DERIVATION OF A PREDICTIVE MODEL FOR NEONATAL ENCEPHALOPATHY REQUIRING THERAPEUTIC HYPOTHERMIA

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Background and Objective

- Eligibility for therapeutic hypothermia (TH) for neonatal encephalopathy (NE) is determined by guidelines, though practice varies among centers.
- Elucidation of perinatal characteristics underlying NE requiring TH is critically needed to better identify and treat these infants.
- To address this knowledge gap, we used perinatal data from a regional registry of NE to develop a predictive model for receiving TH among a sample of newborns evaluated for NE.

Methods

- A predictive model for receiving TH (Y/N) derived using data collected between 2018-2022 as part of the Neonatal Encephalopathy Registry of Massachusetts, a collaboration of 14 centers representing ~50% of deliveries in the state.
- Registry included n=1191 newborns evaluated for NE in one of the four cooling centers and their affiliated community hospitals (TH, n=515 (43.2%); no TH, n=676 (56.8%)).
- Candidate predictors included variables from the 1) demographic, 2) maternal history, 3) delivery, and 4) infant characteristics registry data collection forms.
- Univariate logistic regression used to examine the association between each predictor and TH outcome, followed by Receiver Operating Characteristic (ROC) Area Under the Curve (AUC) analysis to examine predictive performance of TH classification by each significant ($p<0.05$) predictor.
- Predictive models fit using generalized linear mixed models to model binary outcome with random effects to account for clustering by delivery hospitals nested within cooling centers (4). An L1-penalized estimation (lasso) approach was used for variable selection.
- Models were derived progressively with each set of variables added sequentially in chronological order of the assessment forms.

Table 1. Demographic and clinical characteristics

Variables	Statistics	
Gestational age at birth, mean±sd	39.1±1.7	Range: 34.0-42.5
Gestational age category n (%)		
Preterm (34 ≤ GA < 37)	137 (11.5)	
Early term (37 ≤ GA < 39)	306 (25.7)	
Full term (39 ≤ GA < 41)	609 (51.2)	
Late-/post-term (GA ≥ 41)	138 (11.6)	
Infant sex, male, n (%)	714 (60.0)	
Birth weight, g, mean±sd	3250.2±565.0	Range: 1530-4890
Low birthweight (<2500 g), n (%)	118 (9.9)	
Abnormal FHR, n (%)		
Fetal bradycardia	169 (14.2)	
Fetal tachycadia	92 (7.7)	
Early decelerations	16 (1.3)	
Variable decelerations	148 (12.4)	
Late decelerations	115 (9.7)	
Category II tracing	363 (30.5)	
Category III tracing	44 (3.7)	
Mode of delivery: emergency c-section, n (%)	557 (46.8)	
Resuscitation, n (%)		
PPV	898 (75.4)	
CPR (chest compressions)	90 (7.6)	
Epinephrine (required in DR/OR)	44 (3.7)	
Apgar score, median (IQR)		
1 minute	3.0 (2.0-5.0)	
5 minutes	7.0 (5.0-8.0)	< 6, n=345(29.0)
10 minutes	7.0 (6.0-8.0)	
Worst blood gas, median (IQR)		
pH	7.1 (7.0-7.2)	< 7.1, n = 287 (24.4)
Base deficit	11.5 (8.4-14.5)	≥ 10, n = 730 (64.2)
Lactate	8.3 (6.3-11.0)	
HCO_3	17.9 (14.5-20.1)	

[1.] Missing data: gestational age (n = 1); birthweight (n=1); Apgar_1min (n=8); Apgar_5min (n=6); Apgar_10min (n=518); pH (n = 16); bd (n = 35); lactate (487); HCO3 (n = 324). Apgar score at 10 minutes, and blood gases lactate and HCO_3 were excluded as a candidate predictor due to considerable missing data

Figure 1.

