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

## 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 5 medical institutions in Sichuan Province from January 2010 to December 2018.

**Main outcomes/measures** Information of patients with ADR who using Chinese herbal injections containing Panax notoginseng saponin was 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 according to 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 were established by the optimal model selected from the 1080 models.

**Results** A total of 530 patients from 5 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 parameters of the best model, a prediction system for the ADR of Panax notoginseng saponin has been established, which can realize the output of patient ADR risk.

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

**Key words** Adverse drug reactions, Chinese herbal injection, Machine learning, Prediction system, Panax notoginseng saponin

**Strengths and limitations of this study**

- We first used machine learning to predict the ADR of Chinese herbal injection containing Panax notoginseng saponin.
- Eighteen machine learning algorithms were used to establish 1080 ADR prediction models. An ADR prediction system with Chinese herbal injections containing Panax notoginseng saponin developed by the best model had high accuracy and precision, and had potential value for clinical application.
- More than 80 factors including the patient's pathophysiological characteristics, clinical laboratory results, and medication conditions, were incorporated in our study.
- More data were needed to further evaluate the model prediction performance.

## 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 cardio-cerebral vascular system [1-4]. High frequency of adverse drug reactions (ADR) in Chinese herbal containing Panax notoginseng saponin has received widespread attention. Of all the adverse reactions, 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 centralized 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 and avoid 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, Lai et al. [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 collected patients information in the National Center for ADR Monitoring and the Electronic Medical Record (EMR) system by a nested case-control study to establish an ADR prediction model of Chinese herbal injections containing Panax notoginseng saponin, and develop an ADR prediction system based on machine learning algorithms to provide reference for clinical ADR management and prevention.

## METHODS

### Data collection

Information of patients with ADR who using Chinese herbal injections containing Panax notoginseng saponin from the National Center for ADR Monitoring was collected. A nested case-control study was used to randomly match patients without ADR who using Chinese herbal injections containing Panax notoginseng saponin from the EMR system according to 1:4. All patients were from 5 medical institutions in Sichuan Province from January 2010 to December 2018. This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital.

### 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 (CV) <0.1 were deleted.

*Data filling*

There are 4 ways to data filling. No filling means to retain the original data directly. Simple filling refers to use the mean fill for continuous variables, the mode for disordered categorical variables, and the median for ordered categorical variables. Random Forest (RF) filling orders the column according to the number of missing data, and then the missing data was predicted and filled by RF model. RF improve filling refers to predict and fill the column with the least missing data, which was used as the input for the prediction and filling of other missing data.

*Data sampling*

No sampling: directly input the original data into the model. Random over sampler: random replication of data with fewer types to make the sample sizes of different types consistent, while random under sampler is to randomly delete data with more types. Synthetic minority oversampling technique (SMOTE) over sampler: synthesize new data by analyzing a small amount of original data. Borderline SMOTE over sampler: synthesize 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 (Bernoulli NB), Decision Tree (DT), Extra Tree (ET), Gaussian Naïve Bayes (Gaussian NB), Gradient Boosting, K-Nearest Neighbor (KNN), Latent

Dirichlet Allocation (LDA), Logistic Regression (LR), Multinomial Naïve Bayes (Multinomial NB), Passive Aggressive, Quadratic Discriminant Analysis (QDA), RF, Stochastic Gradient Descent (SGD), Support Vector Machine (SVM), eXtreme Gradient Boosting (XGBoost), and Ensemble Learning, were used to build models.

The model establishment was as follows. The data was standardized and divided into a training set and a test set according to 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 used 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. Five algorithms with the largest area under curve (AUC) on each data set were used for ensemble learning.

**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 model with the best predictive performance 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.

**Statistical Analysis**

Categorical variables were expressed as counts and percentages and continuous variables as mean ± standard deviation. 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 were considered statistically significant. Hypothesis testing and Models building were implemented using the stats and sklearn packages in Python (Version3.8), respectively.

## RESULTS

**Research population**

A total of 530 patients were enrolled in this study, of which 106 patients had ADR. ADR patients included 50 (47.17%) males and 56 (52.83%) females.

**Data cleaning**

The assignment of all variables was shown in Supplementary Table 1. After data processing by 4 data filling, 5 data sampling and 3 variable selection methods, we obtained 60 data sets. The results of variable selection by the Lasso and Boruta were shown in Supplementary Figure 1.

### Model establishment

A total of 1080 prediction models were established by 18 machine learning algorithms and the 60 data sets. The results of ten-fold cross-validation were shown in Supplementary Table 2. 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).

### Model evaluation

The AUC, accuracy, precision, recall rate, and F1 value were used to evaluate the performance of the model. The best 5 prediction models were selected and model 1 had the best performance with an AUC of 0.9141 (Table 3). The receiver operating characteristic (ROC) curve of the 5 best model was shown in Figure 1.

### Model interpretation

The importance of each variable to the final prediction model was shown in Figure 2. The result showed that pre-treatment serum levels, renal function, dermatoses, gender and age were the top 5 most important variables contributing to 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 variables was shown in Figure 3. This plot explains how high and low variables values were in relation to SHAP values. According to the prediction model, the higher the SHAP value of a variable, the more likely ADR occurs.

**Sample size assessment**

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

**Develop an ADR prediction system for Panax notoginseng saponin**

According to the parameters of 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 ADR prediction system was shown in Figure 5. The operation and output of the system were shown in Figure 6.

