Development And Assessment Of Machine Learning Models For Predicting Recurrence Risk After Endovascular Treatment In Patients With Intracranial Aneurysms

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Research Article

Keywords: Intracranial aneurysms, Endovascular treatment, Recurrence, Machine learning

Posted Date: June 9th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-551812/v1

Version of Record: A version of this preprint was published at Neurosurgical Review on October 18th, 2021. See the published version at https://doi.org/10.1007/s10143-021-01665-4.

Abstract

Intracranial aneurysms (IAs) remains a major public health concern and endovascular treatment (EVT) has become a major tool for managing IAs. However, the recurrence rate of IAs after EVT is relatively high, which may lead to the risk for aneurysm re-rupture and re-bleed. Thus, we aimed to develop and assess prediction models based on machine learning (ML) algorithms to predict recurrence risk among patients with IAs after EVT in 6 months. Patient population included patients with IAs after EVT between January 2016 and August 2019 in Hunan Provincial People's Hospital, and the data was randomly divided into a training set and a testing set. We developed five ML models and assessed the models. In addition, we used SHapley Additive exPlanations (SHAP) and local interpretable model-agnostic explanation (LIME) algorithms to determine the importance of the selected features and interpret the ML models. A total of 425 IAs were enrolled into this study, and 66 (15.5%) of which recurred in 6 months. Among the five ML models, gradient boosting decision tree (GBDT) model performed best. The area under curve (AUC) of the GBDT model on the testing set was 0.842 (sensitivity: 81.2%; specificity: 70.4%). Our study firstly demonstrated that ML-based models can serve as a reliable tool for predicting recurrence risk in patients with IAs after EVT in 6 months and the GBDT model showed the optimal prediction performance.

Introduction

Intracranial aneurysms (IAs) remains a major public health concern with prevalence of 0.4% – 3% of the general population[27]. Endovascular treatment (EVT) has become a major tool for managing IAs[2, 3]. However, it is estimated that the recurrence rate for IAs is in a range from 6.1–33.6% after EVT[11, 24]. Recurrent aneurysm exposes the patient to risk for aneurysm re-rupture and re-bleed. Therefore, the prediction of recurrence risk is highly meaningful for preventing recurrence and better treatment strategies.

In recent years, Aneurysm Recanalization Stratification Scale (ARSS) [17] have been proposed to predict the recurrence risk after EVT. However, ARSS was not widely used in clinical practice. ARSS is a composite risk score model that has demonstrated moderate discrimination with a C-statistic of 0.799. In addition, nonlinearity and complexity of characteristic variables have not been fully considered in the traditional scoring model that based on the regression analysis. Therefore, new models may be needed to achieve higher accuracy and to deal with nonlinear relationships.

Machine learning (ML) technique, as an application of artificial intelligence, has yielded promising results in the medical field. Compared with traditional methods, ML models learn from instances rather than being programmed with rule[23]. Therefore, ML models avoid the effect of users' intervention and achieve superior accurate results. Several studies have demonstrated that ML methods provide better accuracy and discrimination for the prediction of stroke-associated pneumonia in patients with acute ischemic stroke[12], diagnosis of Parkinson's disease[26] and readmission after hospitalization for chronic obstructive pulmonary disease[9]. Besides, ML-based model enables the computer to process complex non-linear relationships between variables and outcomes to make data-driven predictions[5]. ML includes

multiple algorithms, such as logistic regression (LR), random forest classifier (RFC), support vector machine (SVM), gradient boosting decision tree (GBDT) and fully-connected deep neural network (DNN). However, previous studies using ML to predict recurrence risk after EVT was not found.

Therefore, our study aimed to develop prediction models based on ML algorithms to predict the recurrence risk among patients with IAs after EVT in 6 months, and to evaluate the performance of each ML algorithm.

Methods

Patient population

We collected the patients with IAs who received EVT between January 2016 and August 2019 in Hunan Provincial People's Hospital. The inclusion criteria for participation in this study were patients with intracranial saccular aneurysms who were treated by endovascular coil embolization. The exclusion criteria were patients with dissection, fusiform and blood blister-like aneurysms, patients with cerebral arteriovenous malformations or fistulas, age < 18 years, those who were lost to follow-up after treatment and were unable to provide follow-up data of cerebral angiography. We excluded patients with more than one missing value and missing values in clinical features cannot exceed 8%. According to the follow-up results of DSA after 6 months, the patients were divided into recurrence group and non-recurrence group. Aneurysm recurrence was defined as coil compaction, recanalization, aneurysm regrowth or neck enlargement[8], the angiographic results were evaluated by two neurointerventionalists who were not involved in this study. Multiple aneurysms are counted separately for each aneurysm. The present study was approved by our institution’s ethics committee and patient consent was obtained.

