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Transfontanellar Duplex Brain Ultrasonography Resistive Indices as a Prognostic Tool in Neonatal Hypoxic-Ischemic Encephalopathy Before and After Treatment with Therapeutic Hypothermia

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Abstract

OBJECTIVE—Prior to therapeutic hypothermia (i.e., cooling), transfontanellar duplex brain sonography resistive indices (RI) were studied as bedside non-invasive measures of cerebral hemodynamics in neonates who suffered from hypoxic-ischemic encephalopathy (HIE). We compared pre- and post-cooling RI values and examined the relationships between RI values and specific long-term neurodevelopmental outcomes.

STUDY DESIGN—Transfontanellar duplex brain sonography, including RI, were obtained for 28 neonates prior to brain cooling and for 20 neonates following brain cooling. All RI values were sampled in the anterior cerebral artery at the beginning of each ultrasound study.

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Conflict of Interest

The authors declare no conflict of interest.

Neurodevelopmental assessment was conducted between ages 20-32 months with the *Mullen Scale of Early Learning*. The relationships between pre- and post-cooling RI and cognitive and motor outcomes were studied.

RESULT—Neonates with RI values <0.60 prior to and following cooling were more likely to die or have severe neurodevelopmental disability by ages 20-32 months than those with RI >0.60. Lower RI values were associated with specific neurodevelopmental deficits in motor skill attainment.

CONCLUSION—Pre- and post-cooling transfontanellar duplex brain sonography RI values may be a useful prognostic tool, in conjunction with other clinical information, for neonates diagnosed with HIE. The results of this study suggest that further study of the prognostic value of RI values for short- and long-term outcomes is warranted.

INTRODUCTION

Hypoxic-ischemic encephalopathy (HIE) occurs in 1 to 3 newborns per 1000 live full-term births in developed countries, and is a major cause of neonatal death and neurodevelopmental disability ([1]). Presently, the only empirically proven treatment for neonatal HIE is therapeutic hypothermia (i.e., cooling), which partially mitigates secondary neuronal injury ([2]). This treatment became a standard of care in 2009 after several large multi-center case-control studies demonstrated decreased mortality and improved neurodevelopmental outcome after HIE ([3-5]). Prior to cooling, outcomes following severe to moderate HIE included death, cerebral palsy (CP) and intellectual disability (ID) ([6]), while outcomes of less severe HIE (i.e., moderate to mild) included varying degrees of motor and cognitive dysfunction ([7,8]). Given the range of outcomes following HIE, the identification of prognostic neonatal physiologic biomarkers that are sensitive and specific, as well as time- and cost-effective are critical for optimal acute and post-acute Neonatal Intensive Care Unit (NICU) care, including the identification of neonates who may benefit from adjuvant therapies to cooling as they become available, and referrals for neurodevelopmental follow-up ([9]). In addition, biomarkers may be valuable for monitoring treatment response and may help to better counsel parents about the possible functional outcomes.

Reduced cerebral blood flow velocity within the context of systemic hypotension is a potential precursor to secondary ischemic brain injury([10-12]). Therefore, monitoring cerebral hemodynamics following HIE has been previously proposed as a physiologic biomarker for the identification of neonates at greatest risk of severe disability and death ([13-15]). Transfontanellar duplex sonography with spectral analysis of the cerebral blood flow curve allowing calculation of the resistive index (RI) is a safe, bed-side, and cost-efficient method to measure cerebral hemodynamics, specifically cerebral blood flow velocity and perfusion dynamics following HIE ([16]). Prior to the availability of therapeutic hypothermia, studies demonstrated that low RI values were associated with high rates of severe long-term motor and cognitive impairments or mortality following neonatal HIE ([17,18]). Recent studies have demonstrated that RI values obtained during hypothermia do not have the same predictive value as those obtained after rewarming, suggesting that cooling may change the predictive value ([18]). As such, a better understanding of the utility of comparing pre- and post-cooling RI values is warranted.

In this prospective preliminary study, we aimed to 1) examine the role of normothermic RI values obtained pre- and post-cooling for prognostication of later outcomes, 2) expand classification of long-term outcomes to include severe disability and death, moderate to mild disability, and no disability, and 3) ascertain whether pre- and post-cooling RI values are associated with domain specific neurobehavioral outcomes by early childhood following neonatal HIE.

