The role of expert MRI scores in predicting adverse 18-22-month outcomes for Hypoxic Ischemic Encephalopathy in Neonatal Research Network trials

Ankush Kesri[*1], Rina Bao*[*1,2], Chuan-Heng Hsiao[1], Rutvi Vyas[1], Mohammad Arafat Hussain[1,2], Scott McDonald[3], Jeanette Auman[3], Seetha Shankaran[4], Abbott Laptook[5], Michael Cotten[6], P. Ellen Grant[1,2,#], Yangming Ou[1,2,#]*

Affiliations:
[1] Boston Children's Hospital, Boston, MA, USA
[2] Harvard Medical School, Boston, MA, USA
[3] RTI International, Research Triangle Park, NC, USA
[4] University of Texas at Austin and Dell Medical School, Austin, TX, USA
[5] Brown University, Providence, RI, USA
[6] Duke University, Durham, NC, USA

Background: Hypoxic ischemic encephalopathy (HIE) is a brain injury affecting 1~5/1000 term-born neonates. In high-income countries, despite therapeutic hypothermia reducing mortality and morbidity in developed countries, about one-third of infants with moderate or severe HIE still develop adverse outcomes (i.e., die or suffer from neurocognitive impairment) by the age of two years [1]. A critical need is to predict which HIE patients are at risk of developing adverse 2-year-old outcomes during the neonatal period, so new therapies can be designed and rapidly assessed in high-risk sub-cohorts. In the NICHD Neonatal Research Network (NRN), two HIE trials were conducted in 23 U.S. sites [2, 3]. Experts scored neonatal brain MRIs into 6 levels: 0, 1a, 1b, 2a, 2b, and 3, with a higher score indicating more severe brain injury and usually a higher risk of adverse outcomes around 2 years [4]. Yet, the predictive value of NRN expert MRI scores in the context of other clinical variables has not been investigated.

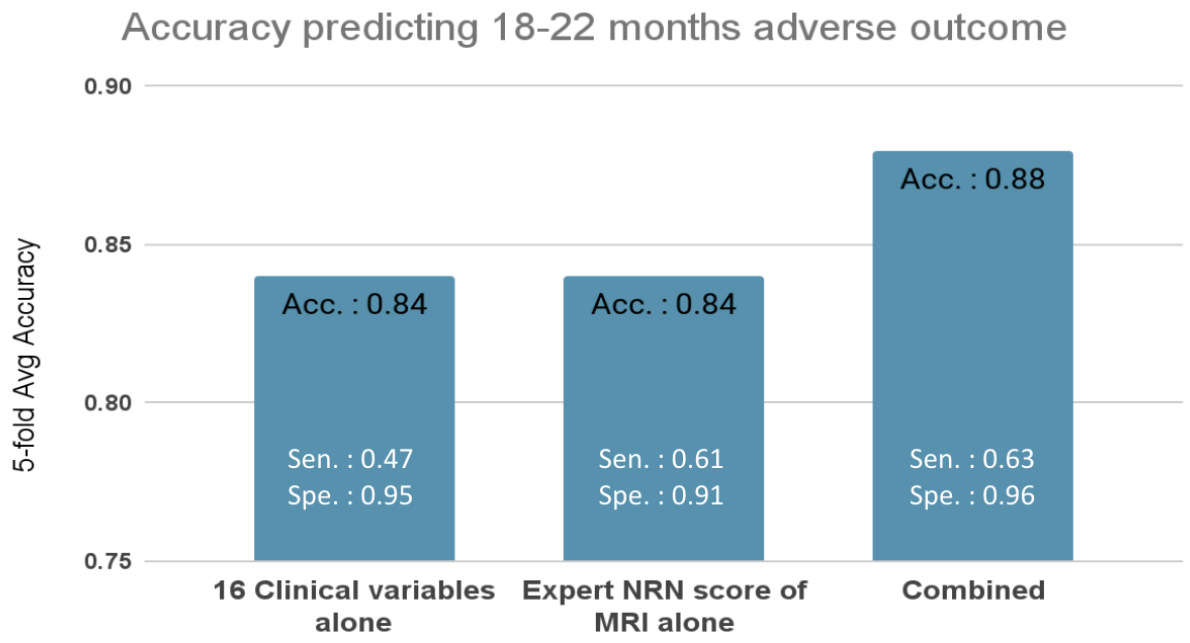
Objective: In neonatal HIE patients, determine how well expert scores from neonatal brain MRIs can predict adverse 18-22-month outcomes and their added value when combined with additional clinical variables.

Methods: We merged two NRN trials, Late Hypothermia (2008-2016, enrollment of infants 6-24 hours of age into cooling and control arms) and Optimizing Cooling (2010-2014, enrollment at <6 hours of age into usual care and longer/deeper cooling arms), into a unified database with 532 HIE patients. A total of 17 features were included in multivariate feature selection and machine learning by the consensus of linear support vector machine (SVM), gaussian-kernel SVM, and random forest (RF). The features include clinical variables (maternal age and education; gestational age at birth, infant sex, birth weight, as well as 1, 5, and 10-minute APGAR scores, age at MRI, umbilical/early-postnatal pH (within 1 hour after birth), seizures at treatment randomization, seizures at discharge, treatment arm, and neurological exam scores at screening, post-treatment, and at discharge from the neonatal intensive care unit [2, 3]. The 17th feature, the NRN expert score of MRI (average of two experts' independent scores, or the single expert's score if the score from the second expert unavailable), was considered alone or in addition to these 16 clinical features. The outcome was measured at age 18-22 months, and was defined as adverse (moderate or severe disability or death, N=95) or otherwise non-adverse (normal or mild

disability, N=312) [2, 3]. We used the forward inclusion and backward elimination (FIBE) algorithm to automatically select the best combination of features that led to the highest accuracy in 5-fold cross-validation [5].

Results: A 6-level expert NRN score alone is as predictive (0.84 accuracy) as the best subset of the 16 clinical features. Combining expert NRN scores with 16 clinical variables led to the highest accuracy (0.88), as well as the most balanced sensitivity (0.63) and specificity (0.96). Clinical variables important to the outcome prediction included 1-min APGAR scores, seizure at screening or discharge, neurological exam scores post-treatment and at discharge, birth weight, and mother's education. In contrast, a recent study found 0.85 accuracy in predicting motor impairment at 12-24 months in 117 infants, with a combination of MRI injury in putamen/globus pallidus, gestational age, and umbilical cord pH [6].

Conclusions: Expert NRN score of neonatal brain MRI is a good predictor of 18-22-month outcomes in HIE patients when used alone and better when combined with other key clinical features. Future studies will explore changes in outcome prediction accuracy with more detailed MRI scores, more sophisticated analysis of MRI, more comprehensive clinical variables (>1000), and more tests of whether the accuracy persists across multi-site datasets.



Selected Features	Discharge Neuro Exam score, Seizure at Discharge, 1-minute APGAR score, Birth Weight, Seizure at Screening	Expert NRN score of MRI	Expert NRN score of MRI, 1-minute APGAR score, Post-treatment Neuro Exam score, Discharge Neuro Exam score, Maternal education

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