All demographic and clinical factors were recorded at the time of admission. Demographic variables included age, sex. Lifestyle variables included smoking and drinking. Aneurysmal characteristics such as aneurysm neck type, longest diameter of the aneurysm, aneurysm shape and so on. Medical history such as hypertension, diabetes mellitus, coronary heart disease and so on. Clinical score included Hunt-Hess grade on admission, Raymond grade immediately after surgery. Wide-necked aneurysms were defined as neck width > 4 mm. Aneurysm location was described as anterior circulation or posterior circulation arteries. Further follow-up data in the study was collected during hospitalization or by telephone interviews.

Statistical Analysis

According to whether the variable was normally distributed, the continuous variable data that conformed to the normal distribution were expressed as mean ± standard deviation, and the t test was used for comparison. The continuous variable data that didn’t conform to the normal distribution was described by the median value and interquartile range, using Mann-Whitney U test for comparison. Categorical variables were expressed as the number of events (percentage of the total), using Pearson's chi-square test or Fisher's exact test. All tests were two sided and p-values less than 0.05 were considered

statistically significant. All statistical analyses were performed using SPSS version 25.0(IBM Corporation, Armonk, NY, USA).

Feature Selection

We initially performed univariate analyses in all variables to select the best clinical factors associated with recurrence in IAs. For the redundant factors may lead to model overfitting and the irrelevant factors may affect the predictive ability of model. Furthermore, all variables with $P < 0.05$ in the univariate analysis were entered into the least absolute selection and shrinkage operator (LASSO) regression using the freely available software python (version 3.7; https://www. python.org/). Finally, variables determined by LASSO regression and variables thought to be independent in the literature were included for constructing ML models.

Model Development and Evaluation

Because we didn't know which ML algorithm would show the best predictive ability ML model, we used 5 ML algorithms: logistic regression (LR), support vector machine (SVM), random forest classifier (RFC), gradient boosting decision tree(GBDT), and deep neural network (DNN).

Before developing the ML prediction model based on the clinical features, we first supplemented the missing values according to the k-nearest neighbor algorithm, and the categorical data were transformed via one-hot encoding. In order to deal with sample imbalance and improve the quality of various algorithms, an adaptive synthesis (ADASYN) sampling method was used to for imbalanced dataset. Dataset were stratified (7:3) into the training datasets for developing models, and the testing was set for evaluating the models' performance through random allocation. In the training step, ten-fold cross-validation was used to tune models. The training set was randomly divided into 90% set for the model derivation and 10% set for inner validation. The process generated ten different derivation and validation subsets to improve the generalization ability. Finally, grid search algorithm was utilized to adjust model hyper-parameters. During the searching process, the area under curve (AUC) of receiver operating characteristic (ROC) was set as scoring, and 10-fold cross-validation was used. After the models were derived, we compared performances of different models on testing sets with scores of AUC of ROC, sensitivity, specificity, precision and accuracy. Delong test was adopted to compare the ROC curves in different models.

Model Interpretation

ML models are often criticized for uninterpretable characteristics,which means the training and validation of ML models are equivalent to packaging in black boxes. In order to improve the interpretability and visualization of the models, we introduced local interpretable model-agnostic explanation(LIME) and SHapley Additive exPlanations (SHAP) approach. LIME algorithm provides local explanation technique by perturbing the selected instance and learning a sparse linear model around it[18]. We used the LIME algorithm to explain specific instances in the best performing model.

The SHAP approach has a high potential for rationalizing the predictions made by complex ML models[25]. Feature importance is represented as SHapley values from game theory, which means the mean marginal contributions of features in the case of all feature sequences. The SHAP approach was used to determine feature importance in the best performing model.

Results

Study Population

Among 436 patients registered to the cohort at the first visit, 64 patients could not be included for a variety of reasons (Fig. 1), a total of 372 patients with 425 IAs were finally included in the study, and 66 (15.5%) IAs recurred. The median age of these patients included was 59 (interquartile range: 49–62) years and 30.6% of them were men. The endpoints of the present study were whether IAs recurred in 6 months. The baseline statistics of both recurrence and non-recurrence groups are described in Table 1.