PATIENTS AND METHODS

This study was approved by the Johns Hopkins Institutional Review Board and written consent was obtained from the legal guardian/parent of each child at the time of the neurodevelopmental follow-up evaluation. Transfontanellar brain sonography with duplex sampling of the intracerebral blood flow velocity was performed per standard of care in the JHH NICU.

Study Population

This study involved a convenience sample from an ongoing prospective and longitudinal study of neonatal predictors of neurodevelopmental outcomes following neonatal HIE. Inclusion criteria for this study were 1) the diagnosis of neonatal HIE based on review of each participant's medical records by a neonatologist (FJN) and pediatric neurologist (VJB), 2) treatment with whole body therapeutic hypothermia, 3) availability of pre- and/or post-cooling RI values, and 4) participation in neurodevelopmental follow-up. Eligible participants for this study were recruited from the Johns Hopkins Hospital NICU covering the period between 2011 and 2013, and only those who provided consent for research participation and had the abovementioned clinical variables were included.

The standard clinical protocol inclusion criteria for therapeutic hypothermia treatment of neonatal HIE at the Johns Hopkins Hospital NICU are birth ≥ 35 weeks gestation, physiologic criteria similar to that reported in the NICHD trials of whole body cooling ([5]), clinical evidence of HIE determined by clinical evaluation of consciousness, neuromuscular control, complex reflexes, autonomic function, and presence of seizures ([19,20]). Hypothermia therapy is initiated within 6 hours of birth. Body temperature is maintained at 33.5 °C for 72 hours, followed by 6 hours of rewarming. Relative exclusion criteria for treatment with hypothermia include severe hemodynamic compromise, profound coagulopathy, strong clinical suspicion of sepsis, likely need for extracorporeal membrane oxygenation (ECMO), and birth weight of less than 1800 grams.

Measures

Transfontanellar duplex sonography Resistive Indices—Transfontanellar brain sonography with spectral analysis of the blood flow velocity curve and subsequent calculation of the RI were performed per standard departmental protocol by an experienced pediatric sonographer (D.S.) 1) during the first 6 hours of life prior to or just at the start of active cooling and 2) following rewarming (≥ 72 hours of life) using state-of-the art equipment (Siemens Acuson S2000, Siemens Medical Solutions, Mountain View, CA; and Z.One, Zonare Medical Systems, Mountain View, CA). The imaging protocol includes

multiplanar anatomical images through the anterior, mastoid and posterior fontanels as well as duplex sonography of the anterior cerebral artery and superior sagittal sinus through the anterior fontanelle. Blood flow velocity is sampled in the sagittal plane through the anterior fontanelle, utilizing a high frequency curved ultrasound transducer with a small foot print matching the size of the fontanelle. The sampling angle is corrected for aliasing. See Figure 1. Duplex measurements were done at the onset of the examination before acquiring anatomical images to limit changes in the cerebral hemodynamics due to compression of the anterior fontanelle. Velocity waveforms were extracted using spectral analysis. RI values were calculated automatically using the following formula: RI = (peak systolic velocity – end diastolic velocity)/peak systolic velocity. Additionally, both pre- and post-cooling transfontanellar anatomical US images were evaluated for focal lesions including hemorrhage or stroke.

Neurodevelopmental outcome—Neurodevelopmental follow-up between the ages of 20-32 months included the *Mullen Scales of Early Learning* and Gross Motor Function Measure, 88 Item Version (GMFM-88).

The *Mullen Scales of Early Learning* is a widely used and comprehensive norm-based measurement of neurodevelopment in children from birth to 68 months of age ([21]). Overall level of cognitive development (Early Learning Composite Standard Score) is determined by performance across four subscales, which can be individually evaluated and reported: visual reception, fine motor, receptive language, and expressive language. The *Gross Motor Function Measure*, *88 Item Version* (*GMFM-88*) is a standardized observational measure, and criterion referenced test of gross motor function for individuals from age 6 months to age 16 years who are at risk for or have diagnoses of cerebral palsy ([22]). It is designed to evaluate a wide variety of specific gross motor movements achieved by an individual, but does not evaluate the specific quality of these motor movements.