**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** | 0.785-0.787 | **0.770±0.070** | 0.769-0.771 | 0.437±0.162 | 0.435-0.438 | **0.546±0.208** | 0.544-0.548 | **0.460±0.142** | 0.459-0.461 |
| | Simple filling | 0.687±0.094 | 0.686-0.688 | 0.761±0.076 | 0.760-0.761 | **0.455±0.180** | 0.453-0.456 | 0.491±0.165 | 0.489-0.492 | 0.442±0.126 | 0.441-0.443 |
| | RF filling | 0.677±0.095 | 0.676-0.678 | 0.759±0.077 | 0.758-0.760 | 0.446±0.181 | 0.444-0.447 | 0.488±0.162 | 0.487-0.490 | 0.440±0.129 | 0.439-0.441 |
| | RF improve filling | 0.678±0.092 | 0.677-0.678 | 0.756±0.077 | 0.755-0.757 | 0.443±0.179 | 0.442-0.445 | 0.485±0.161 | 0.483-0.486 | 0.435±0.125 | 0.434-0.436 |
| | *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** | 0.737-0.739 | **0.823±0.050** | 0.822-0.823 | **0.585±0.229** | 0.583-0.588 | 0.390±0.178 | 0.388-0.391 | 0.441±0.172 | 0.439-0.442 |
| | Random over sampler | 0.718±0.109 | 0.717-0.719 | 0.765±0.070 | 0.764-0.765 | 0.437±0.154 | 0.435-0.438 | 0.531±0.189 | 0.529-0.533 | **0.457±0.135** | 0.456-0.458 |
| | Random under sampler | 0.696±0.106 | 0.695-0.697 | 0.710±0.069 | 0.709-0.711 | 0.364±0.107 | 0.363-0.365 | **0.596±0.161** | 0.594-0.597 | 0.441±0.109 | 0.440-0.442 |
| | SMOTE over sampler | 0.683±0.100 | 0.682-0.684 | 0.755±0.067 | 0.754-0.755 | 0.416±0.137 | 0.414-0.417 | 0.490±0.143 | 0.488-0.491 | 0.435±0.113 | 0.434-0.436 |
| | Borderline SMOTE | 0.699±0.104 | 0.698-0.700 | 0.755±0.072 | 0.755-0.756 | 0.424±0.143 | 0.422-0.425 | 0.506±0.143 | 0.505-0.508 | 0.446±0.115 | 0.445-0.447 |
| | *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 | 0.702-0.703 | 0.758±0.078 | 0.758-0.759 | 0.440±0.184 | 0.438-0.441 | 0.493±0.187 | 0.492-0.494 | 0.434±0.137 | 0.433-0.435 |
| | Lasso selection | **0.713±0.105** | 0.712-0.713 | 0.761±0.074 | 0.760-0.761 | 0.447±0.173 | 0.445-0.448 | **0.513±0.177** | 0.512-0.514 | 0.448±0.128 | 0.447-0.449 |
| | Boruta selection | 0.706±0.103 | 0.705-0.707 | **0.766±0.073** | 0.765-0.766 | **0.449±0.170** | 0.448-0.450 | 0.501±0.166 | 0.500-0.503 | **0.450±0.127** | 0.449-0.451 |
| | *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 | 0.700-0.703 | 0.761±0.061 | 0.760-0.762 | 0.434±0.134 | 0.432-0.436 | 0.538±0.142 | 0.535-0.540 | 0.465±0.105 | 0.463-0.467 |
| Bagging | 0.749±0.083 | 0.748-0.750 | 0.776±0.064 | 0.774-0.777 | 0.457±0.137 | 0.454-0.459 | 0.486±0.159 | 0.483-0.489 | 0.452±0.112 | 0.450-0.454 |
| Bernoulli NB | 0.718±0.099 | 0.716-0.720 | 0.771±0.056 | 0.770-0.772 | 0.444±0.133 | 0.442-0.447 | 0.541±0.141 | 0.538-0.543 | 0.475±0.109 | 0.474-0.477 |
| DT | 0.667±0.085 | 0.665-0.668 | 0.738±0.067 | 0.737-0.739 | 0.388±0.127 | 0.386-0.390 | 0.491±0.151 | 0.489-0.494 | 0.417±0.105 | 0.416-0.419 |
| Ensemble Learning | **0.793±0.083** | 0.791-0.794 | **0.810±0.058** | 0.809-0.811 | **0.545±0.157** | 0.543-0.548 | **0.576±0.162** | 0.573-0.579 | **0.537±0.108** | 0.535-0.539 |
| ET | 0.596±0.097 | 0.594-0.598 | 0.703±0.081 | 0.701-0.704 | 0.308±0.149 | 0.305-0.310 | 0.393±0.186 | 0.390-0.396 | 0.326±0.139 | 0.324-0.329 |
| Gaussian NB | 0.667±0.106 | 0.665-0.669 | 0.720±0.061 | 0.719-0.721 | 0.364±0.106 | 0.362-0.366 | 0.543±0.133 | 0.541-0.545 | 0.429±0.103 | 0.427-0.431 |
| Gradient Boosting | 0.718±0.100 | 0.716-0.720 | 0.783±0.060 | 0.782-0.784 | 0.487±0.161 | 0.484-0.490 | 0.524±0.144 | 0.521-0.526 | 0.481±0.105 | 0.479-0.483 |
| KNN | 0.655±0.101 | 0.654-0.657 | 0.741±0.086 | 0.740-0.743 | 0.394±0.262 | 0.389-0.399 | 0.355±0.217 | 0.351-0.359 | 0.316±0.166 | 0.313-0.319 |
| LDA | 0.724±0.097 | 0.722-0.725 | 0.770±0.065 | 0.769-0.772 | 0.457±0.149 | 0.454-0.459 | 0.561±0.141 | 0.558-0.564 | 0.487±0.110 | 0.485-0.489 |
| LR | 0.728±0.094 | 0.727-0.730 | 0.770±0.070 | 0.769-0.771 | 0.465±0.155 | 0.462-0.467 | 0.580±0.143 | 0.577-0.583 | 0.497±0.110 | 0.495-0.499 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Multinomial NB | 0.727±0.099 | 0.725-0.728 | 0.753±0.071 | 0.752-0.754 | 0.450±0.170 | 0.447-0.453 | 0.570±0.175 | 0.567-0.573 | 0.467±0.111 | 0.465-0.469 |
| Passive Aggressive | 0.686±0.094 | 0.684-0.688 | 0.701±0.087 | 0.699-0.703 | 0.358±0.119 | 0.355-0.360 | 0.558±0.156 | 0.555-0.560 | 0.421±0.107 | 0.419-0.423 |
| QDA | 0.660±0.115 | 0.658-0.662 | 0.774±0.057 | 0.773-0.775 | 0.428±0.178 | 0.425-0.431 | 0.436±0.188 | 0.433-0.440 | 0.411±0.152 | 0.408-0.413 |
| RF | 0.742±0.088 | 0.741-0.744 | 0.792±0.075 | 0.791-0.793 | 0.534±0.194 | 0.531-0.538 | 0.430±0.155 | 0.427-0.432 | 0.444±0.119 | 0.441-0.446 |
| SGD | 0.720±0.099 | 0.718-0.722 | 0.762±0.064 | 0.761-0.764 | 0.452±0.196 | 0.448-0.455 | 0.507±0.213 | 0.503-0.511 | 0.434±0.141 | 0.432-0.437 |
| SVM | 0.735±0.090 | 0.734-0.737 | 0.792±0.073 | 0.790-0.793 | 0.533±0.194 | 0.529-0.536 | 0.443±0.165 | 0.440-0.446 | 0.449±0.115 | 0.447-0.451 |
| XGBoost | 0.740±0.095 | 0.738-0.741 | 0.790±0.074 | 0.789-0.792 | 0.515±0.161 | 0.512-0.518 | 0.513±0.165 | 0.510-0.516 | 0.486±0.112 | 0.484-0.488 |
| *p* value | ***p*<0.0001** | | ***p*<0.0001** | | ***p*<0.0001** | | ***p*<0.0001** | | ***p*<0.0001** | |

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.

**Table 3** Predictive performance indicators of the 5 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 |

## 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 containing Panax notoginseng saponin, including injections, in clinical practice has become more and more common, while the 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%) are the most common, and some cases are even life-threatening [5]. However, the ADR monitoring methods, including spontaneous reporting systems, prescription event monitoring and centralized hospital monitoring system, are reported after the event, and may even have data bias, underreporting or repeated reporting. Therefore, the realization of ADR prediction has important significance for prevent and avoid 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. Sixty data sets, which were from data filling, data sampling and variable selection, were combined with 18 machine learning algorithms to establish 1080 ADR prediction models. The AUC, accuracy, precision, recall rate and F1 value were used to evaluate the predictive performance of the models. According to the parameters of the best model, an ADR prediction system for the Chinese herbal injections containing Panax notoginseng saponin was developed. This predictive system had high accuracy and precision, and had potential value for clinical application.

In recent years, some ADR prediction models based on data mining [6-9], machine learning algorithms [10, 12-15], and statistical methods [16-18], have been developed. 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 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 produced an AUC of 0.83. Compared with these models, the model established in our study had better predictive performance (accuracy was 0.8947, precision was 0.75, recall rate was 0.6667 and AUC was 0.914). As missing data is common in the real-world health system, 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 model with optimal predictive performance selected from the 1080 models, was used to develop the ADR risk prediction system, which is potentially convenient for clinical practice 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 accuracies (78.9–90.2%). Unfortunately, the model ignored the effect of pathological and physiological conditions and the combination medication on ADR. More than 80 factors including the patient's pathophysiological characteristics, clinical laboratory results, and medication conditions, were performed by 3 variable selection methods in our study. Meanwhile, we using the SHAP value to explain the contribution of the variables to the model.

The importance of the variable indicates 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 generalized 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 the 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].

However, our data were all from southwest China, and more data were needed to further evaluate the model prediction performance. In addition, a prospective controlled trial is required to demonstrate the accuracy of the ADR prediction system.

**Contributors** XWW, EWL and RST were involved in the conception and design of the study. XWW drafted the article. JYZ, HC, XWS and YLW analyzed the data.

EWL and RST 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. RST is the guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Ethical approval: This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital (2017-11-01).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** 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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**Figure 1** ROC curve of the 5 best models.

**Figure 2** Importance matrix plot of each variable to the final prediction model. Variable names were shown in Supplementary Table 1. 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, hemoglobin; 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 were shown in Supplementary Table 1. 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, hemoglobin; 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 4** Sample size validation. The vertical bars represent the 95% confidence interval (CI) of AUC of ROC.