Table 1
Admission data of patients with intracranial aneurysms (IAs)

Characteristics	IAs with recurrence (n = 66)	IAs without recurrence (n = 359)	P-value
Male sex, n (%)	16(24.2)	114(31.8)	0.223
Age, years, median, mean ± SD	54.38 ± 7.61	55.18 ± 10.17	0.265
Medical history, n (%)			
Hypertension	42(63.6)	165(46.0)	0.008*
Diabetes mellitus	7(10.6)	15(4.2)	0.062
Hyperlipidemia	2(3.0)	4(1.1)	0.235
Coronary artery disease	6(9.1)	18(5.0)	0.304
Atrial fibrillation	1(1.5)	4(1.1)	0.572
Ischemic stroke	3(4.5)	11(3.1)	0.807
Cerebral hemorrhage	3(4.5)	9(2.5)	0.607
Multiple ruptures of aneurysm, n (%)	0(0.0)	5(1.4)	1.000
Smoking, n (%)	9(13.6)	40(11.1)	0.560
Drinking, n (%)	0(0.0)	16(4.5)	0.163
Ruptured aneurysm, n (%)	38(57.6)	266(74.1)	0.003*
Longest diameter of the aneurysm (mm), mean ± SD	7.71 ± 4.83	5.61 ± 2.71	≤ 0.0001*
Wide-necked aneurysms, n (%)	46(69.7)	187(52.1)	0.008*
Hunt-Hess grade, n (%)			0.014*
□	28(42.4)	88(24.5)	
□	1(1.5)	15(4.2)	
□	30(45.5)	221(61.6)	
□	7(10.6)	25(7.0)	
□	0(0.0)	10(2.8)	
Embolization methods, n (%)			0.396
Stent-assisted embolization	40(60.6)	237(66.0)	
Non-stent assisted embolization	26(39.4)	122(34.0)	

Characteristics	IAs with recurrence (n = 66)	IAs without recurrence (n = 359)	P-value
Location of the aneurysm, n (%)			0.372
Anterior circulation	62(94.0)	325(90.5)	
Posterior circulation	4(6.1)	34(9.5)	
Multiple aneurysms, n (%)	28(42.4)	127(35.4)	0.274
Aneurysm shape, n (%)			0.026*
Quasi circle	27(40.9)	148(41.2)	
Irregular	24(36.4)	174(48.5)	
Long strip	6(9.1)	15(4.2)	
Lobular	2(3.0)	10(2.8)	
Oval	7(10.6)	12(3.3)	
Raymond grade, n (%)			≤ 0.0001*
□	50(75.8)	357(99.4)	
□	16(24.2)	2(0.6)	
Data are expressed as count (%) or mean ± standard deviation (SD). *, P < 0.05.			

Feature Selection

7 variables were significantly different between the two groups with univariate analyses **(Table 1)**, then these variables were enrolled for the LASSO regression. Though embolization methods were not significantly different between the two groups with univariate analyses, whether endovascular coil embolization with stent or not is considered to be related to recurrence in previous study[28]. Thus, we also introduced the variable for the LASSO regression. The results of LASSO regression excluded the variable of Hunt-Hess grade. Finally, wide-necked aneurysms, ruptured aneurysm, longest diameter of the aneurysm, Raymond grade, embolization methods, hypertension and aneurysm shape were incorporated into ML models.

Model Performance

The selected hyper-parameters used for model development are provided in **Supplemental Table 1**. The AUC, sensitivity, specificity and accuracy of each model on the testing set were provided in **Table 2** and **Fig. 2a**. **Fig. 2b** showed ROCs of ML models in the training set of models.

Table 2
Model performance on testing cohort

Model	AUC (95% CL)	Sensitivity	Specificity	Accuracy
LR	0.757 (0.692–0.821)	61.4 %	66.7 %	64.1 %
RFC	0.809 (0.752–0.867)	69.3 %	75.9 %	72.7 %
SVM	0.796 (0.735–0.856)	69.3 %	75.0 %	72.2 %
GBDT	0.842 (0.790–0.895)	81.2 %	70.4 %	75.6 %
DNN	0.781 (0.720–0.844)	60.4 %	71.3 %	66.0 %

AUC, area under curve of receiver operating characteristic; CL, confidence interval; LR, logistic regression; RFC, random forest classifier; SVM, support vector machine; GBDT, gradient boosting decision tree; DNN, deep neural network.

