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Develop an ADR prediction system of Chinese herbal injections containing Panax notoginseng saponin: a nested case–control study using machine learning

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ABSTRACT

Objective This study aimed to develop an adverse drug reactions (ADR) antecedent prediction system using machine learning algorithms to provide the reference for security usage of Chinese herbal injections containing Panax notoginseng saponin in clinical practice.

Design A nested case–control study.

Setting National Center for ADR Monitoring and the Electronic Medical Record (EMR) system.

Participants All patients were from five medical institutions in Sichuan Province from January 2010 to December 2018.

Main outcomes/measures Data of patients with ADR who used Chinese herbal injections containing Panax notoginseng saponin were collected from the National Center for ADR Monitoring. A nested case–control study was used to randomly match patients without ADR from the EMR system by the ratio of 1:4. Eighteen machine learning algorithms were applied for the development of ADR prediction models. Area under curve (AUC), accuracy, precision, recall rate and F1 value were used to evaluate the predictive performance of the model. An ADR prediction system was established by the best model selected from the 1080 models.

Results A total of 530 patients from five medical institutions were included, and 1080 ADR prediction models were developed. Among these models, the AUC of the best capable one was 0.9141 and the accuracy was 0.8947. According to the best model, a prediction system, which can provide early identification of patients at risk for the ADR of Panax notoginseng saponin, has been established.

Conclusion The prediction system developed based on the machine learning model in this study had good predictive performance and potential clinical application.

STRENGTHS AND LIMITATIONS OF THIS STUDY

- ⇒ To the best of our knowledge, this study was the first to develop an adverse drug reaction (ADR) prediction system for Chinese herbal injection containing Panax notoginseng saponin using machine learning.
- ⇒ Data of patients with ADR came from the National Center for Adverse Drug Reaction Monitoring, which is highly representative.
- ⇒ In order to obtain the best model, the data processing adopted 4 data filling, 5 data sampling, 3 variable selection methods and 18 machine learning algorithms were applied for model establishment.
- ⇒ The area under curve, accuracy, precision, recall rate and F1 value were used to evaluate the predictive performance of the model.
- ⇒ As the study population was all from southwest China, the results may be biased while the prediction system was applied in other medical institutions.

INTRODUCTION

Panax notoginseng saponins, as the main ingredients of Panax notoginseng (Buck.) F.H.Chen, has been widely used in the disease therapy of nervous system and cardiocerebral vascular system.[1–4] High frequency of adverse drug reactions (ADR) in Chinese herbal containing Panax notoginseng saponin has received widespread attention. Among these ADR, about 69.57% were caused by injections, mainly manifested as drug eruption (50.5%), allergic reaction (20.4%) and anaphylactic shock (9.7%), which can be life-threatening in severe cases.[5]

At present, ADR is mainly monitored by spontaneous reporting system, case–control study, cohort study, prescription event monitoring and centralised hospital monitoring system. However, most of these methods have obvious hysteresis. Therefore, there is an increasing need to develop an ADR antecedent prediction system to prevent the occurrence of ADR in Chinese herbal injections containing Panax notoginseng saponin.

Machine learning, the core technology of artificial intelligence, is commonly used to build prediction models. In recent years, some prediction models for ADR have been established.[6–10] Based on a clustering method for the postprocessing of association rules, Wei and Scott[6] developed an application of stepwise association rule mining to identify the associations between vaccine and multiple adverse events. In addition, Imai *et al*[10] used artificial neural networks to evaluate vancomycin-induced nephrotoxicity. However, small sample size, incomplete patient information and unsatisfactory predictive performance restrict the application of ADR prediction models in clinical practice. In view of these challenges, this study aimed to develop an ADR prediction system of Chinese herbal injections containing Panax notoginseng saponin based on machine learning algorithms and provide reference for clinical ADR management and prevention.

METHODS

Data collection

Patients with ADR who used Chinese herbal injections containing Panax notoginseng included in this study were from the National Center for Adverse Drug Reaction Monitoring reported by five hospitals in Sichuan Province from January 2010 to December 2018. Then, a nested case–control study was used to randomly match patients without ADR from the Electronic Medical Record system of the five medical institutions. The ratio of patients with ADR to those without ADR was 1:4. For multiple lab results, in order to facilitate clinical application, we selected the last results of patients before the usage of medication. And for multiple admissions, all patients were included according to their first admission.

Data cleaning

Variable assignment

Binary-state variables were directly assigned values of 0 or 1. According to whether in the normal range, clinical laboratory variables were assigned values of 1, 2 and 3 (1, below the normal range; 2, within the normal range and 3, above the normal range).

Column deletion

Variables with missing data >90%, or a single category >90%, or the coefficient of variation <0.1 were deleted.

Data filling

There are four ways to data filling. No filling: retained the original data. Simple filling: missing data of continuous variables replaced by the mean or median and categorical variables by the mode. Random Forest (RF) filling: used the RF model to predict and replace the missing data directly. RF improve filling: ordered variables based on the number of missing data that were replaced by RF filling next.

Data sampling

No sampling: built models from the original data. Random over sampler: randomly replicated the data of fewer categories to match the sample size to that of more categories. Random under sampler: deleted the data of more categories to match the sample size to that of fewer categories. Synthetic minority oversampling technique (SMOTE) over sampler: synthesise new data from a small amount of original data. Borderline SMOTE over sampler: synthesise new data from borderline data.

Variable selection

No variable selection or use Lasso or Boruta for variable selection.

Model establishment

Through different data filling, data sampling and variable selection, 60 data sets were obtained. Eighteen machine learning algorithms, including AdaBoost, Bagging, Bernoulli Naïve Bayes, Decision Tree, Extra Tree, Gaussian Naïve Bayes, Gradient Boosting, K-Nearest Neighbour, Latent Dirichlet Allocation, Logistic Regression, Multinomial Naïve Bayes, Passive Aggressive, Quadratic Discriminant Analysis, RF, Stochastic Gradient Descent, Support Vector Machine, eXtreme Gradient Boosting and Ensemble Learning, were used to build models.

