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# Development and external validation of a machine learning model for brain injury in pediatric patients on extracorporeal membrane oxygenation

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## Abstract

**Background** Patients supported by extracorporeal membrane oxygenation (ECMO) are at a high risk of brain injury, contributing to significant morbidity and mortality. This study aimed to employ machine learning (ML) techniques to predict brain injury in pediatric patients ECMO and identify key variables for future research.

**Methods** Data from pediatric patients undergoing ECMO were collected from the Chinese Society of Extracorporeal Life Support (CSECLS) registry database and local hospitals. Ten ML methods, including random forest, support vector machine, decision tree classifier, gradient boosting machine, extreme gradient boosting, light gradient boosting machine, Naive Bayes, neural networks, a generalized linear model, and AdaBoost, were employed to develop and validate the optimal predictive model based on accuracy and area under the curve (AUC). Patients were divided into retrospective cohort for model development and internal validation, and one cohort for external validation.

**Results** A total of 1,633 patients supported by ECMO were included in the model development, of whom 181 experienced brain injury. In the external validation cohort, 30 of the 154 patients experienced brain injury. Fifteen features were selected for the model construction. Among the ML models tested, the random forest model achieved the best performance, with an AUC of 0.912 for internal validation and 0.807 for external validation.

**Conclusion** The Random Forest model based on machine learning demonstrates high accuracy and robustness in predicting brain injury in pediatric patients supported by ECMO, with strong generalization capabilities and promising clinical applicability.

**Keywords** Random forest model, Brain injury, Prediction model, ECMO, Machine learning

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## Introduction

Extracorporeal membrane oxygenation (ECMO) is considered a life-saving intervention for patients with severe, reversible respiratory or circulatory dysfunction that is refractory to conventional medical management. Moreover, its indications have expanded to include use as a bridge to both cardiac and lung transplants, as well as support for lung resections in unstable patients [1–3]. Despite advances in ECMO technology, the observed mortality rates at hospital discharge for ECMO support remain high, with rates of 59–69%, 50–64%, and 45–57% in neonates, pediatric patients, and adults, respectively [2, 4–6].

One study reported that ECMO complications include mechanical device failure, clots, bleeding complications, hemolysis, hyperbilirubinemia, brain injury, and renal injury [7]. Among these, brain injury is a major contributor to morbidity and mortality in children on ECMO support [8, 9]. The types of neurological complications documented in the ELSO registry include brain death, clinically and electroencephalographically determined seizures, diffuse central nervous system ischemia on imaging, central nervous system infarction, and hemorrhage, including central nervous system and intraventricular central nervous system hemorrhages [10].

According to a recent study, the incidence of brain injury under ECMO support is higher in patients with cardiac indications rather than in those with respiratory indications. Moreover, the study indicated that neurologic complications increased with decreasing age; for example, seizures (clinical or Electroencephalography) for cardiac indications were 6.8%, 31.1%, and 74.9% in adults, pediatric, and neonatal patients, respectively [4].

While studies focused on the risk factors for brain injury in patients supported by ECMO exist [11, 12], few have been conducted on brain injury prediction models. Given the high mortality associated with ECMO-related neurologic complications [13], ensuring early detection and treatment of this condition remains crucial. Furthermore, early detection and timely intervention are recognized as essential for improving outcomes [14]. Therefore, we developed a risk-prediction model to help clinicians identify high-risk patients at an early stage, thereby enabling timely and individualized measures to prevent and treat ECMO-related brain injury.

## Methods

### Study design and sample sources

Our study follows the Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis guideline, which is used to aid the reporting of studies developing prediction models [15]. And this

study was not registered because it is not a clinical trial. Retrospectively, up to September 15, 2023, clinical data of 1643 patients (Data 1) supported by ECMO were extracted from the Chinese Society of Extracorporeal Life Support (CSECLS) registry database, which is a multi-center observational study. As the ECMO-related data, including demographic information, comorbidities, main diagnosis, pre-ECMO details, ECMO indication, ECMO support details including complications, weaning trial details and outcomes, were submitted on a standardized electronic form by 112 ECMO centers in China mainland ECMO centers to CSECLS database. While external validation data (Data 2) were collected from The Seventh Medical Center of Chinese PLA General Hospital, Beijing, and The Children's Hospital Affiliated to Zhengzhou University, Zhengzhou. This study was approved by the Medical Ethics Committee of West China Second University Hospital of Sichuan University (Number: 2023–078). Data in this study are available from the corresponding author upon reasonable request.