The predictive performance was observed in LR (AUC, 0.757; 95% CL, 0.692-0.821), RFC (AUC, 0.809; 95% CL, 0.752-0.867), GBDT (AUC, 0.842; 95% CL, 0.790-0.895), SVM (AUC, 0.796; 95% CL, 0.735-0.856) and DNN (AUC, 0.781; 95% CL, 0.720-0.844) in the testing dataset (**Fig. 2a)**. Although the AUC of GBDT model reached 0.842, significant difference in AUCs was not found between the GBDT model and the RFC model **(Supplementary Table 2)**. In general, the prediction model we built aimed to identify as many patients with recurrence as possible, so the sensitivity of the model is particularly important. Due to the highest sensitivity and AUC, we choose the GBDT model as the final prediction model.

Model Interpretation

We presented a patient with recurrence that had been correctly predicted by GBDT model. LIME algorithm indicated that the patient from the “true positive” group had a high probability (68%) of recurrence in 6 months. The prediction is correctly mainly based on the variables included ruptured aneurysms, longest diameter of the aneurysm and wide-necked aneurysms, while Raymond grade had a wrong effect on the prediction of the results **(Fig. 3a)**. And we selected a patient from the “true negative” group randomly, LIME model indicated that the prediction is correctly mainly based on the variables included Raymond grade, longest diameter of the aneurysm and wide-necked aneurysms **(Fig. 3b)**.

To determine the importance of each feature, we implemented the SHAP algorithm on the best performing model(GBDT). As can be seen from **Fig. 4a**, the top four risk features were longest diameter of the aneurysm, ruptured aneurysm, embolization methods and wide-necked aneurysms. **Fig. 4b** showed the specific distribution of SHAP values for each variable in the GBDT model. The redder the color of the dot, the higher the value of the variable for the case. And positive SHAP values are associated with recurrence. Therefore, The higher the values of the longest diameter of the aneurysm, the more likely the chance of recurrence. patients with wide-necked aneurysms, unruptured aneurysms have a higher recurrence rate. compared to simple conventional coil, stent-assisted coil (SAC) embolization can result in lower recurrence rate.

Discussions

In the present study, it is the first work predicting the recurrence risk of IAs with ML models. We developed five ML models using 7 variables to predict recurrence of patients with IAs after EVT in 6 months and GBDT model showed the best prediction performance. In addition, two interpretation algorithms were introduced to explain the GBDT model. The significance of our study in clinical practice is that we provide an effective tool for deciding on individual intervention strategies in patients with IAs.

ML models make our study more close-linked to the clinical setting, and have a broader application prospects. ML models have advantages in handling variables with non-linear relationship, interaction, and missing values. Besides, ML models generate an individualized probability of outcome for a patient, which is different from traditional scoring system. As the technology matures, ML algorithms can be integrated into decision-making systems which can process large amounts of data automatically. The decision-making system is helpful to make clinical judgments and to provide patients with individual treatment. Furthermore, electronic patient record (EPR) system makes it convenient to the application of ML models.

As a popular ensemble method, GBDT algorithm has been successfully applied in medical fields[6] because of favorable discrimination performance and ability to capture complex relationships[29]. Among the five ML models in our study, GBDT model displayed best discriminatory ability (AUC, 0.842; 95% CL, 0.790–0.895), which suggested that it is a powerful model for predicting recurrence of patients with IAs in 6 months. GBDT model has a sensitivity of 81.5%, which means only 18.5% of aneurysms with recurrence are not identified correctly. From clinical perspective, unnecessary intervention for non-recurrent aneurysm is acceptable, but it will cause serious consequences if recurrent aneurysms cannot be correctly predicted. Thus, it is more valuable to identify IAs with recurrence than IAs without recurrence. That is to say, sensitivity is more important than specificity in our ML models. Our GBDT model with best AUC and sensitivity among five models contributes to predict the recurrence risk of IAs.

An ADASYN sampling method was used to tackle the issue of class imbalance in our study. Among 425 cases of IAs treated with EVT, 66 cases recurred postoperatively, with a total recurrence rate of 15.5%, which was consistent with the results of previous studies[11, 24]. Thus, there was a significant sample imbalance between recurrence group and non-recurrence group. Obviously, misclassification of IAs with recurrence (minority class) will lead to more serious costs than IAs without recurrence (majority class), that’s why the identification of IAs with recurrence (minority class cases) is of greater need in medical diagnosis. Assuming that all the cases are classified into the majority class, the overall accuracy of the model is still high, but it is a false reliable model actually. Due to the above assumption, we adopted ADASYN sampling approach to generate more synthetic data for IAs with recurrence (minority class cases), which has been introduced in previous studies[13]. This kind of sampling technique can reduce the bias due to class imbalance by changing the data distribution. Therefore, our GBDT model which considering class imbalance has a reliable performance to identify IAs with high risk of recurrence.

