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Traditional Chinese Medicine Constitution and Clinical Data Association with Machine Learning for Prediction of Spontaneous Abortion

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ABSTRACT

Background: Early prevention of Spontaneous Abortion (SA) is essential for the treatment of recurrent spontaneous abortion.
Objective: In this retrospective study, a variety of machine learning methods were used to develop predictive models and diagnose the potential risk of SA.
Methods: A total of 663 pregnant women participated in the case-control study, 586 of which were SA patients and 77 were normal parturition women. The research data included 25 features of Traditional Chinese Medicine (TCM) constitution and clinical data related to SA. This work utilized 8 machine learning techniques including logistic regression, gradient boosting decision tree, k-nearest neighbor, classification and r-egression tree, multi-layer perceptron, support vector machine, random forest and XG-Boost to predict SA. The performances of the applied models were evaluated by using the method of 10-fold cross-validation and by computing the diagnostic test characteristics, including accuracy, precision, recall, F_1 score, and the AUC of ROC curve.
Results: The F_1 scores of these eight machine learning techniques were all above 97.5%. Among them, gradient boosting decision tree had the best prediction result on SA. The accuracy, precision, recall, F_1 score, and the AUC of ROC curve of gradient boosting decision tree were 97.9%, 99%, 98.6%, 98.8%, and 97.3%, respectively.
Conclusion: The paper has accurately predicted the risk of SA combined with TCM constitution and clinical data.

1. Introduction

Spontaneous abortion (SA), or miscarriage, is defined as fetal loss before 28 gestational weeks in China (Xu et al., 2020). Recently, the prevalence of SA in pregnant women in the world is as high as 8% to 20% (Cubo et al., 2019). The latest expert consensus pointed out that the risk of SA increases with the number of abortions and age, which causes huge emotional harm to women and their partners, seriously affecting family life (Carp, 2019). In recent years, several studies had shown that some clinical and laboratory indicators could predict the risk of SA (Lee et al., 2019; Wang et al., 2017). However, public available statistical methods only found a modest correlation between some factors and SA. Machine learning can provide better SA prediction performance. The purpose of this study is to fill in the gaps in the existing machine learning models for predicting the risk of SA.

Machine learning is a combination of artificial intelligence (AI) and computing, which can provide an accurate diagnosis of diseases and predict results (Chen et al., 2018; Han et al., 2015). For example, predictive models based on machine learning were established to help the screening of intracranial aneurysms (Heo et al., 2020). Yang et al. collected the real-world clinical medical records and utilize the convolution neural network (CNN) to complete the auxiliary diagnosis (Yang et al., 2018). The top 20 risk factors for cardiovascular events were determined through Random Forest Classifier (RFC), which performed better than traditional risk calculators (Ambale-Venkatesh et al., 2017). Therefore, machine learning has become an effective and reliable tool for physicians to carry out the clinical practice.

Traditional Chinese Medicine (TCM) has been guiding health maintenance and disease treatment for thousands of years, which has been widely used in countries all over the world. TCM is a personalized medicine. TCM constitution studies the overall physical condition affected by congenital and acquired factors. Among them, Yin and Yang are the general terms describing two opposite, yet complementary and inter-related forces found in all matter in nature (Stoltzfus, 2011). where

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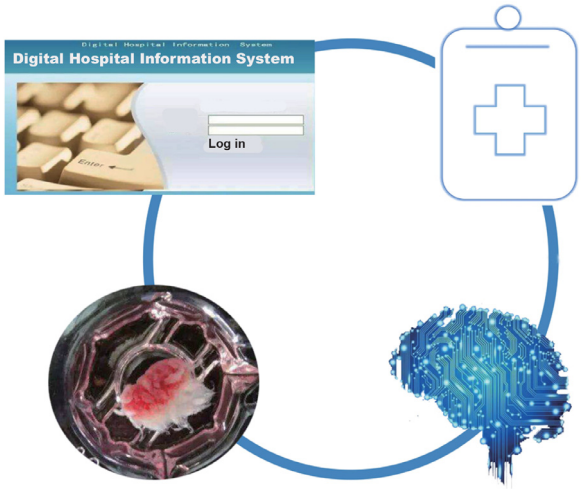

Fig. 1. Schematic diagram of proposed method.

in external, excess and heat syndromes are indicators of yang deficiencies, while internal, deficiency and cold syndromes reveal yin deficiencies.

In this article, we predict the existence of the risk of SA by considering the characteristics of 25 TCM constitution and clinical data features, and a large number of pregnant women samples are used for predicting SA with 8 machine learning techniques.

The schematic diagram of the proposed method in this paper is illustrated in Fig. 1. A binary probability classifier of a machine learning algorithm can determine whether the pregnant woman is at risk of SA through their TCM constitution and clinical data.

2. Materials and Methods

2.1. Rsesearch object

The case-control study retrospectively selected 663 data entries from women between the ages of 22 and 45 from December 2018 to December 2019, with an average age of 34 years from the Department of Reproductive Immunology, Tongde Hospital of Zhejiang Province. The research had passed the ethics approval (Batch number: No. [2020]039).