**Figure 5** The development of ADR prediction system.

**Figure 6** The operation (A) and output (B) of the ADR prediction system.

385

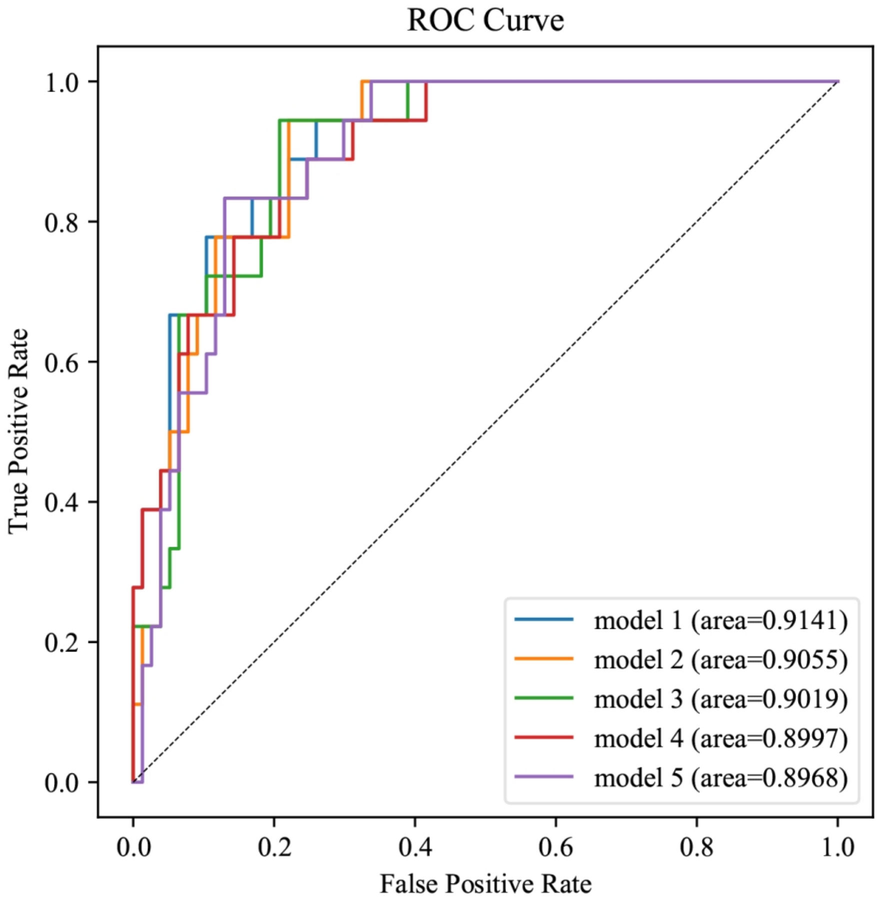


Figure 1 ROC curve of the 5 best models.

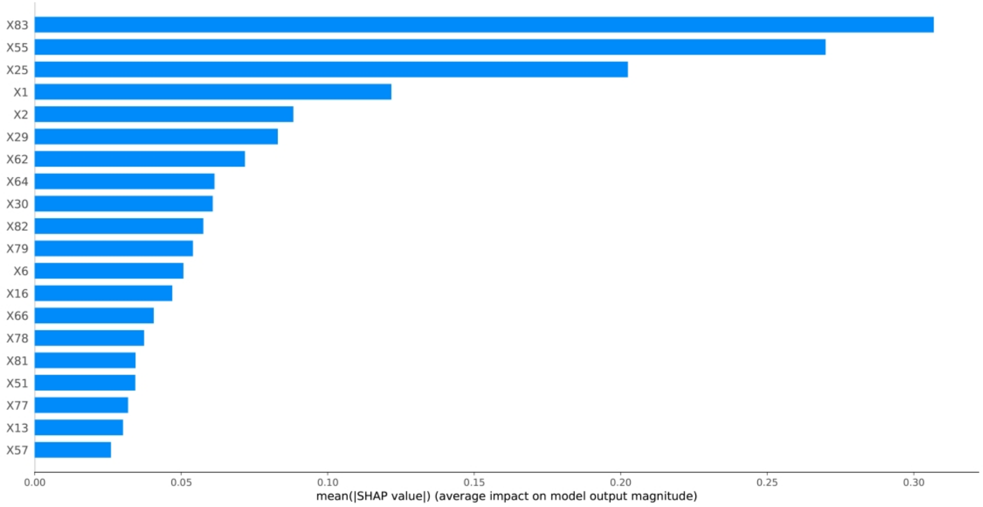


Figure 2 Importance matrix plot of each variable to the final prediction model.

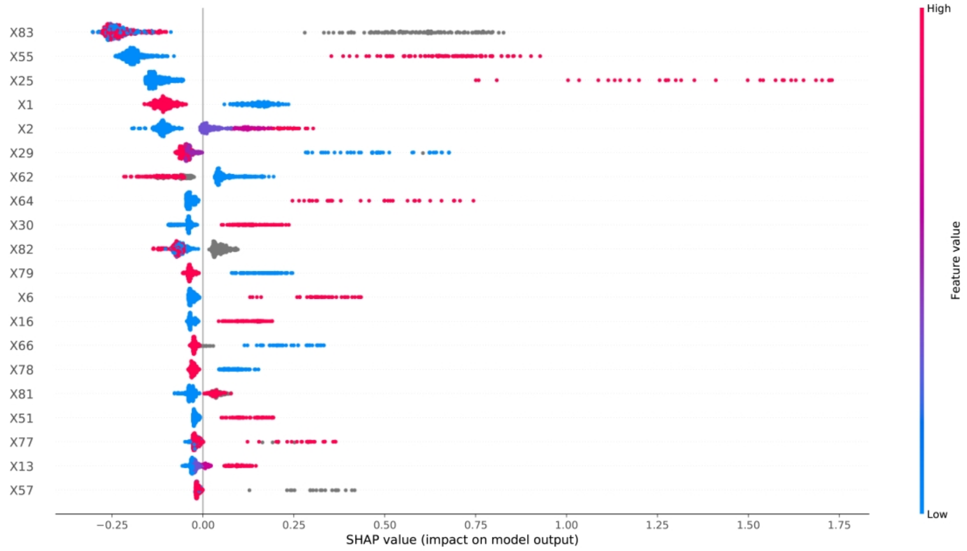


Figure 3 SHAP summary plot of the top 20 variables of the model.

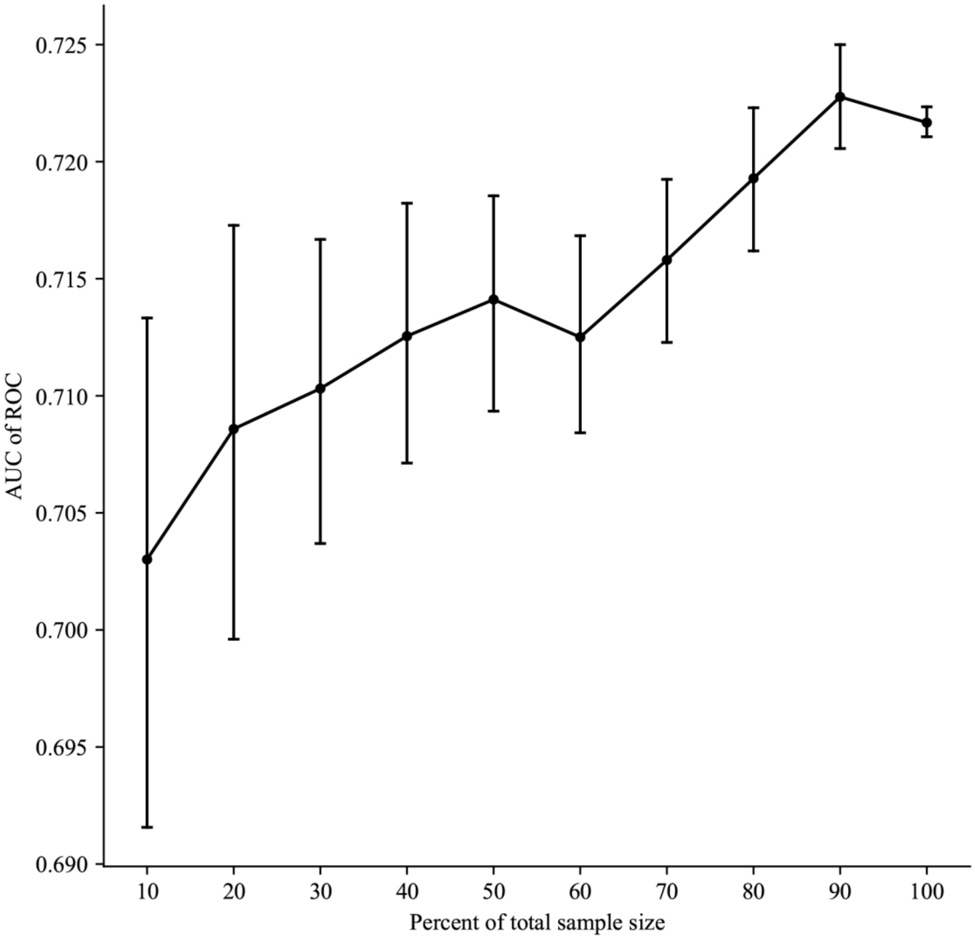


Figure 4 Sample size validation.

