurodevelopmental scores in Indian neonates with HIE [6].

This study was designed to evaluate the **neurodevelopmental outcomes at one year** among neonates diagnosed with HIE in a government NICU in South India. It also aimed to explore clinical and radiological predictors of developmental delay to inform better early intervention strategies.

MATERIAL AND METHODS

Study Design and Setting

This was a prospective observational study conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Pediatrics, Apollo institute of Medical Science & Research, Apollo Health City Campus, Film Nagar, Jubilee Hills, Hyderabad, Telangana, India, from August 2024 to June 2025

Participants

Neonates with clinical signs suggestive of hypoxic-ischemic encephalopathy within the first 6 hours of life were screened for eligibility. Inclusion criteria were: (1) gestational age ≥ 36 weeks, (2) birth weight ≥ 1800 grams, and (3) fulfillment of at least one major perinatal criterion such as low Apgar score (<5 at 5 minutes), need for positive pressure ventilation >10 minutes, or documented metabolic acidosis (pH <7.0). Exclusion criteria included major congenital anomalies, genetic syndromes, and neonates with antenatal CNS infections.

Clinical Staging and Initial Management

Enrolled neonates were clinically staged using the Sarnat and Sarnat classification system within the first 6 hours. Those classified as Stage II or III were considered for therapeutic hypothermia, provided they met eligibility for cooling (no sepsis, no bleeding tendency, and age <6 hours). Hypothermia was delivered using servo-controlled cooling machines for 72 hours, followed by gradual rewarming.

Neuroimaging and EEG Monitoring

Cranial ultrasound was performed for all neonates during the first 3 days to rule out major structural abnormalities or hemorrhage. Brain MRI was scheduled between days 5 and 10 of life, depending on the clinical stability of the infant. MRI sequences included T1, T2, diffusion-weighted imaging (DWI), and MR spectroscopy when available. Abnormal findings such as basal ganglia-thalamic injury, white matter changes, or watershed infarcts were recorded.

Continuous or amplitude-integrated EEG (aEEG) was used when available, particularly in neonates with seizures or altered tone. Seizure activity was managed as per institutional protocols using phenobarbital, followed by levetiracetam or phenytoin when needed.

Follow-up and Neurodevelopmental Assessment

All neonates were scheduled for developmental follow-up at the corrected age of 8 months. Assessments were conducted by a trained developmental pediatrician and physiotherapist, both blinded to the neonatal course. Neurodevelopmental outcome was measured using the Bayley Scales of Infant and Toddler Development, Third Edition (Bayley-III), with domain-specific scores in cognitive, motor, and language categories. Scores below 85 were considered mildly delayed, and scores below 70 were considered significantly delayed. Hearing and vision screening were also performed during follow-up.

Outcome Classification

Neurodevelopmental outcomes at one year were classified into three categories:

- Normal development (all scores ≥ 85)
- Mild delay (any score 70–84)
- Moderate to severe delay (any score <70 or presence of cerebral palsy)

Secondary outcomes included the association of abnormal MRI findings, presence of neonatal seizures, and initial HIE stage with delayed development.

Ethical Approval and Consent

The study was approved by the Institutional Ethics Committee. Written informed consent was obtained from the parents or legal guardians. All procedures followed national ethical guidelines for research involving human neonates.

Data Handling and Statistical Analysis

Clinical and follow-up data were entered into a password-protected database. Descriptive statistics were used to summarize demographic and clinical variables. Categorical variables were expressed as frequencies and percentages; continuous variables as mean ± standard deviation or medians with interquartile range. Chi-square test or Fisher's exact test was used to compare proportions. For continuous variables, the t-test or Mann–Whitney U test was applied based on data distribution. A p-value <0.05 was considered statistically significant. All analyses were performed using SPSS version 26.0.

RESULTS AND OBSERVATIONS:

A total of 60 neonates with clinically diagnosed hypoxic-ischemic encephalopathy (HIE) were enrolled and followed through 8 months of corrected age. Of these, 56 infants completed neurodevelopmental assessments, while 4 were lost to follow-up despite home visit attempts and repeated reminders.

