Combining 47 clinical and neuroimaging variables to predict adverse 18-22-month outcomes for Hypoxic Ischemic Encephalopathy in Neonatal Research Network trials

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Background: Hypoxic ischemic encephalopathy (HIE) affects in 1~5/1000 term infants. Despite treatment, 1/3 of neonates with HIE shown adverse outcomes by age 2 years. The Consortium Of Biomarker In Neonatal Encephalopathy (COMBINE, since 2022), aims to predict 2-year adverse outcomes in the neonatal stage, toward improving care in early time windows. We merged 2 HIE trials - Late Hypothermia (2008-16, late/standard cooling or control arms, 21 sites) [1] and Optimizing Cooling (2010-14, standard/longer/deeper cooling arms, 18 sites) [2].

Objective: Develop a multivariate machine learning predictor and quantify the accuracy in predicting 18-22-month adverse outcomes.

Methods: We started with 47 variables based on clinical knowledge (Table 1). Experts scored the severity of brain injury in neonatal brain MRI, using the Neonatal Research Network (NRN) scoring system: 0 no injury, 1a, 1b, 2a, 2b, and 3 devastating injuries [3]. Outcome was adverse (N=312, moderate/severe disability, or death), or normal (N=95) by 18-22 months. Our algorithm automatically selected the subset of variables with the highest prediction accuracy compared to other variable combinations, by a consensus of linear support vector machine, gaussian SVM and random forest. Accuracy was defined as the percentage of neonates being predicted correctly, in 5-fold cross-validation (80% patients training; 20% patients testing; repeated 5 times so every patient has been tested once and only once).

Results: Expert NRN score of neonatal brain MRI alone achieved 0.84 accuracy. When the NRN expert score of MRI was not used, machine learning selected 12 out of 46 clinical variables for a 0.84 accuracy. The highest accuracy, 0.89, was obtained by combining the NRN expert score and clinical variables. Of the 9 variables finally selected to predict outcomes, the most predictive variables were NRN expert score of MRI, treatment variables (Sarnat scores at discharge and post-treatment, intubation), neonatal characteristics (1min Apgar, gestational age), maternal demographics (age, race), and delivery mode. In contrast, [4] found 0.85 accuracy predicting motor impairment at 1-2 years in 117 infants, combining MRI injury in putamen/globus pallidus, gestational age, and umbilical cord pH.

Conclusions: Expert NRN score of neonatal brain MRI, treatment, neonatal characteristics, maternal demographics, and delivery mode jointly predicted 18-22-month adverse outcomes with

0.89 accuracy. Future work will add more sophisticated MRI analysis, more comprehensive clinical variables, and more tests of accuracy stability across multi-site data.

Table 1. The 47 clinical and MRI variables we have included as predictors in this study.

Categories	Variables	
Demographics (3)	Maternal age at delivery (years) Mother ethnicity	Mother race
Socioeconomics (1)	Mother's education	
Pregnancy Conditions (4)	Antepartum hemorrhage (y/n) Mother diabetes (y/n)	Thyroid malfunction (y/n) Hypertension eclampsia (y/n)
Delivery (5)	Delivery mode Fetal decelerated heart rate (y/n)	Infant outborn (y/n) Chorioamnionitis (infection of fetal membrane, y/n) Histologic chorioamnionitis (y/n)
Sentinel Events (9)	Umbilical cord mishap (y/n Placental problem (y/n) Maternal hemorrhage (y/n) Maternal cardio-respiratory arrest (y/n)	Uterine rupture (y/n) Shoulder dystocia (y/n) Maternal trauma (y/n) Maternal seizure (y/n)
	Perinatal sentinel event (y if y in any events in this category)	
Neonatal Characteristics (9)	Gestational age at birth (weeks) Birth length (cm) Apgar score: 1min Apgar score: 5min Apgar score: 10min	Birth weight (g) Birth head circumference (cm) Infant sex Umbilical cord blood gas pH
Treatment (13)	Intubation, respiratory support type Discharge enteral feed start (day) Seizure in screening neuro-exam Length of stay in NICU (days) Sarnat score at screening Sarnat score at discharge Sarnat score post-treatment	Respiratory FiO2 Seizure at discharge Random treatment assigned Placental pathology performed (y/n) Discharge: home therapy gavage tube feed Discharge: home therapy gastrostomy tube feed
Neuroimaging (2)	Age at MRI (days)	NRN expert score of infant brain MRI
Site information (1)	Hospital	

Accuracy predicting adverse outcomes at 18-22 months

NRN score alone — Acc: 0.84, Sen: 0.61, Spe: 0.91
Non-MRI clinical variables — Acc: 0.84, Sen: 0.53, Spe: 0.97
Combined — Acc: 0.89, Sen: 0.66, Spe: 0.96