We collected relevant TCM constitution and clinical data of all participants, including basic information, numbers of previous abortions, Western medicine-related auxiliary examination results, and TCM constitution results, which were used as raw data analysis to predict the risk of SA. In these clinical data, the positive is denoted as 1 and the negative is 0. In TCM constitution, the scoring and classification criteria of the balanced constitution in TCM constitution are as follows: if the transformation scores of the other 8 constitutions are all less than 40 and the transformation score of the balanced constitution is greater than or equal to 60, we classify the balanced constitution as 1; if the transformation scores of the other 8 constitutions are all less than 30 and the transformation score of the balanced constitution is greater than or equal to 60, we classify the balanced constitution as 2; if the above two conditions are not met, we classify the balanced constitution as 0. We classify other biased constitutions as 0 with a score of less than 30. We classify other biased constitutions as 1 with the score from 30 to 39. And we classify other biased constitutions as 2 with the score greater than or equal to 40. As shown in Fig. 2.

Fig. 2 shows the distribution of the raw data, which can be visualized between each feature and SA. In Fig. 2A, the majority of Yang deficiency and Qi deficiency are more than 40 points, which may be most related to abortion. Among the previous abortions, people with a history of abortion may be more likely to have an abortion. In addition, in the original data, the distribution of the sample is unbalanced, the number of abortions samples obviously exceeds the number of normal births samples. It is necessary to perform data preprocessing in later chapters.

Table 1
Numbers of training and test data.

	Abortion	Normal labor	Total
Training set	71	525	596
Pre-processed by SMOTE	525	525	1050
Test set	6	61	67

Fig. 2B shows the correlation heat map of the original data. INS is highly correlated with Yin deficiency. T is highly correlated with Yin deficiency. LPD is positively correlated with phlegm dampness, APL-Ab is highly correlated with blood stasis, EmAbIt is highly positively correlated with special intrinsic, and TORCH, UU, CT infection indexes are positively correlated with damp heat.

2.2. Proposed methods

This paper utilizes eight machine learning techniques including logistic regression (LR), gradient boosting decision tree (GBDT), k nearest neighbor (KNN), classification and regression tree (CART), multilayer perceptron (MLP), support vector machines (SVM), random forest classifier (RFC), extreme gradient boosting (XGboost) for the prediction of the risk of SA associated with clinical data and TCM constitution. The system diagram of the proposed method is shown in Fig. 3.

2.3. Data pre-processing

By analyzing the raw data, it is clear that there are several missing values in the data and the dynamic range of the data are inconsistent. To increase the prediction accuracy of the model, processing missing values and data discretization are important for our prediction model.

There are several missing values in the discrete features of AsAb, EmAb, ANA, ATA, APL-Ab, and INS in the raw, so data filtering is an important step for data preprocessing. The missing values are filled with the mode of the missing features. And then patient number features are deleted in raw data that are not affect the prediction result at all.

To solve the phenomenon of different dynamic ranges, the input data is pre-processed by binning with custom intervals. According to the "TCM Constitution Classification and Decision Table" developed by Professor Wang Qi of TCM Constitution, we divide nine continuous features including yang_deficiency, yin_deficiency, qi_deficiency, phlegm_dampness, damp_heat, blood_stasis, special_intrinsic, qi_depression and balanced_constitution into three categories: class 0, class 1 and class 2.

10-fold cross-validation is used to divide the raw data into training and test set as shown in Fig. 4. The data numbers illustrated by one fold are detailed in Table 1. For the prediction of SA, the numbers for training and test set are 596 (class 0:71, class 1:525) and 67 (class 0:6, class 1:61). It is obvious that class 0 and class 1 in the dataset are unbalanced. This potential issue could be reduced by applying the synthetic minority over-sampling technique (SMOTE). The training data for class 1 are pre-processed by SMOTE to 525 as shown in Table 1.

2.4. Machine learning models

2.4.1. Logistic regression

Logistic regression (Xiang et al., 2019) is applied to estimate the possibility of something happening. It is a classification algorithm used to assign observation data to a discrete set of classes, which is used in our method as shown in Fig. 5A. LR is a generalized linear regression analysis model, defined as an Eq. (1)-((2):

