Risk Assessment of Fetuses for Hypoxic-Ischemic Encephalopathy Using Antepartum Clinical Data

Ethan Grooby[1], Johann Vargas-Calixto[1], Aditi Lahiri[2],
Yvonne W Wu[3], Lawrence David Gerstley[2], Michael William Kuzniewicz[2],
Marie-Coralie Cornet[3], Emily Hamilton[1,4], Philip Warrick[1,4], Robert E Kearney[1]

[1] McGill University, Montreal, Canada, [2] Kaiser Permanente Northern California, Oakland, USA
[3] University of California, San Francisco, USA, [4] PeriGen Inc., North Carolina, USA

Abstract

Neonatal hypoxic-ischemic encephalopathy (HIE), a brain injury caused by oxygen deprivation near birth, can lead to death or long-term neurodevelopmental impairment. This study identified at-risk populations for HIE based on known clinical risk factors and developed a HIE risk score. Maternal, pregnancy, labour, and infant data from a retrospective cohort of singleton infants ($\geq$ 35 weeks) were analysed. Three outcome classes were defined based on blood gas value, neurological exams, and the presence of clinical interventions at birth: (1) HIE (n=420), (2) acidosis alone (n=3,384), and (3) healthy (n=242,645). 10-fold cross-validation was performed with the best-performing risk score having an area under the receiver operating characteristic curve of 0.71. Notable risk factors included parity, prior c-section, gestational age, gestational hypertension, and fetal sex.

1. Introduction

Neonatal hypoxic-ischemic encephalopathy (HIE), a brain injury caused by oxygen deprivation near birth [1], affects 1.3-1.7 [2] and 1.5-26.5 [2–4] per 1,000 live births in high-income and low-to-middle-income countries, respectively. It is a major cause of long-term neurodevelopmental issues [1,4–6], death in the first month of life [3,4] and medical malpractice claims [5, 6]. Overall, there is a need for timely detection of fetal oxygen deprivation to prevent HIE.

Cardiotocography (CTG), a tool to assess fetal well-being, acquires fetal heart rate (FHR) and maternal uterine pressure (UP) signals. So far, FHR with conventional clinical guidelines and novel automated decision support software have shown promising but variable improvement in HIE outcomes compared with traditional intermittent auscultation [6–9]. However, the usage of CTG has resulted in a rise in unnecessary Caesarean sections (C-sections), which are costly, divert resources away from other essential health services, and are associated with short- and long-term health risks for the woman, child, and future pregnancies [7,10]. This clinical ineffectiveness can be attributed to high inter- and intra-observer variability in interpretation [7, 8], clinical misinterpretation of FHR data [6], and limited specificity and utility of current clinical guidelines with the majority of signals falling under the suspicious category [8,9]. Furthermore, while obstetricians integrate clinical risk factors into their FHR interpretation, current clinical guidelines do not [8, 9].

This paper explored using pre-labour clinical information to improve HIE outcome detection and reduce unnecessary C-sections. Sub-populations are identified based on HIE risk. Populations with higher HIE risk may require more in-depth clinical and automated decision-support evaluation. A risk score is also developed, which could assist in reducing the burden of monitoring.

2. Dataset

CTG records linked to clinical information about the infant, mother, pregnancy, labour, and outcome were obtained from 16 Northern California Kaiser Permanente (KP) Hospitals between 2011-2019, amounting to over 250,000 births [11]. The outcome label of HIE was defined as a combination of acidosis (indicating hypoxia) and encephalopathy (indicating brain dysfunction). Acidosis was determined based on blood gas assessment (at least one pH$<$7 or base deficit $\geq$10 mmol/L from any cord blood, or a base deficit $\geq$10 mmol/L on the first infant blood gas before 2 hours of age). Encephalopathy was defined as at least one of the following: abnormal neurological exam lasting $\geq$6 hours, seizures in the first 24 hours of life, or received therapeutic hypothermia.

