

Original Research Article

Resistive index as an early prognostic marker in neonatal hypoxic-ischemic encephalopathy: a prospective observational study

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ABSTRACT

Background: Hypoxic-ischemic encephalopathy (HIE) remains a leading cause of neonatal morbidity and mortality. The resistive index (RI), measured via cranial Doppler ultrasound, has emerged as a potential prognostic marker for early neurological outcomes. This study aims to assess the prognostic value of RI in neonates with HIE.

Methods: A prospective observational study was conducted on 110 neonates diagnosed with HIE at a Neonatal Intensive Care Unit (NICU) of Guru Gobindsingh Government Hospital, Jamnagar. RI was measured at 6 and 12 hours of life using Cranial Doppler ultrasound. Data on perinatal risk factors and clinical outcomes were collected. Neurological assessments were performed at 3 and 6 months. Standard statistical tests, including chi-square analysis, were used for data interpretation.

Results: A significant association was found between RI values at 6 hours and adverse neurological outcomes at 3 months ($\chi^2 = 11.45$, $p = 0.009$) and at 6 months ($\chi^2 = 10.89$, $p = 0.012$). Similar associations were observed for RI at 12 hours. Higher RI values correlated with increased mortality and adverse neurodevelopmental outcomes.

Conclusions: RI measurement via cranial Doppler ultrasound serves as a valuable early prognostic indicator in neonates with HIE. Routine incorporation of RI assessments in neonatal care protocols may aid in early risk stratification and targeted interventions to improve long-term outcomes.

Keywords: Cranial Doppler ultrasound, Hypoxic-ischemic encephalopathy, Neonatal prognosis, Resistive index

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) is a severe neurological condition caused by perinatal asphyxia, resulting in reduced oxygen and blood supply to the brain. It remains a significant cause of neonatal morbidity and mortality, particularly in low-resource settings. HIE affects approximately 1 to 2 per 1000 live births in developed nations, with higher prevalence rates in developing countries due to inadequate perinatal care and delayed interventions. The consequences of HIE can range from mild developmental delays to severe neurological impairments such as cerebral palsy, epilepsy, and cognitive deficits, which may persist

throughout life, impacting both the affected individuals and their families.¹

The pathophysiology of HIE involves a two-phase injury mechanism. The primary phase occurs due to acute oxygen deprivation, leading to energy failure in brain cells, disruption of ion homeostasis, and increased intracellular calcium accumulation. This is followed by a secondary phase, which occurs hours after the initial insult and is characterized by oxidative stress, excitotoxicity, and inflammation. This delayed neuronal injury contributes significantly to long-term neurological deficits.² During the early stages of HIE, autoregulation of cerebral blood flow is often impaired, which

exacerbates brain injury. This alteration in cerebral hemodynamic has led researchers to investigate various neuroimaging and hemodynamic markers, such as cranial Doppler ultrasound, to identify early prognostic indicators of neurological outcomes.³

The severity of HIE is typically classified using clinical scoring systems such as the Sarnat and Sarnat staging system, which categorizes infants into mild, moderate, or severe HIE based on neurological findings. Infants with moderate to severe HIE are at the highest risk for long-term complications and often require therapeutic interventions such as therapeutic hypothermia. Therapeutic hypothermia has been the most significant advancement in HIE management, demonstrating neuroprotective effects by reducing metabolic demand, mitigating secondary injury, and improving neurodevelopmental outcomes.⁴

However, despite these advancements, a substantial proportion of neonates still experience adverse neurological outcomes, necessitating additional prognostic tools for risk stratification and targeted interventions. Identifying neonates at the highest risk of poor outcomes remains challenging, as conventional clinical assessments may not fully predict long-term neurodevelopmental impairment. Therefore, there is an urgent need for non-invasive, reliable, and early biomarkers to guide clinical decision-making and optimize neonatal care.⁵