Y-axis: 5-fold cross-valdiated accuracy

Selected features:

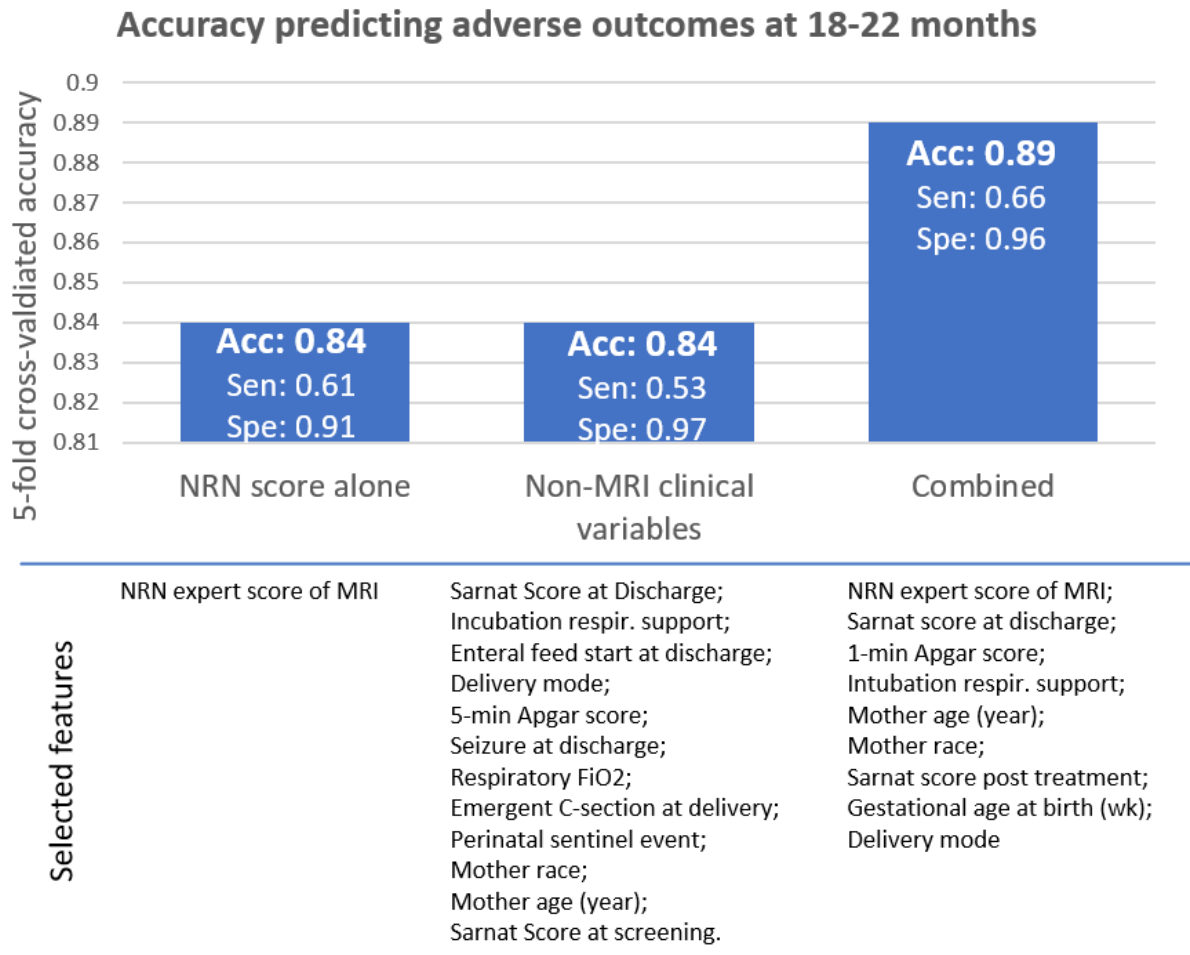| NRN score alone	Non-MRI clinical variables	Combined
NRN expert score of MRI	Sarnat Score at Discharge; Incubation respir. support; Enteral feed start at discharge; Delivery mode; 5-min Apgar score; Seizure at discharge; Respiratory FiO2; Emergent C-section at delivery; Perinatal sentinel event; Mother race; Mother age (year); Sarnat Score at screening.	NRN expert score of MRI; Sarnat score at discharge; 1-min Apgar score; Intubation respir. support; Mother age (year); Mother race; Sarnat score post treatment; Gestational age at birth (wk); Delivery mode

Fig 1. Accuracies and auto-selected variables in three experiments for outcome prediction.

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