The model establishment was as follows. The data were randomly divided into a training set and a test set by the ratio of 8:2. The training set was used to build models, and the test set was used to evaluate the predictive performance of the models. Ten-fold cross-validation on the training set was applied for internal validation of the model, and 200 Bootstrapping samples from the test set for the evaluation of the impact of different data processing methods or machine learning algorithms on model predictive performance. Ensemble learning models were developed by five machine learning algorithms with the largest area under curve (AUC) on each data set.

Model evaluation

We used the AUC, accuracy, precision, recall rate and F1 value to evaluate the predictive performance of the model. Five models with the largest AUC were compared, and the best model was selected to develop an ADR prediction system of Chinese herbal injections containing Panax notoginseng saponin. SHapley Additive exPlanations (SHAP) helped to explain the contribution of variables to the model.

Sample size assessment

To evaluate the influence of different sample sizes on model predictive performance, randomly extracted 10%, 20%, 30% to 100% subsets from the training set by Bootstrapping. The 10 subsets were used to establish models, respectively. Repeated the procedure 100 times and the AUC, calculated from the testing set, was used for sample size examination.

Patient and public involvement

Patients and/or the public were not directly involved in this study.

Table 1 The effect of different data processing methods on model prediction performance (bootstrapping)

	AUC		Accuracy		Precision		Recall rate		F1 value	
	Mean±SD	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**
Data filling										
No filling	**0.786±0.101**	0.785 to 0.787	**0.770±0.070**	0.769 to 0.771	0.437±0.162	0.435 to 0.438	**0.546±0.208**	0.544 to 0.548	**0.460±0.142**	0.459 to 0.461
Simple filling	0.687±0.094	0.686 to 0.688	0.761±0.076	0.760 to 0.761	**0.455±0.180**	0.453 to 0.456	0.491±0.165	0.489 to 0.492	0.442±0.126	0.441 to 0.443
RF filling	0.677±0.095	0.676 to 0.678	0.759±0.077	0.758 to 0.760	0.446±0.181	0.444 to 0.447	0.488±0.162	0.487 to 0.490	0.440±0.129	0.439 to 0.441
RF improve filling	0.678±0.092	0.677 to 0.678	0.756±0.077	0.755 to 0.757	0.443±0.179	0.442 to 0.445	0.485±0.161	0.483 to 0.486	0.435±0.125	0.434 to 0.436
p value	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**	
Data sampling										
No sampling	**0.738±0.101**	0.737 to 0.739	**0.823±0.050**	0.822 to 0.823	**0.585±0.229**	0.583 to 0.588	0.390±0.178	0.388 to 0.391	0.441±0.172	0.439 to 0.442
Random over sampler	0.718±0.109	0.717 to 0.719	0.765±0.070	0.764 to 0.765	0.437±0.154	0.435 to 0.438	0.531±0.189	0.529 to 0.533	**0.457±0.135**	0.456 to 0.458
Random under sampler	0.696±0.106	0.695 to 0.697	0.710±0.069	0.709 to 0.711	0.364±0.107	0.363 to 0.365	**0.596±0.161**	0.594 to 0.597	0.441±0.109	0.440 to 0.442
SMOTE over sampler	0.683±0.100	0.682 to 0.684	0.755±0.067	0.754 to 0.755	0.416±0.137	0.414 to 0.417	0.490±0.143	0.488 to 0.491	0.435±0.113	0.434 to 0.436
Borderline SMOTE	0.699±0.104	0.698 to 0.700	0.755±0.072	0.755 to 0.756	0.424±0.143	0.422 to 0.425	0.506±0.143	0.505 to 0.508	0.446±0.115	0.445 to 0.447
p value	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**	
Variable selection										
No selection	0.702±0.109	0.702 to 0.703	0.758±0.078	0.758 to 0.759	0.440±0.184	0.438 to 0.441	0.493±0.187	0.492 to 0.494	0.434±0.137	0.433 to 0.435
Lasso selection	**0.713±0.105**	0.712 to 0.713	0.761±0.074	0.760 to 0.761	0.447±0.173	0.445 to 0.448	**0.513±0.177**	0.512 to 0.514	0.448±0.128	0.447 to 0.449
Boruta selection	0.706±0.103	0.705 to 0.707	**0.766±0.073**	0.765 to 0.766	**0.449±0.170**	0.448 to 0.450	0.501±0.166	0.500 to 0.503	**0.450±0.127**	0.449 to 0.451
p value	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**	

AUC, area under curve; RF, random forest; SMOTE, synthetic minority oversampling technique.

Table 2 The effect of different machine learning algorithms on model prediction performance (bootstrapping)