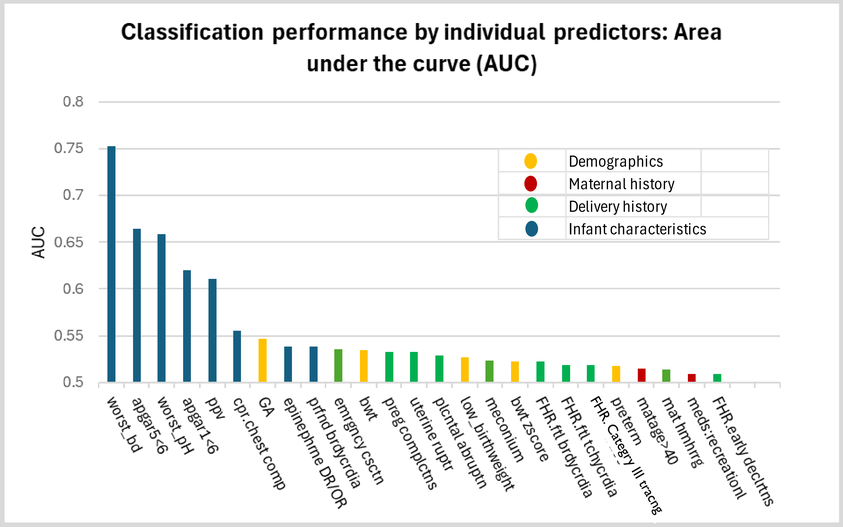
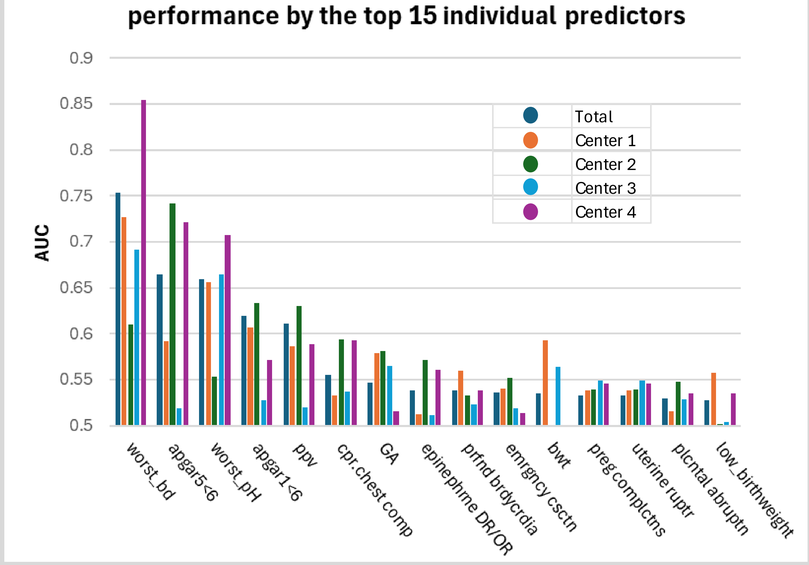


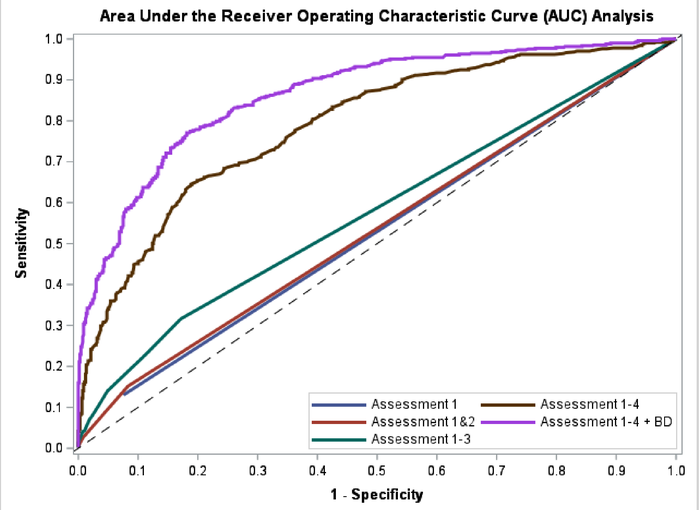
Figure 2.