$$z = w_n x_n + w_{n-1} x_{n-1} + \ldots + w_1 x_1 + w_0 \quad (1)$$

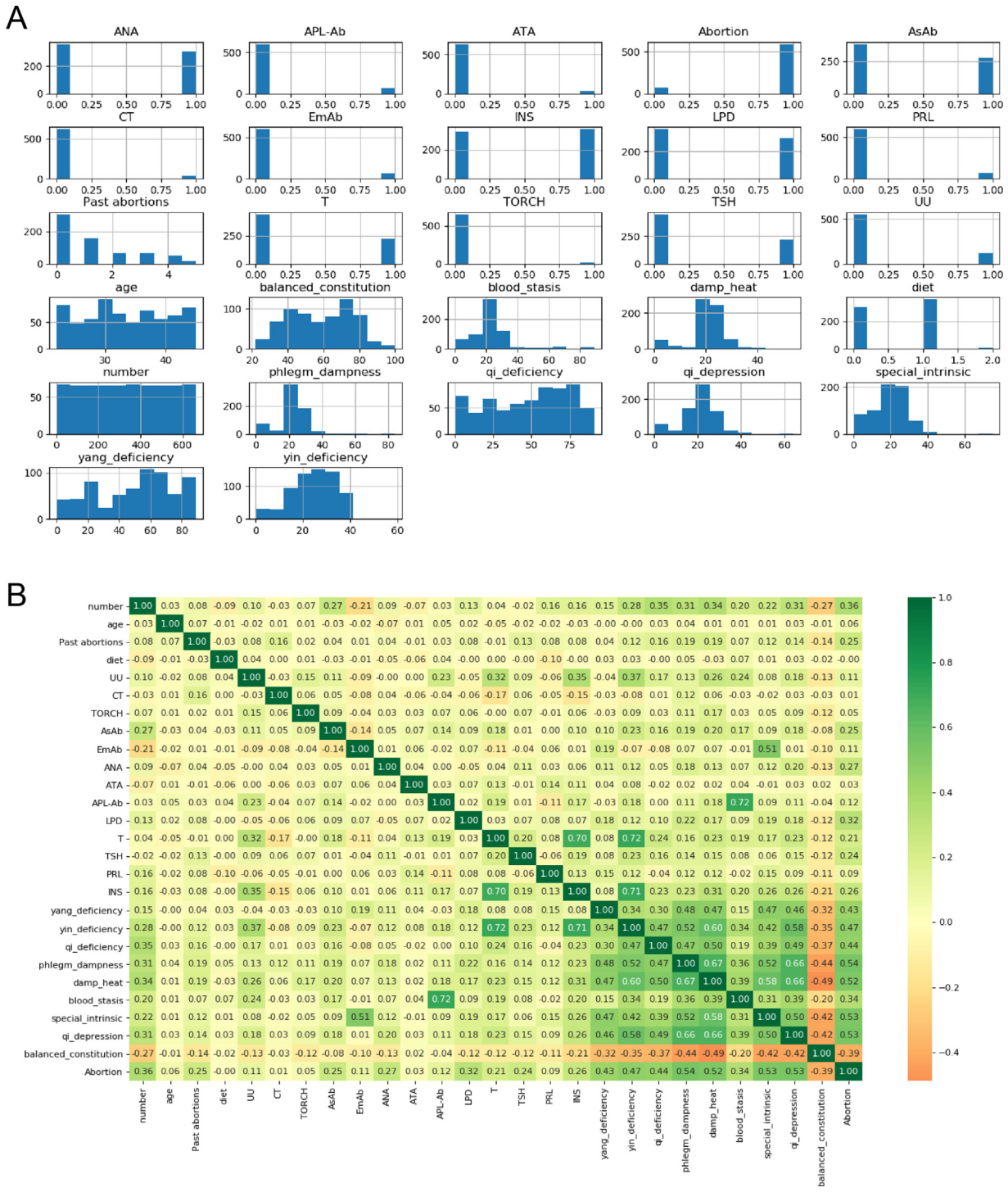

Fig. 2. Histogram and heat map of raw data to predict spontaneous abortion. (A) Histogram is mainly used to express the contrast relationship between each feature and SA. (B) Heat map shows the relative abundances of each feature and SA.

$$y = f_{sigmoid}(z) = \frac{e^z}{1+e^z} = \frac{1}{1-e^{-z}} \tag{2}$$

where $x_1 \sim x_n$ denote the input variables and $w_1 \sim w_n$ denote the weights being learned. And n represents the number of features after preprocessing, which is 25 in our paper. Logistic regression convert its output y using the logistic sigmoid function to return a probability value.

Grid search and learning curve are used to optimize the hyper parameters in our method. The number of max iterations of the LR algorithm is the hyper parameter to be optimized parameters.

2.4.2. Gradient boosting decision tree

Gradient boosting decision tree (GBDT) (Luna et al., 2019) is an ensemble machine learning method. GBDT constructs multiple decision trees through the gradient boosting method, which is helpful to overfitting. GBDT can combine the performance of the weak learner of a single