	AUC		Accuracy		Precision		Recall rate		F1 value	
	Mean±SD	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**	**Mean±SD**	**95% CI**
Machine learning algorithms										
AdaBoost	0.702±0.104	0.700 to 0.703	0.761±0.061	0.760 to 0.762	0.434±0.134	0.432 to 0.436	0.538±0.142	0.535 to 0.540	0.465±0.105	0.463 to 0.467
Bagging	0.749±0.083	0.748 to 0.750	0.776±0.064	0.774 to 0.777	0.457±0.137	0.454 to 0.459	0.486±0.159	0.483 to 0.489	0.452±0.112	0.450 to 0.454
Bernoulli NB	0.718±0.099	0.716 to 0.720	0.771±0.056	0.770 to 0.772	0.444±0.133	0.442 to 0.447	0.541±0.141	0.538 to 0.543	0.475±0.109	0.474 to 0.477
DT	0.667±0.085	0.665 to 0.668	0.738±0.067	0.737 to 0.739	0.388±0.127	0.386 to 0.390	0.491±0.151	0.489 to 0.494	0.417±0.105	0.416 to 0.419
Ensemble Learning	**0.793±0.083**	0.791 to 0.794	**0.810±0.058**	0.809 to 0.811	**0.545±0.157**	0.543 to 0.548	**0.576±0.162**	0.573 to 0.579	**0.537±0.108**	0.535 to 0.539
ET	0.596±0.097	0.594 to 0.598	0.703±0.081	0.701 to 0.704	0.308±0.149	0.305 to 0.310	0.393±0.186	0.390 to 0.396	0.326±0.139	0.324 to 0.329
Gaussian NB	0.667±0.106	0.665 to 0.669	0.720±0.061	0.719 to 0.721	0.364±0.106	0.362 to 0.366	0.543±0.133	0.541 to 0.545	0.429±0.103	0.427 to 0.431
Gradient boosting	0.718±0.100	0.716 to 0.720	0.783±0.060	0.782 to 0.784	0.487±0.161	0.484 to 0.490	0.524±0.144	0.521 to 0.526	0.481±0.105	0.479 to 0.483
KNN	0.655±0.101	0.654 to 0.657	0.741±0.086	0.740 to 0.743	0.394±0.262	0.389 to 0.399	0.355±0.217	0.351 to 0.359	0.316±0.166	0.313 to 0.319
LDA	0.724±0.097	0.722 to 0.725	0.770±0.065	0.769 to 0.772	0.457±0.149	0.454 to 0.459	0.561±0.141	0.558 to 0.564	0.487±0.110	0.485 to 0.489
LR	0.728±0.094	0.727 to 0.730	0.770±0.070	0.769 to 0.771	0.465±0.155	0.462 to 0.467	0.580±0.143	0.577 to 0.583	0.497±0.110	0.495 to 0.499
Multinomial NB	0.727±0.099	0.725 to 0.728	0.753±0.071	0.752 to 0.754	0.450±0.170	0.447 to 0.453	0.570±0.175	0.567 to 0.573	0.467±0.111	0.465 to 0.469
Passive aggressive	0.686±0.094	0.684 to 0.688	0.701±0.087	0.699 to 0.703	0.358±0.119	0.355 to 0.360	0.558±0.156	0.555 to 0.560	0.421±0.107	0.419 to 0.423
QDA	0.660±0.115	0.658 to 0.662	0.774±0.057	0.773 to 0.775	0.428±0.178	0.425 to 0.431	0.436±0.188	0.433 to 0.440	0.411±0.152	0.408 to 0.413
RF	0.742±0.088	0.741 to 0.744	0.792±0.075	0.791 to 0.793	0.534±0.194	0.531 to 0.538	0.430±0.155	0.427 to 0.432	0.444±0.119	0.441 to 0.446
SGD	0.720±0.099	0.718 to 0.722	0.762±0.064	0.761 to 0.764	0.452±0.196	0.448 to 0.455	0.507±0.213	0.503 to 0.511	0.434±0.141	0.432 to 0.437
SVM	0.735±0.090	0.734 to 0.737	0.792±0.073	0.790 to 0.793	0.533±0.194	0.529 to 0.536	0.443±0.165	0.440 to 0.446	0.449±0.115	0.447 to 0.451
XGBoost	0.740±0.095	0.738 to 0.741	0.790±0.074	0.789 to 0.792	0.515±0.161	0.512 to 0.518	0.513±0.165	0.510 to 0.516	0.486±0.112	0.484 to 0.488
p value	**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**		**p<0.0001**	

AUC, area under curve; DT, Decision Tree; ET, Extra Tree; KNN, K-Nearest Neighbour; LDA, Latent Dirichlet Allocation; LR, Logistic Regression; NB, Naïve Bayes; QDA, Quadratic Discriminant Analysis; SGD, Stochastic Gradient Descent; SVM, Support Vector Machine.

Table 3 Predictive performance indicators of the five best models

	AUC	Accuracy	Precision	Recall rate	F1 value
Model 1	**0.9141**	**0.8947**	**0.75**	0.6667	**0.7059**
Model 2	0.9055	0.8105	0.5	**0.7778**	0.6087
Model 3	0.9019	0.8421	0.6154	0.4444	0.5161
Model 4	0.8997	0.8632	0.6316	0.6667	0.6486
Model 5	0.8968	0.8316	0.5357	0.8333	0.6522

AUC, area under curve.

Statistical analysis

Categorical variables were expressed as counts and percentages and continuous variables as mean±SD. Analysis of variance will be used if the data were normally distributed and the variances were equal, otherwise, Kruskal-Wallis test will be used. p value <0.05 was considered statistically significant. Hypothesis testing and models building were implemented using the stats and sklearn packages in Python (V.3.8), respectively.

RESULTS

Research population

A total of 530 patients were enrolled in this study, of which 106 patients had ADR. The patients included 250 (47.17%) men and 280 (52.83%) women. The demographic and clinical characteristics of the patients are shown in online supplemental table 1.

Data cleaning

The results of 83 variables assignment are shown in online supplemental table 2. After the column deletion, 63 variables were included in the following study (online supplemental table 3). Then, four data filling methods were used for replacing the 1290 (3.86%) missing data. We used Lasso or Boruta for variable selection, and the results are shown in online supplemental table 3. Using four data filling, five data sampling and three variable selection methods for data processing, respectively, 60 data sets were obtained.

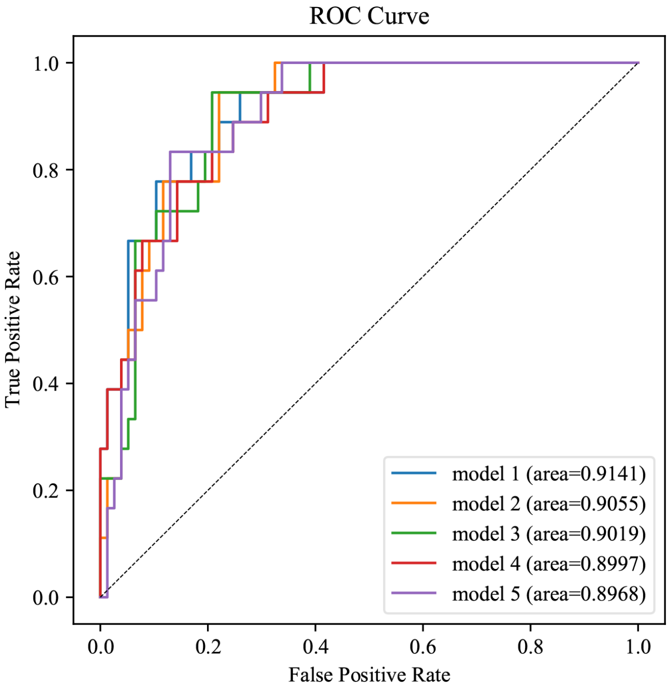


Figure 1 ROC curve of the five best models. ROC, receiver operating characteristic.