Data Analysis

Descriptive analyses (means, standard deviations, and percentages) were calculated to ascertain sample characteristics including gestational age, gender, umbilical cord pH and base deficit, RI values pre- and post-cooling, *Mullen Scales of Early Learning* composite score, and *GMFM-88* raw score.

Neurodevelopmental outcomes by RI were explored using a Chi Square analysis, and a p-value ≤ .05 was set to determine significant group differences. For this analysis, RI values were divided into five different ranges: 0.40-0.49; 0.50-0.59; 0.60-0.69; 0.70-0.79; and 0.80-0.89, as opposed to using a cut-off value of <0.55. Given the small and preliminary nature of this dataset, this allowed for the most robust examination of outcomes across a wide range of RI. Neurodevelopmental outcomes were categorized as 1) severe disability: Early Learning Composite score <50 on the Mullen or death, 2) moderate/mild disability: a Mullen Early Learning Composite score ≥ 50 and < 85 or a Mullen Early Learning Composite score ≥ 85 with a specific Mullen subscale t-score < 40, and 3) no disability: a Mullen Early Learning Composite score of ≥ 85 with no Mullen subscale t-scores < 40.

Relationships between specific neurodevelopmental domains and pre- and post-cooling RI values were explored using a Spearman Rho correlation analysis, and a p-value ≤ .05 was set to determine a significant correlation. Domain-specific neurodevelopmental variables included in this analysis were Mullen Scales of Early Learning Visual Reception, Fine Motor, *Receptive Language*, and *Expressive Language* subtest T-scores, and *GMFM-88* total raw score.

RESULTS

Sample Characteristics

Twenty-eight neonates had pre-cooling transfontanellar brain sonography obtained during the first 6 hours of life with calculated RI values, and 21 neonates had post-cooling transfontanellar brain sonography obtained 6-24 hours after rewarming was completed with calculated RI values (Figure 1 and Figure 2). Sample characteristics are presented in Table 1. Post-cooling RI values could not be obtained for 5 neonates who died during cooling therapy and for two additional newborns who did not have post-cooling transfontanellar brain sonography completed. Additionally, one child for whom pre and post-cooling transfontanellar brain sonography was obtained, died following NICU discharge. Of the neonates who died during or after hypothermia therapy, 50% were male. The mean pre-hypothermia RI values for the entire clinical sample fell within the lower limits of the normal range (M = .65, SD = .12), as did the mean post-cooling RI value (M = .65, SD = .09).

Those participants who were living between ages 20 and 32 months and returned for a follow-up research evaluation, completed the *Mullen Scales of Early Learning* (N = 22) and the *GMFM-88* (N=18). Thus a total of 18 children completed both the *Mullen Scales of Early Learning* and the *GMFM-88*. Post-cooling, RI was not obtained for two children in this subgroup who completed both the *Mullen Scales of Early Learning* and the *GMFM-88* at age 20-32 months. The mean *Mullen Scales of Early Learning* Early Learning Composite Score for all children who completed neurodevelopmental follow-up fell in the low average range (M = 89.5, SD = 18.86), and the total mean percentage for all 88 items successfully completed on the *GMFM-88* was 85.16% (range 7.20% - 95.20%).

RI Values and Clinical Outcome

Chi Square analyses examining the differences between pre-cooling RI value ranges and outcomes were significant, X^2 (8, N = 28) = 18.90, p = .015 (Figure 3). Differences between post-cooling RI value ranges and outcomes were not significant, X^2 (6, N = 21) = 12.36, p = .055 (Figure 4). Outcomes of severe disability and death occurred more frequently among neonates with pre-cooling RI values at or below the 0.60 to 0.69 range, and the mean pre-cooling RI values for the neonates who died during hypothermia therapy (N = 6) was 0.59 (SD =07).

Spearman Rho correlations between pre- and post-cooling RI values and specific subtest T-scores on the *Mullen Scales of Early Learning*, including the Visual Reception, Fine Motor, Receptive Language, and Expressive Language, were not significant. There was also no

significant association between pre-cooling RI values and the total raw score on the *GMFM-88*; however, there was a statistically significant correlation between post-cooling RI values and the total raw score on the *GMFM-88* (Spearman Rho correlation coefficient = .51, $p = .042$).