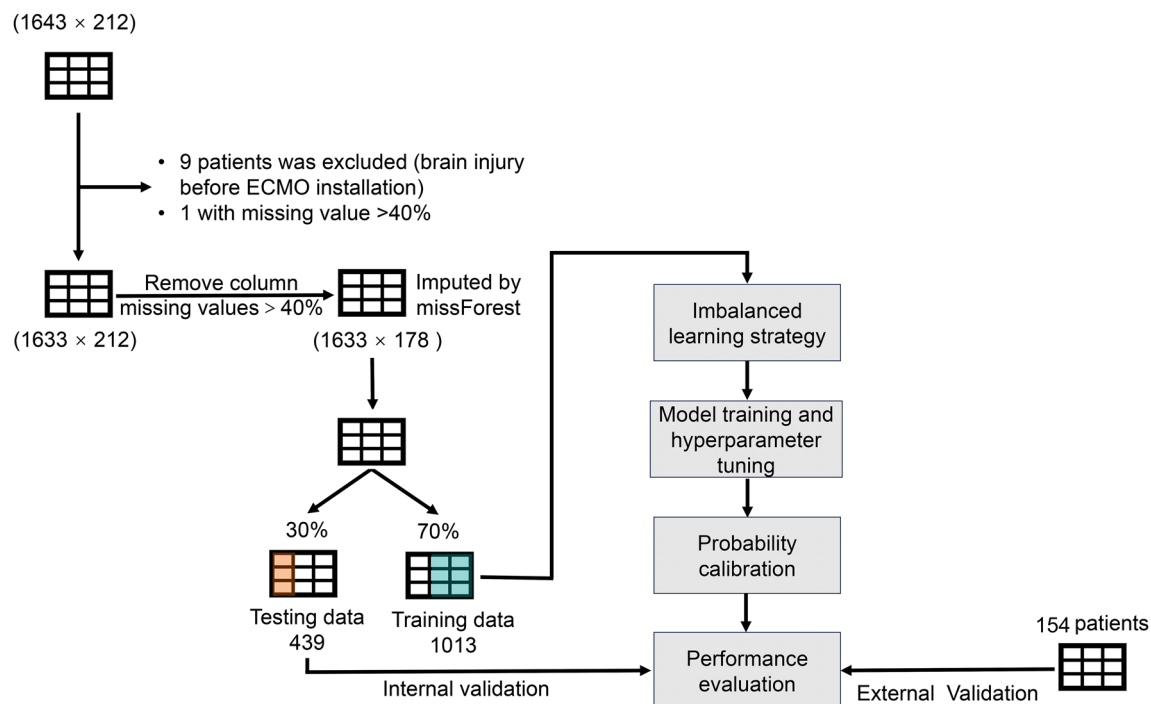
### Inclusion exclusion criteria

Inclusion criteria: 1. Patients aged < 18 years; 2. Patients receiving ECMO support; and 3. Patients with missing data < 40%.

Exclusion criteria: 1. Patients aged  $\geq 18$  years; 2. Patients with severe multi-organ failure before ECMO; 3. Patients with brain injury (including intracranial hemorrhage, infarction and severe craniocerebral trauma) or craniotomy before ECMO support; 4. Patients with severe coagulation disorders; and 5. Patients with missing data  $\geq 40\%$ .

### Definition of outcome and data collection

ECMO-related neurological complications include ischemic stroke, hemorrhage stroke, brain death, and seizures. Methods recommended to diagnose these complications include clinical manifestations, electroencephalography, computed tomography (CT)/magnetic resonance imaging (MRI), or head ultrasound [16]. Previous studies have indicated that factors such as premature birth, lower body weight, congenital heart disease, cardiac failure, pre-ECMO cardiac arrest, acidosis, hypoxemia, hypocarbia, hypotension, and impairment of cerebral autoregulation are associated with neurological complications in patients receiving ECMO support [17]. Thus, features perceived to be related to neurological injury during ECMO support were collected.



**Fig. 1** Machine learning pipeline

## Statistical analysis

### Descriptive statistics

Categorical and numerical variables were presented as frequencies (percentage) and mean (interquartile range [IQR]), respectively. Additionally, to assess the relationships between predictors and brain injury, univariate analysis was conducted using the Chi-squared Test (for categorical data where all frequencies exceed 5) or Fisher's Exact Test (for categorical data with one or more frequencies below 5) and the Wilcoxon rank-sum test (for data with non-normal distribution) as appropriate. A priori significance was set at  $P < 0.05$ .

### Data preparation

The original data1 contained 212 features, and any features or patients with over 40% missing values were removed from the dataset, leaving 178 features and 1633 patients. Also, when data 2 shows poor data quality (missing value was too higher), the data processing method was the same as in data 1. The remaining missing values were imputed using several modern imputation methods, including missForest [18, 19], k-nearest neighbor, and multiple imputation using chained equations [20].

Notably, the classes were highly skewed, as the incidence of brain injury was 11.1%; thus, the following approaches were applied to handle this condition:

synthetic oversampling of the minority class using the synthetic minority oversampling technique algorithm (SMOTE) [21]; and adaptive synthetic sampling (ADASYN), an advanced oversampling technique, which generates synthetic instances for the minority class. This method adapts the creation of synthetic samples based on the local density of instances, thereby enhancing the model's performance in managing imbalanced data [22]. Tomek Links, an extensively used under-sampling method, effectively reduces noise and borderline instances in the majority class, thus minimizing overfitting and bias [23]. SMOTE+Tomek Links (SMOTETomek) combines SMOTE and Tomek Links, with the benefit of mitigating overfitting and underfitting issues [24].

However, these methods are only applicable to continuous variables, and face challenges when dealing with categorical variables. Therefore, one-hot coding on the categorical variables was applied to enable it to proceed. However, one-hot encoding increases the dimensionality of the data and may result in inaccurate distance calculations. Another synthetic minority oversampling technique for nominal and continuous features (SMOTE\_NC) is suitable for handling datasets containing both numeric and categorical variables [25]. Further technical details and the entire machine-learning pipeline are presented in Fig. 1.

### Feature selection

For feature selection, the number of features was predetermined to be 15 to balance the information gain and complexity of data acquisition. Until this step, data process was done in a supervised manner to avoiding data leakage. First, the features were filtered based on data quality and other concerns, and features with low variance and high collinearity ( $r > 0.7$ ) were removed [26]. Finally, we apply recursive feature elimination to select features. In the RFE process, both a logistic regression model and a linear support vector machine were fitted to the training dataset. For each model, five features with the smallest coefficients were identified, and from those common to both models, one was selected for elimination based on our general feature selection strategy (explainability, face validity, potential causal relationship with brain injury, and ease/reliability of data acquisition). This process was continued until a final set of 15 features remained [27].

### Model construction

Ten machine learning (ML) algorithms, including Random Forest (RF), Generalized Linear Model (GLM), Support vector machine (SVM), Gradient boosting machines (GBM) [28, 29], eXtreme Gradient Boosting (XGBoost) [30], Light Gradient Boosting Machine (LGBM), Naive Bayes, Neural Networks, Decision tree (DT) [31], and AdaBoost [32], were applied to develop the prediction model of brain injury in children and neonates on ECMO support.

Model development, validation and assessment.