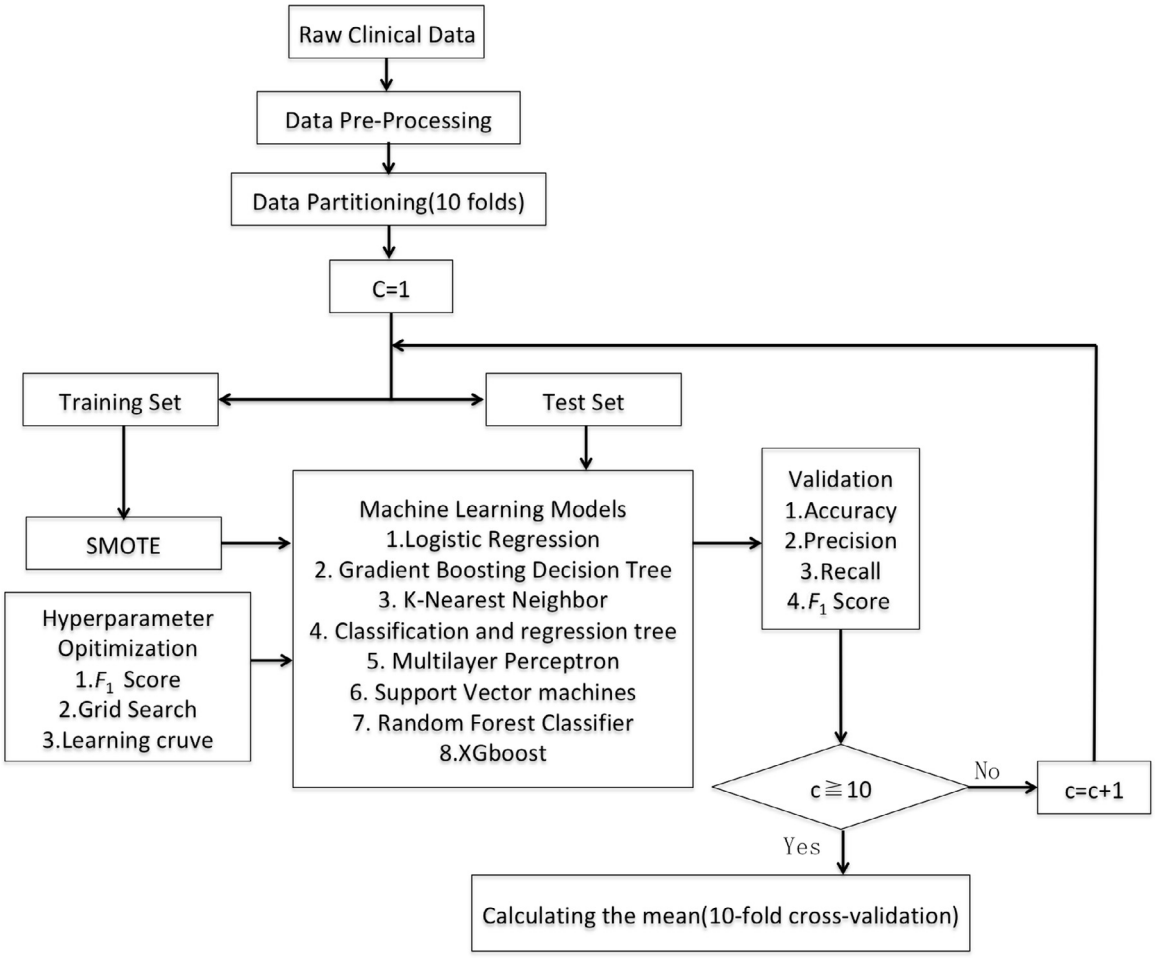

Fig. 3. Flow chart of the proposed method.

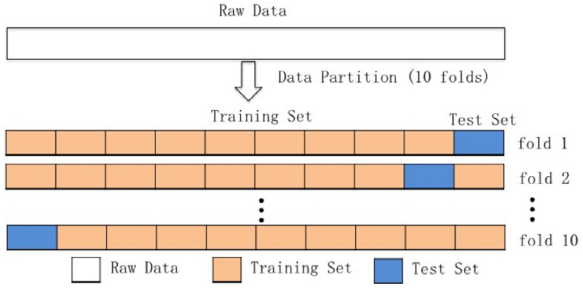

Fig. 4. Data partition of 10-fold cross validation for training and test sets.

decision tree into a single strong learner. Our algorithm selects the Nestimators and max feature as hyper parameters to improve prediction accuracy.

2.4.3. K-nearest neighbors

The k-nearest neighbors algorithm (KNN) is a non-parametric statistical method used for classification and regression (Yu et al., 2016). In KNN classification, the input consists of the k closest training examples in the feature space and the output is a class membership. An object is classified by a plurality vote of its neighbors, with the object being assigned to the class most common among its k nearest neighbors. The selection of k value, distance measurement, and classification decision rules are the three basic elements of the KNN algorithm. There are several ways to measure the distance between points in the space, such as Manhattan distance and Euclidean distance calculation. The Euclidean distance is usually used in the KNN algorithm, defined as an Eq. (3):

$$\rho = \sqrt{(x_2 - x_1)^2 + (y_2 - y_1)^2} \tag{3}$$

where (x_1, x_2), (y_1, y_2)denote two different points, represents the distance between the two points. The number of Nearest Neighbors parameter is optimized in our method to obtain higher prediction accuracy.

2.4.4. Classification and regression tree

Classification and regression tree (CART) is a decision tree algorithm, which can summarize decision rules from a series of data with features and labels, and present these rules with a tree structure to solve classification and regression problems. Our method uses the CART algorithm (Zhu and Fang, 2016), which builds a classification model in the form of a tree structure, as shown in Fig. 5B. The maximum tree depth is the hyper parameter optimized n CART.

2.4.5. Multilayer perceptron

Multilayer perceptron (MLP) is also called an artificial neural network (ANN). MLP consists of an input layer, a hidden layer, and an output layer (Heddam, 2016). The simplest MLP is a three-layer structure, which contains only one hidden layer, as shown in Fig. 5C. MLP can be regarded as a logistic regress-ion classifier. In fully connected MLP, each node in one layer is connected with a certain weight to each node in the next layer wit. The maximum number of iteration is the hyper-parameter in our method.