DISCUSSION

The present findings demonstrate that transfontanellar duplex brain sonography ultrasound RI values below 0.60 prior to cooling provides differentiation of the specific categorical outcome of severe neurodevelopmental disability or death by age 20-32 months. These findings are consistent with previous findings in term neonates diagnosed with HIE who did not receive cooling ([16]). Results of the present study also suggest that pre-cooling RI <0.60 may broadly differentiate neonates who are more likely to have outcomes of severe neurodevelopmental disability or death by ages 20-32 months while post-hypothermia RI values <.60 may be specifically associated with worse functional gross motor outcomes. In previous studies, RI values ≤ 0.55 were associated with severe disability, including CP, as well as death among children with a history of neonatal HIE ([16–18,23–25]). Two of three studies examining RI values as a long-term predictors of outcome found worse outcomes among neonates with RI values ≤ 0.55, including those neonates who were treated with cooling ([17,18]). Elstad et al. found that RI values ≤ 0.55 during cooling (i.e., 48 to 72 hours of life) had a sensitivity of 58% and a specificity of 83% for prediction of outcome ([17]). Skranes and colleagues suggested that cooling may lead to cerebral vasoconstriction and subsequently higher RI values during cooling ([18]). Skranes and colleagues calculated the sensitivity and specificity of RI following rewarming and found that an RI ≤ 0.55 had a sensitivity of 43% and a specificity of 100% for long-term outcomes ([18]). As such the findings of Elstad et al. and Skranes et al. suggest that the validity of RI values alone is limited for predicting broad and categorical long-term outcomes ([17,18]). These findings are also consistent with studies, which have demonstrated relationships between low RI values and worse outcomes secondary to other disease processes and treatments ([16,26]), such as chronic liver disease ([27]), vascular malformations, and intervention with ECMO ([26]).

Previous studies examining the long-term predictive value of RI values following neonatal HIE have utilized broad categorical classifications (e.g., death, severe/moderate disability, and no disability) and did not correlate RI values with specific domains of neurobehavioral outcome ([16–18]). The present study demonstrated a relationship between post-cooling RI and gross motor outcome, but no relationship between pre-cooling RI and motor outcomes. In general, RI values should generally stabilize into the normal range 48 hours post-injury ([12]). Failure to do so more than 72 hours post-injury, which equates with the time period in which post-cooling RI values were obtained, may therefore suggest a more severe brain injury and subsequently worse motor outcome.

There was no association between pre- and post-cooling RI and other neurobehavioral domains (i.e., fine motor function, visual perceptual abilities, and language) between ages 20-32 months; however, gross motor function in young children is more easily quantified than difficulties in other neurobehavioral domains. It remains unclear based on present research whether worse performance in these other neurobehavioral domains may be

observed later in childhood development among survivors of neonatal HIE, when neurobehavioral tests are more sensitive and children have to demonstrate substantially more skills of higher complexity in order to perform well. Presently, long-term follow-up of specific domains of neurobehavioral or cognitive function among children who have a history of neonatal HIE with cooling therapy is extremely limited. The TOBY study group recently compared childhood outcomes at ages 6-7 years; among survivors of neonatal HIE who were cooled versus those who were not cooled. The results of this long-term follow-up included higher rates of survival with IQ ≥ 85 and less severe motor impairments, such as cerebral palsy, among children who had undergone cooling therapy ([28]). Therefore, it is possible that the classic pattern of neurobehavioral outcome in neonatal HIE , in which there is greater motor impairment than cognitive impairment, has been mitigated by cooling therapy; however, some degree of motor impairment may remain among those with lower RI values post-cooling within the context of worse brain injury.

In conclusion, the present study confirms a role for RI measurements, in conjunction with other clinical information, as a safe and cost-efficient method for prognostication of outcome in neonatal HIE. Pre-cooling RI values may predict poor outcome including severe disability and death very early in the course of the disease. Thus, neonates with pre-hypothermia RI values below 0.60 might benefit from adjuvant treatments to therapeutic hypothermia as soon as such treatments become available. In contrast, post-cooling RI values may predict level of gross motor function by ages 20-32 months and thus provide a means to determine which neonates may require early and targeted therapeutic interventions (e.g., physical therapy).