The resistive index (RI), a Doppler ultrasound-derived parameter, has gained attention as a potential prognostic marker in neonates with HIE. RI is calculated using the peak systolic velocity and end-diastolic velocity in cerebral arteries and serves as an indirect measure of cerebrovascular resistance. A higher RI is indicative of increased vascular resistance, which may reflect cerebral oedema, impaired autoregulation, or evolving hypoxic-ischemic injury. Conversely, a lower RI suggests decreased vascular resistance, potentially due to vasoparalysis or evolving ischemic injury.⁶ Several studies have explored the role of RI in predicting outcomes in neonates with HIE. Elevated RI values in the anterior cerebral artery and middle cerebral artery have been associated with poor neurological outcomes, including death and neurodevelopmental impairment.⁷ The non-invasive nature of RI measurement makes it an attractive tool for bedside assessment, allowing continuous monitoring of cerebral hemodynamic without additional risks. However, variability in measurement techniques and a lack of standardized RI thresholds pose challenges in clinical application.⁸

The prognostic utility of RI in HIE remains an area of ongoing research. While some studies have demonstrated strong associations between abnormal RI values and adverse outcomes, others have reported inconsistent findings due to differences in study populations, timing of RI assessment, and methodological variations.⁹

Standardizing the timing of RI measurement and establishing reference ranges for different stages of HIE could enhance its clinical utility. Additionally, integrating RI assessments with other neuroimaging modalities, such as MRI and amplitude-integrated EEG, may provide a more comprehensive evaluation of cerebral injury and improve prognostic accuracy.¹⁰ As neonatal intensive care continues to evolve, there is a growing emphasis on early identification of at-risk neonates to facilitate timely interventions. Understanding the relationship between RI and HIE outcomes could significantly contribute to improving neonatal neurocritical care and reducing long-term disability.

The present study aims to evaluate the prognostic significance of RI in neonates with HIE by assessing its correlation with short-term neurological outcomes. Specifically, this study investigates RI measurements at 6 and 12 hours of life and their association with mortality and neurodevelopmental impairment at 3 and 6 months. By identifying early hemodynamic alterations, this research seeks to establish RI as a non-invasive biomarker for predicting adverse outcomes in neonates with HIE, thereby aiding in early risk stratification and clinical decision-making.

METHODS

Study design and settings

This study was designed as a prospective observational analysis aimed at evaluating the prognostic value of the resistive index (RI) in neonates diagnosed with hypoxic-ischemic encephalopathy (HIE). The investigation was conducted in the Neonatal Intensive Care Unit (NICU) of the Department of Paediatrics at Guru Gobindsingh Government Hospital and Shri M. P. Shah Government Medical College, Jamnagar. The study was conducted over a one-year period from May 2023 to May 2024.

Ethical approval for the study was obtained from the institutional review board (Ref. No: 50/01/2023), and written informed consent was secured from the parents or legal guardians of all participating neonates.

Study participants

Neonates diagnosed with HIE were enrolled, and the resistive index was measured using Doppler ultrasound within the first 24 hours of life. Clinical data, including gestational age, birth weight, and Apgar scores, were meticulously recorded. The neonates were closely monitored for neurological outcomes throughout their NICU stay and followed up for six months post-discharge.

The inclusion criteria comprised neonates clinically diagnosed with HIE based on established criteria such as Apgar scores and clinical signs of moderate to severe encephalopathy. Only neonates born at or beyond 35

weeks of gestation were included to ensure a relatively uniform study population and minimize variability associated with prematurity. Additionally, participants were required to undergo a transcranial Doppler ultrasound examination within the first 72 hours of life, with feasibility confirmed prior to inclusion.

Neonates with major congenital anomalies, particularly those affecting the central nervous or cardiovascular systems, as well as those with pre-existing neurological conditions or metabolic disorders that could influence cerebral blood flow and RI measurements, were excluded from the study. Further exclusion criteria included cases where obtaining parental or guardian consent was not possible, instances of severe co-morbid conditions such as severe sepsis or multi-organ failure, and technical difficulties in obtaining accurate RI measurements due to poor acoustic windows or patient instability.

Sample size determination

The sample size was determined based on previous studies and pilot data assessing neonatal HIE and resistive index abnormalities. Statistical power and confidence intervals were taken into consideration to ensure robustness and reliability. Given the variability in clinical settings, the final sample size was adjusted to 110 neonates to enhance the statistical power of the study and allow for a more comprehensive analysis.