Model establishment

A total of 1080 prediction models were established by 18 machine learning algorithms and 60 data sets. The results of 10-fold cross-validation are shown in online supplemental table 4. Using 200 Bootstrapping samples from the test set to evaluate the impact of different data processing methods or machine learning algorithms on model predictive performance. The results showed that differences of model predictive performance exist by different data filling, data sampling, variable selection (table 1) and machine learning algorithms (table 2). The ensemble learning model had the best performance with an AUC of 0.793±0.083 (table 2).

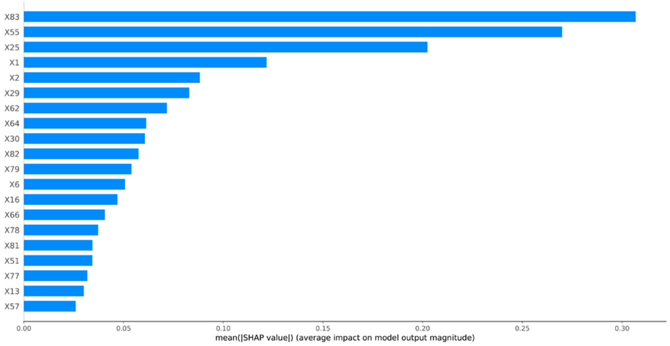


Figure 2 Importance matrix plot of each variable to the final prediction model. Variable names are shown in online supplemental table 2). X83, pre-treatment serum levels; X55, renal function; X25, dermatoses; X1, gender; X2, age; X29, dose; X62, low-density lipoprotein; X64, hypoproteinemia; X30, anti-infective agents; X82, pre-treatment indicators of carcinoma; X79, haemoglobin; X6, history of allergy; X16, respiratory diseases; X66, albumin/globulin; X78, red blood cell; X81, hypersensitive C reactive protein; X51, dermatology medication; X77, eosinophils; X13, Charlson comorbidity index (Score); X57, serum potassium.

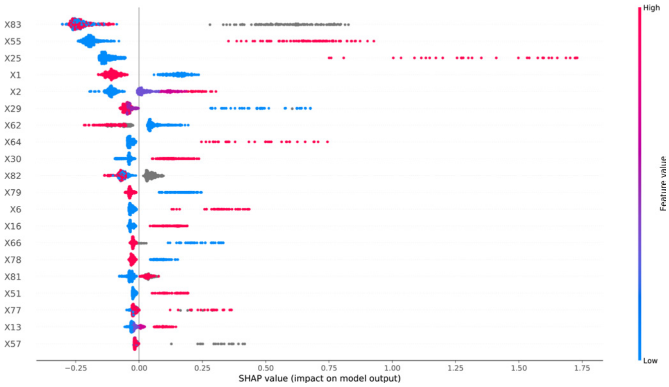


Figure 3 SHAP summary plot of the top 20 variables of the model. Red represents higher variable values, and blue represents lower variable values. Variable names are shown in online supplemental table 2). X83, pre-treatment serum levels; X55, renal function; X25, dermatoses; X1, gender; X2, age; X29, dose; X62, low-density lipoprotein; X64, hypoproteinemia; X30, anti-infective agents; X82, pre-treatment indicators of carcinoma; X79, haemoglobin; X6, history of allergy; X16, respiratory diseases; X66, albumin/globulin; X78, red blood cell; X81, hypersensitive C reactive protein; X51, dermatology medication; X77, eosinophils; X13, Charlson comorbidity index (Score); X57, serum potassium. SHAP, SHapley Additive exPlanations.

Model evaluation

The AUC, accuracy, precision, recall rate and F1 value were used to evaluate the performance of the model. The best five models were selected and model 1 had the best performance with an AUC of 0.9141 (table 3). The receiver operating characteristic curve of the five best models is shown in figure 1.

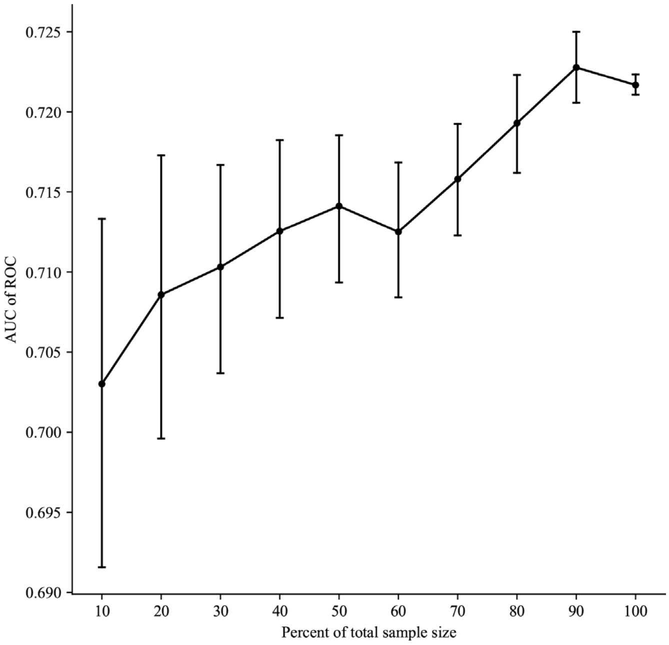


Figure 4 Sample size validation. The vertical bars represent the 95% CI of AUC of ROC. AUC, area under curve; ROC, receiver operating characteristic.

Model interpretation

The importance of each variable to the final prediction model is shown in figure 2. The result showed that pretreatment serum levels, renal function, dermatoses, gender and age were the top five most important variables for the model. We used the SHAP value to explain the contribution of the variables to the model, and the SHAP value of the top 20 is shown in figure 3. This plot explains how high and low variable values were in relation to SHAP values. For the prediction model, the higher the SHAP value of a variable, the more likely ADR occurs.