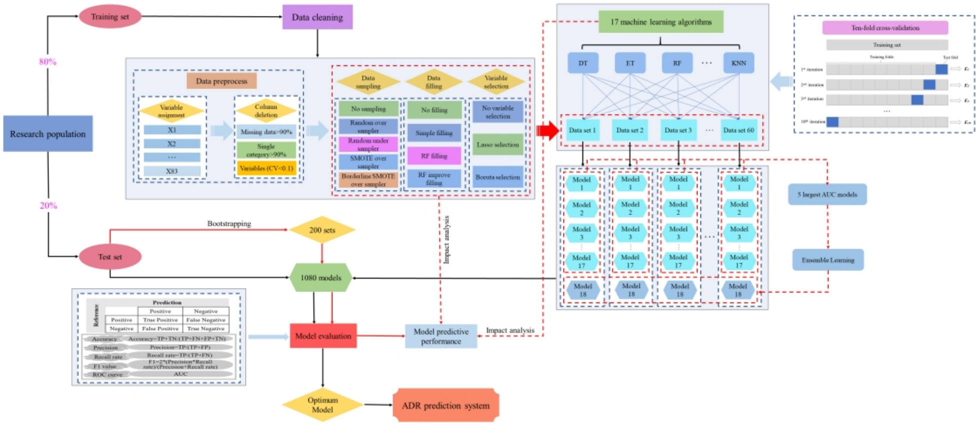
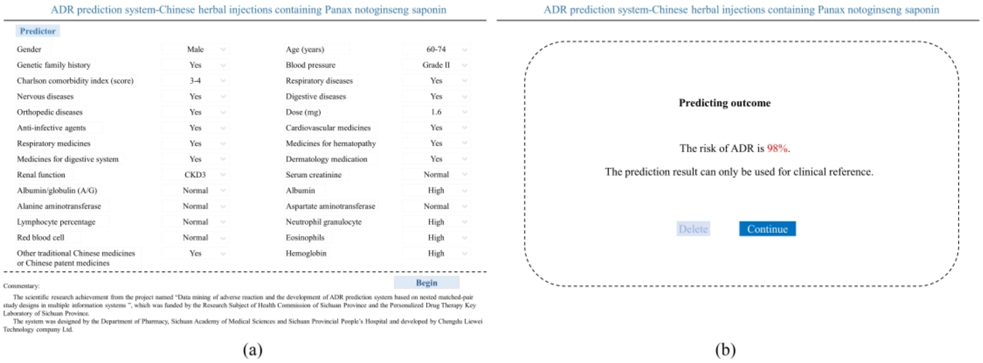


Figure 5 The development of ADR prediction system.

1050x472mm (96 x 96 DPI)



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 |

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.

(b)

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

1899x688mm (96 x 96 DPI)

**Table 1** 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 (°C) | 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 2** 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.

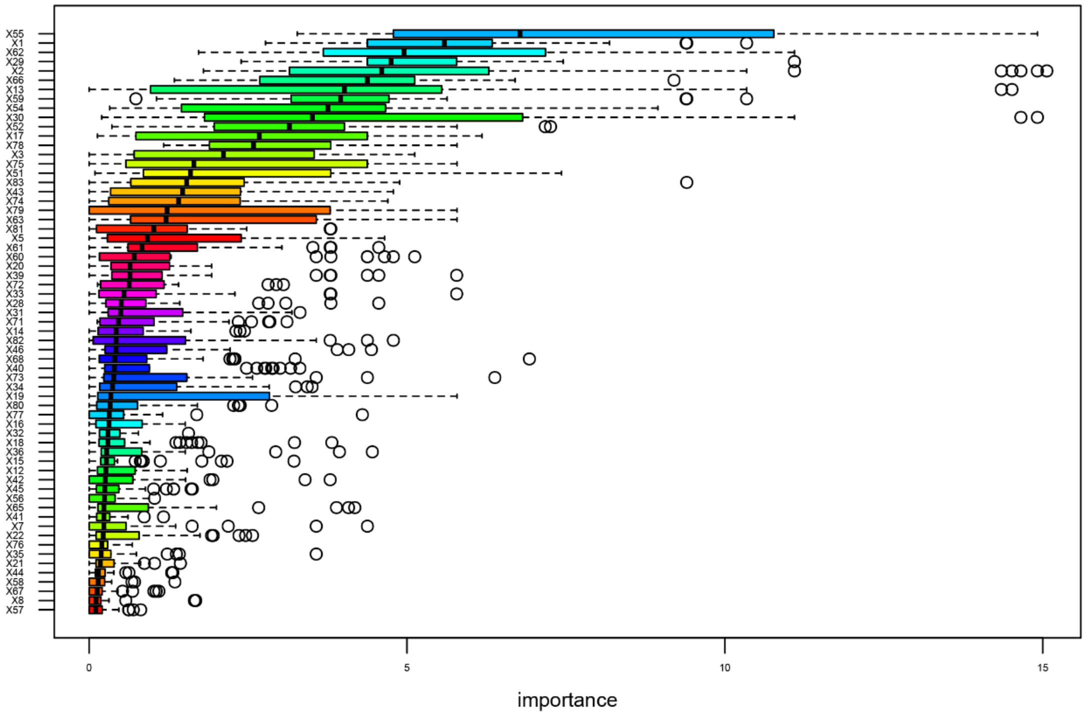


**Figure 1** Variable selection by Lasso and Boruta. Variable names were shown in Table S1.

# Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

Upload your completed checklist as an extra file when you submit to a journal.

In your methods section, say that you used the TRIPODreporting guidelines, and cite them as:

Collins GS, Reitsma JB, Altman DG, Moons KG. Transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD): The TRIPOD statement.

| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title** | | | |
| | #1 | Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted. | 1 |
| **Abstract** | | | |

| | | | |
|---|---|---|---|
| | #2 | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 2 |
| **Introduction** | | | |
| | #3a | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 3 |
| | #3b | Specify the objectives, including whether the study describes the development or validation of the model or both. | 4 |
| **Methods** | | | |
| Source of data | #4a | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | 5 |
| Source of data | #4b | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 5 |
| Participants | #5a | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | 5 |
| Participants | #5b | Describe eligibility criteria for participants. | 5 |
| Participants | #5c | Give details of treatments received, if relevant | 5 |

| | | | |
|---|---|---|---|
| Outcome | #6a | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | 7 |
| Outcome | #6b | Report any actions to blind assessment of the outcome to be predicted. | 7 |
| Predictors | #7a | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured | 6 |
| Predictors | #7b | Report any actions to blind assessment of predictors for the outcome and other predictors. | 6 |
| Sample size | #8 | Explain how the study size was arrived at. | 5 |
| Missing data | #9 | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 6 |
| Statistical analysis methods | #10a | If you are developing a prediction model describe how predictors were handled in the analyses. | 6 |
| Statistical analysis methods | #10b | If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 7 |
| Statistical analysis methods | #10c | If you are validating a prediction model, describe how the predictions were calculated. | 7 |
| Statistical analysis methods | #10d | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 7 |

| | | | |
|---|---|---|---|
| Statistical analysis methods | #10e | If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done | 7 |
| Risk groups | #11 | Provide details on how risk groups were created, if done. | 7 |
| Development vs. validation | #12 | For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors. | 7 |
| **Results** | | | |
| Participants | #13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | 8 |
| Participants | #13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | 8 |
| Participants | #13c | For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome). | 8 |
| Model development | #14a | If developing a model, specify the number of participants and outcome events in each analysis. | 9 |
| Model development | #14b | If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome. | 9 |

|  |  |  |  |
|---|---|---|---|
| Model specification | #15a | If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | 9 |
| Model specification | #15b | If developing a prediction model, explain how to the use it. | 9 |
| Model performance | #16 | Report performance measures (with CIs) for the prediction model. | 9 |
| Model-updating | #17 | If validating a model, report the results from any model updating, if done (i.e., model specification, model performance). | 9 |
| **Discussion** |  |  |  |
| Limitations | #18 | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | 17 |
| Interpretation | #19a | For validation, discuss the results with reference to performance in the development data, and any other validation data | 15 |
| Interpretation | #19b | Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. | 15 |
| Implications | #20 | Discuss the potential clinical use of the model and implications for future research | 16 |

