Development and Validation of a Seizure Prediction Model in Neonates Following Cardiac Surgery

Running Head: Neonatal Seizure Prediction Model

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ABSTRACT

BACKGROUND: Electroencephalographic seizures (ES) following neonatal cardiac surgery are often subclinical and have been associated with poor outcomes. An accurate ES prediction model could allow targeted continuous electroencephalographic monitoring (CEEG) for high-risk neonates.

METHODS: Development and validation of ES prediction models in a multi-center prospective cohort where all postoperative neonates with cardiopulmonary bypass (CPB) underwent CEEG.

RESULTS: ES occurred in 7.4% of neonates (78 of 1053). Model predictors included gestational age, head circumference, single ventricle defect, DHCA duration, cardiac arrest, nitric oxide, ECMO, and delayed sternal closure. The model performed well in the derivation cohort (c-statistic 0.77, Hosmer-Lemeshow p=0.56), with a net benefit (NB) over monitoring all and none over a threshold probability of 2% in decision curve analysis (DCA). The model had good calibration in the validation cohort (Hosmer-Lemeshow, p=0.60); however, discrimination was poor (c-statistic 0.61) and in DCA there was no NB of the prediction model between the threshold probabilities of 8% and 18%. Using a cut-point that emphasized negative predictive value (NPV) in the derivation cohort, 32% (236 of 737) of neonates would not undergo CEEG, including 3.5% (2 of 58) with ES (NPV 99%, sensitivity 97%).

CONCLUSIONS: In this large prospective cohort, a prediction model of ES in neonates following CPB had good performance in the derivation cohort with a NB in DCA. However, performance in the validation cohort was weak with poor discrimination, calibration, and no NB in DCA. These findings support CEEG monitoring of all neonates following CPB.

Continuous electroencephalographic monitoring (CEEG) has identified postoperative electroencephalographic seizures (ES) in neonates following surgery with cardiopulmonary bypass (CPB) which are usually subclinical. [1-7] Postoperative ES are associated with worse neurodevelopmental outcomes, abnormal neuroimaging and neurologic examinations.[1,8-11] Based on these data, an American Clinical Neurophysiology Society's (ACNS) guideline recommends performing CEEG following neonatal cardiac surgery.[12] However, CEEG is resource intense so widespread implementation has not occurred.[13] Targeting CEEG to neonates at high risk of ES would enable more efficient use of CEEG resources. The aim of this investigation was to develop and validate a prediction model for ES with the hypothesis that preoperative and operative characteristics would predict the probability of postoperative ES.

PATIENTS AND METHODS

Derivation and validation cohorts

Models were developed and validated in a prospectively acquired cohort from three centers: Children's Hospital of Philadelphia (CHOP), Riley Children's Hospital (RCH), and University of Virginia Children's Hospital (UVA), where postoperative neonates (≤30 days, corrected gestational age ≤44 weeks from June 2012 through 2018 at CHOP, May 2014 through 2018 at RCH, and May 2016 through 2018 at UVA) underwent CEEG. The cohort was identified through the Society of Thoracic Surgeon's database for the individual institution. For multiple operations during the neonatal period, only the index operation was included. Exclusion criteria were infants >30 days, no CPB and no CEEG. Each institutional review board approved the study with waiving informed consent as this was chart review of existing clinical data.

Primary outcome

The primary outcome ES was defined as an abnormal, paroxysmal EEG event different from the background, >10 seconds (or shorter if associated with a clinical seizure), with a plausible EEG field, that evolved in frequency, voltage, morphology and/or spatial distribution within 48 hours postoperatively.

EEG Monitoring

Postoperative CEEG was initiated within six hours of returning to the intensive care unit (ICU). CEEG was performed with the international 10-20 system (modified for neonates) using portable acquisition machines networked to the main EEG server, allowing EEG review at the bedside, from multiple sites in the hospital, and remotely. If an ES was identified, the ICU Service was alerted by the EEG technologist or electroencephalographer, and neurology consultation was obtained. CEEG was continued on all neonates for 48 hours. In those with ES, CEEG was continued for 24 hours following the termination of the last ES. Antiseizure medication choice was at the discretion of the treating cardiac intensivist and neurologist.

