Predicting Long-term Neurocognitive Outcome after Pediatric Intensive Care Unit Admission - Exploring the Potential of Machine Learning

European Journal of Pediatrics

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Regression Trees

Regression Trees is a non-parametric machine learning algorithm with high interpretability of outcomes.[1] In order to increase its predictive power and to reduce the risk of overfitting, the bootstrap aggregating (bagging) method was used.[2] The bagging method consists of three steps: (1) generate n bootstrapped samples out of the training dataset; (2) train a regression tree from every sample; (3) take the average predictions from all trained trees. Bagging automatically leaves out 33% of the data within each sample, the out-of-bag sample, which is used for cross-validating the accuracy of the models. A hyperparameter for the bagging method is the optimal number of bagging samples to be generated, which is found by creating a hyper-grid to loop over several different combinations of hyperparameters. It generates 90 models with 10 to 100 bagging samples. Thereafter the error per model is plotted against the number of samples (as increasing the number of samples reduces the error) in order to find the n where the error stabilizes. This n is used as the number of bagging samples. Finally, the models are cross-validated and evaluated based on the performance metrics and the performance of the bagged regression trees is compared to the outcomes of the single tree. The importance of each predictor variable is rated from 0-100% and indicates for how many of the bagging samples this specific variable was used. Variable importance of the bagged Regression Trees in this study is displayed in eTable 3.

eTable 3. Variable importance of the bagged Regression Trees

Neurocognitive outcomes	Predictor variables	Variable importance (%)
FSIQ		
	Birth weight (grams)	100
	Mean difference between PIP and PEEP (cmH_2O)	89.6
	Socioeconomic status	79.3
	Minimum SpO_2/FiO_2 ratio	69.4
	Mean airway pressure (cmH_2O)	65.6
	Number of times pH > 7.45	65.3
	Mean SpO_2/FiO_2 ratio	64.4
	Glucose (mmol/L)	64.2
	Duration of invasive mechanical ventilation (hours)	63.0
	Gestational age (weeks)	58.7
	Age at follow-up (years)	47.9
	Length of PICU stay (days)	44.8
	Weight at PICU admission (grams)	42.7
	Number of times pCO_2 > 6.4 kPa	34.0
	Number of times $etCO_2$ > 6.5 kPa	33.1
	PIM 2 score	30.8
	Age at PICU admission (days)	26.3
	Number of times $etCO_2$ < 3.5 kPa	15.3
	Number of times pH < 7.35	13.3
	Maximum FiO_2 (%)	12.7
	Sex	12.1
	Number of times SpO_2 < 85%	10.1
	Number of times SpO_2 < 90%	9.2
	Number of times glucose > 10 mmol/L	5.9
	Breastfed in past	0.7
	Number of times pCO_2 < 4.7 kPa	0.5
	Minimum FiO_2 (%)	0.0
Speed and attention		
	Age at follow-up (years)	100
	Mean airway pressure (cmH_2O)	48.7
	Duration of invasive mechanical ventilation (hours)	47.0
	Birth weight (grams)	45.1
	Mean difference between PIP and PEEP (cmH_2O)	45.1
	PIM 2 score	42.4
	Glucose (mmol/L)	41.4
	Number of times $etCO_2$ > 6.5 kPa	39.4
	Weight at PICU admission (grams)	37.7
	Mean SpO_2/FiO_2 ratio	37.0
	Gestational age (weeks)	31.3
	Age at PICU admission (days)	29.9
	Minimum SpO_2/FiO_2 ratio	29.3
	Number of times pH < 7.35	26.6
	Socioeconomic status	23.8
	Number of times pCO_2 > 6.4 kPa	22.8
	Number of times SpO_2 < 90%	16.4
	Number of times $etCO_2$ < 3.5 kPa	15.9
	Length of PICU stay (days)	13.1
	Maximum FiO_2 (%)	12.3
	Number of times pCO_2 < 4.7 kPa	11.9
	Number of times pH > 7.45	10.0
	Sex	6.6
	Number of times glucose > 10 mmol/L	6.4
	Minimum FiO_2 (%)	4.3

	Number of times SpO_2 < 85%	2.0
	Breastfed in past	0.0
Verbal memory		
	Birth weight (grams)	100
	Age at follow-up (years)	94.2
	Number of times pCO_2 > 6.4 kPa	91.7
	Weight at PICU admission (grams)	87.1
	Gestational age (weeks)	79.4
	Age at PICU admission (days)	73.0
	Duration of invasive mechanical ventilation (hours)	62.2
	Number of times pH < 7.35	59.1
	Number of times $etCO_2$ > 6.5 kPa	53.5
	Glucose (mmol/L)	53.2
	Mean airway pressure (cmH_2O)	53.1
	Minimum SpO_2/FiO_2 ratio	50.8
	PIM 2 score	38.7
	Mean SpO_2/FiO_2 ratio	38.6
	Mean difference between PIP and PEEP (cmH_2O)	36.7
	Number of times SpO_2 < 90%	35.9
	Socioeconomic status	34.9
	Number of times $etCO_2$ < 3.5 kPa	33.1
	Length of PICU stay (days)	27.1
	Number of times pCO_2 < 4.7 kPa	24.1
	Number of times pH > 7.45	19.3
	Number of times glucose > 10 mmol/L	14.1
	Maximum FiO_2 (%)	13.5
	Breastfed in past	2.7
	Sex	0.4
	Minimum FiO_2 (%)	0.4
	Number of times SpO_2 < 85%	0.0

Note. The importance of each predictor variable is rated from 0-100% and indicates for how many of the bagging samples this specific variable was used.

k-Nearest Neighbors

K-Nearest Neighbor is a proximity based algorithm that uses 'feature similarity' in order to predict the outcomes of new data that is provided to the model. The distance metric used to determine the relative closeness of the datapoint is the euclidean distance. First, the numerical variables were scaled by transformation into z-scores. Second, the categorical variables were converted to dummy coded variables (1 = presence, 0 = absence). Third, the optimal value of the number of neigbors (k) was determined by incorporating a hyperparameter tuner that searches for the optimal value for k out of 20 different values for k. After every increment of k by 1 the model was cross-validated and the performance metrics were calculated.

The outcome value for a new patient is determined by the proximity of its features to that of other patients. For example: a new patient's value for FSIQ is determined by the weighted average of FSIQ values of the k patients whose patient and PICU-related characteristics are most similar. As k-Nearest Neighbors models are never trained, all predictors in the model are equally important to predict an outcome.

References

1. Breiman L, Friedman J, Stone CJ, Olshen RA. Classification and regression trees. CRC press1984.
2. Breiman L. Bagging predictors. Machine learning1996. p. 123–40.