Strengths and Limitations

The present study provides both pre- and post-hypothermia measurements, as well as the use of standardized and norm-referenced measures of neurobehavioral function in early childhood. This study is also one of the first to examine the relationship between neonatal RI values following HIE and specific neurobehavioral outcomes in early childhood. While all of these factors are particular areas of strength in the present study, these findings have to be interpreted cautiously within the context of a small sample size, which is a significant limitation. Furthermore, given the small number of neonates in the present study, it was not appropriate to calculate the sensitivity and specificity of RI values for prediction of long-term outcomes by ages 20-32 months. Finally, the RI values were sampled only within a single artery of the anterior circle of Willis. Additional measurements within the middle and posterior cerebral artery may be collected in a future study. Given these limitations, further examination of these findings within the context of a larger cohort of patients is warranted.

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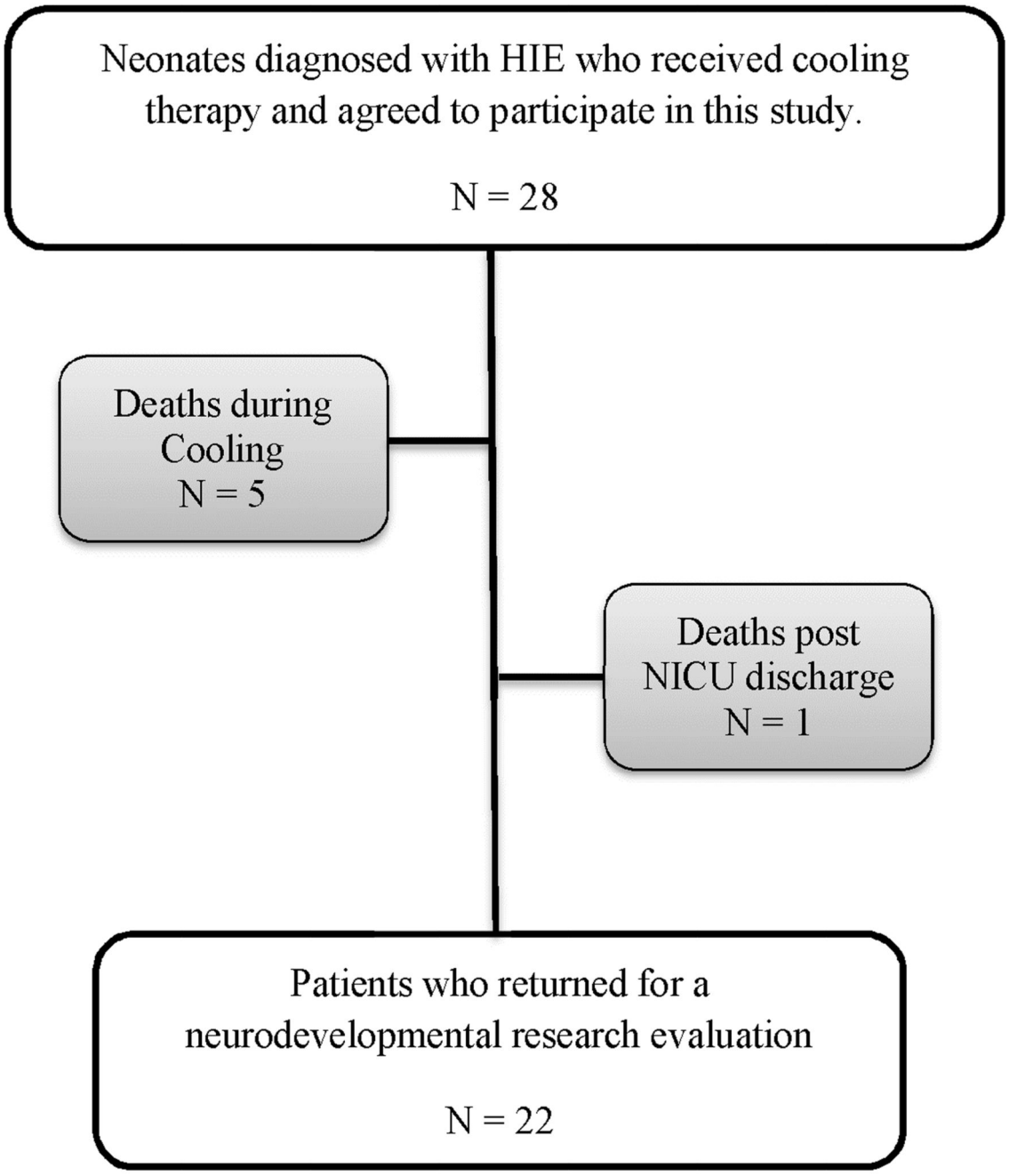