The data were randomly partitioned into training (70%) and testing (30%) sets to avoid overfitting in the model predictions and ensure robust generalization during testing [33]. To train these (ML) models (with different methods balancing the training sets), the training set was employed in a double-nested cross-validation process, which included five k-fold cross-validation loops (with  $k=5$  in each loop). These loops were utilized for hyperparameter optimization, probability calibration, and to obtain an unbiased and conservative performance estimate [34].

We trained these ML models using different methods to balance the training data. The final model was determined by the better receiver operating characteristic curve of the testing data. Results were considered statistically significant if the  $p$  value was  $< 0.05$ . The performance of the final model was assessed using the AUC, accuracy, specificity, sensitivity, positive predictive value, negative predictive value, receiver operating characteristic curve, precision-recall curve, and balanced accuracy using a confusion matrix. The testing data were used for internal validation, and the validation data were applied

to this model for external validation. The feature importance of the predictive model performance was estimated and validated using the RFE technique, logistic LASSO, and Boruta methods [35].

### Explainability

Random forest feature selection was applied to identify the most to least important features for classification [36]. Regarding the explainability of the ML models, Shapley Additive Explanations (SHAP), a model-agnostic explanation method, was applied to interpret the results from a predictive model. Specifically, the SHAP values from the ML feature space were transformed to the corresponding clinical variable space, where each SHAP value was mapped back to the original variables, and a SHAP summary plot was drawn to visualize the contribution of the feature to the final model's output [37, 38].

R software (version 4.3.3) was applied for all statistical analyses, model development, validation and figure drawing. And the key analysis code was reported in Supplementary files.

## Results

### Characteristics of the study population

The baseline of the patients (Data 1) supported by ECMO is shown in Table 1, with the missing value percentage in Table S1. The characteristics of the validation data (Data 2) are shown in Table 2. In Data 1, nine patients were excluded due to brain injury before ECMO support, and one patient was excluded due to missing values larger than 40%. Finally, 1633 patients were included in this study for model construction.

In detail, patients with brain injury show a lower age (71.7 [73.7] vs 46.4 [58.3] months,  $p < 0.001$ ), height (103.55 [90] vs 89.87 [60] cm,  $p < 0.001$ ), and weight (26.66 [34.5] vs 15.36 [15.5] Kg,  $p < 0.001$ ); while the sex shows no difference (529 [36.43%] vs 67 [37.02%] in female and 923 [63.57%] vs 114 [62.08%] in male,  $p = 0.94$ ). Moreover, circulation status before ECMO, including systolic blood pressure (SBP) and diastolic blood pressure (DBP), was significantly lower in patients with ECMO-related brain injury than in those without ( $p < 0.001$ ); while the heart rate (HR) shows no significant difference. In addition, the pH, partial pressure of oxygen (PO<sub>2</sub>), partial pressure of carbon dioxide (PCO<sub>2</sub>), and lactate (Lac) in patients with ECMO-related brain injury before installation also showed a significant decrease than without brain injury (all  $p < 0.01$ ). After ECMO, the brain injury group continued to show worse metabolic and respiratory conditions, with significantly lower pH and higher levels of PCO<sub>2</sub> and Lac (all  $p < 0.01$ ). Moreover, ECMO flow at the 4th hour was lower in brain injury patients ( $p < 0.001$ ).

**Table 1** Characteristic of the cohorts

Characteristic		N = 1633	Non-brain injury (n = 1452)	Brain injury (n = 181)	P value
Age, mean (SD), m		68.87 (72.54)	71.7 (73.7)	46.4 (58.3)	< 0.001
SEX (%)	Female	596 (36.50)	529 (36.43)	67 (37.02)	0.94
	Male	1037 (63.5)	923 (63.57)	114 (62.08)	
Height, median (IQR), cm		95(86)	103.57 (90)	89.88 (60)	< 0.001
Weight, median (IQR), kg		14.3(32.5)	26.66 (34.5)	15.36 (15.5)	< 0.001
Before ECMO installation					
SBP, median (IQR), mmHg		60 (35)	62.71 (34)	54.48 (30)	< 0.001
DBP, median (IQR), mmHg		40 (20)	39.37 (20)	34.11 (18.08)	< 0.001
HR, median (IQR), beat/min		135 (68)	120.27 (62.15)	119.12 (97)	0.45
PH, median (IQR)		7.29 (0.22)	7.26 (0.21)	7.22 (0.26)	< 0.001
HCO <sub>3</sub> , median (IQR), mmol/L		20.36 (8.7)	20.62 (8.42)	21.8 (10.7)	0.60
PO <sub>2</sub> , median (IQR), mmHg		75.04 (78)	103.2 (76.61)	92.22 (68)	< 0.01
PCO <sub>2</sub> , median (IQR), mmHg		43 (17.86)	47.09 (17.07)	52.50 (25.1)	< 0.01
Lac, median (IQR), mmol/L		5.7 (8.16)	7.13 (7.81)	9.02 (9.91)	< 0.002
After ECMO installation					
PH, median (IQR)		7.38 (0.11)	7.37 (0.11)	7.34 (0.11)	< 0.01
HCO <sub>3</sub> , median (IQR), mmol/L		22.51 (5.6)	22.19 (5.55)	22.32 (6.02)	0.93
PO <sub>2</sub> , median (IQR), mmHg		151.33 (107.77)	159.56 (112.79)	156.29 (112.76)	0.69
PCO <sub>2</sub> , median (IQR), mmHg		39.17 (7.29)	39.06 (7.5)	41.42 (7.6)	< 0.001
Lac, median (IQR), mmol/L		4.42 (6)	6.06 (5.81)	7.57 (6.84)	< 0.001
ECMO flow 4 h, median (IQR), L/min		1.2 (1.6)	1.54 (1.7)	1.22 (1.1)	< 0.001
ECMO model					
V-A (%)		1463 (89.59)	1289	174	< 0.01*
V-V (%)		154 (9.43)	148	6	
A-V (%)		3 (0.18)	3	0	
V-A-V (%)		6 (0.37)	6	0	
V-V-A (%)		7 (0.43)	6	1	
Clinical indications					< 0.001
Circulation (%)		1127 (69.01)	1003	124	
Respiratory (%)		455 (27.86)	404	51	
ECPR (%)		249 (15.25)	197	52	
CO <sub>2</sub> removal (%)		8 (0.48)	6	2	
ECMO assist time, median (IQR), Hours		115.37 (114.92)	154.89 (115.45)	149.74 (110.37)	0.8
Bleeding complication (%)	No	1132	1053 (72.52)	79 (30.38)	< 0.0001
	Yes	501 (30.68)	399 (27.48)	102 (69.62)	
Pulmonary complication (%)	No	1561	1395 (96.07)	166 (91.71)	< 0.05
	Yes	72 (4.41)	57 (3.93)	15 (8.29)	
Extremity complications (%)	No	1543	1372 (94.49)	171 (94.48)	1
	Yes	90 (5.51)	80 (5.51)	10 (5.52)	
Machine Complications (%)	No	1449	1301 (89.60)	148 (81.77)	< 0.01
	Yes	184 (11.27)	151 (10.40)	33 (18.23)	
Outcome					< 0.001
Death during assistance (%)		296 (18.08)	254 (17.49)	42 (23.20)	
Death after weaning (%)		402 (24.57)	340 (23.42)	62 (34.25)	
Survive discharge (%)		935 (57.35)	858 (59.09)	77 (42.54)	