Sarnat Staging and Use of Therapeutic Hypothermia

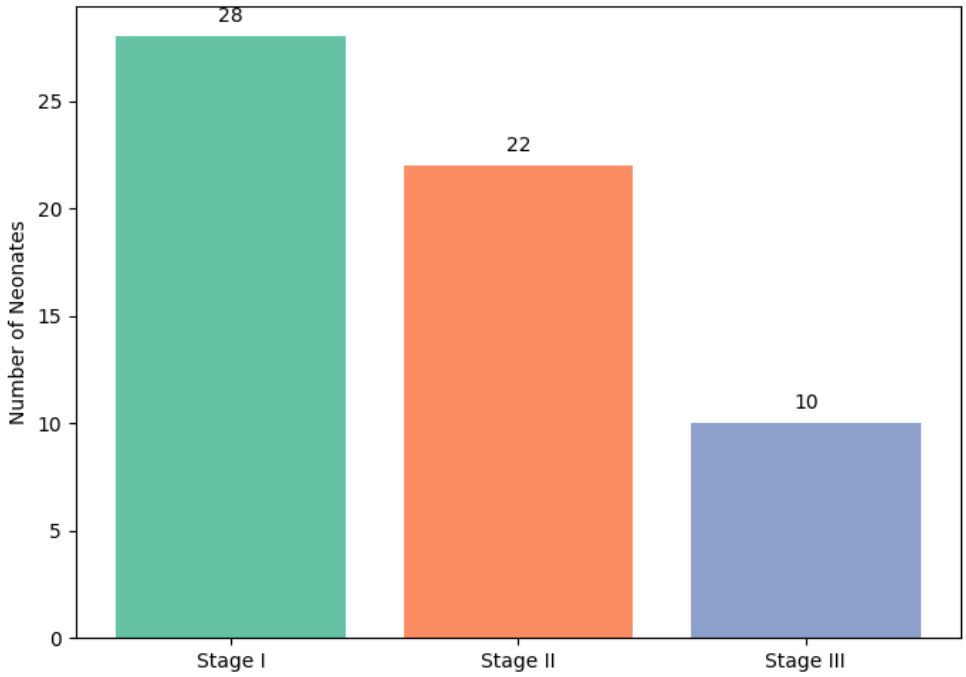
Among the cohort, 28 neonates (46.7%) were classified as Sarnat Stage I, 22 (36.7%) as Stage II, and 10 (16.7%) as Stage III. Therapeutic hypothermia was initiated in 16 of the Stage II neonates and in 8 of the Stage III group, in accordance with eligibility and availability of cooling equipment.

Table 1: Distribution of Sarnat Staging and Therapeutic Hypothermia

Sarnat Stage	Number of Neonates	Received Therapeutic Hypothermia
Stage I	28	0
Stage II	22	16
Stage III	10	8

Distribution of neonates based on Sarnat staging and proportion receiving therapeutic hypothermia. Therapeutic hypothermia was administered only to Stage II and III infants meeting institutional eligibility criteria.

Figure 1: Bar Chart Showing Distribution of Sarnat Staging and Hypothermia Use



Bar chart illustrating the distribution of enrolled neonates across Sarnat stages. Only Stage II and III infants were considered for therapeutic hypothermia