Figure 1.
Study enrollment at birth and participation in later neurodevelopmental follow-up.

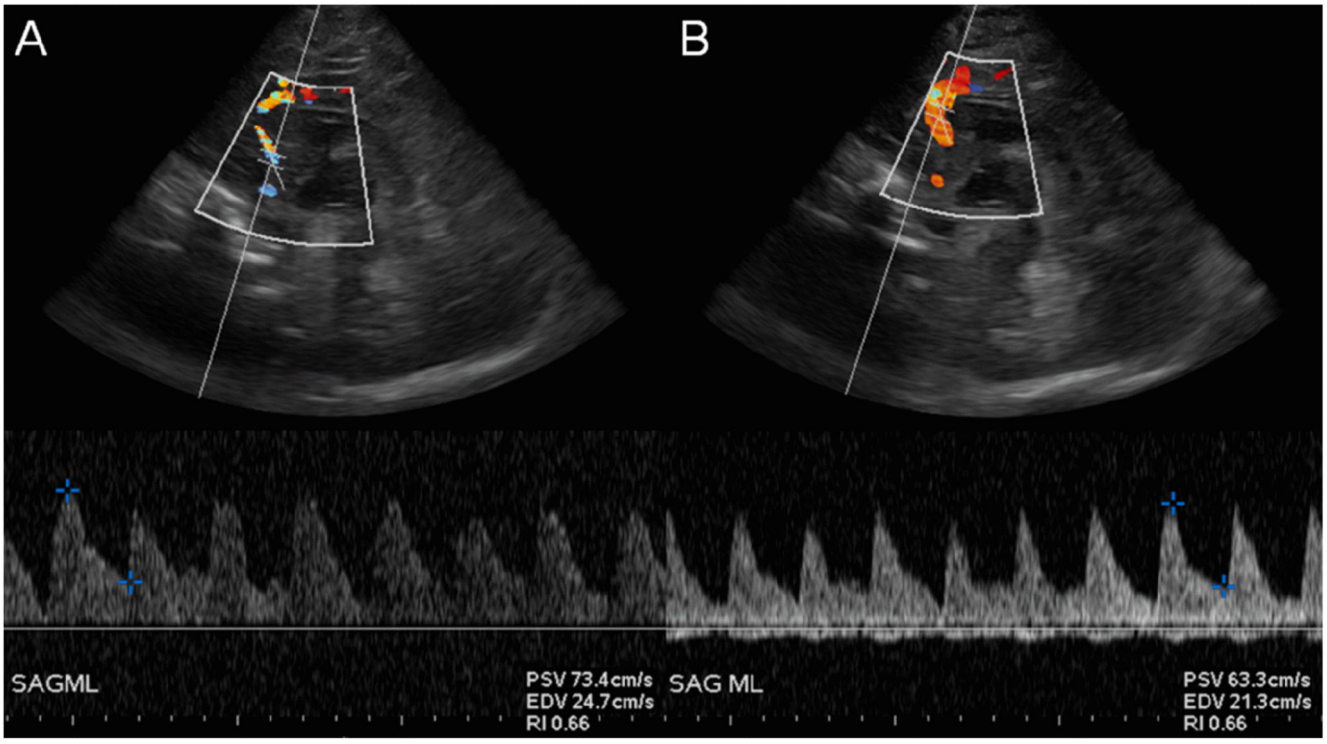

Figure 2.