Another significant advantage of our GBDT model is its visualization and interpretability. ML models for clinical applications have a fatal drawback that the relationship between clinical factors and reactions is

invisible to doctors. However, it is impossible for doctors to trust a ML diagnosis without a reasonable explanation. LIME algorithm explains the prediction of ML models in an interpretable manner, and LIME algorithm was applied to investigate feature contributions for individual instances. In previous ML models for clinical predictions, researchers usually used feature importance to explain the contribution of each feature to the prediction capability of the model. compared with conventional feature importance, SHAP determines whether the influence of a feature is positive or negative. Therefore, we Introduced LIME and SHAP algorithms to explain the recurrence prediction of ML models. The above two algorithms can greatly increase the clinicians' trust in the model and experts can provide knowledge-based validation for the interpretation of ML model.

In our study, several predictors of recurrence in patients with IAs have been established. On the one hand, Longest diameter of the aneurysm, Raymond grade and wide-necked aneurysms have been confirmed as risk factors, which is consistent with previous studies[17, 19, 24, 28]. Our study also confirms that stent-assisted coil (SAC) embolization is associated with lower recurrence compared with simple conventional coil, and this finding was also reported by previous studies[22, 28]. On the other hand, Our results indicated that ruptured aneurysms related to lower recurrence rate in SHAP analysis, which is consistent with that of Peluso (2008) who found ruptured aneurysms associated with lower re-treatment rates[20]. This finding may be due to the larger size of unruptured aneurysms in our study. In addition, our found that history of hypertension was an independent predictor of recurrence. Previous studies have reported that hypertension remains a risk factor in the steady prognosis of IAs after EVT[14, 21]. Biological evidence shows that that abnormal hemodynamic status are related to vascular remodeling and the generation of aneurysms, particularly, self-hypertension often contributes to the development and enlargement of aneurysms[16]. However, a previous study indicated that hypertension was not a predictor of recurrence[15]. Although further research on hypertension and recurrence has to be implemented, our study strongly suggests that blood pressure should be effectively monitored in the postoperative stage. In addition, smoking is also a known risk factor for aneurysm development and aneurysmal subarachnoid hemorrhage[10]. But the relationship between smoking and aneurysm recurrence was still controversial [1, 7]. Our study found that smoking was not significantly associated with aneurysm recurrence.

Our study also has some limitations. First, patients with IAs were selected from a single hospital and no external validation was performed, the generalizability performance of the ML models merits investigation in patients treated at other institutions and by other neurologists. Second, several patients potentially eligible for our study could not be contacted and the cases were excluded. Thus, it is unclear whether we have overestimated or underestimated the risk of recurrence. Finally, data of possible hemodynamic predictors of recurrence such as flow momentum[4] were not available in our study. Future prospective studies will have to assess whether incorporating novel predictors may improve the performance of predictive model.

Conclusion

This study firstly demonstrated that ML-based models for prediction of recurrence risk in patients with IAs can serve as a reliable tool and the GBDT model achieved the optimal prediction performance. In future, with external verification, the GBDT model will potentially assist clinicians to promptly target the high risk of recurrence among patients with IAs after EVT in 6 months.

Declarations

Authors' contributions STL, YZ and JH contributed equally to this work. STL: drafting the manuscript, statistical analyses, interpreting the results; YZ: drafting the manuscript; JH, LX, LHG, XPL and DZZ: data collection; XPG, HL, XMD and ZHZ: scientific supervision; JJZ: manuscript revisions.

Funding This study was funded by National Natural Science Foundation of China grant 81673511, Jiangsu key Research and Development Plan grant BE2017613, Jiangsu Six Talent Peaks Project grant WSN-151 and Hunan innovation guidance grant of clinical medical technology 2020SK50920.

Data availability None.

Code availability SPSS version 25.0, python version 3.7.

Conflict of interest The authors declare that they have no conflict of interests.

Ethics approval Data collection and scientific use were approved by the institutional ethics committee of Hunan Provincial People's Hospital ([2015]-10).

Consent to participate Data collection and scientific use were approved by the patients according to regulations by the ethics committee.

Consent for publication All authors agreed to the publication of the manuscript.