Procedure

Resistive index measurements were conducted on all enrolled neonates within 72 hours of birth using pulse wave Doppler ultrasound with a 3.5 MHz transducer. The signal was obtained from the anterior cerebral artery (ACA) in the sagittal plane while maintaining an inclination angle as close to 15 degrees as possible. To ensure accuracy, all imaging and RI measurements were independently verified by an expert paediatrician. The RI was calculated using the formula: $RI = (PSV - PDV) / PSV$, where PSV represents the peak systolic velocity and PDV represents the peak diastolic velocity. An RI within the range of 0.56 to 0.80 was considered normal, and neonates were classified accordingly.

Outcome measures

The primary outcomes was neonatal mortality and discharge status. Secondary outcomes focused on the evaluation of abnormal neurodevelopmental outcomes at three and six months of age. These outcomes were assessed through standardized neurodevelopmental examinations, providing insight into the prognostic value of RI in neonates diagnosed with HIE.

Statistical analysis

The statistical analysis was conducted using IBM SPSS Statistics for Windows, Version 25.0 (released 2017,

IBM Corp., Armonk, NY). Statistical methods included expressing continuous variables as mean±standard deviation and comparing them using independent t-tests. Categorical variables were presented as frequencies and percentages and compared using chi-square tests. Logistic regression assessed associations between Resistive Index (RI) and outcomes. A p value <0.05 was considered statistically significant.

AI declaration statement

In preparing this manuscript, we used AI language models (ChatGPT (OpenAI, San Francisco, California) and Claude (Anthropic, San Francisco, California) solely to improve language and readability. These tools assisted with grammar and text fluency only. All scientific content, methodology, and conclusions are entirely our own work. AI tools are not listed as authors.

RESULTS

The figure summarizes the gestational age distribution of neonates diagnosed with Hypoxic-Ischemic Encephalopathy (HIE). A significant majority, 82.72% of neonates, were born between 37-40 weeks, while 17.27% were born after 40 weeks (Figure 1).

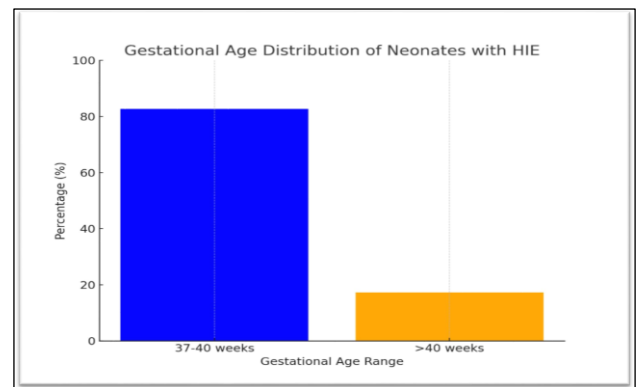


Figure 1: Gestational age of neonates with HIE.

Table 1 presents the relationship between Resistive Index (RI) values, arterial blood gas (ABG) pH levels, and neonatal outcomes (expired vs. discharged). Neonates were categorized based on RI as normal (0.56-0.8) or abnormal (<0.56 or >0.8), with further division based on pH levels (<6.8 or >6.8). The chi-square analysis ($\chi^2=29.77$, $df=3$, $p<0.001$) indicates a statistically significant association between RI, pH, and neonatal outcomes, suggesting that abnormal RI and lower pH are linked to higher mortality (Table 1).

Figure 2 presents the primary outcomes among patients in a study, with four categories: discharge, expired, Discharge on Request (DOR), and Discharge against Medical Advice (DAMA). Most patients (77.27%) were discharged, while 17.27% expired. Both DOR and DAMA each accounted for 2.72% of the outcomes.

Table 2 summarizes the neurodevelopmental outcomes of neonates diagnosed with hypoxic-ischemic encephalopathy at two follow-up intervals: 3 months and 6 months. The majority of neonates showed normal development (67.27% at 3 months and 63.64% at 6 months).

A small proportion exhibited abnormal outcomes (11.82% at 3 months and 13.63% at 6 months), while a few cases were lost to follow-up. Mortality rates decreased over time, with 1.82% expired at 3 months and 0.91% at 6 months (Table 2).

Table 1: Association of Resistive Index (RI) and Arterial Blood Gas (ABG) pH with neonatal outcomes.