(A) Pre- and (B) post-cooling transfontanellar duplex head ultrasound with measurement of RI values within the anterior cerebral artery in a neonate after HIE; pre- and post-cooling RI values are 0.66, respectively.

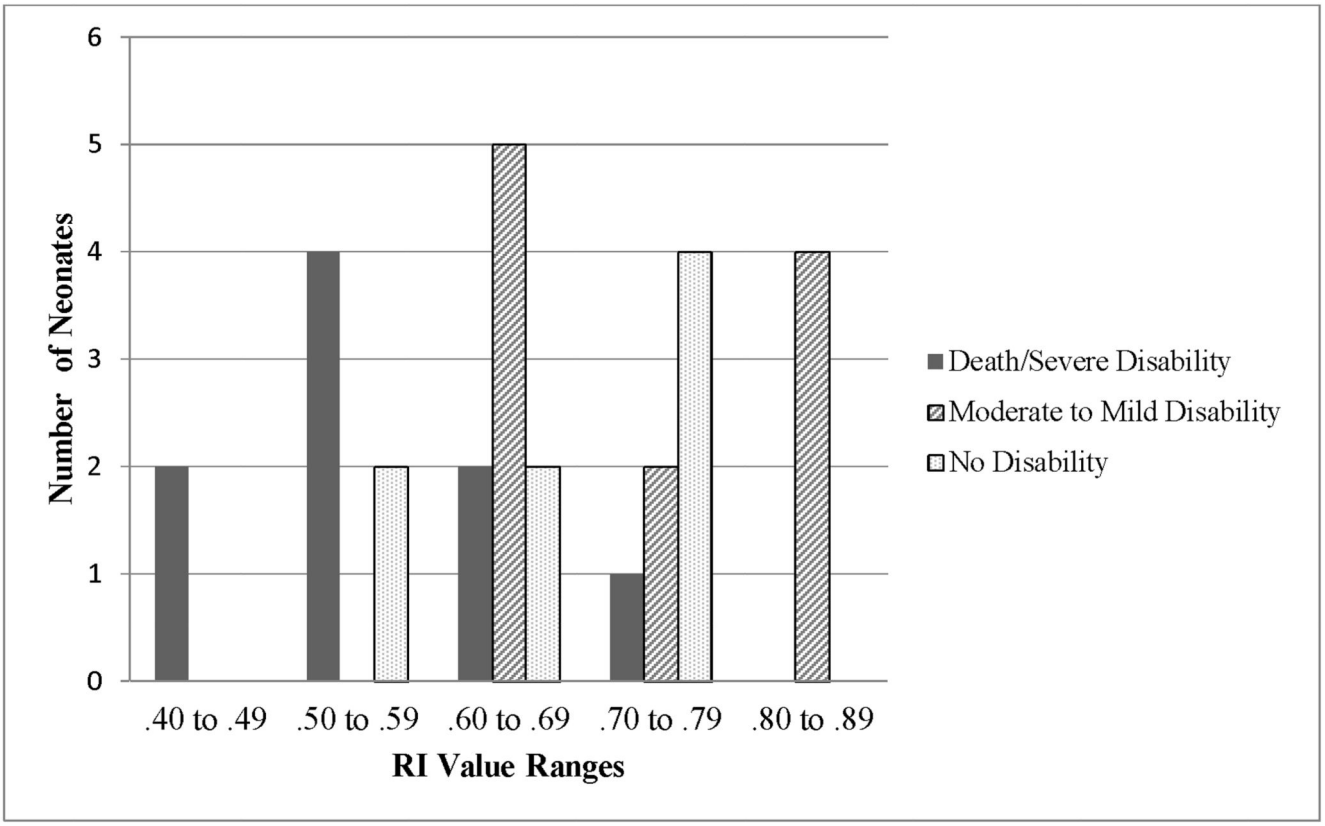

Figure 3.

This figure represents the number of neonates (Y-axis) with RI values within the specified value ranges (X-axis) pre-cooling therapy. The color or pattern of each bar, as specified in the legend, indicates clinical outcome.