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Figures

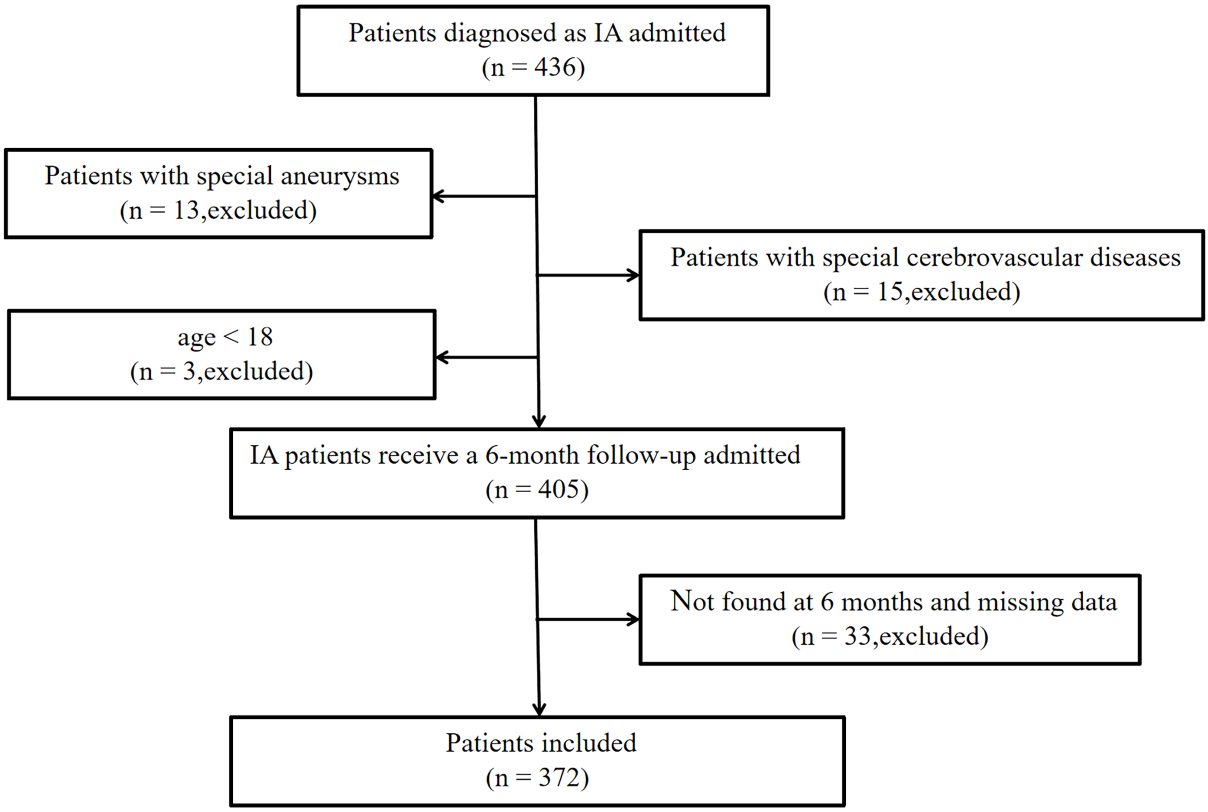
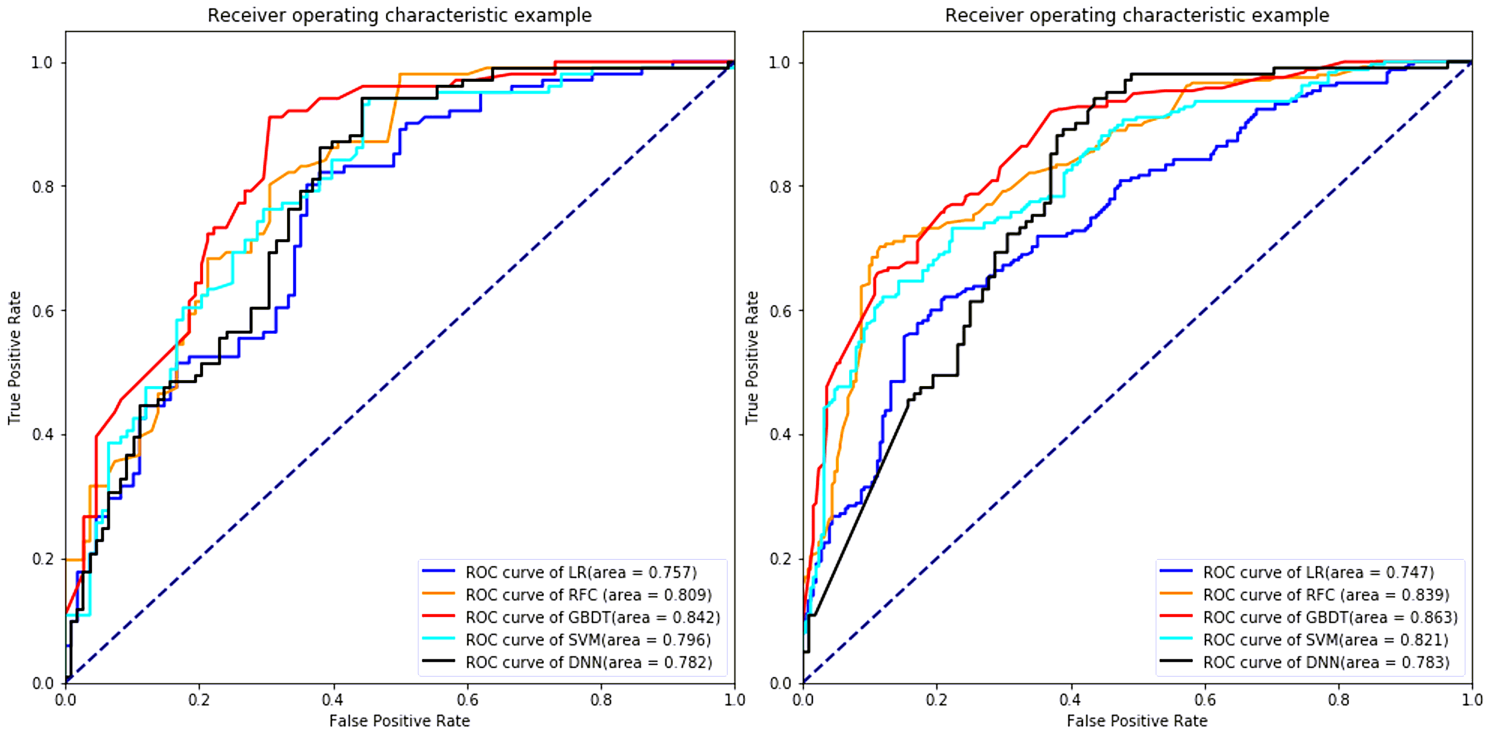