Inclusion criteria were singleton and cephalic presentation pregnancies with a gestational age $\geq$35 wks. Exclusion criteria were stillbirths, death $\leq$ 6 hours after birth,

and neonates without HIE that required intervention at birth [11]. In total, there were 420 infants with HIE, 3,384 infants with acidosis alone, and 242,645 healthy cases. 31,237 of these records had missing data. Two binary label sets were considered for classification. (1) healthy vs acidosis (HIE + acidosis alone). (2) healthy vs HIE cases.

3. Identifying At-Risk Groups

Known risk factors for maternal and fetal conditions were extracted, namely, pre-existing maternal conditions (diabetes, depression, anxiety, hypertension), gestational conditions (depression, diabetes, hypertension, anxiety, intrauterine growth restriction), gestational age, maternal age and weight, parity, prior C-section, Group B Streptococcus status and fetal sex.

Logistic regression and decision tree models were explored to identify at-risk populations for HIE. Continuous variables were converted into categorical variables based on standard medical definitions, i.e., body mass index (BMI) into underweight to obese classes, gestational age into pre- to post-term classes, and parity in terms of nulliparity. Additionally, maternal age was categorised in bins.

Logistic Regression The reference groups are indicated in Table 1. Adjusted odds ratios were calculated as the exponential of the coefficients of the fitted model. The odds ratio is the odds of the event (HIE or acidosis) occurring when a risk factor is present divided by the odds of the event occurring when the risk factor is absent. The Benjamini-Kreger and Yekatieli [12] method was used for statistical testing for multiple comparisons. It is a 2-stage adaptive method with the false discovery rate set at 0.05.

Decision Tree Our tree-split limit of 10 and risk-factor selection is based on interaction-curvature tests [13]. These choices ensure that a combination of a small set of key clinical risk factors is considered and to minimise the bias of selecting risk factors with more distinct values.

4. Risk Scores

Existing Risk Score Comorbidity point score, version 2 (COPS2) summarises the diagnoses over the preceding 12 months for an individual and is currently used in KP hospitals [14]. For our study, COPS2 is calculated for the mother at delivery admission.

Proposed Risk Scores We considered logistic regression and decision trees or ensembled decision trees using bagging or AdaBoost. Decision tree-based classifiers utilised surrogate splits to address missing data. To avoid overfitting, stepwise backward feature elimination of the full logistic regression model based on the Akaike information criterion was performed. For decision-tree models, we retained 20 features using maximum relevance minimum redundancy with mutual information quotient [15].

4.1. Evaluation

We performed 10-fold cross-validation stratified by hospital site, delivery method, and outcome. The calibration performance was assessed using calibration intercept and slope, and the discrimination performance was assessed using AUROC and the number needed to evaluate (NNE).

5. Results and Discussion

Table 1 presents the adjusted odds ratios from the logistic regression model for statistically significant risk/protective factors. Notable individual factors include parity$>$0, pre-existing diabetes, moderate to late pre-term gestational age, and delivery age of above 40.

Figure 1 shows that the subset of five clinical features can separate the population into 8 groups. In particular, parity$>$0 with no prior c-section is the lowest at-risk group, capturing 43.2% of total births, with an HIE odds ratio of 0.26. This is a potential sub-population to exclude from further evaluation, reducing the burden on clinicians and unnecessary C-sections. Conversely, nulliparity in combination with pre-term or late to post-term gestational age or gestational hypertension are notable at-risk groups for further evaluation, with HIE odds ratios exceeding 2.

Table 2 shows risk-score performance. The existing COPS2 score had poor discriminability with an AUROC of 0.48 for HIE cases, highlighting the need for an HIE-specific risk score. This can be attributed to the fact that COPS2 does not consider obstetrical information such as parity. Logistic regression showed good performance in both calibration and discriminability, but cannot consider missing data. Decision Trees with AdaBoost showed the best performance with AUROC of 0.71, and calibration slope and intercept of 0.98 and 0.00 for HIE cases on the entire dataset. However, Figure 2 highlights that NNE is still high for the top-performing classifiers, as HIE is rare.