Sample size assessment

With the continuously increased size of sample data, the AUC values of the testing sets continued to increase, which shows a sufficient sample size included in this study (figure 4).

Develop an ADR prediction system for Panax notoginseng saponin

According to the best model, a prediction system for the ADR of Panax notoginseng saponin has been developed and we had obtained the software copyright. The development of the ADR prediction system is shown in figure 5. The operation and output of the system are shown in figure 6.

DISCUSSION

Traditional Chinese medicine has been used for the prevention and treatment of diseases for centuries.[11] In recent years, the application of Chinese herbal injections containing Panax notoginseng saponin has become more and more common in clinical practice, while ADR often causes concerns. Studies have shown that the Chinese herbal ingredients, traditional Chinese medicine preparation and combination medication are the important factors for the ADR of Chinese herbal injections containing Panax notoginseng saponin. Drug eruption (50.5%), allergic reactions (20.4%) and anaphylactic shock (9.7%) were the most common, and some cases were even life threatening.[5] However, the ADR monitoring methods, including spontaneous reporting systems, prescription event monitoring and centralised hospital monitoring system, were all reported after the event and may even have data bias, under-reporting or repeated reporting. Therefore, the realisation of ADR prediction has important significance for preventing ADR of Chinese herbal injections containing Panax notoginseng saponin in clinical practice.

In our study, a nested case–control study was performed for data collection. In order to obtain the best model, we used four data filling, five data sampling and three variable selection methods for data processing and combined 18 machine learning algorithms to establish 1080 ADR prediction models. By comparing the AUC, accuracy, precision, recall rate and F1 value of these models, the best one was selected to develop an ADR prediction system

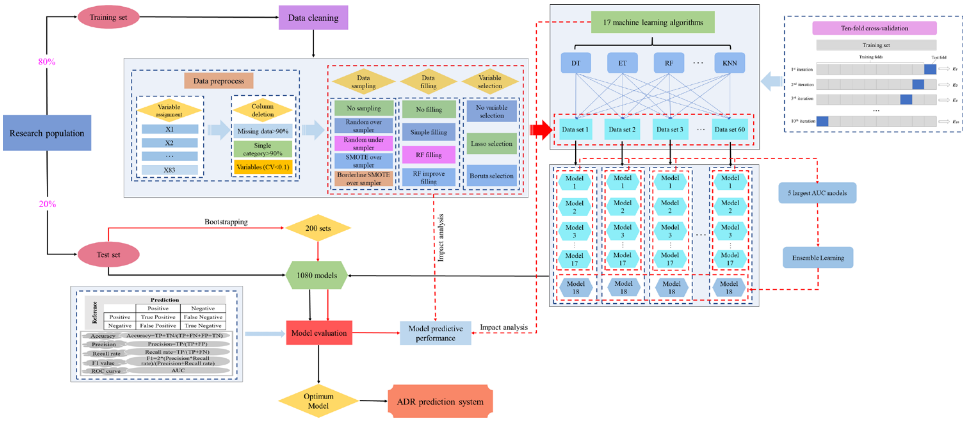
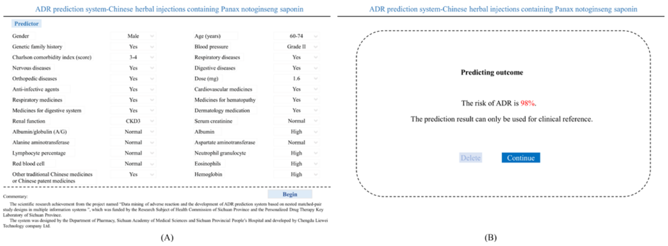


Figure 5 The development of ADR prediction system. ADR, adverse drug reaction; AUC, area under curve; DT, Decision Tree; ET, Extra Tree; FN. false negative; FP, false positive; KNN, K-Nearest Neighbour; RF, Random Forest; TP, true positive; TN, true, negative.

for the Chinese herbal injections containing Panax notoginseng saponin.

In recent years, some ADR prediction models have been developed based on data mining,[6–9] machine learning algorithms[10 12–15] and statistical methods.[16–18] Tangiisuran *et al*[16] combined univariate analysis and multivariate binary logistic regression for the identification of clinical risk factors to develop an ADR risk model. The AUC of the model at the internal and external validation stage was 0.74 and 0.73, respectively, the sensitivity was 80% and 84%, and the specificity was 55% and 43%.[16] Imai *et al*[10] used artificial neural networks to predict the ADR risk and made an AUC of 0.83. Compared with other studies, the model established in our study had better predictive performance (accuracy was 0.8947, precision was 0.75, the recall rate was 0.6667 and AUC was 0.914). As missing data are common in clinical practice, the methods of data filling used in our study may be advantageous for the deal with imbalanced data in clinical real-world research. More importantly, the system developed by the best model was potentially convenient for clinical application because of its' simple operation, fast calculation and high accuracy.

It is worth noting that Hammann *et al*[19] established a decision tree model based on the chemical, physical and structural properties of compounds for the prediction of ADR occurrence and the model had high predictive accuracy (78.9–90.2%). However, the model was difficult to interpret as it ignored the effect of pathological and physiological conditions and the combination medication on ADR. This made the model unlikely to be accepted by clinicians. In our study, we collected more than 80 factors including the patient's pathophysiological characteristics, clinical laboratory results and medication conditions. Meanwhile, the critical predictors associated with the ADR were identified by the SHAP values. Although using the SHAP values as a generalised approach to identify the important clinical determinants of ADR caused by Chinese herbal injections containing Panax notoginseng saponin is not possible, it may help generate clinical hypotheses for some specific clinical events.