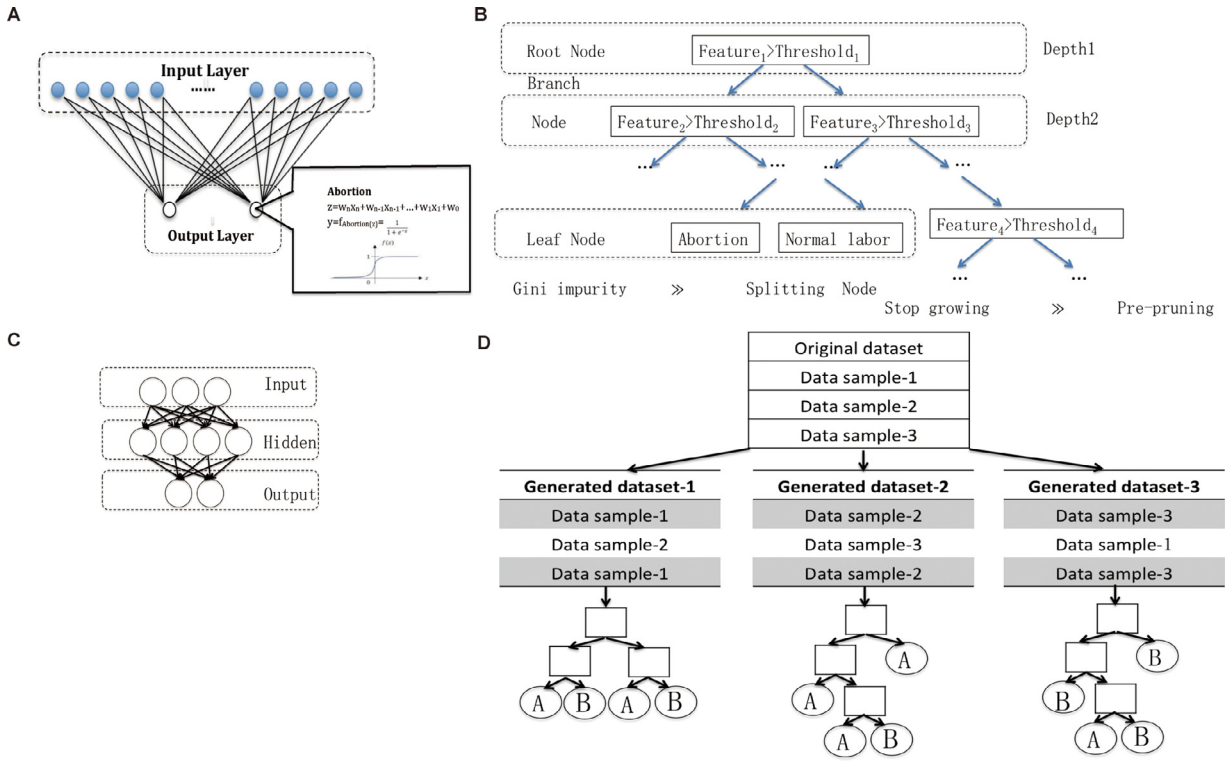

Fig. 5. Illustration of machine learning models used in the proposed method. (A) logistic regression; (B) classification and regression tree; (C) multilayer perceptron; (D) random forest classifier.

2.4.6. Support vector machines

Support vector machine (SVM) constructs a hyperplane or a set of hyper-planes in a high-dimensional or infinite-dimensional space, which can be used for classification, regression, or outlier detection (Wang et al., 2017). Our proposed method utilizes a Gaussian kernel function, and the data point is regarded as a 25-dimensional vector. We use a linear SVM to construct the hyper-spaced hyperplane to separate these points to distinguish different classes. The algorithm prevents overfitting and improves model accuracy by optimizing the penalty term C and the kernel coefficient gamma hyper parameter.

2.4.7. Random forest classifier

Random forest classifier (RFC) (Chowdhury et al., 2019) is an ensemble machine learning technique, constructs multiple decision trees, and collects them together for classification as shown in Fig. 5D. RFC has established multiple CART models with different samples and different initial variables. In each decision tree, a random subset of features is utilized to split the nodes. There is no correlation between each individual tree, and our method does not prune trees in random forests. The final prediction result is based on the majority vote model in multiple decision trees. RFC combines the advantages of feature selection and packaging. The number of DT is the hyper-parameter in our method.

2.4.8. Extreme gradient boosting

Extreme gradient boosting (XGboost) is one of the boosting algorithms, which is a machine learning method that integrates individual learners into more complex learners (Ogunleye and Wang, 2020). The XGboost algorithm grows a tree by continuously performing feature splitting. Then learning a tree every round, and fitting the residual between the predicted value and the actual value of the previous round model. According to the features of a sample, there will be a corresponding leaf node in each tree, and each leaf node corresponds to a score. Finally, the sum of the scores corresponding to each tree is the predicted value of the sample. The number of DT and the maximum tree depth are the hyper parameters in our method. The key optimized hyper parameter for the eight machine learning methods mentioned above is shown in Table 2. The most suitable assessment method to measure the prediction of the risk of SA among the eight machine learning methods is F_1 score as shown in Eq. (4). So the hyper parameter optimization is executed by grid search and learning curve of F_1 score. And the accuracy, precision, and recall and the area under the ROC curve will be defined in the next section.