Data collection

Data were collected and managed using REDCap (Research Electronic Data Capture), hosted at the CHOP Research Institute.[14] Clinical data were obtained from the medical record. Neonates were categorized according to a classification that incorporates cardiac anatomy and perioperative physiology, which has been shown to predict perioperative mortality.[15] A list of operations and comparison across centers is provided in the Supplemental Material (**Supplemental Table 1**). ES were classified as status epilepticus if any ES lasted longer than 30 minutes or if recurrent ES lasted more than 30 minutes in any one-hour epoch (50% seizure burden). ES were classified as EEG-only ES (no clinical signs observed by bedside caregivers or on video review) or electroclinical ES.

Candidate predictors

Candidate predictors included 23 preoperative and operative variables (**Supplemental Table 2**). In neonates with CHD seizures, brain injury and neurodevelopmental dysfunction have been associated with age at surgery, sex, race, gestational age, low birth weight, head circumference, genetic syndrome, cardiac defect, duration of deep hypothermic circulatory arrest (DHCA), open sternum, cardiac arrest, low hematocrit on bypass and extracorporeal membrane oxygenation (ECMO).[1,2,4,5,7,11,16-20] Racial and ethnic disparities have also been observed with CHD outcomes.[21-24] Regional cerebral perfusion (RCP) has been proposed as a neuroprotective strategy during CPB to avoid DHCA, although ES have been associated with its use.[4,7,25] Longer duration of CPB, and inhaled nitric oxide were used as surrogates for a sicker postoperative neonate.

Model building strategy

Statistical analyses were performed using Stata 14.2 (College Station, TX). The association of each predictor with ES was examined using the chi-square or Fisher's exact test for categorical variables and the Wilcoxon's rank sum test for continuous variables. Significant center variation was observed in preoperative and operative variables (**Supplemental Table 3**). Therefore, the initial building strategy to derive a model in the CHOP dataset which comprised 70% (739 of 1053) of the cohort was abandoned. These models had inadequate fit in datasets from RCH and UVA (**Supplemental Tables 4, 5, 6 and 7**). To make the model more generalizabile to centers other than those in this study a combined dataset was used to incorporate the variability in neonatal cardiac surgery perioperative care.[26-28] The cohort from the three centers was combined with a random 70:30 split for derivation and validation of the model, respectively. Variables with a p-value of <0.2 (two-sided) were entered into a model using either logistic regression with backward elimination or with Least Absolute Shrinkage and Selection Operator regression (lasso). In backward elimination, variables were sequentially

removed based on their beta coefficients with comparison of the area under the receiver operating characteristic curve (AUC) until the model was deemed adequate. Lasso regression is a machine learning algorithm that both shrinks coefficients of variables towards zero to avoid overfitting and selects a subset of predictor variables into the model based on a penalty on the absolute value of the coefficients in the modelzero.[29]

Model assessment and validation

In the derivation cohort, internal validation was performed using the following: (1) predictive accuracy was assessed by the Brier score (variation explained by predictor, a Brier score of 0 indicates a perfect model whereas 0.25 indicates a non-informative model);[30,31] (2) discrimination (ability of the model to separate neonates with ES to those without ES) was assessed using the discrimination slope (difference of average predictions in neonates with and without ES),[31] sensitivity, specificity, and the AUC with the concordance statistic (c-statistic); (3) calibration (accuracy of predictions) was measured using the Hosmer-Lemeshow goodness of fit test and by a calibration plot that assessed agreement between predicted and observed ES;[31] and (4) decision curve analysis (DCA) was conducted to measure the net benefit (NB) of making decisions based on model predictions. In DCA, the NB of the prediction model is calculated across a range of threshold probabilities for ES, defined as the minimal probability of ES at which EEG monitoring would be warranted. In DCA the prediction model is compared to the default strategies of monitoring all or none. The interpretation of DCA is that the strategy with the highest NB at a particular threshold probability has the highest clinical value.[31,32] Cross-validation using 10-folds was performed in lasso with selection of the lasso tuning parameter that minimized the estimate of out of sample prediction error.