RI outcomes	pH	Expired	Discharged	Total
Normal RI (0.56-0.8)	pH<6.8	32	4	73
	pH>6.8	41	1	
Abnormal RI (<0.56 & >0.8)	pH<6.8	16	10	37
	pH>6.8	21	4	

$\chi^2=29.77$, df = 3, p value= <0.001**, *p value <0.05 – Significant, **p value <= 0.001 -Highly Significant

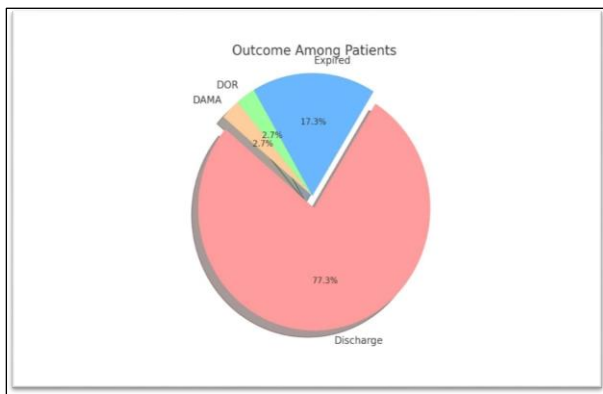


Figure 2: Outcome among patients.

Table 2: Follow-up outcomes of neonates with hypoxic-ischemic encephalopathy at 3 and 6 months.

Time of follow up	Count (n)	Percentage (%)
Outcome at 3 months		
Normal	74	67.27
Abnormal	13	11.82
Lost to follow up	3	2.73
Expired	2	1.82
Outcome at 6 months		
Normal	70	63.64
Abnormal	14	13.63
Lost to follow up	4	3.64
Expired	1	0.91

Table 3: Resistive Index (RI) measurements at 6 and 12 hours and their association with neonatal outcomes.

Outcomes	Count (n)	RI values				p value
		Mean	Std	Min	Max	
Outcomes at 6 hours						
DAMA	3	0.64	0.1	0.57	0.71	0.009*
Discharged	85	0.77	0.2	0.55	1.24	
DOR	3	0.76	0.19	0.65	0.98	
Expired	19	0.96	0.35	0.6	1.3	
Outcomes at 12 hours						
DAMA	3	0.62	0.12	0.54	0.71	0.001**
Discharged	85	0.77	0.2	0.55	1.26	
DOR	3	0.77	0.21	0.65	1.01	
Expired	19	1.0	0.31	0.7	1.31	

*p value <0.05-Significant, **p value <= 0.001-Highly Significant

Table 3 presents the mean, standard deviation (Std), minimum (Min), and maximum (Max) values of Resistive Index (RI) measured at 6- and 12-hours post-birth in neonates diagnosed with hypoxic-ischemic encephalopathy. Outcomes are categorized as Discharged, Expired, Discharge on Request (DOR), and Discharge Against Medical Advice (DAMA). The mean RI was highest in expired neonates (0.96 at 6 hours and 1.0 at 12 hours), indicating a significant association between elevated RI and poor prognosis. The chi-square analysis yielded statistically significant p values (0.009 at

6 hours and 0.001 at 12 hours), suggesting that higher RI values correlate with increased mortality risk (Table 3).

Table 4 illustrates the distribution of neonatal outcomes based on Resistive Index (RI) categories measured at 6- and 12-hours post-birth. Outcomes include Discharge, Expired, Discharge on Request (DOR), and Discharge Against Medical Advice (DAMA). A higher proportion of neonates with altered RI values expired (15 at both time points), whereas those with normal RI had significantly better outcomes, with more being discharged (50 at 6 hours and 55 at 12 hours). Chi-square

analysis indicates a statistically significant association between RI and outcomes ($p=0.024$ at 6 hours; $p=0.0063$

at 12 hours), suggesting that altered RI correlates with increased mortality and poorer prognosis (Table 4).

Table 4: Association of Resistive Index (RI) at 6 and 12 hours with neonatal outcomes.