\* This P value was calculated based on V-A and V-V only; SD: Standard deviation; IQR: Interquartile range; ECMO: extracorporeal membrane oxygenation; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; PH: potential of hydrogen; HCO<sub>3</sub>: Hydrogen carbonate; PO<sub>2</sub>: Partial pressure of oxygen; PCO<sub>2</sub>: Partial pressure of carbon dioxide; Lac: Lactic acid; ECMO models: V-A: Veno-arterial; V-V: Veno-venous; A-V: Arterio-venous; V-A-V: veno-arterial-venous; V-V-A: Veno-venous-arterial; ECPR: Extracorporeal cardio-pulmonary resuscitation

**Table 2** Comparison of characteristic of external data and internal data

Characteristic	Internal data n = 1633	External data n = 154	P value
Age, mean (SD), month	68.87(72.54)	32.02(49.25)	3.71E-15
Female (%)	596(36.50)	54(35.06)	0.79
Height, median (IQR), cm	102.06(86)	78.87(49.5)	3.33E-11
Weight, median (IQR), kg	25.41(32.5)	12.44(11.6)	5.27E-12
<i>Before ECMO installation</i>			
SBP, median (IQR), mmHg	61.80(35)	68.74(35.81)	0.0076
DBP, median (IQR), mmHg	38.79(19.67)	43.57(21.50)	0.0072
HR, median (IQR), beat/min	120.14(68)	135.49(48.50)	0.0135
PH, median (IQR)	7.25(0.22)	7.29(0.20)	0.29
HCO <sub>3</sub> , median (IQR), mmol/L	20.75(8.64)	22.32(9.85)	0.02
PO <sub>2</sub> , median (IQR), mmHg	101.98(76)	79.55(45.75)	1.92E-06
PCO <sub>2</sub> , median (IQR), mmHg	47.69(17.86)	51.52(27.57)	0.153
Lac, median (IQR), mmol/L	7.34(8.16)	7.33(7.53)	0.66
<i>After ECMO installation</i>			
pH, median (IQR)	7.36(0.11)	7.43(0.13)	1.91E-11
HCO <sub>3</sub> , median (IQR), mmol/L	22.20(5.6)	24.18(5.65)	3.05E-04
PO <sub>2</sub> , median (IQR), mmHg	159.2(107.77)	130.40(121.88)	6.05E-08
PCO <sub>2</sub> , median (IQR), mmHg	39.32(7.29)	37.89(15.4)	0.015
Lac, median (IQR), mmol/L	6.23(6)	5.92(6.39)	0.275
ECMO flow 4 h, median (IQR), L/min	1.5(1.6)	0.89(0.88)	6.77E-12
<i>ECMO model</i>			
V-A (%)	1463(89.59)	145(94.16)	
V-V (%)	154(9.43)	9(5.84)	
A-V (%)	3(0.18)	0	
V-A-V (%)	6(0.38)	0	
V-V-A (%)	7(0.42)	0	
Brain injury	181(11.08)	29(18.83)	6.47E-03

SD: Standard deviation; IQR: Interquartile range; ECMO: extracorporeal membrane oxygenation; SBP: systolic blood pressure; DBP: diastolic blood pressure; HR: heart rate; PH: potential of hydrogen; HCO<sub>3</sub>: Hydrogen carbonate; PO<sub>2</sub>: Partial pressure of oxygen; PCO<sub>2</sub>: Partial pressure of carbon dioxide; Lac: Lactic acid; ECMO models: V-A: Veno-arterial; V-V: Veno-venous; A-V: Arterio-venous; V-A-V: veno-arterial-venous; V-V-A: Veno-venous-arterial; ECPR: Extracorporeal cardio-pulmonary resuscitation

Regarding the ECMO modes, the V-A mode accounted for 89.59%, whereas the V-V mode accounted for 9.43%. The remaining three modes collectively account for less than 1% of the total. Consequently, we focused our analysis on the brain function outcomes in the V-A and V-V modes. Statistical analysis revealed a significant difference in the incidence of neurological complications between the two modes ( $p < 0.01$ ). Regarding the indications for ECMO support, 69.01% and 27.86% of patients used ECMO for circulatory and respiratory reasons, respectively. More importantly, the results showed a statistically significant association between the occurrence of brain injury and patient outcomes during assistance. Specifically, the mortality rates (including death during assistance and death after weaning) were higher among patients who developed brain injury. Additionally, there is

no significant difference between the training data and testing data in the main included characteristics (shown in Table S2).