Overall, Figure 1 highlights suitable sub-populations to exclude and include for further evaluation. Logistic Regression and AdaBoost models show good calibration performance to obtain prior probabilities for HIE risk with promising discriminability performance. However, due to the high NNE, these models cannot be used in isolation for determining a C-section. Instead, the identified risk factors and developed risk score should be utilised in conjunction with CTG analysis, labour progress, and maternal vital signs for improved performance and interpretability.

6. Conclusion

Relevant individual and groups of risk factors for identifying at-risk populations of HIE were determined. The existing COPS2 risk score is not appropriate for HIE risk. The developed risk score provides reasonable estimates of

Table 1: Logistic Regression Adjusted Odds Ratios for Statistically Significant Risk/Protective Factors

Risk Factor	Healthy	Acidosis Alone	HIE	OR (Healthy vs HIE)	OR (Healthy vs Acidosis)
Prior C-Section (Ref No)	208,438	2,928	372		
Yes	34,205	456	48	1.66 (1.15-2.41)	1.74 (1.55-1.96)
Parity (Ref Nulliparity)	97,462	2,132	284		
Parity>0	138,818	1,108	112	0.23 (0.18-0.31)	0.30 (0.28-0.33)
Fetal Sex (Ref Female)	119,433	1,484	168		
Male	123,141	1,899	252	1.43 (1.16-1.77)	1.14 (1.16-1.33)
Gestational Conditions					
Diabetes	226,789	3,136	393		
Yes	15,856	248	27	1.08 (0.78-1.48)	1.12 (1.00-1.24)
Hypertension	206,971	2,577	297		
Yes	35,674	807	123	1.84 (1.45-2.33)	1.46 (1.34-1.58)
Anxiety	220,992	2,983	355		
Yes	21,653	401	65	1.97 (1.31-2.96)	1.28 (1.11-1.48)
Intrauterine Growth Restriction	237,353	3,296	405		
Yes	5,292	88	15	1.78 (1.04-3.06)	1.27 (1.02-1.58)
Pre-Existing Conditions					
Diabetes	240,176	3,307	403		
Yes	2,469	77	17	3.31 (1.95-5.62)	2.00 (1.59-2.51)
Gestational Age					
Ref Full-Term [39,41)	148,187	1,911	217		
Moderate to Late Pre-Term [35,37)	7,456	153	37	2.87 (1.99-4.13)	1.55 (1.32-1.82)
Early-Term [37.39)	57,466	657	88	0.88 (0.67-1.15)	0.86 (0.79-0.95)
Late-Term [41,42)	28,496	635	71	1.26 (0.93-1.171)	1.49 (1.46-1.64)
Post-Term ≥42	1,040	28	7	2.55 (1.04-6.24)	1.56 (1.05-2.31)
Delivery Maternal Age					
Ref [20,30)	87,887	1,223	136		
<20	5,582	102	15	1.19 (0.65-2.16)	1.05 (0.85-1.29)
[30,40)	138,062	1,888	239	1.36 (1.07-1.71)	1.20 (1.11-1.29)
≥40	11,110	171	30	2.04 (1.31-3.17)	1.47 (1.25-1.73)
Pre-pregnancy BMI					
Ref Healthy [18.5,25)	100,910	1,280	165		
Underweight <18.5	6,650	61	9	0.88 (0.45-1.73)	0.73 (0.57-0.94)
Overweight [25,30)	59,225	835	106	1.16 (0.90-1.49)	1.15 (1.06-1.26)
Obese ≥30	50,341	880	102	1.18 (0.9-1.55)	1.39 (1.27-1.52)

Ref=Reference, OR=Odds Ratio, Shading: Statistically Significant Risk Factor (red) or Protective Factor (green) based on Benjamini-Kreger and Yekatieli method [12]. 95% confidence intervals are shown in brackets.