ADR prediction system-Chinese herbal injections containing Panax notoginseng saponin

Predictor

Gender	Male	Age (years)	60-74
Genetic family history	Yes	Blood pressure	Grade II
Charlson comorbidity index (score)	3-4	Respiratory diseases	Yes
Nervous diseases	Yes	Digestive diseases	Yes
Orthopedic diseases	Yes	Dose (mg)	1.6
Anti-infective agents	Yes	Cardiovascular medicines	Yes
Respiratory medicines	Yes	Medicines for hematopathy	Yes
Medicines for digestive system	Yes	Dermatology medication	Yes
Renal function	CKD3	Serum creatinine	Normal
Albumin/globulin (A/G)	Normal	Albumin	High
Alanine aminotransferase	Normal	Aspartate aminotransferase	Normal
Lymphocyte percentage	Normal	Neutrophil granulocyte	High
Red blood cell	Normal	Eosinophils	High
Other traditional Chinese medicines or Chinese patent medicines	Yes	Hemoglobin	High

Begin

Commentary:

The scientific research achievement from the project named "Data mining of adverse reaction and the development of ADR prediction system based on nested matched-pair study designs in multiple information systems ", which was funded by the Research Subject of Health Commission of Sichuan Province and the Personalized Drug Therapy Key Laboratory of Sichuan Province.

The system was designed by the Department of Pharmacy, Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital and developed by Chengdu Liewei Technology company Ltd.

(A)

ADR prediction system-Chinese herbal injections containing Panax notoginseng saponin

Predicting outcome

The risk of ADR is 98%.

The prediction result can only be used for clinical reference.

Delete Continue

(B)

Figure 6 The operation (A) and output (B) of the ADR prediction system. ADR, adverse drug reaction.

The results of SHAP indicated that whether the patients have dermatoses will significantly affect the models' predictive performance. Cutaneous ADR is one of the most common adverse reactions of Panax notoginseng, such as erythema multiforme, urticaria, severe erythema multiforme and acute generalised exanthematous pustulosis.[20 21] Therefore, those patients with original dermatoses are more likely to have ADR after using Panax notoginseng. In addition, we found that age and gender are related to the occurrence of Panax notoginseng-induced ADR, which is consistent with the results reported by Yang *et al*.[22]

This study had some limitations. First, the small sample size of this study might affect the model prediction performance. Second, as the study population was all from southwest China, the results may be biased while the prediction system was applied in other medical institutions. Finally, a prospective controlled trial is required to demonstrate the accuracy of the ADR prediction system.

Contributors X-WW, E-WL and R-ST were involved in the conception and design of the study. X-WW drafted the article. J-YZ, HC, X-WS and Y-LW analysed the data. E-WL and R-ST revised the manuscript. All authors gave final approval of the version to be published. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. R-ST is the guarantor.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Patient consent for publication Not applicable.

Ethics approval This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital (2017-11-01). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Data are available upon reasonable request. Data may be obtained from a third party and are not publicly available. The first author (7190175@uestc.edu.cn) will share any publicly available data if requested by email.

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Table 1 Demographic and clinical characteristics of the patients

Parameter	Number
Gender	
Male	250(47.17)
Female	280(52.83)
Age (years)	
≤ 44	121(22.83)
45 ≤ Age ≤ 59	193(36.42)
60 ≤ Age ≤ 74	132(24.91)
≥ 75	84 (15.85)
Body mass index (BMI, kg/m^2)	
< 18.5	48(9.06)
18.5 ≤ BMI ≤ 23.9	275(51.89)
≥ 24	175(33.02)
Charlson comorbidity index (Score)	
0	104(19.62)
1 or 2	190(35.85)
3 or 4	123(23.21)
≥ 5	113(21.32)

Data presented as number (%)

Table 2 Variable assignment

Number	Variable	Assignment
	Adverse drug reaction	1, Yes; 0, No
X1	Gender	1, Male; 0, Female
X2	Age (years)	1, ≤ 44; 2, 45 ≤ Age ≤ 59; 3, 60 ≤ Age ≤ 74; 4, ≥ 75
X3	Body mass index (BMI, kg/m^2)	1, < 18.5; 2, 18.5 ≤ BMI ≤ 23.9; 3, ≥ 24
X4	Asians	1, Yes; 0, No
X5	Genetic family history	1, Yes; 0, No
X6	History of allergy	1, Yes; 0, No
X7	Smoking	1, Yes; 0, No
X8	Alcohol	1, Yes; 0, No
X9	Temperature (℃)	1, < 36.1; 2, 36.1 ≤ Temperature ≤ 37.2; 3, > 37.3
X10	Pulse (beats/min)	1, < 60; 2, 60 ≤ Pulse ≤ 100, 3, > 100
X11	Breathe (times/min)	1, < 12; 2, 12 ≤ Breathe ≤ 20; 3, > 20
X12	Blood pressure	0, Normal (systolic pressure ≤ 139 mmHg or diastolic pressure ≤ 89 mmHg); 1, Grade I (140 mmHg ≤ systolic pressure ≤ 159 mmHg or 90 mmHg ≤ diastolic pressure ≤ 99 mmHg); 2, Grade II (160 mmHg ≤ systolic pressure ≤ 179 mmHg or 100 mmHg ≤ diastolic pressure ≤ 109 mmHg); 3, Grade III (systolic pressure ≥180 mmHg or diastolic pressure ≥110 mmHg)
X13	Charlson comorbidity index (Score)	1, 0; 2, 1 or 2; 3, 3 or 4; 4, ≥ 5
X14	Cardiovascular disease	1, Yes; 0, No

X15	Endocrine diseases	1, Yes; 0, No
X16	Respiratory diseases	1, Yes; 0, No
X17	Nervous diseases	1, Yes; 0, No
X18	Digestive diseases	1, Yes; 0, No
X19	Neoplastic diseases	1, Yes; 0, No
X20	Orthopedic diseases	1, Yes; 0, No
X21	Genito-urinary diseases	1, Yes; 0, No
X22	Hematopathy	1, Yes; 0, No
X23	Oculopathy	1, Yes; 0, No
X24	Ear-nose-throat diseases	1, Yes; 0, No
X25	Dermatoses	1, Yes; 0, No
X26	Immune rheumatism	1, Yes; 0, No
X27	Other diseases	1, Yes; 0, No
X28	Solvent	1, 0.9% sodium chloride injection; 2, 5% glucose injection; 3, Other solvents
X29	Dose (mg)	1, < 1.6; 2, =1.6; 3, > 1.6
X30	Anti-infective agents	1, Yes; 0, No
X31	Cardiovascular medicines	1, Yes; 0, No
X32	Medicines for digestive system	1, Yes; 0, No
X33	Respiratory medicines	1, Yes; 0, No
X34	Nervous system medicines	1, Yes; 0, No
X35	Medication in mental disorders	1, Yes; 0, No