Figure 1

Flowchart of patient inclusion and exclusion process.



a b

Figure 2

The receiver operating characteristic curve (ROC) of five models on testing set (a) and ROC of five models in the training set (b).

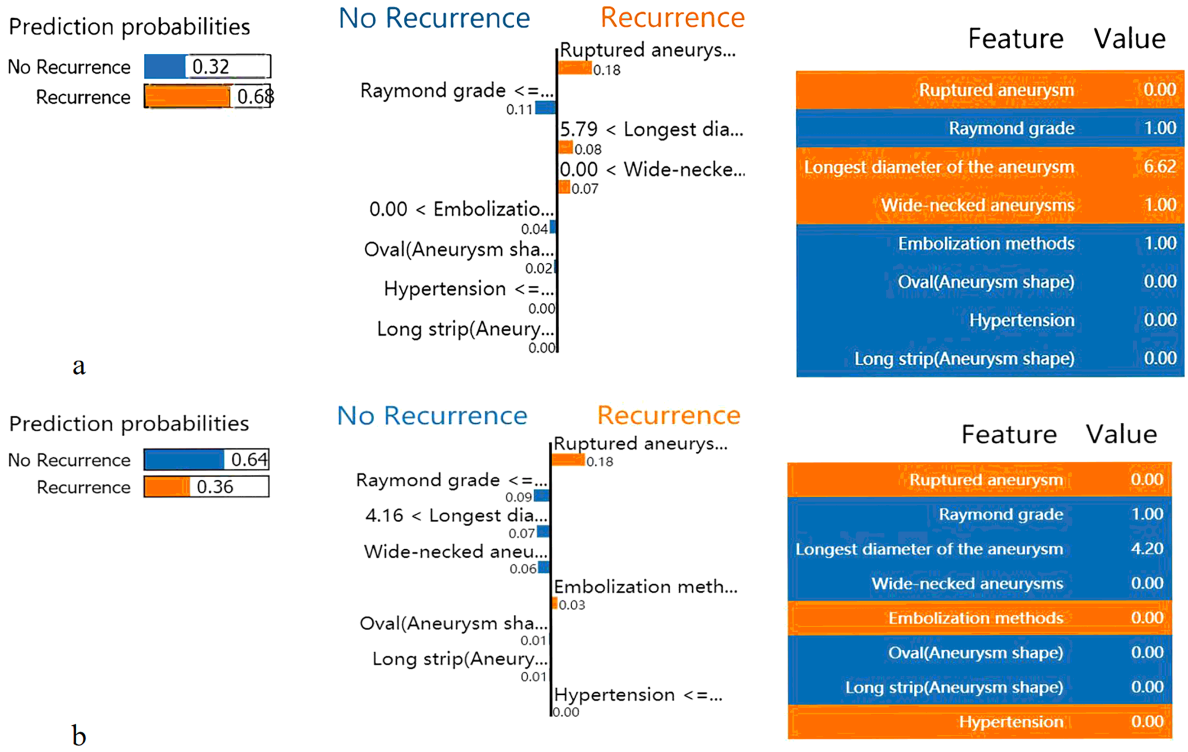


Figure 3

LIME plot for individual case explanation on 2 random patients from the testing set of the GBDT model. LIME plot included he patient from the “true positive” group