Notably, the characteristics of Data 2 differ significantly from those of Data 1. In Table 2, the age, height, and weight of Data 2 are significantly lower than those of Data 1, with p-values of 3.71E-15, 3.33E-11, and 5.27E-12, respectively. Additionally, circulation metrics (SBP, DBP, and HR), blood gas parameters (HCO<sub>3</sub> and PO<sub>2</sub>), and ECMO flow at 4 h also show significant differences between the two datasets. Finally, the incidence of brain injury in the two groups was significantly different: 11.08% in Data 1 and 18.83% in Data 2 ( $p = 6.47E-03$ ).

#### Feature selection

Our models included the following features: height, age, worst HR before installation, lowest DBP (before installation), worst HCO<sub>3</sub> 6 h before installation, worst Lac



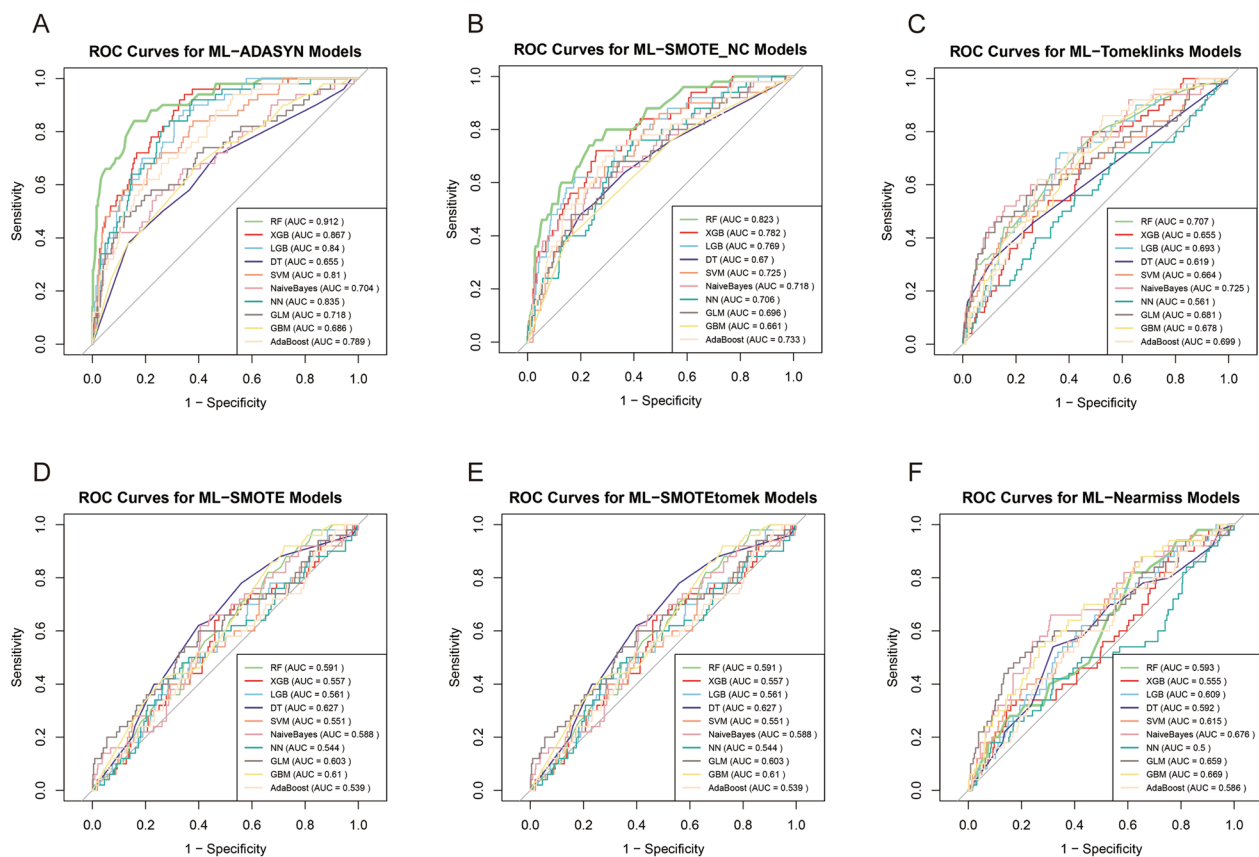
6 h before installation, worst PCO<sub>2</sub> 6 h before installation, “clinical Indication 4” (ECPR), septicemia, cardiac arrest before ECMO, “ECMO catheter method 2” (Percutaneous), “ECMO catheter method 3” (surgical incision), “machine complications Types 32” (Thrombus), “Bleeding complications” (have or not), “bleeding complications32” (bleeding complications other than gastrointestinal bleeding, bleeding at intubation, surgery-related bleeding, hemolytic Fhb > 50 mg/dl, and DIC).