Table 2: Risk Score Performance

Model	Acidosis Calibration		HIE Calibration		AUROC	
	Slope	Intercept	Slope	Intercept	Acidosis	HIE
COPS2	NA	NA	NA	NA	0.49 ± 0.01	0.48 ± 0.02
Logistic Regression*	0.97 ± 0.05	0.00 ± 0.03	0.91 ± 0.12	0.00 ± 0.10	0.68 ± 0.01	0.73 ± 0.02
Decision Tree	0.97 ± 0.06	0.00 ± 0.03	1.18 ± 0.20	0.00 ± 0.10	0.63 ± 0.01	0.66 ± 0.02
Bagged Decision Trees	0.34 ± 0.03	-0.04 ± 0.03	0.38 ± 0.08	-0.30 ± 0.10	0.62 ± 0.01	0.64 ± 0.02
Decision Trees with AdaBoost	0.80 ± 0.04	0.00 ± 0.03	0.98 ± 0.13	0.00 ± 0.10	0.68 ± 0.01	0.71 ± 0.04

95% Confidence Intervals Shown, *for records with no missing values

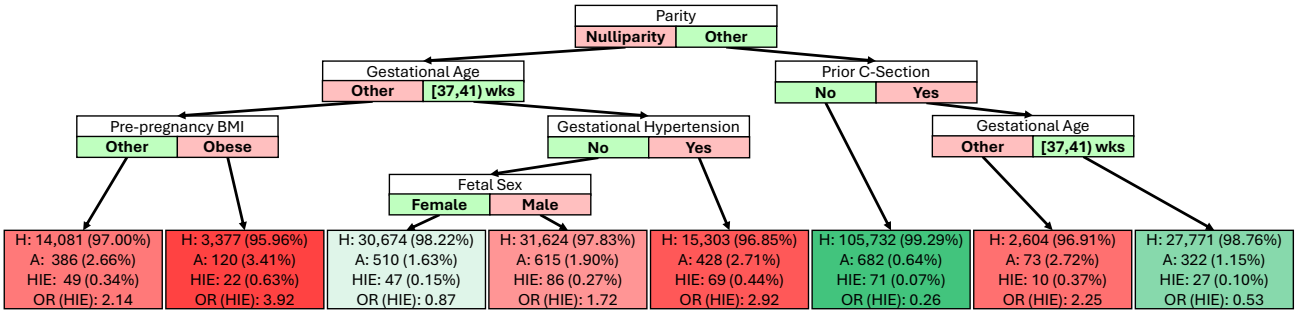

Figure 1: Segmented Populations based on HIE Risk
Red/Green Shading=Risk/Protective Factor, OR (HIE)=Odds Ratio (Healthy vs HIE), H=Healthy, A=Acidosis Alone

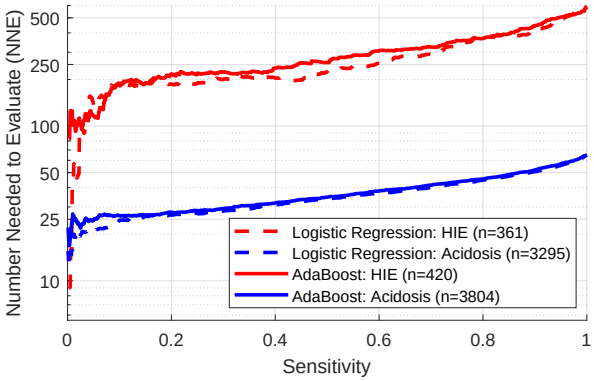

Figure 2: Number Needed to Evaluate (NNE) Plots

acidosis and HIE risk. Future work involves incorporating clinical risk factors and scores with maternal vital signs, labour progress, signs for infection, and FHR analysis.

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Address for correspondence:

Ethan Grooby
3775 Rue University, Montreal, QC H3A 2B4, Canada
ethan.grooby@mcgill.ca