$$F_1 = \frac{2 \times prcision \times recall}{precision + recall} \tag{4}$$

2.5. Assessment measurement

The performance of the applied models in this paper is evaluated by computing the diagnostic test characteristics, including accuracy, precision, recall, F_1score, and area under the receiver operating characteristic (ROC). The accuracy, precision, and recall are redefined by true positives (TP), true negatives (TN), false positives (FP), and false negatives (FN) are denoted in Eqs. (5)-(7):

$$\text{Accuracy} = \frac{TP + TN}{TP + TN + FP + FN} \tag{5}$$

$$\text{Precision} = \frac{TP}{TP + FP} \tag{6}$$

$$\text{Recall} = \frac{TP}{TP + FN} \tag{7}$$

where TP is the number of the samples that the actual values are aborted women and the predicted values are also aborted women. TN is the number of the samples that the actual values are normal pregnant women and the predicted values are also normal pregnant women. FP is the number of the samples that the actual values are normal pregnant women and the predicted values are aborted women. FN is the number of the samples that the actual values are aborted women and the predicted values are normal pregnant women.

Table 2
Hyper parameter optimization.

Model	Hyper parameter	Beginning value	Ending value	Interval	Optimum value
LR	max_iter	1	20	1	6
GBDT	N_estimators	170	200	1	172
KNN	N_neighbors	1	10	1	7
CART	max_depth	1	20	1	9
MLP	max_iter	1	250	1	201
SVM	C	0	10	0.01	0.54
RFC	N_estimators	30	60	1	48
XGboost	N_estimators	25	40	1	30

Table 3
Performance comparisons of eight machine learning methods.

	Accuracy	Precision	Recall	F_1 score	ROC AUC
LR	97.1%	98.0%	99.0%	98.4%	97.4%
GBDT	97.9%	99.0%	98.6%	98.8%	97.3%
KNN	95.8%	98.4%	96.9%	97.5%	97.3%
CART	96.4%	99.0%	96.9%	97.9%	95.5%
MLP	97.4%	98.4%	98.8%	98.6%	97.5%
SVM	97.1%	97.5%	99.5%	98.4%	97.3%
RFC	97.4%	98.9%	98.3%	98.6%	97.0%
XGboost	97.1%	98.6%	98.3%	98.4%	97.6%

Table 4
Performance comparisons of eight machine learning methods with sklearn default parameters.

	Accuracy	Precision	Recall	F_1 score	ROC AUC
LR	97.0%	97.8%	99.0%	98.3%	97.5%
GBDT	96.8%	98.7%	97.8%	98.2%	97.6%
KNN	95.0%	97.9%	96.6%	97.1%	96.5%
CART	94.4%	99.0%	94.7%	96.7%	95.7%
MLP	97.3%	98.2%	98.8%	98.5%	97.5%
SVM	96.5%	97.6%	98.6%	98.1%	97.5%
RFC	97.1%	98.8%	98.1%	98.4%	97.2%
XGboost	96.7%	98.1%	98.3%	98.1%	97.0%

3. Results

In this paper, the accuracy, precision, recall, F_1 score, and the area under the ROC curve are used to evaluate our prediction model, and 10-fold cross-validation method is applied to evaluate the optimized performance for the eight machine learning techniques. The results are shown in Table 3. The eight machine learning methods proposed in this paper shows a good effect on the prediction for SA. The prediction accuracy of all machine learning algorithms is all above 95.8%, and F_1 scores are above 97.5%

The performance comparisons of eight machine learning techniques proposed in this paper are shown in Fig. 6. From the perspective of the evaluation accuracy, GBDT has the best prediction effect. The second is RFC and MLP. It is easy to find that the prediction effect of the three tree-based methods is excellent. So the integrated classification model based on the decision tree is suitable for predicting SA. And the overall prediction effects of RFC, GBDT, and XGboost are better than CART.

4. Discussion

The learning curves of the key hyper parameters for the eight proposed machine learning methods for predicting SA are shown in Fig 7. The curves of the eight methods all show good convergence. The learning curves of the LR and MLP are shown as Fig. 7A and Fig. 7E, respectively. When the maximum number of iterations of LR and MLP are 6 and 201, respectively, the prediction effect is the best. The number of decision trees has a great influence on the prediction model for the ensemble classification algorithm based on the decision tree.