## Other information

|  |  |  |  |
|---|---|---|---|
| Supplementary information | #21 | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | 18 |
| Funding | #22 | Give the source of funding and the role of the funders for the present study. | 18 |

BMJ Open

# 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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| | |

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

## 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 5 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 was 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 5 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.

**Key words** Adverse drug reactions, Chinese herbal injection, Machine learning, Prediction system, Panax notoginseng saponin

**Strengths and limitations of this study**

- To the best of our knowledge, this study was the first to develop an ADR prediction system for Chinese herbal injection containing Panax notoginseng saponin using machine learning.
- Data of ADR patients 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 cardio-cerebral 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 centralized 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 ~~and avoid~~ 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, Lai et al. [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

ADR patients who used Chinese herbal injections containing Panax notoginseng included in this study were from the National Center for Adverse Drug Reaction Monitoring reported by 5 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 (EMR) system of the 5 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.

This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People's Hospital. Due to the retrospective nature of the study, informed consent was waived. And we hid the patients' personal information during the study.

### 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 (CV) <0.1 were deleted.

*Data filling*

There are 4 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: synthesize new data from a small amount of original data. Borderline SMOTE over sampler: synthesize 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 (Bernoulli NB), Decision Tree (DT), Extra Tree (ET), Gaussian Naïve Bayes (Gaussian NB), Gradient Boosting, K-Nearest Neighbor (KNN), Latent Dirichlet Allocation (LDA), Logistic Regression (LR), Multinomial Naïve Bayes (Multinomial NB), Passive Aggressive, Quadratic Discriminant Analysis (QDA), RF, Stochastic Gradient Descent (SGD), Support Vector Machine (SVM), eXtreme Gradient Boosting (XGBoost), 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 5 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.

### Statistical Analysis

Categorical variables were expressed as counts and percentages and continuous variables as mean ± standard deviation. 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 were considered statistically significant. Hypothesis testing and models building were implemented using the stats and sklearn packages in Python (Version3.8), 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%) males and 280 (52.83%) females. The demographic and clinical characteristics of the patients were shown in Supplementary Table 1.

### Data cleaning

The results of 83 variables assignment were shown in Supplementary Table 2. After the column deletion, 63 variables were included in the following study (Supplementary Table 3). Then, 4 data filling methods were used for replacing the 1,290 (3.86%) missing data. We used Lasso or Boruta for variable selection, and the results were shown in Supplementary Table 3. Using 4 data filling, 5 data sampling and 3 variable selection methods for data processing respectively, 60 data sets were obtained.

**Model establishment**

A total of 1080 prediction models were established by 18 machine learning algorithms and 60 data sets. The results of ten-fold cross-validation were shown in Supplementary 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).

**Model evaluation**

The AUC, accuracy, precision, recall rate, and F1 value were used to evaluate the performance of the model. The best 5 models were selected and model 1 had the best performance with an AUC of 0.9141 (Table 3). The receiver operating characteristic (ROC) curve of the 5 best models were shown in Figure 1.

**Model interpretation**

The importance of each variable to the final prediction model was shown in Figure 2. The result showed that pre-treatment serum levels, renal function, dermatoses, gender and age were the top 5 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 was shown in Figure 3. This plot explains how high and low variables 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 was shown in Figure 5. The operation and output of the system were shown in Figure 6.