The model was then applied to the validation cohort to test its performance using all the measures above. Predicted ES probabilities were calculated from the model and sensitivity, specificity, positive predictive values, negative predictive values (NPV), and the proportion of

patients undergoing CEEG were assessed at various model cutoffs assuming that those above the cutoff would be selected for CEEG.

RESULTS

Postoperative CEEG occurred in 739 of 745 (99.2%) neonates at CHOP, 188 of 188 (100%) at RCH and 126 of 130 (96.9%) at UVA. ES occurred in 7.4% (78 of 1053) of neonates, including 8% (59 of 739) at CHOP, 9% (17 of 188) at RCH, and 1.6% (2 of 126) at UVA. **Table 1** provides summary characteristics in the derivation and validation cohorts. ES occurred in 7.9% (58 of 737) of the derivation cohort and 6.3% (20 of 316) of the validation cohort, p=0.38. In the derivation cohort, ES occurred in 8.5% (55 of 521) from CHOP, 10.4% (13 of 125) from RCH, and 1.1% (1 of 91) from UVA. In the validation cohort, ES occurred in 6.9% (15 of 281) from CHOP, 6.4% (4 of 63) from RCH, and 2.9% (1 of 35) from UVA. The final model (**Table 2**) was developed using the lasso due to its superior performance in the validation cohort (**Table 3**) when compared to backward elimination (**Supplemental Tables 8 and 9**). In the derivation cohort, the model performed well with a Brier Score of 0.06 indicating an informative prediction. Model discrimination was fair with the predicted probability of ES 11% higher in neonates with versus without ES (c-statistic of 0.77) (**Figure 1** *Upper* left). Hosmer-Lemeshow suggested adequate fit (χ^2=2.27, p-value 0.56). DCA in the derivation cohort is shown in **Figure 2** (left). Below the threshold probability of 2% there was no difference in the NB of monitoring all and monitoring based on the model, with a higher NB for these strategies compared to monitoring none. Above the threshold probability of 2% the NB of the model was higher than the NB of monitoring all and none.

In the validation cohort the Brier Score was 0.06 indicating an informative prediction. Model discrimination was poor with the predicted probability 6% higher in neonates with versus those without ES (c-statistic of 0.61) (**Figure 1** *Upper* right). Hosmer-Lemeshow suggested adequate fit (χ^2=6.42, p value 0.60); however, the calibration plot (**Figure 1** *Middle* right)

showed that predicted probabilities of ES underestimated the observed probabilities. There were a number of neonates in whom the model predicted a low probability of ES, but in whom the actual probability was considerably higher. DCA in the validation cohort (**Figure 2** right) showed no difference in the strategy of monitoring all and monitoring based on the model below a threshold probability of 5%. Above a threshold probability of ES of 5% to a probability of 8% the model had a NB over monitoring all and none. Above this probability the model had no NB until a threshold probability of 18% above which it was beneficial till a probability of 50%.

Tables 4 and 5 provide model characteristics in the derivation and validation cohorts at different cutoffs. At a cutoff of 0.03 that maximizes sensitivity and NPV, 32% (236 of 737) of neonates in the derivation cohort would not undergo CEEG, including 3.5% (2 of 58) of neonates with ES (NPV 99%, sensitivity 97%). In the validation cohort 25.6% (81 of 316) of neonates would not undergo CEEG, including 10% (2 of 20) of neonates with ES (NPV 97.5%, sensitivity 90%).

COMMENT

A predictive model based on clinical characteristics was developed and validated to enable efficient use of resources to target CEEG to neonates with a high probability of ES. In the derivation cohort the model overall had good performance with fair discrimination and good calibration. In the validation cohort the model was informative, however discrimination was poor, and although the calibration appeared adequate, the predicted probabilities underestimated the observed probabilities, particularly for neonates with low predicted probabilities. In DCA, the model had some NB in the validation cohort; however, there was no benefit observed between threshold probabilities of 8% to 18%. Given that the reported probability of postoperative ES is 1.5% to 20% and >8% in most reports, centers with abundant CEEG resources would likely monitor neonates above the threshold probability of 8% to 10%.[1-7] Given that in the validation cohort the model had no NB in this range it is not of clinical value in centers with abundant