### Model performance

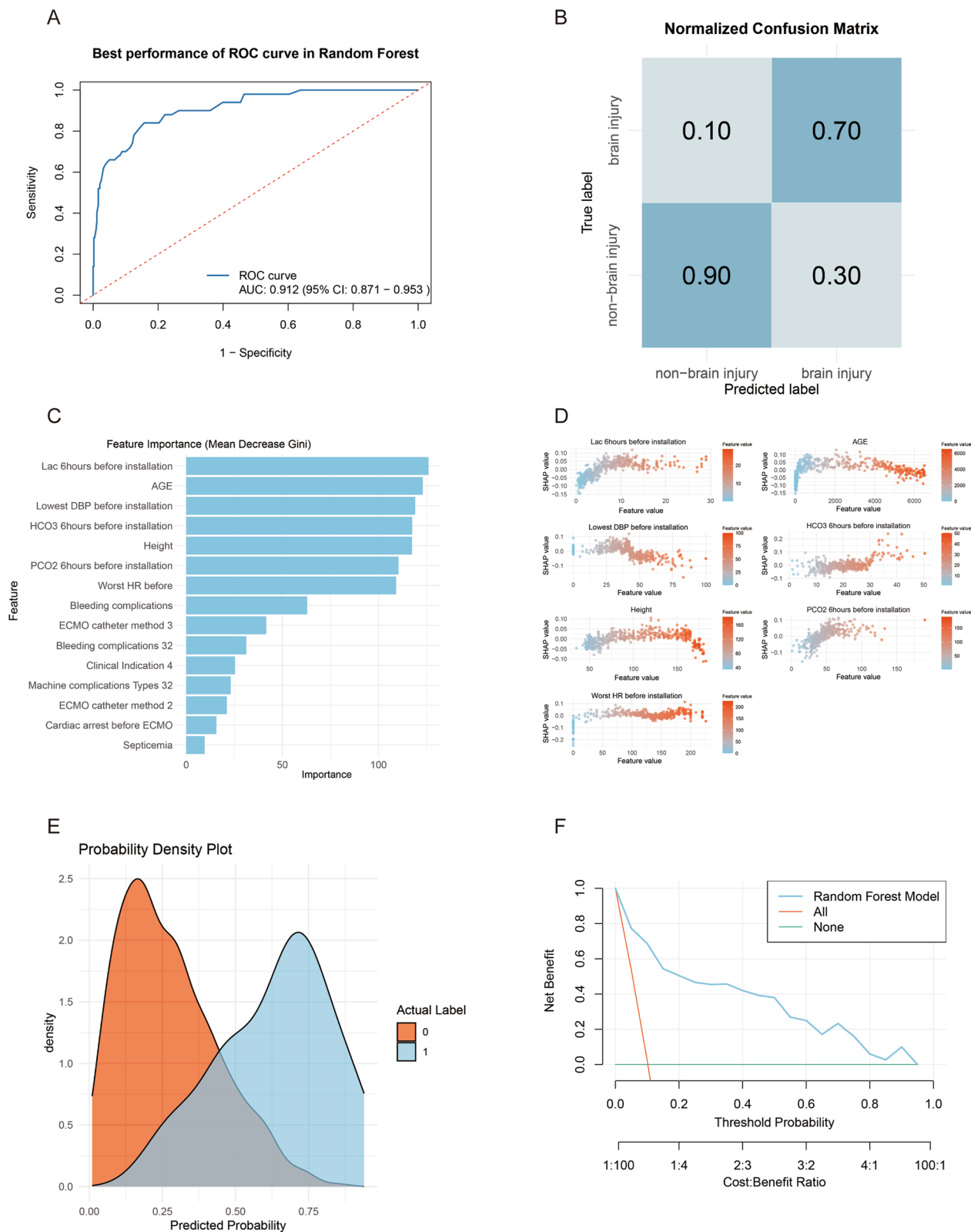
In Fig. 2, the results show that the ROC curves and AUC values of the ML methods were combined with methods to tackle class imbalance. As clearly shown in this figure, regardless of the ML methods that were used, data processed by ADASYN had the best performance regarding AUC, while SMOTE and SMOTETomek methods had a relatively low AUC. Additional details are provided in Table S3. Moreover, regardless of the method used to counter the effects of class imbalance

problems, we observed that Random Forest showed the best performance in terms of AUC.

The best prediction performance was achieved using the random forest method combined with the ADASYN method. The AUC was 0.912 (95% CI, 0.871–0.953), as shown in Fig. 3A). The performances of all ML models (trained by data balanced by ADASYN) are presented in Table 3. Specificity and sensitivity, the common metrics used for evaluating the utility of binary classification models in medical applications, were selected, and the confusion matrix showed a specificity of 0.90 and sensitivity of 0.70 (Fig. 3B). The model obtained an accuracy of 0.879, with a false positive rate, false negative rate, and F1 values of 0.037, 0.557, and 0.931, respectively. The positive predictive value (PPV) and negative predictive value (NPV) values were 0.963 and 0.443, respectively. The Brier score was 0.108. Moreover, the positive likelihood ratio and negative likelihood ratio were 14.551 and 0.555, respectively.



**Fig. 2** ROC curves of machine learning methods with different methods tackling data imbalance; **A.** ADASYN; **B.** SMOTE\_NC; **C.** Tomeklinks; **D.** SMOTE; **E.** SMOTETomek; **F.** Nearmiss



**Fig. 3** Model diagnostics for the random forest machine algorithm combined with ADASYN resampling technique. **A.** The receiver operating curve of internal validation; **B.** Pooled normalized confusion matrix; **C.** Feature importance based on random Forest algorithm. **D.** SHAP dependence plot for the seven continuous features of the model. The x-axis represents the actual values and the y-axis represents the SHAP values. **E.** Probability density plot of internal validation. **F.** Decision curve analysis of internal validation



**Table 3** Performance of internal validation models (using data balanced by ADASYN method)

Model	AUC	AUPRC	Accuracy	TPR	TNR	FPR	FNR	PPV	NPV	F1	AIC	Brier Score	PLR	NLR
RF	0.912	0.670	0.879	0.900	0.700	0.037	0.557	0.963	0.443	0.931	190.753	0.108	14.551	0.555
XGB	0.867	0.423	0.791	0.800	0.720	0.038	0.710	0.962	0.290	0.873	244.613	0.137	5.622	0.756
LGB	0.840	0.433	0.804	0.825	0.620	0.050	0.713	0.950	0.287	0.883	257.834	0.135	7.675	0.722
DT	0.655	0.184	0.712	0.736	0.500	0.072	0.823	0.928	0.177	0.821	312.022	0.202	2.350	0.901
SVM	0.810	0.372	0.777	0.795	0.620	0.052	0.744	0.948	0.256	0.865	266.943	0.160	5.177	0.783
NaiveBayes	0.704	0.257	0.816	0.861	0.420	0.071	0.744	0.929	0.256	0.894	297.572	0.147	4.408	0.747
NN	0.835	0.334	0.779	0.790	0.680	0.044	0.730	0.956	0.270	0.865	258.970	0.165	6.444	0.763
GLM	0.718	0.288	0.697	0.708	0.600	0.060	0.810	0.940	0.190	0.808	294.173	0.200	3.113	0.863
GBM	0.686	0.203	0.808	0.856	0.380	0.076	0.768	0.924	0.232	0.889	308.991	0.243	2.547	0.910
AdaBoost	0.789	0.360	0.785	0.806	0.600	0.053	0.739	0.947	0.261	0.871	279.334	0.151	4.342	0.799