**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** | 0.785-0.787 | **0.770±0.070** | 0.769-0.771 | 0.437±0.162 | 0.435-0.438 | **0.546±0.208** | 0.544-0.548 | **0.460±0.142** | 0.459-0.461 |
| | Simple filling | 0.687±0.094 | 0.686-0.688 | 0.761±0.076 | 0.760-0.761 | **0.455±0.180** | 0.453-0.456 | 0.491±0.165 | 0.489-0.492 | 0.442±0.126 | 0.441-0.443 |
| | RF filling | 0.677±0.095 | 0.676-0.678 | 0.759±0.077 | 0.758-0.760 | 0.446±0.181 | 0.444-0.447 | 0.488±0.162 | 0.487-0.490 | 0.440±0.129 | 0.439-0.441 |
| | RF improve filling | 0.678±0.092 | 0.677-0.678 | 0.756±0.077 | 0.755-0.757 | 0.443±0.179 | 0.442-0.445 | 0.485±0.161 | 0.483-0.486 | 0.435±0.125 | 0.434-0.436 |
| | *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** | 0.737-0.739 | **0.823±0.050** | 0.822-0.823 | **0.585±0.229** | 0.583-0.588 | 0.390±0.178 | 0.388-0.391 | 0.441±0.172 | 0.439-0.442 |
| | Random over sampler | 0.718±0.109 | 0.717-0.719 | 0.765±0.070 | 0.764-0.765 | 0.437±0.154 | 0.435-0.438 | 0.531±0.189 | 0.529-0.533 | **0.457±0.135** | 0.456-0.458 |
| | Random under sampler | 0.696±0.106 | 0.695-0.697 | 0.710±0.069 | 0.709-0.711 | 0.364±0.107 | 0.363-0.365 | **0.596±0.161** | 0.594-0.597 | 0.441±0.109 | 0.440-0.442 |
| | SMOTE over sampler | 0.683±0.100 | 0.682-0.684 | 0.755±0.067 | 0.754-0.755 | 0.416±0.137 | 0.414-0.417 | 0.490±0.143 | 0.488-0.491 | 0.435±0.113 | 0.434-0.436 |
| | Borderline SMOTE | 0.699±0.104 | 0.698-0.700 | 0.755±0.072 | 0.755-0.756 | 0.424±0.143 | 0.422-0.425 | 0.506±0.143 | 0.505-0.508 | 0.446±0.115 | 0.445-0.447 |
| | *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 | 0.702-0.703 | 0.758±0.078 | 0.758-0.759 | 0.440±0.184 | 0.438-0.441 | 0.493±0.187 | 0.492-0.494 | 0.434±0.137 | 0.433-0.435 |
| | Lasso selection | **0.713±0.105** | 0.712-0.713 | 0.761±0.074 | 0.760-0.761 | 0.447±0.173 | 0.445-0.448 | **0.513±0.177** | 0.512-0.514 | 0.448±0.128 | 0.447-0.449 |
| | Boruta selection | 0.706±0.103 | 0.705-0.707 | **0.766±0.073** | 0.765-0.766 | **0.449±0.170** | 0.448-0.450 | 0.501±0.166 | 0.500-0.503 | **0.450±0.127** | 0.449-0.451 |
| | *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 | 0.700-0.703 | 0.761±0.061 | 0.760-0.762 | 0.434±0.134 | 0.432-0.436 | 0.538±0.142 | 0.535-0.540 | 0.465±0.105 | 0.463-0.467 |
| Bagging | 0.749±0.083 | 0.748-0.750 | 0.776±0.064 | 0.774-0.777 | 0.457±0.137 | 0.454-0.459 | 0.486±0.159 | 0.483-0.489 | 0.452±0.112 | 0.450-0.454 |
| Bernoulli NB | 0.718±0.099 | 0.716-0.720 | 0.771±0.056 | 0.770-0.772 | 0.444±0.133 | 0.442-0.447 | 0.541±0.141 | 0.538-0.543 | 0.475±0.109 | 0.474-0.477 |
| DT | 0.667±0.085 | 0.665-0.668 | 0.738±0.067 | 0.737-0.739 | 0.388±0.127 | 0.386-0.390 | 0.491±0.151 | 0.489-0.494 | 0.417±0.105 | 0.416-0.419 |
| Ensemble Learning | **0.793±0.083** | 0.791-0.794 | **0.810±0.058** | 0.809-0.811 | **0.545±0.157** | 0.543-0.548 | **0.576±0.162** | 0.573-0.579 | **0.537±0.108** | 0.535-0.539 |
| ET | 0.596±0.097 | 0.594-0.598 | 0.703±0.081 | 0.701-0.704 | 0.308±0.149 | 0.305-0.310 | 0.393±0.186 | 0.390-0.396 | 0.326±0.139 | 0.324-0.329 |
| Gaussian NB | 0.667±0.106 | 0.665-0.669 | 0.720±0.061 | 0.719-0.721 | 0.364±0.106 | 0.362-0.366 | 0.543±0.133 | 0.541-0.545 | 0.429±0.103 | 0.427-0.431 |
| Gradient Boosting | 0.718±0.100 | 0.716-0.720 | 0.783±0.060 | 0.782-0.784 | 0.487±0.161 | 0.484-0.490 | 0.524±0.144 | 0.521-0.526 | 0.481±0.105 | 0.479-0.483 |
| KNN | 0.655±0.101 | 0.654-0.657 | 0.741±0.086 | 0.740-0.743 | 0.394±0.262 | 0.389-0.399 | 0.355±0.217 | 0.351-0.359 | 0.316±0.166 | 0.313-0.319 |
| LDA | 0.724±0.097 | 0.722-0.725 | 0.770±0.065 | 0.769-0.772 | 0.457±0.149 | 0.454-0.459 | 0.561±0.141 | 0.558-0.564 | 0.487±0.110 | 0.485-0.489 |
| LR | 0.728±0.094 | 0.727-0.730 | 0.770±0.070 | 0.769-0.771 | 0.465±0.155 | 0.462-0.467 | 0.580±0.143 | 0.577-0.583 | 0.497±0.110 | 0.495-0.499 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Multinomial NB | 0.727±0.099 | 0.725-0.728 | 0.753±0.071 | 0.752-0.754 | 0.450±0.170 | 0.447-0.453 | 0.570±0.175 | 0.567-0.573 | 0.467±0.111 | 0.465-0.469 |
| Passive Aggressive | 0.686±0.094 | 0.684-0.688 | 0.701±0.087 | 0.699-0.703 | 0.358±0.119 | 0.355-0.360 | 0.558±0.156 | 0.555-0.560 | 0.421±0.107 | 0.419-0.423 |
| QDA | 0.660±0.115 | 0.658-0.662 | 0.774±0.057 | 0.773-0.775 | 0.428±0.178 | 0.425-0.431 | 0.436±0.188 | 0.433-0.440 | 0.411±0.152 | 0.408-0.413 |
| RF | 0.742±0.088 | 0.741-0.744 | 0.792±0.075 | 0.791-0.793 | 0.534±0.194 | 0.531-0.538 | 0.430±0.155 | 0.427-0.432 | 0.444±0.119 | 0.441-0.446 |
| SGD | 0.720±0.099 | 0.718-0.722 | 0.762±0.064 | 0.761-0.764 | 0.452±0.196 | 0.448-0.455 | 0.507±0.213 | 0.503-0.511 | 0.434±0.141 | 0.432-0.437 |
| SVM | 0.735±0.090 | 0.734-0.737 | 0.792±0.073 | 0.790-0.793 | 0.533±0.194 | 0.529-0.536 | 0.443±0.165 | 0.440-0.446 | 0.449±0.115 | 0.447-0.451 |
| XGBoost | 0.740±0.095 | 0.738-0.741 | 0.790±0.074 | 0.789-0.792 | 0.515±0.161 | 0.512-0.518 | 0.513±0.165 | 0.510-0.516 | 0.486±0.112 | 0.484-0.488 |
| *p* value | ***p*<0.0001** | | ***p*<0.0001** | | ***p*<0.0001** | | ***p*<0.0001** | | ***p*<0.0001** | |

208 Bernoulli NB, Bernoulli Naïve Bayes; DT, Decision Tree; ET, Extra Tree; Gaussian NB, Gaussian Naïve Bayes; KNN, K-Nearest Neighbor;
209 LDA, Latent Dirichlet Allocation; LR, Logistic Regression; Multinomial NB, Multinomial Naïve Bayes; QDA, Quadratic Discriminant
210 Analysis; SGD, Stochastic Gradient Descent; SVM, support vector machine. XGBoost, eXtreme Gradient Boosting.

**Table 3** Predictive performance indicators of the 5 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 |

## 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 centralized hospital monitoring system, were all reported after the event, and may even have data bias, underreporting or repeated reporting. Therefore, the realization 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 4 data filling, 5 data sampling and 3 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 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 is 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 generalized 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.

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 generalized 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** XWW, EWL and RST were involved in the conception and design of the study. XWW drafted the article. JYZ, HC, XWS and YLW analyzed the data. EWL and RST 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. RST is the guarantor.

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**Competing interests** None declared.

**Patient consent for publication** Not required.

**Ethics approval** Ethical approval: This study was approved by the Ethics Committee of Sichuan Academy of Medical Sciences and Sichuan Provincial People’s Hospital (2017-11-01).

**Provenance and peer review** Not commissioned; externally peer reviewed.

**Data availability statement** 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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**Figure 1** ROC curve of the 5 best models.

**Figure 2** Importance matrix plot of each variable to the final prediction model. Variable names were shown in Supplementary 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, hemoglobin; 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 were shown in Supplementary 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, hemoglobin; 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 4** Sample size validation. The vertical bars represent the 95% confidence interval (CI) of AUC of ROC.

**Figure 5** The development of ADR prediction system.

**Figure 6** The operation (A) and output (B) of the ADR prediction system.

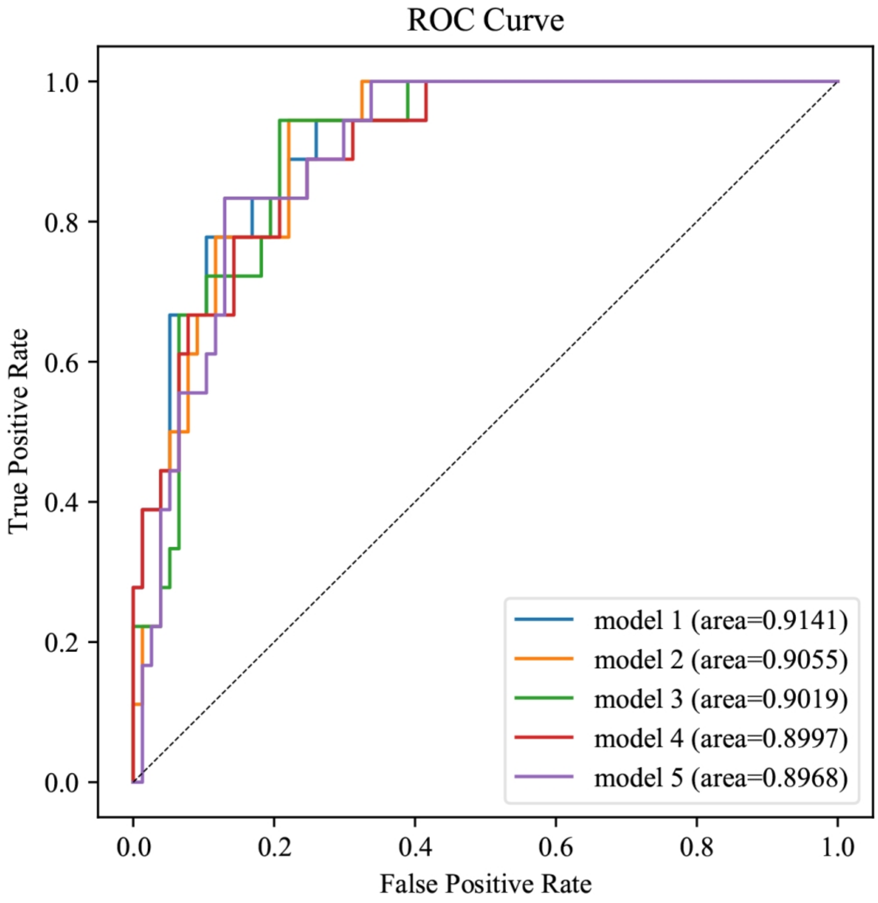


Figure 1 ROC curve of the 5 best models.