CEEG resources.[17,33,34]In centers with limited CEEG resources where higher threshold probabilities for seizures may be used e.g. 50% the model again had no NB in the validation cohort therefore would not be of clinical value. Therefore, although this model performed well in the derivation cohort, validation was poor indicating the model should not be used for targeting CEEG. These data support the current recommended practice of performing CEEG for all neonates following surgery with CPB.[12]

Despite the current ACNS guideline, the data on the incidence of postoperative ES, and the association of ES with worse outcomes, CEEG in postoperative neonates has not been widely implemented given the resource requirements. [1-12,17] Many centers monitor neonates considered to be at the highest risk of ES, including those on ECMO support or following a cardiac arrest.[35,36] Therefore, a prediction model could allow targeted CEEG. However, although there was a similar ES incidence in 2 of 3 the centers, significant center variation was observed in the timing of surgery, the use of open sternum, intraoperative strategies for neuroprotection including DHCA and RCP, and other factors associated with neurological injury including the lowest hematocrit on CPB, cardiac arrest, and ECMO. The model was therefore developed in a multicenter cohort to enable generalizability.

There are limitations to these data. First, exclusion of CEEG background may have led to information bias. As the goal of this study was to develop a prediction model based on preoperative and operative variables, background CEEG variables were not included. Initial CEEG background has been shown to be useful when incorporated into an ES prediction model in children admitted with acute encephalopathy to the pediatric ICU.[37] Second, perioperative brain injury evident on neuroimaging is an important variable that was not included in the prediction model as all neonates did not have routine perioperative neuroimaging. Third, given the multicenter nature of study misclassification of ES and differences in EEG interpretation may have occurred. A standard definition of ES and ES identification was used which is known to be reliable across encephalographers.[38,39] Fourth, the study was designed to for a sample size of

750 neonates in the validation cohort with 60 ES to achieve a sensitivity of 98% (anticipated 95% CI 92-100%) and specificity of 50% (anticipated 95% CI of 47-53%). The total sample size was achieved, and the number of ES (57) approached the target value. However, in the derivation dataset, while a sensitivity of 97% was obtained for the lower cutoff of the receiver operating characteristics curve (**Table 4**), the specificity was only 34.5%, well outside the specified range, and which drove down the NPV. Alternatively, in order to achieve a specificity near 50%, the sensitivity dropped to 85%. This suggests that key predictors needed to achieve these levels of accuracy were missing even from the derivation model. Not surprisingly this resulted in poor performance in the validation cohort.

In conclusion, ES in neonates following surgery with CPB were not accurately predicted by a model using preoperative and operative variables. These findings support continued CEEG in all neonates following surgery with CPB.

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Table 1. Comparison of variables in the derivation and validation cohorts

Variable	Derivation (n=737)	Validation (n=316)	*p* value[*]
Age at surgery median (IQR)	6 (4,9)	6 (4,11)	0.27
Male sex n (%)	444 (60.2)	198 (62.7)	0.46
Race n (%)			
White	451 (61.0)	196 (62.0)	0.64
Black	94 (12.7)	35 (11.1)	
Other	192 (26.1)	85 (26.9)	
Gestational age at birth (weeks) median (IQR)	39 (38,39)	39 (37,39)	0.07
Birth weight (kg) median (IQR)	3.2 (2.8,3.5)	3.1 (2.8,3.5)	0.07
Head circumference (cm) median (IQR)	33.5 (32,34.5)	33.5 (32,34.5)	0.25
Prenatal diagnosis n (%)	537 (72.8)	233 (73.7)	0.77
Genetic diagnosis n (%)	144 (19.5)	74 (23.4)	0.16
Cardiac defect n (%)			
Single ventricle	254 (34.5)	102 (32.3)	0.49
Two ventricles without arch obstruction	315 (42.7)	150 (47.5)	0.16
Two ventricles with arch obstruction	168 (22.8)	64 (20.3)	0.36
Single ventricle without arch obstruction	54 (7.3)	24 (7.6)	0.88
Single ventricle with arch obstruction	200 (27.1)	78 (24.7)	0.41
CPB duration (minutes) median (IQR)	60 (42,109)	60 (41,101)	0.47
DHCA n (%)	355 (48.2)	145 (45.9)	0.50
DHCA duration (minutes) median (IQR)	37 (24, 47)	40 (25,47)	0.30
RCP n (%)	103 (14.0)	34 (10.8)	0.16
RCP duration (minutes) median (IQR)	62 (39,98)	52 (29,72)	0.09
Lowest hematocrit on CPB (%) median (IQR)	28 (26,31)	28 (26,31)	0.89
Nitric oxide in OR n (%)	153 (20.8)	64 (20.3)	0.85
Cardiac arrest in OR n (%)	6 (1)	1 (0)	0.36
ECMO in OR n (%)	30 (4)	9 (3)	0.34
Open chest in OR n (%)	205 (27.8)	92 (29.1)	0.67
Electrographic seizures n (%)	58 (7.9)	20 (6.3)	0.38