explained by LIME algorithm (a) and a patient from the “true negative” group explained by LIME algorithm (b).

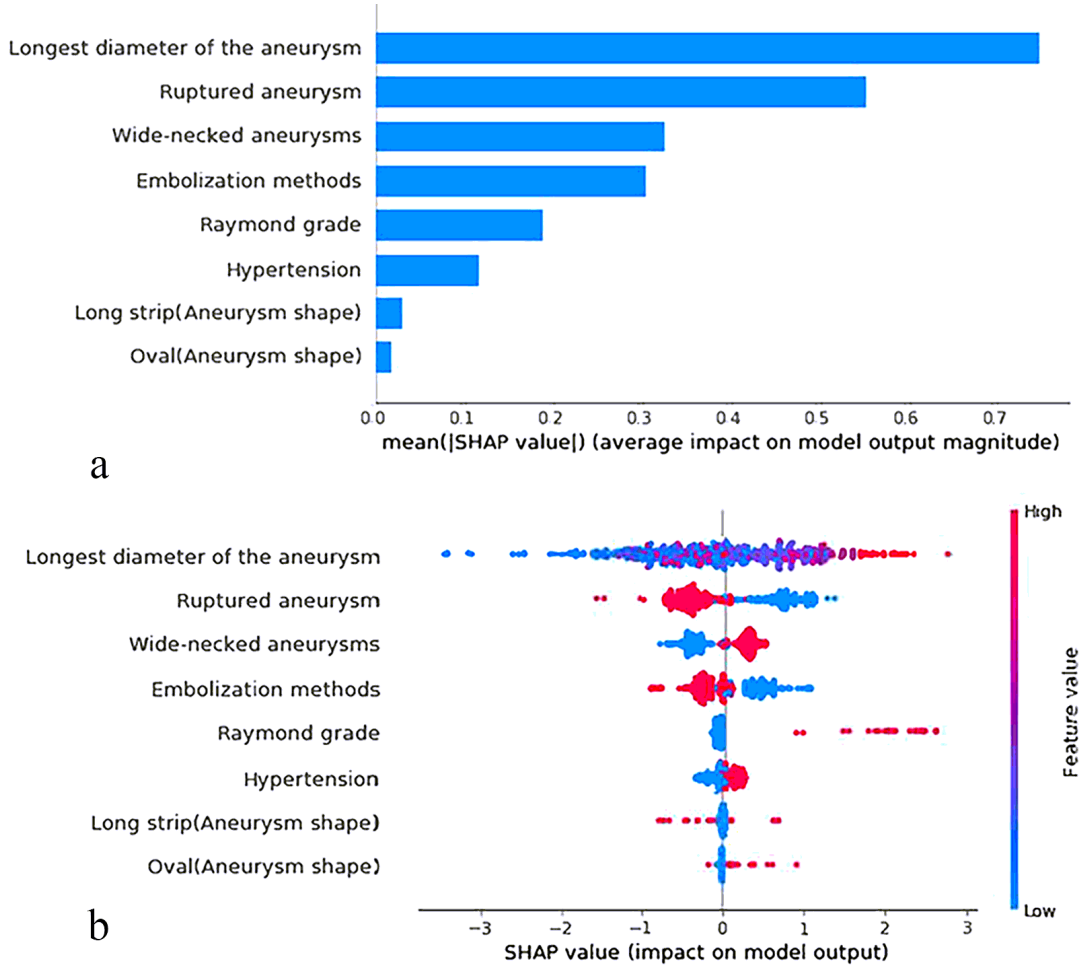


Figure 4

SHAP summary plot of the GBDT model. The plot showed the importance of each variable (a) and the specific distribution between variables and SHAP values (b) using SHAP algorithm.

Supplementary Files

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