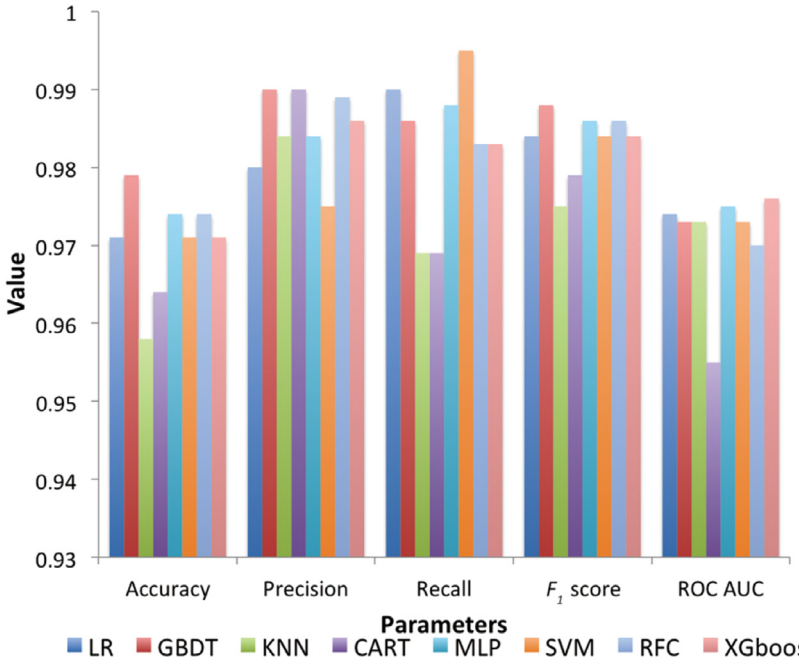

Fig. 6. Performance of different machine learning methods for prediction of SA.

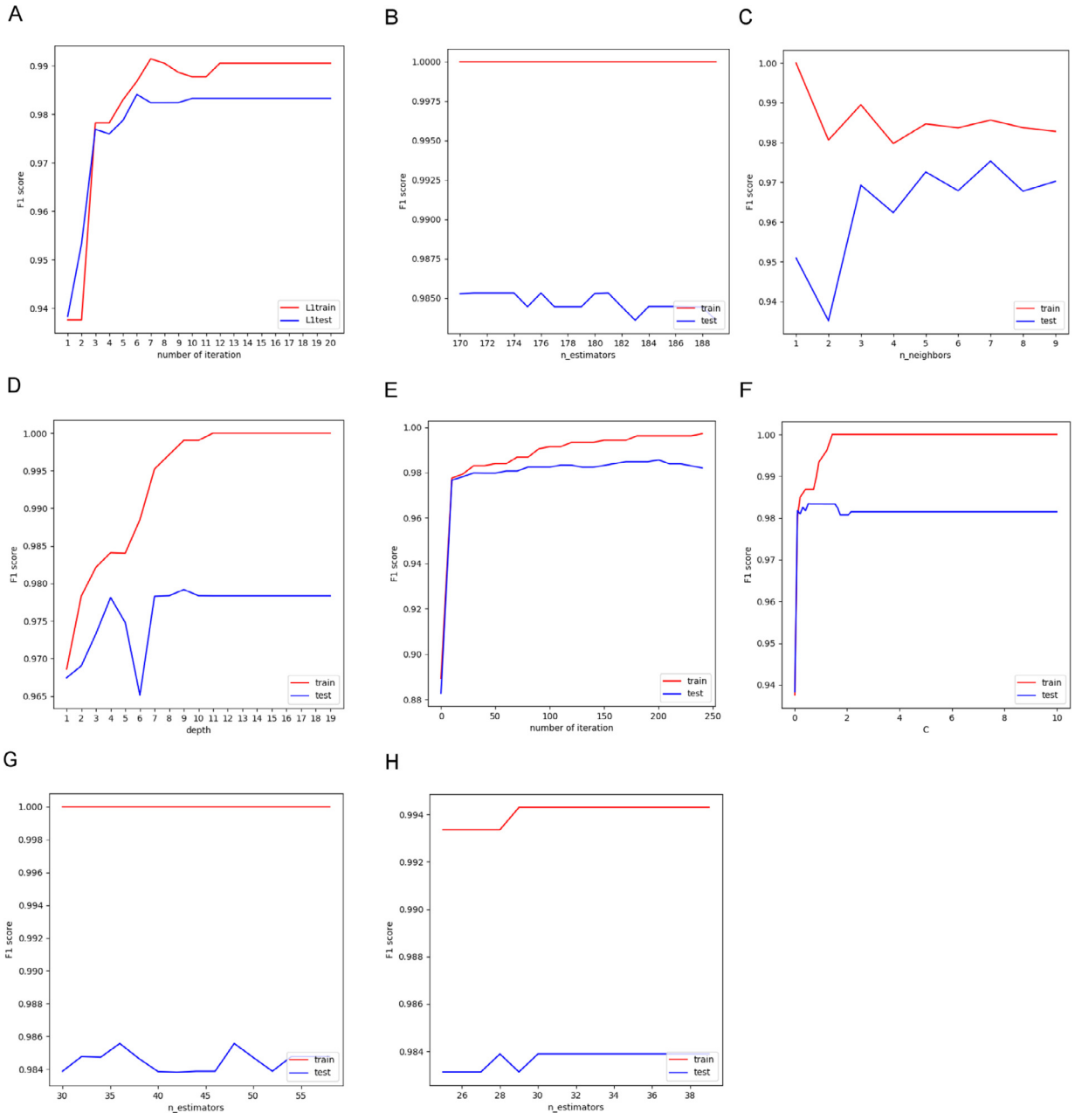

Fig. 7. A set of learning curves for each of the eight machine learning method. (A) logistic regression; (B) gradient boosting decision tree; (C) k-nearest neighbor; (D) classification and regression tree; (E) multilayer perceptron; (F) support vector machines; (G) random forest classifier; (H) XGboost.