Abbreviations: n, number; IQR, interquartile; kg, kilogram; cm, centimeters; CPB, cardiopulmonary bypass; DHCA, deep hypothermic circulatory arrest; RCP, regional cerebral perfusion; ECMO, extracorporeal membrane oxygenation; OR, operating room

Table 2. Prediction model[*] coefficients

Parameter	Coefficient
Intercept	6.802
Gestational age (weeks)	-0.117
Head circumference (cm)	-0.181
Single ventricle (yes versus No)	0.555
DHCA duration (minutes)	0.018
Nitric oxide in OR (yes versus no)	0.710
Cardiac arrest in OR (yes versus no)	1.645
ECMO in OR (yes versus no)	1.114
Open chest in OR (yes versus no)	0.580

[*]The final prediction model in the derivation dataset was derived from LassoLogit

Table 3. Model performance in the derivation and validation cohorts

Statistic	Derivation	Validation
Likelihood Ratio	59.99	
Pseudo-R-square	0.148	
C-statistic	0.7678	0.606
Brier Score	0.064	0.058
Hosmer-Lemeshow χ^2 (*p* value)	2.27 (0.56)	6.42 (0.60)

Table 4. Model characteristics at various cutoffs in derivation dataset

Model cutoff Predicted probability of ES	Sensitivity	Specificity	PPV	NPV	Proportion with CEEG
0.02	96.6	15.9	8.9	98.2	85.1
0.03	96.6	34.5	11.2	99.2	68.0
0.04	89.7	44.9	12.2	98.1	57.8
0.05	84.5	53.8	13.5	97.6	49.3
0.06	74.1	61.1	14.0	96.5	41.7
0.07	67.2	67.2	14.9	96.0	35.6
0.08	58.6	72.5	15.4	95.3	30.0
0.09	55.2	76.6	16.8	95.2	25.9
0.10	53.4	80.4	18.9	95.3	22.5
0.20	31.0	94.7	33.3	94.1	7.3

Abbreviations: ES, electrographic seizures; PPV, positive predictive value; NPV, negative predictive value

Table 5. Model characteristics at various cutoffs in validation dataset

Model cutoff Predicted probability of ES	Sensitivity	Specificity	PPV	NPV	Proportion with CEEG
0.02	95.0	11.5	6.8	97.1	88.9
0.03	90.0	26.7	7.7	97.5	74.4
0.04	70.0	42.2	7.6	95.4	58.5
0.05	65.0	50.7	8.2	95.5	50.3
0.06	50.0	59.5	7.7	94.6	41.1
0.07	45.0	66.2	8.3	94.7	34.5
0.08	40.0	71.3	8.6	94.6	29.4
0.09	35.0	74.7	8.5	94.4	26.0
0.10	30.0	76.4	7.9	94.2	24.1
0.20	20.2	95.3	22.2	94.6	5.7

Figure Legends

Figure 1. Characteristics for the derivation (left) and validation (right) cohorts**.** *Top* Receiver operating characteristic curve. *Middle* Scatter plots of predicted compared to observed probabilities showing model calibration. *Bottom* Box plots of predicted probabilities showing model discrimination*.*

Figure 2. Decision curve analysis of the prediction model for the derivation (left) and validation (right) cohorts.