Outcomes	Dama	Discharge	Dor	Expired
RI at 6 hours category				
Altered	1	35	1	15
Normal	2	50	2	4
Chi square: 9.38, dF: 3, p value=0.024*				
RI at 12 hours category				
Altered	1	30	1	15
Normal	2	55	2	4
Chi square : 12.32 dF: 3 P value: 0.0063*				

*p value <0.05-Significant, **p value <= 0.001-Highly Significant

Table 5: Neurological examination and Recovery Interval (RI) category outcomes at 3 and 6 months.

Time of neurological examination and RI	Abnormal	Expired	Lost to follow up	Normal
Neurological examination at 3 months RI at 6 hours category				
Altered	10	2	1	25
Normal	3	0	2	49
Chi square:11.45, df:3, p value=0.009*				
Neurological examination at 6 months RI at 6- and 12-hours category				
Altered	9	1	3	19
Normal	6	0	1	52
Chi square: 10.89, df:3, p value=0.012*				

*p value <0.05-Significant, **p value <= 0.001-Highly Significant

Table 5 presents the results of a neurological examination and recovery interval (RI) categorization at two time points-3 months and 6 months. The outcomes are classified into four categories: abnormal, expired, lost to follow-up, and normal. The analysis includes the correlation between the altered or normal neurological examination findings and the corresponding recovery interval (6 hours for the 3-month assessment and 12 hours for the 6-month assessment). The chi-square values (11.45 for 3 months, 10.89 for 6 months) and their respective p values (0.009 for 3 months and 0.012 for 6 months) suggest a significant association between the neurological status and recovery interval (Table 5).

DISCUSSION

The present study aimed to evaluate the prognostic value of the resistive index (RI) measured via cranial Doppler ultrasound in neonates diagnosed with hypoxic-ischemic encephalopathy (HIE). Our findings demonstrate a significant association between RI values recorded at 6- and 12-hours post-birth and adverse neurological outcomes observed at 3 and 6 months. These results align with previous studies investigating cerebral hemodynamics in neonates with HIE, reinforcing the potential role of RI as an early biomarker for neurodevelopmental prognosis.

The majority of neonates included in our study were born between 37 and 40 weeks of gestation, representing

82.72% of the total cohort. A smaller proportion (17.27%) were post-term neonates, which is consistent with existing literature suggesting that full-term neonates face an increased risk of developing HIE due to complications during labor and the heightened oxygen demands associated with delivery.¹¹ Birth asphyxia and perinatal stress are more commonly observed in term infants, as they experience a transition from intrauterine to extrauterine life that requires precise physiological adaptation. The slightly lower proportion of post-term neonates in our study could be attributed to a lower incidence of prolonged pregnancies in the population sampled, but this does not negate the fact that both full-term and post-term infants remain at risk of developing HIE when exposed to perinatal complications.

A key finding of our study was the prevalence of low Apgar scores among neonates diagnosed with HIE. The mean Apgar score recorded was 4.40, indicating poor neonatal adaptation to extrauterine life. The Apgar score is widely recognized as a critical measure of neonatal well-being immediately after birth, and its correlation with HIE severity has been well-documented. Studies have consistently demonstrated that lower Apgar scores reflect perinatal asphyxia, which results in cerebral hypoxia and subsequent brain injury.^{12,13} The direct relationship between low Apgar scores and HIE highlights the importance of immediate resuscitative efforts and continuous monitoring of neonates presenting with early signs of distress. These findings further

emphasize the need for vigilant neonatal care to mitigate the potential for long-term neurological impairment in affected infants.

Our study revealed that the mean RI values at 6 hours (0.71) and 12 hours (0.73) were significantly associated with adverse neurological outcomes ($p=0.008$). This observation is consistent with findings from previous studies, which have reported elevated RI values in neonates who later exhibited poor neurodevelopmental outcomes during follow-up assessments.^{14,15} Abnormal RI values have been linked to increased cerebral vascular resistance, a key factor contributing to brain injury in HIE.^{16,17} The resistive index serves as a quantitative measure of cerebral blood flow dynamics, and its elevation may indicate an underlying disruption in autoregulation, which is commonly observed in neonates suffering from hypoxic-ischemic insults. The results from our study support the notion that cranial Doppler ultrasound can provide valuable prognostic information by identifying neonates at higher risk for neurological impairment based on RI measurements obtained within the first few hours of life.