The learning curves of the RFC, GBDT, and XGboost are shown as Fig. 7G, Fig. 7B, and Fig. 7H, respectively. When the number of decision trees of RFC, GBDT, and XGboost is 48, 172, and 30, respectively, the prediction effect is the best. In addition, as shown in Fig. 7D, when the maximum tree depth is 9, CART obtains the best prediction effect. As shown in Fig. 7C, when the number of neighbors is 7, the prediction effect of KNN is the best. As shown in Fig. 7F, when the penalty coefficient C is 0.54, SVM obtains the best prediction effect. In addition to the above hyper-parameters, other hyper parameters are also optimized. For example, when optimizing the GBDT model, the maximum number of features is 10. When optimizing the XGboost model, the maximum tree depth is 6. When optimizing the SVM model, the RBF kernel function is used, and the gamma hyper parameter is 0.45. What' is more, it is easy to find out that machine learning is an excellent way to predict SA. We can also get good prediction effects with the default parameters of the Scikit learn library, as shown in Table 4.

In this work, we intensively searched related works of literature from PubMed, WOS, Embase, CNKI, WanFang, and other databases by April 1, 2020. We identified a study in the diagnosis of SA patients using the SVM model in machine learning (Bruno et al., 2020), which used the SVM algorithm for predicting SA. This paper used 18 selected features after data processing for model prediction, which obtained a maximum accuracy of 93.85. Compared with the literature (Wang et al., 2017), the accuracy obtained by the GDBT algorithm proposed in our paper has improved by 4.05%. In addition, incorporating TCM constitution recognition is not considered, and the performance between different machine learning techniques is not discussed for risk prediction models. Therefore, there is an urgent need to further study the prognostic value of the test results used in the abortion population (van Dijk et al., 2020).

TCM has been widely used in the treatment of SA in China for thousands of years (Luo et al., 2012). Our team has conducted clinical and experimental studies on the correlation between SA and TCM consti-

tution for nine years (Ye et al., 2011; Ye et al., 2013) and created Yiqi Bushen Recipe for the treatment of SA. The clinical effect is remarkable, and a series of experimental demonstrations have been carried out (Ye et al., 2015; Ye et al., 2016). In the new era of precision medicine, an increasing area of interest is whether the research of diseases can provide practical health benefits at a population level. The combination of clinical data and TCM constitution to predict SA came into being. This method leads to a unified perspective in SA prediction and management that can be simultaneously tailored to each pregnancy and applied at any gestational age, even before pregnancy. The paper applies TCM constitution and clinical data to the risk prediction model of SA, which helps guide clinicians for further follow-up. The prediction results of this model show good prediction performance.

There are potential improvements to our approach. First, the candidate features are identified from the secondary analysis of the data, which do not include all potential risk factors, such as smoking, home care support, and details of surgery or medication. However, this study included the most common and representative features reported in other relevant literature (Bagis et al., 2001; Kianpour et al., 2019; Rasti et al., 2016; Soules et al., 1989; Zuily et al., 2015). Secondly, the data size is small, which may affect the performance of the model. Similarly, we failed to collect all the information about the results of the patient's risk of SA. However, there are still 40% of unexplained recurrent miscarriages, which indicates that the cause is complex. We included common causes, such as endocrine factors (T, PRL, INS, TSH, LPD), immune factors (APL, ANA, ATA, EmAb, AsAb), infection factors (TORCH infection, reproductive tract infection) (Bagis et al., 2001; Kianpour et al., 2019; Rasti et al., 2016; Soules et al., 1989; Zuily et al., 2015), into the SA prediction model in this paper. In addition, our work is a single-center study, and the prevalence of patients in other regions needs further studies from patients in other geographical locations are demanded. This study may have an impact on clinicians, patients, and decision-makers. The risk prediction model provides an accurate and simple method to classify patients into clinically meaningful risk groups upon discharge and promotes further management in local communities and families. In short, we have determined the clinical indicators for predicting the risk of SA with integrated Chinese and Western medicine. We have also developed a predictive model that allows clinicians to estimate the risk of SA based on these features. The application of this model may intervene and prevent the patient's abortion in advance, and reduce the patient's abortion rate to a certain extent, but the patient needs appropriate treatments and follow-up.

5. Conclusion

Our study uses machine learning techniques for SA prediction with several TCM constitution and clinical data dimensions training. This paper utilizes eight machine learning techniques to predict SA. The results show that GBDT has the best prediction effect. Machine learning technology can improve the performance of predicting SA. It provides the application of clinical practice guidelines, facilitates shared decision making around SA through individualized risk prediction, and improves clinical outcomes through appropriate TCM use in high-risk SA patients. It is a new and feasible tool for clinicians to screen aborted patients with a high-risk rate in the process of integrating Chinese and Western medicine diagnosis and treatment. The important goal in the future is to incorporate this model into the hospital electronic medical system as a doctor's auxiliary tool and to evaluate the effect of this method in clinical practice guidelines.

Ethical Approval

Batch No. [2020]039.

Data Availability

Nil.

Funding

Nil.

Declaration of Competing Interest

All authors declare that they have no competing interests.

CRediT authorship contribution statement

YL, YYG and LQY analyzed and interpreted the data, and was a major contributor in writing the manuscript. QTW, STX and LYWH participated in data collection. PY was a major contributor in reviewing the manuscript, and handled the project supervision. All authors read and approved the final manuscript.

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Supplementary Materials

Nil.

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