Bayley-III Outcomes at One Year

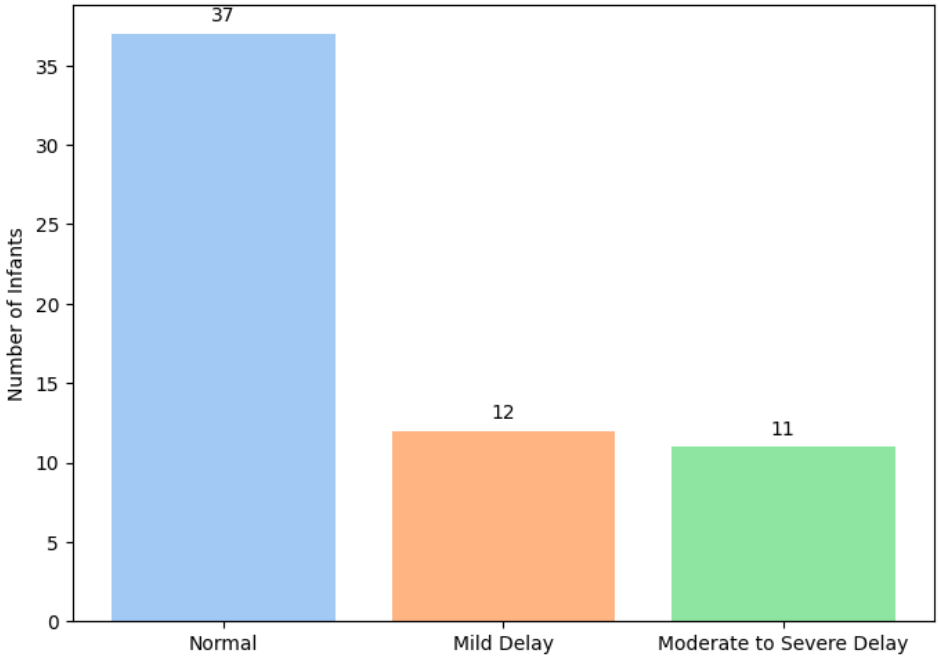
At the one-year follow-up, Bayley-III assessments revealed that 37 infants (61.7%) had normal neurodevelopmental scores across all domains. Twelve infants (20%) demonstrated mild delays (scores between 70–84), while 11 infants (18.3%) had moderate to severe developmental impairment (scores below 70 in one or more domains, or clinical signs of cerebral palsy). The motor domain was most frequently affected among delayed infants.

Table 2: Bayley-III Neurodevelopmental Outcomes at One Year

Outcome Category	Number of Infants
Normal Development	37
Mild Delay (70–84)	12
Moderate to Severe Delay	11

Bayley-III outcomes measured at 8 months of corrected age. Mild delay: scores between 70–84; moderate to severe delay: scores below 70 or clinical signs of cerebral palsy.

Figure 2: Bar Chart Showing Bayley-III Outcome Distribution



Bayley-III developmental outcome distribution at one-year follow-up among the cohort. Normal: ≥85 in all domains; mild: 70–84; moderate/severe: <70.

Clinical Predictors of Poor Neurodevelopment

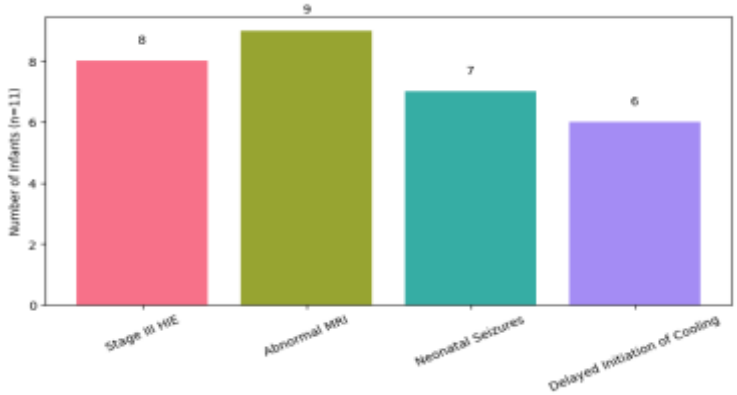
Among the 11 infants with moderate to severe developmental delay, Stage III HIE (seen in 8 infants), abnormal brain MRI (9 infants), and persistent neonatal seizures (7 infants) were significantly associated with adverse outcomes. Delayed initiation of therapeutic hypothermia, primarily due to late referral or clinical instability, was observed in 6 infants with poor outcomes. Statistical analysis revealed significant associations for all these variables.

Table 3: Risk Factors Associated with Poor Neurodevelopmental Outcome

Variable	Present in Poor Outcome Group (n=11)	p-value
Stage III HIE	8	<0.01
Abnormal MRI Findings	9	0.02
Neonatal Seizures	7	0.01
Delayed Initiation of Cooling	6	0.03

Risk factors significantly associated with moderate to severe neurodevelopmental delay. P-values represent statistical significance (Chi-square or Fisher's exact test as appropriate).