Results

- Descriptive statistics (**Table 1**): Mean GA 36.1±1.7, 11.5% preterm, 9.9% bwt<2500g, 60% male; resuscitation (PPV (75.4%); CPR (7.6%),epinephrine (3.7%); Apgar 5min <6 (29%), worst gas (pH<7.1(24.4%), bd≥10 (64.2%)
- Among 93 variables evaluated, n=25 significantly associated with TH.(**Figure 1**) . Five predictors with AUC >0.6, all from the infant characteristics form.
- Strongest predictors were worst base deficit (AUC = 0.75), Apgar5<6 (0.66), worst pH (0.66), Apgar1<6 (0.62), and PPV resuscitation (0.61)
- Among the top performing predictors, there was considerable variability in performance among the different cooling centers and their affiliated delivery hospitals. (**Figure 2**)
- As derived from an empty means, random intercept model, receiving TH had an intraclass correlation (ICC) = 0.17 indicating 17% of the variance in cooling status was between cooling centers and their affiliated delivery hospitals
- Performance of each multivariable predictive model improved with the addition of variables from subsequent forms with the largest improvement with the inclusion of those from the infant characteristics form.(**Figure 3**)
- The optimal model (Low birthweight (<2500 g), maternal recreational drug use, fetal tachycardia, Apgar 1 and 5 < 6, and worst base deficit; AUC=0.86 (**Table 2**)) exhibited good diagnostic metrics (sensitivity:0.77, specificity:0.82, PPV:0.76, NPV:0.83) at the Youden's Index cut-off.

Figure 3.



AUC 0.53: Low birthweight (< 2500 g)

AUC 0.53: Low birthweight (< 2500 g); Medications: recreational

AUC 0.58: Low birthweight (< 2500 g); Medications: recreational; Placental abruption; FHR: Fetal tachycardia; FHR; Early decelerations (FHR)

AUC 0.79: Low_birthweight (<2500 g); Medications: recreational; Placental abruption; FHR: Fetal tachycardia; Resuscitation (epinephrine) Apgar 1 < 6; Apgar 5 < 6; worst pH

AUC 0.86: Low birthweight (<2500 g); Medications: recreational; FHR: Fetal tachycardia ; Apgar 1 < 6, Apgar 5 < 6; worst base deficit

Table 2.

Predictors in final model	OR	95% CI	
Medication: recreational	7.05	(1.67, 29.71)	*
Apgar 1 min < 6	3.32	(2.16, 5.11)	*
Apgar 5 min < 6	2.42	(1.70, 3.43)	*
Low birthweight (<2500 g)	2.31	(1.40, 3.81)	*
FHR. Fetal tachycardia	1.95	(1.12, 3.38)	*
Worst base deficit	1.21	(1.16, 1.25)	*

*$p < 0.05$

[1.] All predictors binary with exception of worst BD which is continuous

Conclusions

- Derivation of a prediction model of TH using perinatal variables exhibited good diagnostic metrics.
- Variables with the best predictive performance were those collected during infant delivery.
- The final model included significant predictors from the 1) demographic, 2) maternal history, 3) delivery, and 4) infant characteristics registry data collection forms.
- This study highlights the effectiveness of a predictive model that utilizes immediate perinatal data to determine the necessity for TH in neonates with encephalopathy. By integrating similar models into clinical practice, we can achieve more personalized assessments and initiate timely interventions.

References

1. The Therapeutic Hypothermia Guidelines: Recommendations of the Neonatal Encephalopathy Task Force. https://www.rmf.harvard.edu/-/media/Files/_Global/KC/PDFs/ Guidelines/crico_neonates.pdf.
2. El-Dib M, El-Shibiny H, Walsh B, Cherkerzian S, Boulanger J, Bates SV, Culic I, Gupta M, Hansen A, Herzberg E, Joung K, Keohane C, Patrizi S, Soul JS, Inder T; CRICO Neonatal Encephalopathy Registry. Establishing a regional registry for neonatal encephalopathy: impact on identification of gaps in practice. Pediatr Res. 2024 Jan;95(1):213-222.

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