AUC Area under the curve; AUPRC: the area under the precision-recall curve; TPR: True positive rate; TNR: True negative rate; FPR: False positive rate; FNR: False negative rate; PPV: Positive predictive value; NPV: Negative predictive value; AIC: Akaike Information Criterion; PLR: Positive likelihood ratio; NLR: Negative likelihood ratio

Of the included fifteen features influencing the predictions, seven were continuous features. According to the SHAP framework, which is presented in Fig. 3D, both the SHAP value and feature value are presented to illustrate the contribution of features. Specifically, Fig. 3C shows the feature importance calculated from the random forest model using the Gini impurity reduction as a metric. The results show that ‘HCO3 6 h before installation’, ‘Lac 6 h before installation’, and ‘PCO2 6 h before installation’ are the most important features and play a crucial role in the classification task of the model. They contribute the most to reducing data impurities and improving classification accuracy.

The probability density plot (Fig. 3E) shows that the predicted probabilities for the majority of true negative samples are concentrated between 0 and 0.3, whereas the predicted probabilities for true positive samples predominantly fall within 0.6–1. Although there is a clear separation between the predicted probabilities of the most positive and negative cases, a degree of overlap exists within the probability range of 0.3–0.6. The decision curve analysis (Fig. 3F) indicated that in contrast to the ‘Treat All’ and ‘Treat None’ strategies, over the wide threshold range of up to 0.9, the net benefit predicted by the model (blue curve) is significantly higher than that of the Treat All (red curve) and Treat None (green curve) strategies. While, with the rise of threshold probability, the net benefit is decreasing, and the cost: benefit ratio increased rapidly. Moreover, after the application of the Platt Scaling calibration method (Figure S1 A and B), the predicted probabilities of the model were closer to the actual frequency of occurrence.

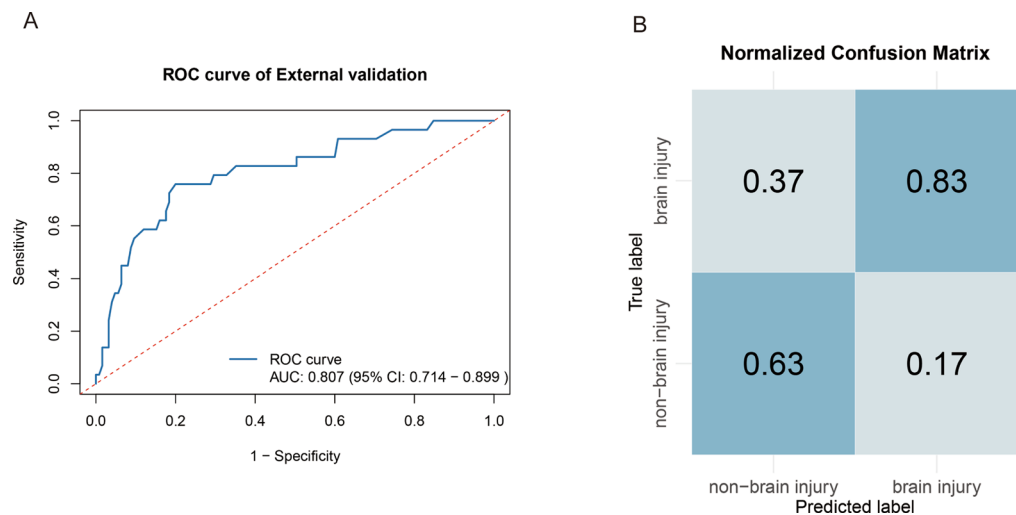
### External validation performance

External validation was performed using Data 2. The ROC curve for this model, shown in Fig. 4A, achieved an AUC of 0.807 (95% confidence interval: 0.714–0.899) on the external validation dataset. Furthermore, the normalized confusion matrix for the classification model, illustrated in Fig. 4B, indicates a sensitivity of 0.83 and a specificity of 0.63 on the external validation dataset.

### Discussion

In this study, we developed a fairly accurate ML technique to estimate the individual risk of brain injury in children supported by ECMO. To our knowledge, this is the first model to predict the occurrence of brain injury in pediatric patients under ECMO support, achieving an AUC of 0.912 in internal validation and 0.807 in external validation. The model incorporates 15 variables, with 12 could be collected before ECMO installation and three representing ECMO-related complications. This suggests that early patient information and the emergence of complications can help predict the onset of ECMO-related brain injury. So that timely interventions, such as optimizing anticoagulation and enhanced neurological monitoring, could be given to high-risk patients to improve treatment strategies and long-term prognosis.

ML techniques have been extensively used to develop predictive models for various clinical scenarios, including brain injury. For instance, in a retrospective case–control study, ML and multivariable logistic regression models were developed to predict moderate-to-severe traumatic brain injury in pediatric patients [39]. A light gradient boosting machine model was developed to help identify patients with sepsis-associated acute brain injury [40]; and deep transfer learning reliably identified normal-appearing HIBI on HCT performed within 3 h of



**Fig. 4** Performance of RF model on validation data. **A.** The receiver operating curve of external validation; **B.** Pooled normalized confusion matrix

return of spontaneous circulation in comatose survivors of cardiac arrest [41]. Furthermore, a neural network was applied to predict radiographic brain injury in pediatric patients treated with ECMO, thereby achieving an AUC of 0.76, 73% sensitivity, and 80% specificity [42].