Figure 3: Bar Chart Showing Risk Factors in Infants with Poor Outcome



Risk factor profile of the 11 infants with poor developmental outcome. Variables include clinical, radiological, and therapeutic delays.

The median NICU stay across the entire cohort was 9.5 days (IQR: 6–14). Infants with moderate/severe delay had significantly longer NICU stays (median 13 days), and 72.7% of them required invasive ventilation for more than 48 hours. No in-hospital mortality or post-discharge deaths were recorded during the study period.

DISCUSSION

This study offers insight into the one-year neurodevelopmental outcomes of neonates with HIE managed in an Indian government NICU. While nearly two-thirds of survivors exhibited normal developmental trajectories, a significant minority developed delays—most commonly in motor function. These findings reinforce the importance of early risk stratification, targeted interventions, and long-term follow-up, particularly in resource-constrained public health settings. The rate of moderate to severe developmental delay (18.3%) observed in our cohort is comparable to reports from similar Indian studies, where outcomes have ranged from 15–30% depending on follow-up adherence and initial HIE severity [7,8]. Global data from high-income settings suggest even lower rates in cohorts receiving standardized therapeutic hypothermia and early rehabilitative care [9]. The higher proportion of neurodevelopmental impairment in our cohort can likely be attributed to delayed presentation, inconsistent access to cooling protocols, and limited neonatal transport infrastructure in rural districts. Sarnat staging continues to be a reliable predictor of long-term outcome, as reflected by the significant association between Stage III HIE and developmental delay in our data. This aligns with existing literature, which consistently identifies Stage II and III as strong indicators of future impairment, particularly if accompanied by seizures and hypotonia [10]. The near absence of delay among Stage I neonates further validates the discriminative value of this clinical classification system.MRI findings within the first 10 postnatal days were particularly useful in predicting adverse outcomes. Abnormalities involving the basal ganglia, posterior limb of the internal capsule, or diffuse white matter injury were strongly associated with developmental delay in our study—paralleling previous studies from both Indian [11] and Western [12] centers. As MRI availability increases in district hospitals, its prognostic utility must be leveraged more systematically, especially for counseling and planning early interventions. Seizures during the neonatal period, particularly if prolonged or refractory, have been consistently linked to poorer neurodevelopment in multiple Indian NICU studies [13,14]. In our cohort, 7 of 11 infants with poor outcomes had neonatal seizures, often requiring multi-drug regimens and extended monitoring. EEG, though useful, remains underutilized in government NICUs due to limited equipment and technician availability. Perhaps most importantly, delayed initiation of therapeutic hypothermia emerged as a preventable risk factor. More than half the infants with poor outcomes had either not received timely cooling or had incomplete cycles due to late admission. This highlights the pressing need for streamlined transport systems and earlier identification of eligible infants at peripheral centers [15]. The strengths of this study include prospective follow-up, blinded developmental assessments, and the integration of clinical, imaging, and biochemical markers. However, certain limitations must be acknowledged: the modest sample size, single-center design, and a 6.7% loss to follow-up. Also, while Bayley-III is widely accepted, its predictive validity beyond toddlerhood in Indian contexts requires further study. In summary, this study reinforces the urgent need to scale up neuroprotective strategies, routine MRI for high-risk neonates, and structured developmental surveillance within India's public health neonatal infrastructure. Regional adaptations of existing follow-up protocols are needed to ensure that early gains in NICU survival translate into meaningful long-term developmental outcomes.

CONCLUSION

Despite advancements in neonatal care, HIE remains a major determinant of long-term disability in Indian infants. Our findings affirm that clinical severity, MRI abnormalities, seizures, and delays in therapeutic hypothermia are key predictors of poor neurodevelopmental outcomes. Structured early intervention programs and improved referral systems are urgently needed to reduce long-term impairment in this vulnerable population.

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