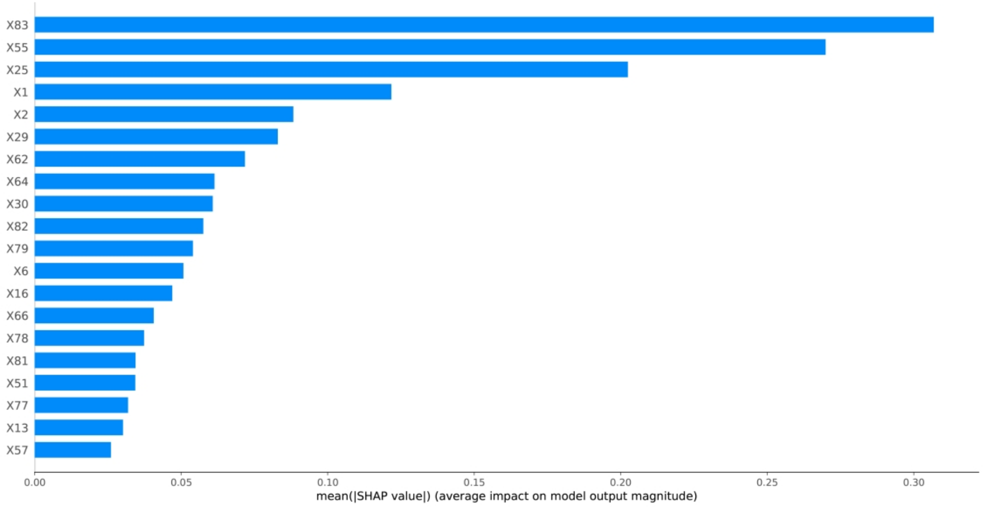


Figure 2 Importance matrix plot of each variable to the final prediction model.

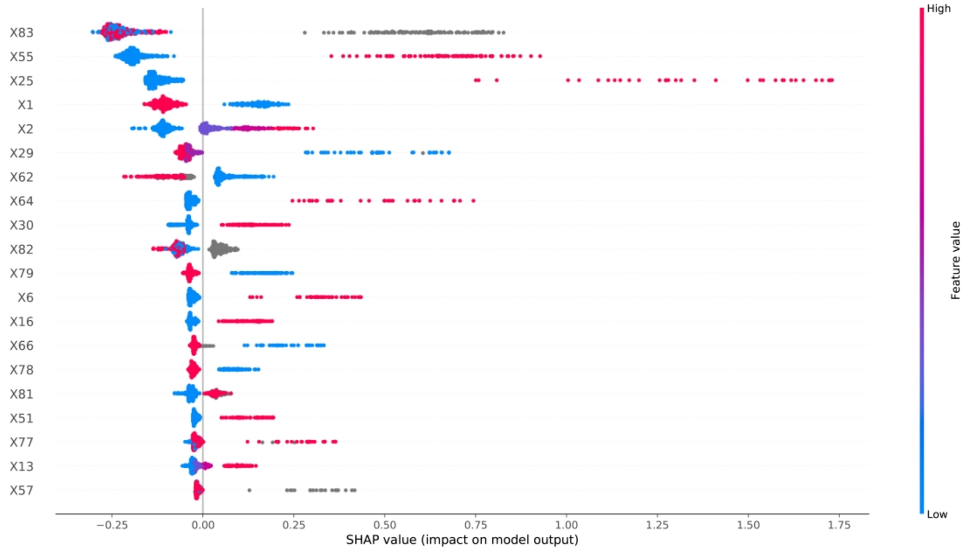


Figure 3 SHAP summary plot of the top 20 variables of the model.

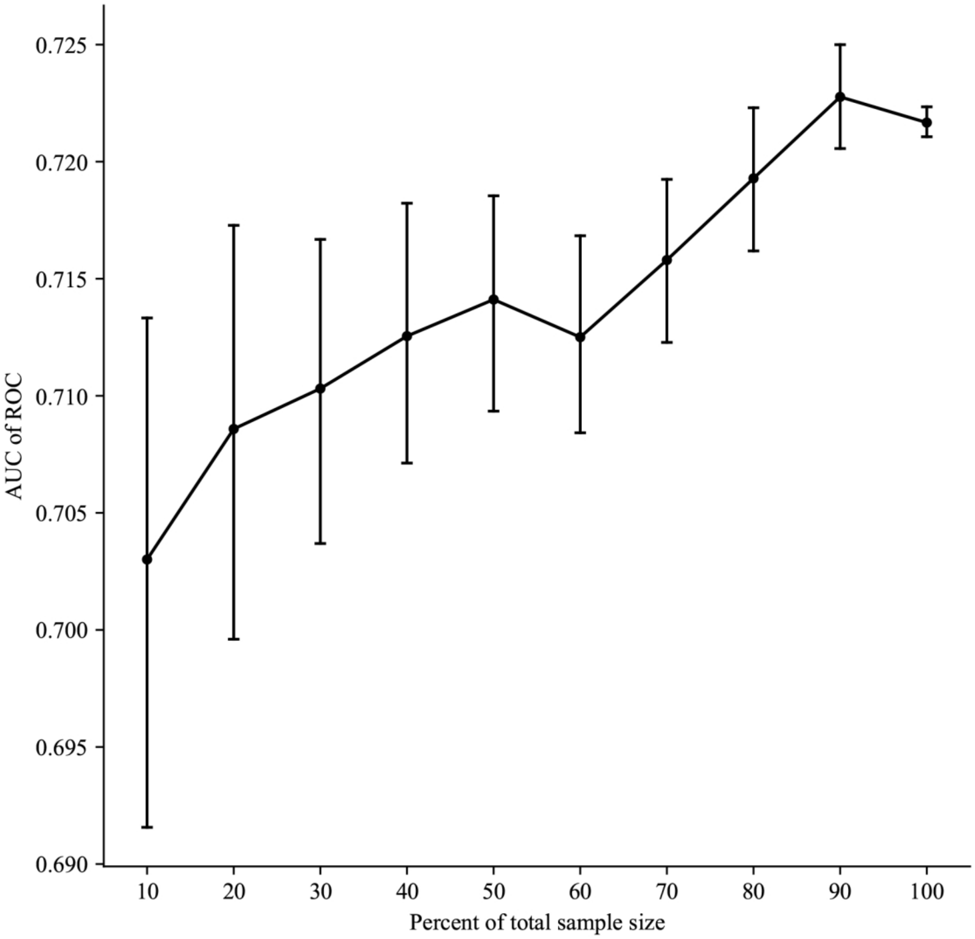


Figure 4 Sample size validation.