Moreover, a brain injury risk prediction model for adult patients on ECMO support was published earlier this year [43]. In that study, a machine learning approach was employed to predict neurological complications in ECMO patients, revealing that longer ECMO duration, older age, and higher 24-h ECMO pump flow were associated with acute brain injury. However, despite utilizing four different machine learning methods to develop the prediction model, the reported performance was suboptimal, with an AUC of only 0.67. Furthermore, the standard feature selection process was inadequate, leading to a large number of features in the prediction model, which could limit its usability.

In addition to brain injury, several studies have focused on predicting outcomes in patients receiving ECMO. To begin with, one single-institution study [44], published in 2020 used features such as lactate, age, total bilirubin, and creatinine to predict survival to discharge. Another study [45], based on data from the international Extracorporeal Life Support Organization (ELSO) registry, aimed to predict in-hospital mortality. Additionally, in Abbasi's study [46], applied machine learning to predict ECMO complications, including hemorrhage and thrombosis; however, the results of this study were not fully reported.

Unlike previous studies, involving 1,633 pediatric patients from 112 centers, our research is a multicenter study in the model development process and involved external validation. During model construction, five imputation methods were tested for handling missing

values, with MissForest demonstrating the best performance regarding AUC and the area under the precision-recall curve (AUPRC) (Table S4). Subsequently, ten ML methods were evaluated using data balanced by six different techniques. The random forest model balanced with ADASYN exhibited the best performance.

In patients with and without brain injury, the clinical characteristics showed significant differences. Among the 15 included features, arterial blood gas and hemodynamic status indicators including 'HCO<sub>3</sub> 6 h before installation', 'Lac 6 h before installation', 'PCO<sub>2</sub> 6 h before installation', 'cardiac arrest before ECMO', 'clinical indication 4 (ECPR)', 'worst HR before (installation)' and 'lowest DBP before installation' (also presented in Fig. 2C) were notably important for the occurrence of brain injury in pediatric s supported by ECMO. While causality could not be determined from this analysis, these findings suggest that focusing on hemodynamic parameters may be a promising avenue for future research. Previous studies have reported that these features are related to acute brain injury in ECMO patients [2, 47–49]. Demographic information such as age and height indicated that patients with brain injuries were generally smaller, aligning with previous research showing a higher incidence in neonates. Additionally, bleeding complications, machine-related thrombus, septicemia, and ECMO catheter methods (percutaneous and surgical incision) align with previous research, suggesting that coagulation disturbances are associated with brain injury [50, 51]. Thus, it may suggest that adjusting anticoagulation strategies may not only reduce the occurrence of bleeding complications but also reduce the occurrence of brain injury [52].

The model demonstrates superior performance through several evaluation metrics, particularly when

handling positive and negative sample-imbalanced data. Its AUPRC was significantly higher than that of the other models, indicating that it performed outstandingly in identifying positive samples. Additionally, the model's precision was high, demonstrating its excellent performance in reducing false positives and false negatives. The Akaike information criterion (AIC) and Brier scores further supported the stability and generalizability of the model. Moreover, the highest PLR and lowest NLR of RF model among these models also indicated that the application of our model was superior to identify the occurrence of brain injury. While the NPV of the model was low, indicating that room for improvement exists in predicting negative-class samples, the model shows strong applicability and reliability in prediction tasks.

Several neuromonitoring techniques are available for patients receiving ECMO. Head Ultrasound and near-infrared spectroscopy are non-invasive, portable, and cost-effective methods; however, they have limitations regarding sensitivity and reproducibility. Conversely, head CT and MRI offer high sensitivity for detecting structural changes, with MRI avoiding radiation. However, they are expensive and require sedation. Electroencephalography provides crucial cerebral activity data but requires skilled interpretation and can be affected by artifacts and sedation [53].

Our study also had several limitations. First, the external validation results significantly differed from the internal results, likely because of the significant differences between Data 1 and Data 2, including population composition and clinical characteristics, as shown in Table 2. Furthermore, as our study was retrospective, despite the promising results from both internal and external validations, additional cohort and prospective studies are required to strengthen the evidence and confirm the clinical utility of the model. Moreover, algorithmic bias is unavoidable in the process of model development. Subgroup analyses based on populations (such as neonates and pediatric patients), indications, and ECMO types were not conducted because of the limited number of cases in each subgroup; hence, the clinical application of the model may be limited in some aspects.

## Conclusions

We developed a clinical model using ML to predict the occurrence of brain injury in children supported by ECMO. This model achieved a considerable AUC (0.912). Notably, 12 of the 15 included features can be collected in the early stages of ECMO, making the model both efficient and easily applicable. Thus, collecting these included features and applying the model would help clinicians to identify children at risk of brain injury early and provide valuable insights for

the treatment of ECMO-related brain injury. Further research is required to validate and calibrate this model.

## Abbreviations

ECMO	Extracorporeal membrane oxygenation
AUC	Area under the curve
AUPRC	Area under the precision-recall curve
ML	Machine learning
ROC	Receiver operating characteristic curve

## Supplementary Information

The online version contains supplementary material available at <https://doi.org/10.1186/s13054-024-05248-9>.

Additional file 1.

Additional file 2.

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Not applicable.

## Author contributions

Drs Bixin, Deng, Zhe, Zhao and conceptualized and designed the study, performed the analyses drafted the initial manuscript; Drs Tiechao Ruan, Ruixi Zhou, Chang'e Liu, Qiuping Li, Wenzhe Cheng, Jie Wang, Feng Wang, Haixiu Xie, Chenglong Li, Zhongtao Du, Wenting Lu coordinated data collection, collected data, and reviewed the manuscript; Drs Xiaohong Li, Junjie Ying, Tao Xiong, Xiaotong Hou, Xiaoyang Hong, and Dezhi Mu, revised the manuscript for important intellectual content; and all authors approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

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## Data availability

The datasets used and/or analyzed during the study are available from the corresponding author on reasonable request.

## Declarations

## Competing interests

The authors have no conflicts of interest relevant to this article to disclose.

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