One of the most notable findings of our study was the significantly higher mortality rate observed in neonates with an RI greater than 0.8 ($p<0.001$). This result aligns with previous research indicating that impaired cerebral autoregulation in HIE can lead to fluctuating blood flow patterns, which can be effectively detected using Doppler ultrasound.¹⁸ When cerebral autoregulation is compromised, neonates are more susceptible to hypoxic injury and cerebral edema, both of which can contribute to increased RI values.¹⁹ Given these findings, RI could serve as a critical parameter for risk stratification, allowing clinicians to identify neonates who may require more intensive monitoring and early therapeutic intervention. The role of Doppler ultrasound in neonatal encephalopathy assessment has been increasingly recognized, with studies suggesting that RI values can complement MRI findings to enhance prognostic accuracy.²⁰ As a non-invasive and readily accessible imaging modality, Doppler ultrasound presents a practical option for early bedside assessment of cerebral hemodynamics in neonates with suspected HIE.

At the follow-up assessments conducted at 3 and 6 months, 67.27% and 63.64% of neonates, respectively, exhibited normal neurodevelopmental outcomes. In contrast, 11.82% and 13.63% of neonates demonstrated abnormalities in neurodevelopmental assessments. These rates are in line with previous studies reporting similar outcomes in neonates diagnosed with HIE. The persistence of neurodevelopmental abnormalities in a subset of infants underscores the need for early intervention programs aimed at improving long-term outcomes for at-risk neonates.²¹ Neonatal brain plasticity presents an opportunity for rehabilitation, and early therapeutic interventions such as physiotherapy, occupational therapy, and specialized

neurodevelopmental follow-up programs may help optimize cognitive and motor function in affected infants.

Therapeutic hypothermia has emerged as the standard intervention for managing neonates with moderate to severe HIE. By reducing metabolic demand and limiting neuronal injury, hypothermia has been shown to improve neurodevelopmental outcomes in affected neonates. Research suggests that this intervention may stabilize cerebral blood flow and potentially normalize RI values over time.²² Although our study did not specifically examine the effects of therapeutic hypothermia on RI trends, future research should explore whether differences exist between treated and untreated neonates in terms of RI progression and long-term neurological outcomes. Understanding these trends could provide further insight into the mechanisms by which hypothermia exerts its neuroprotective effects and refine clinical protocols for optimizing patient outcomes.

In conclusion, our study highlights the prognostic significance of the resistive index in neonates with hypoxic-ischemic encephalopathy. Elevated RI values within the first 12 hours of life were significantly associated with adverse neurological outcomes at 3 and 6 months, reinforcing the potential of RI as an early biomarker for neurodevelopmental prognosis. The association between RI and increased mortality further underscores the importance of early hemodynamic assessment in neonates with HIE. While therapeutic hypothermia remains the cornerstone of HIE management, future studies should investigate how RI values change in response to treatment and whether they can be used to guide individualized therapeutic strategies. The integration of RI measurements with other imaging modalities, such as MRI, could enhance the accuracy of prognostic assessments and contribute to improved neonatal care strategies. Given the potential of Doppler ultrasound as a non-invasive and accessible tool, its role in neonatal neurology warrants further investigation to optimize early diagnosis and intervention for neonates at risk of long-term neurological impairment.

This study has few limitations. Despite its strengths, this study has several limitations. First, the sample size, while adequate for statistical analysis, may limit generalizability to larger populations. Second, variations in RI measurement techniques across different neonatologists could introduce observer bias. Standardized Doppler protocols should be implemented to improve reproducibility. Third, the study's observational design prevents establishing causation between RI values and outcomes. A multicenter study with a larger cohort and longer follow-up periods could provide more definitive conclusions.

CONCLUSION

This study highlights the prognostic significance of resistive index measurements in neonates with hypoxic-

ischemic encephalopathy. Doppler ultrasound serves as a valuable, non-invasive tool for early risk stratification, aiding in timely interventions. The findings underscore the potential of RI as an objective marker for predicting adverse neurological outcomes. Integrating RI assessments into routine neonatal care can enhance clinical decision-making, optimize treatment strategies, and improve long-term neurodevelopmental prognoses, ultimately contributing to better neonatal health outcomes.

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