X36	Non-steroidal anti-inflammatory drugs	1, Yes; 0, No
X37	Antiallergic agent	1, Yes; 0, No
X38	Genito-urinary system medicines	1, Yes; 0, No
X39	Medicines for hematopathy	1, Yes; 0, No
X40	Endocrine agents or hormone drugs	1, Yes; 0, No
X41	Antineoplastic drugs	1, Yes; 0, No
X42	Amino acids, vitamins, minerals or other nutrition preparations	1, Yes; 0, No
X43	Regulating water, electrolyte or acid-base balance drugs	1, Yes; 0, No
X44	Adjuvant agents to anesthesia or anesthetics	1, Yes; 0, No
X45	Diagnostic agents	1, Yes; 0, No
X46	Biological agents	1, Yes; 0, No
X47	Obstetrical-gynecological drugs	1, Yes; 0, No
X48	Stomatological preparations	1, Yes; 0, No
X49	Ophthalmic medication	1, Yes; 0, No
X50	Ear-nose-throat medication	1, Yes; 0, No
X51	Dermatology medication	1, Yes; 0, No
X52	Other traditional Chinese medicines	1, Yes; 0, No

	or Chinese patent medicines	
X53	Urea	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X54	Serum creatinine	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X55	Renal function	1, Glomerular filtration rate ≥ 90 ml/(min·1.73m^2); 2, 60ml/(min·1.73m^2) ≤ Glomerular filtration rate ≤ 89ml/(min·1.73m^2); 3, 30ml/(min·1.73m^2) ≤ Glomerular filtration rate ≤59 ml/(min·1.73m^2); 4, 15ml/(min·1.73m^2) ≤ Glomerular filtration rate ≤29 ml/(min·1.73m^2); 5, Glomerular filtration rate < 15 ml/(min·1.73m^2)
X56	Blood glucose	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X57	Serum potassium	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X58	Serum sodium	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X59	Total cholesterol	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X60	Triglyceride	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X61	High-density lipoprotein	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X62	Low-density lipoprotein	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X63	Albumin	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X64	Hypoproteinemia	1, Yes; 0, No
X65	Globulin	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X66	Albumin/globulin (A/G)	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X67	Aspartate aminotransferase	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X68	Alanine aminotransferase	1, Below the normal range; 2, Within the normal range; 3, Above the normal range

X69	Liver function	1, Less than 3 times upper limit of normal range of liver function tests (ULN of LFTs); 2, 3~5 times ULN of LFTs; 3, More than 5 times ULN of LFTs
X70	Total bilirubin	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X71	Lactic dehydrogenase	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X72	Creatine kinase	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X73	White blood cell	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X74	Neutrophil granulocyte	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X75	Lymphocyte percentage	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X76	Monocyte percentage	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X77	Eosinophils	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X78	Red blood cell	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X79	Hemoglobin	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X80	Platelet count	1, Below the normal range; 2, Within the normal range; 3, Above the normal range
X81	Hypersensitive C-reactive protein	0, Within the normal range; 1, Above the normal range
X82	Pre-treatment indicators of carcinoma	0, Within the normal range; 1, Above the normal range
X83	Pre-treatment serum levels	0, Within the normal range; 1, Above the normal range

Table 3 Results of different variable preprocessing methods

Method	Included variables
Column deletion	X1, X2, X3, X5, X7, X8, X12, X13, X14, X15, X16, X17, X18, X19, X20, X21, X22, X28, X29, X30, X31, X32, X33, X34, X35, X36, X39, X40, X41, X42, X43, X44, X45, X46, X51, X52, X54, X55, X56, X57, X58, X59, X60, X61, X62, X63, X65, X66, X67, X68, X71, X72, X73, X74, X75, X76, X77, X78, X79, X80, X81, X82, X83
Lasso	X1, X2, X18, X29, X30, X31, X33, X51, X52, X54, X55, X65, X66, X68, X78
Boruta	X1, X2, X5, X12, X13, X16, X17, X18, X20, X29, X30, X31, X33, X39, X40, X51, X52, X54, X55, X63, X66, X67, X68, X74, X75, X77, X78, X79

Variable names were shown in Supplementary Table 2.

Table 4 The effect of different data processing methods and machine learning algorithms on model prediction performance (Ten-fold cross-validation)

		AUC		**Accuracy**		**Precision**		**Recall rate**		**F1 value**	
		Mean±SD	95%CI	Mean±SD	95%CI	Mean±SD	95%CI	Mean±SD	95%CI	Mean±SD	95%CI
Data filling											
	No filling	0.868±0.099	0.864-0.872	0.820±0.093	0.816-0.823	0.772±0.190	0.765-0.779	0.720±0.254	0.710-0.730	0.729±0.217	0.721-0.737
	Simple filling	0.881±0.097	0.877-0.885	0.828±0.100	0.824-0.832	0.793±0.165	0.787-0.799	0.746±0.243	0.737-0.756	0.751±0.197	0.744-0.759
	RF filling	0.885±0.095	0.881-0.888	0.831±0.095	0.827-0.835	**0.802±0.157**	0.796-0.808	0.749±0.237	0.740-0.759	**0.757±0.189**	0.750-0.764
	RF improve filling	**0.887±0.094**	0.883-0.890	**0.832±0.096**	0.828-0.835	0.799±0.158	0.793-0.806	**0.751±0.240**	0.742-0.760	0.757±0.191	0.749-0.764
	p value	***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**	
Data sampling											
	No sampling	0.824±0.088	0.820-0.828	0.832±0.050	0.830-0.835	0.641±0.271	0.629-0.653	0.399±0.197	0.391-0.408	0.464±0.193	0.455-0.472
	Random over sampler	**0.923±0.063**	0.920-0.925	0.858±0.085	0.854-0.861	**0.849±0.079**	0.845-0.852	0.872±0.118	0.867-0.877	0.857±0.089	0.854-0.861
	Random under sampler	0.815±0.107	0.810-0.819	0.732±0.104	0.728-0.737	0.783±0.145	0.776-0.789	0.678±0.188	0.670-0.686	0.707±0.132	0.701-0.713
	SMOTE over sampler	0.920±0.072	0.917-0.923	0.857±0.081	0.853-0.860	0.844±0.071	0.841-0.848	0.875±0.125	0.869-0.880	0.856±0.089	0.852-0.860
	Borderline SMOTE	0.919±0.077	0.916-0.923	**0.859±0.085**	0.855-0.862	0.841±0.074	0.837-0.844	**0.885±0.130**	0.879-0.890	**0.859±0.093**	0.855-0.863
	p value	***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**	
Variable selection											