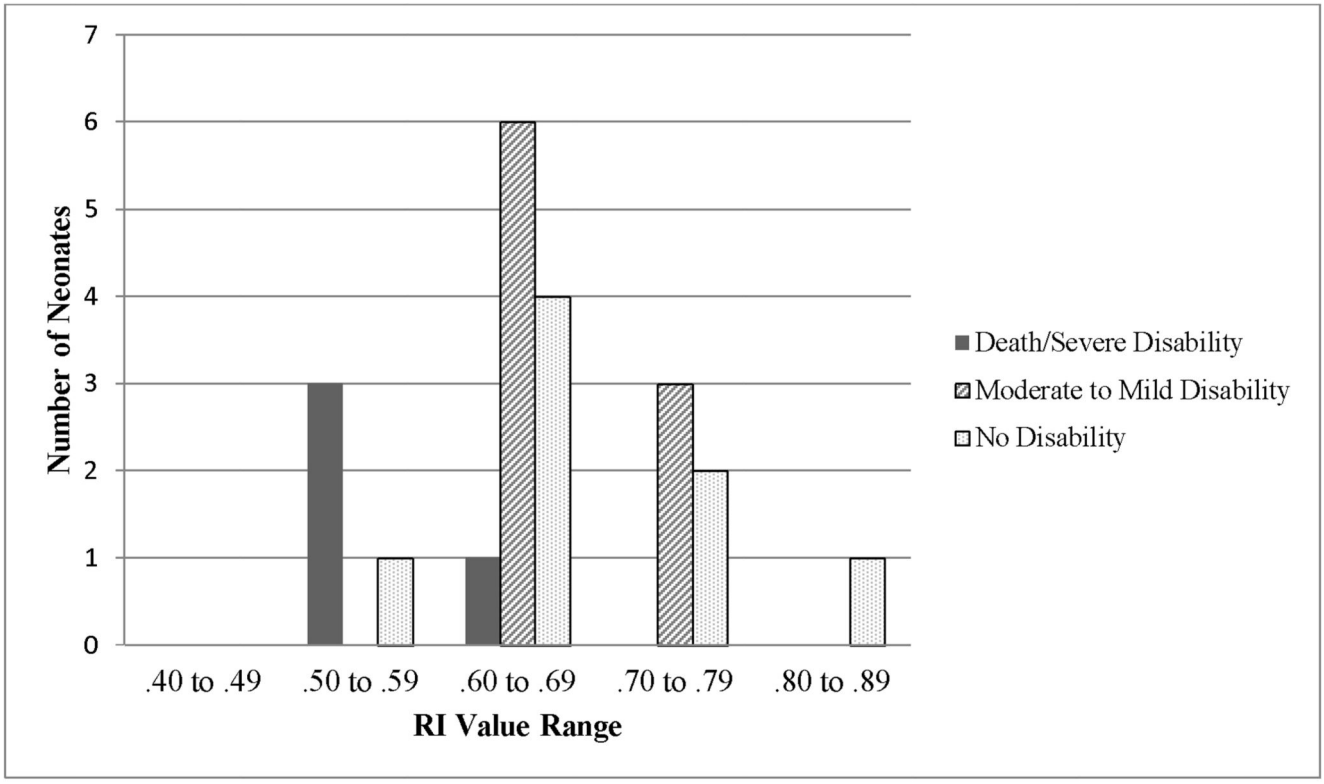

Figure 4.

This figure represents the number of neonates (Y-axis) with RI values within the specified value ranges (X-axis) post-cooling therapy. The color or pattern of each bar, as specified in the legend, indicates clinical outcome.

Table 1

Participant characteristics

Gestational Age: *Mean (SD) Weeks*	38.31 (1.97)
Male: *N (%)*	15 (54%)
Umbilical Cord Gas: *Mean (SD)*	6.93 (.14)
Base Deficit (mmol/l): *Mean (SD)*	−17.21 (5.42)
Pre-Hypothermia Head Ultra Sound RI: *Mean (SD)*	.65 (.12)
Post-Hypothermia Head Ultra Sound RI: *Mean (SD)*	.65 (.09)
Mullen Scales of Early Learning Composite: *Mean (SD)*	90 (19)
GMFM Total Raw Score: *Mean (SD)*	423 (99)