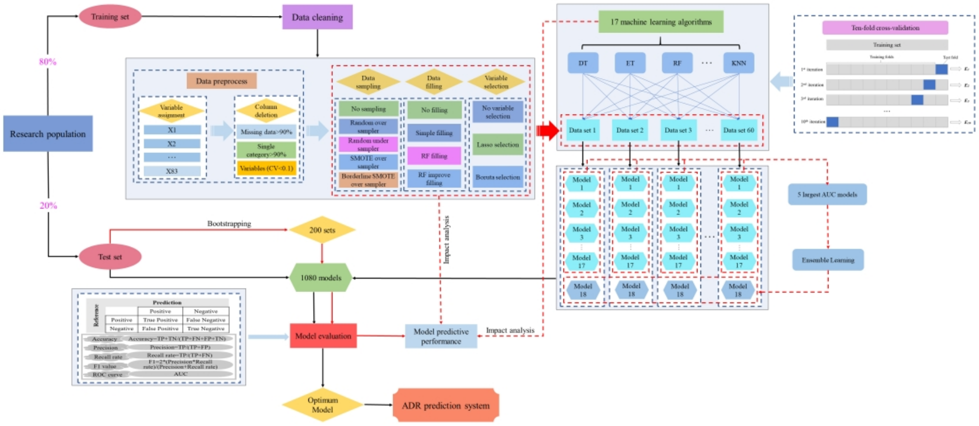
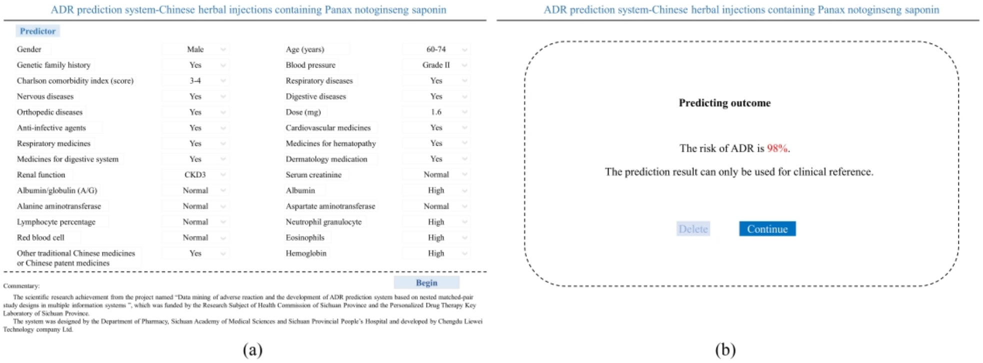


Figure 5 The development of ADR prediction system.

1050x472mm (96 x 96 DPI)



ADR prediction system-Chinese herbal injections containing Panax notoginseng saponin

| | | | |
|---|---|---|---|
| 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 |

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.

(b)

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

1899x688mm (96 x 96 DPI)

**Table 1** Demographic and clinical characteristics of the patients

| Parameter | Number |
|---|---|
| Gender | |
| Male | 250(47.17) |
| Female | 280(52.83) |
| Age (years) | |
| $\leq 44$ | 121(22.83) |
| $45 \leq \text{Age} \leq 59$ | 193(36.42) |
| $60 \leq \text{Age} \leq 74$ | 132(24.91) |
| $\geq 75$ | 84 (15.85) |
| Body mass index (BMI, kg/m$^2$) | |
| $< 18.5$ | 48(9.06) |
| $18.5 \leq \text{BMI} \leq 23.9$ | 275(51.89) |
| $\geq 24$ | 175(33.02) |
| Charlson comorbidity index (Score) | |
| 0 | 104(19.62) |
| 1 or 2 | 190(35.85) |
| 3 or 4 | 123(23.21) |
| $\geq 5$ | 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, $\leq 44$; 2, $45 \leq$ Age $\leq 59$; 3, $60 \leq$ Age $\leq 74$; 4, $\geq 75$ |
| X3 | Body mass index (BMI, kg/$m^2$) | 1, $< 18.5$; 2, $18.5 \leq$ BMI $\leq 23.9$; 3, $\geq 24$ |
| 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 (°C) | 1, $< 36.1$; 2, $36.1 \leq$ Temperature $\leq 37.2$; 3, $> 37.3$ |
| X10 | Pulse (beats/min) | 1, $< 60$; 2, $60 \leq$ Pulse $\leq 100$, 3, $> 100$ |
| X11 | Breathe (times/min) | 1, $< 12$; 2, $12 \leq$ Breathe $\leq 20$; 3, $> 20$ |
| X12 | Blood pressure | 0, Normal (systolic pressure $\leq 139$ mmHg or diastolic pressure $\leq 89$ mmHg); 1, Grade I (140 mmHg $\leq$ systolic pressure $\leq 159$ mmHg or 90 mmHg $\leq$ diastolic pressure $\leq 99$ mmHg); 2, Grade II (160 mmHg $\leq$ systolic pressure $\leq 179$ mmHg or 100 mmHg $\leq$ diastolic pressure $\leq 109$ mmHg); 3, Grade III (systolic pressure $\geq$180 mmHg or diastolic pressure $\geq$110 mmHg) |
| X13 | Charlson comorbidity index (Score) | 1, 0; 2, 1 or 2; 3, 3 or 4; 4, $\geq 5$ |
| 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

# Reporting checklist for prediction model development/validation.

Based on the TRIPOD guidelines.

## Instructions to authors

Complete this checklist by entering the page numbers from your manuscript where readers will find each of the items listed below.

Your article may not currently address all the items on the checklist. Please modify your text to include the missing information. If you are certain that an item does not apply, please write "n/a" and provide a short explanation.

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In your methods section, say that you used the TRIPODreporting guidelines, and cite them as:

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| | | Reporting Item | Page Number |
|---|---|---|---|
| **Title** | | | |
| | #1 | Identify the study as developing and / or validating a multivariable prediction model, the target population, and the outcome to be predicted. | 1 |
| **Abstract** | | | |

| | | | |
|---|---|---|---|
| | #2 | Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions. | 2 |
| **Introduction** | | | |
| | #3a | Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models. | 3 |
| | #3b | Specify the objectives, including whether the study describes the development or validation of the model or both. | 4 |
| **Methods** | | | |
| Source of data | #4a | Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable. | 5 |
| Source of data | #4b | Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up. | 5 |
| Participants | #5a | Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centres. | 5 |
| Participants | #5b | Describe eligibility criteria for participants. | 5 |
| Participants | #5c | Give details of treatments received, if relevant | 5 |

| | | | |
|---|---|---|---|
| Outcome | #6a | Clearly define the outcome that is predicted by the prediction model, including how and when assessed. | 7 |
| Outcome | #6b | Report any actions to blind assessment of the outcome to be predicted. | 7 |
| Predictors | #7a | Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured | 6 |
| Predictors | #7b | Report any actions to blind assessment of predictors for the outcome and other predictors. | 6 |
| Sample size | #8 | Explain how the study size was arrived at. | 5 |
| Missing data | #9 | Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method. | 6 |
| Statistical analysis methods | #10a | If you are developing a prediction model describe how predictors were handled in the analyses. | 6 |
| Statistical analysis methods | #10b | If you are developing a prediction model, specify type of model, all model-building procedures (including any predictor selection), and method for internal validation. | 7 |
| Statistical analysis methods | #10c | If you are validating a prediction model, describe how the predictions were calculated. | 7 |
| Statistical analysis methods | #10d | Specify all measures used to assess model performance and, if relevant, to compare multiple models. | 7 |

| | | | |
|---|---|---|---|
| Statistical analysis methods | #10e | If you are validating a prediction model, describe any model updating (e.g., recalibration) arising from the validation, if done | 7 |
| Risk groups | #11 | Provide details on how risk groups were created, if done. | 7 |
| Development vs. validation | #12 | For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictors. | 7 |
| **Results** | | | |
| Participants | #13a | Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful. | 8 |
| Participants | #13b | Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome. | 8 |
| Participants | #13c | For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome). | 8 |
| Model development | #14a | If developing a model, specify the number of participants and outcome events in each analysis. | 9 |
| Model development | #14b | If developing a model, report the unadjusted association, if calculated between each candidate predictor and outcome. | 9 |

| | | | |
|---|---|---|---|
| Model specification | #15a | If developing a model, present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point). | 9 |
| Model specification | #15b | If developing a prediction model, explain how to the use it. | 9 |
| Model performance | #16 | Report performance measures (with CIs) for the prediction model. | 9 |
| Model-updating | #17 | If validating a model, report the results from any model updating, if done (i.e., model specification, model performance). | 9 |
| **Discussion** | | | |
| Limitations | #18 | Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data). | 17 |
| Interpretation | #19a | For validation, discuss the results with reference to performance in the development data, and any other validation data | 15 |
| Interpretation | #19b | Give an overall interpretation of the results, considering objectives, limitations, results from similar studies, and other relevant evidence. | 15 |
| Implications | #20 | Discuss the potential clinical use of the model and implications for future research | 16 |

## Other information

| | | | |
|---|---|---|---|
| Supplementary information | #21 | Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets. | 18 |
| Funding | #22 | Give the source of funding and the role of the funders for the present study. | 18 |