	No selection	0.870±0.105	0.867-0.874	0.820±0.104	0.817-0.824	0.780±0.178	0.774-0.786	0.733±0.254	0.725-0.742	0.737±0.208	0.730-0.744
	Lasso selection	**0.889±0.089**	0.886-0.892	**0.835±0.090**	0.832-0.838	**0.801±0.165**	0.796-0.807	**0.751±0.240**	0.743-0.759	**0.758±0.196**	0.752-0.765
	Boruta selection	0.881±0.094	0.878-0.884	0.827±0.093	0.824-0.830	0.794±0.162	0.788-0.799	0.741±0.236	0.733-0.749	0.750±0.191	0.744-0.757
	p value	***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**	
machine learning algorithms											
	AdaBoost	0.871±0.092	0.864-0.879	0.813±0.093	0.806-0.820	0.784±0.136	0.773-0.795	0.731±0.202	0.715-0.747	0.745±0.160	0.733-0.758
	Bagging	0.907±0.102	0.898-0.915	0.854±0.101	0.846-0.863	0.805±0.158	0.793-0.818	0.791±0.245	0.771-0.810	0.785±0.196	0.769-0.801
	Bernoulli NB	0.866±0.082	0.860-0.873	0.802±0.085	0.795-0.809	0.771±0.144	0.759-0.783	0.719±0.178	0.705-0.733	0.736±0.148	0.724-0.748
	DT	0.815±0.110	0.806-0.824	0.805±0.089	0.797-0.812	0.773±0.158	0.760-0.786	0.715±0.237	0.696-0.734	0.724±0.184	0.709-0.739
	ET	0.829±0.110	0.821-0.838	0.809±0.092	0.801-0.816	0.767±0.164	0.754-0.780	0.714±0.255	0.694-0.735	0.720±0.207	0.704-0.737
	Gaussian NB	0.845±0.089	0.838-0.852	0.786±0.085	0.779-0.793	0.734±0.155	0.722-0.747	0.743±0.164	0.730-0.756	0.730±0.143	0.719-0.742
	Gradient Boosting	0.891±0.102	0.883-0.899	0.841±0.099	0.833-0.849	0.822±0.149	0.810-0.834	0.746±0.252	0.725-0.766	0.762±0.194	0.747-0.778
	KNN	0.896±0.084	0.890-0.903	0.830±0.098	0.822-0.838	0.747±0.296	0.724-0.771	0.687±0.381	0.656-0.717	0.674±0.326	0.648-0.700
	LDA	0.897±0.073	0.891-0.903	0.835±0.081	0.829-0.842	0.805±0.117	0.796-0.815	0.768±0.191	0.753-0.783	0.777±0.144	0.765-0.788
	LR	0.893±0.076	0.886-0.899	0.834±0.082	0.827-0.840	0.815±0.119	0.805-0.824	0.754±0.216	0.737-0.772	0.767±0.157	0.755-0.780
	Multinomial NB	0.839±0.071	0.834-0.845	0.773±0.078	0.766-0.779	0.753±0.161	0.740-0.766	0.653±0.235	0.634-0.672	0.676±0.190	0.660-0.691
	Passive Aggressive	0.836±0.098	0.828-0.844	0.780±0.091	0.772-0.787	0.723±0.161	0.711-0.736	0.720±0.205	0.703-0.736	0.712±0.172	0.698-0.725

QDA	0.915±0.081	0.909-0.922	0.860±0.089	0.853-0.868	0.827±0.152	0.814-0.839	0.798±0.184	0.783-0.812	0.805±0.156	0.792-0.817
RF	0.919±0.097	0.911-0.926	0.871±0.100	0.863-0.879	0.843±0.154	0.831-0.856	0.775±0.268	0.753-0.796	0.788±0.214	0.771-0.805
SGD	0.895±0.075	0.889-0.901	0.832±0.082	0.825-0.839	0.803±0.197	0.787-0.819	0.710±0.287	0.687-0.733	0.726±0.238	0.707-0.745
SVM	**0.926±0.086**	0.919-0.933	**0.875±0.096**	0.867-0.883	**0.858±0.144**	0.847-0.870	0.776±0.271	0.754-0.797	0.791±0.217	0.773-0.808
XGBoost	0.922±0.092	0.914-0.929	0.869±0.100	0.861-0.877	0.825±0.153	0.812-0.837	**0.810±0.229**	0.792-0.828	**0.808±0.185**	0.793-0.822
p value	***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**		***p*<0.0001**	

AUC, Area under curve; RF, Random Forest; SMOTE, Synthetic minority oversampling technique; Bernoulli NB, Bernoulli Naïve Bayes; DT, Decision Tree; ET, Extra Tree; Gaussian NB, Gaussian Naïve Bayes; KNN, K-Nearest Neighbor; LDA, Latent Dirichlet Allocation; LR, Logistic Regression; Multinomial NB, Multinomial Naïve Bayes; QDA, Quadratic Discriminant Analysis; SGD, Stochastic Gradient Descent; SVM, support vector machine. XGBoost, eXtreme Gradient Boosting