

Machine Learning Models in Type 2 Diabetes Risk Prediction: Results from a Cross-sectional Retrospective Study in Chinese Adults*

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Summary: Type 2 diabetes mellitus (T2DM) has become a prevalent health problem in China, especially in urban areas. Early prevention strategies are needed to reduce the associated mortality and morbidity. We applied the combination of rules and different machine learning techniques to assess the risk of development of T2DM in an urban Chinese adult population. A retrospective analysis was performed on 8000 people with non-diabetes and 3845 people with T2DM in Nanjing. Multilayer Perceptron (MLP), AdaBoost (AD), Trees Random Forest (TRF), Support Vector Machine (SVM), and Gradient Tree Boosting (GTB) machine learning techniques with 10 cross validation methods were used with the proposed model for the prediction of the risk of development of T2DM. The performance of these models was evaluated with accuracy, precision, sensitivity, specificity, and area under receiver operating characteristic (ROC) curve (AUC). After comparison, the prediction accuracy of the different five machine models was 0.87, 0.86, 0.86, 0.86 and 0.86 respectively. The combination model using the same voting weight of each component was built on T2DM, which was performed better than individual models. The findings indicate that, combining machine learning models could provide an accurate assessment model for T2DM risk prediction.

Key words: type 2 diabetes; risk prediction; machine learning

Type 2 diabetes mellitus (T2DM) is a major disease with a high prevalence around the globe, and a trend that is still on the rise^[1, 2]. T2DM is a leading cause of morbidity and mortality and contributes to increased risks of cardiovascular risk diseases by 2 to 4 times^[1]. As a large developing country in the world, China has now joined the world epidemic of T2DM with its

rapid economic growth over the past three decades^[2-4]. Although it is increasing rapidly both in urban and rural areas, the prevalence of T2DM is significantly higher in urban than in rural population^[2]. Recent studies indicate that T2DM can be prevented and early screening and diagnosis are thus central to effective prevention strategies^[5-8]. Accordingly, more attention should be paid to the early diagnosis of T2DM in urban areas in consideration of its great health burden.

To this end, a series of clinical prediction methods have been developed to identify individuals with unknown diabetes or those at high risk of developing diabetes over recent years^[9-13]. However, these models may not be readily applicable to patients reporting to a hospital for different types of services. Still, considering differences in ethnic specificity and economic development in different regions, it is necessary to develop a risk prediction system for T2DM, that can meet the characteristics of the Chinese population, especially in urban areas.

Machine learning and data mining models are increasingly utilized in the field of science^[14-19]. The main objective of these models is to determine effective variables and the relationship between them^[19]. These models can also be used for prediction and estimation^[14, 15].

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Machine learning models can be defined as a process to design a model that is learned through experience and to improve its performance. These models are a field of artificial intelligence and are an active field of research in different sciences. Also, in medical science, machine learning techniques are widely used for the diagnosis of T2DM^[15, 17-19]. For example, decision tree models have been widely used to predict diabetes^[20] and experimental results showed that the weighted voting method not only improves the classification accuracy, but also has a strong generalization ability and universality^[21, 22].

The aim of this study is to create a diabetes risk prediction model using available data in a retrospective study aimed at preventing development of overt T2DM among Chinese urban adults in Nanjing. Therefore, we implemented in this study five different machine-learning techniques such as Multilayer Perceptron (MLP), Ada Boost (AD), Trees Random Forest (TRF), Support Vector Machine (SVM) and Gradient Tree Boosting (GTB) to model T2DM and analyze the performance.

1 MATERIALS AND METHODS

1.1 Data Collection and Indicator Selection

We collected physical examination data from 8000 people with non-diabetes and 3845 people with T2DM from the Nanjing Drum Tower Hospital. This study was approved by the Ethics Review Committee of Nanjing Drum Tower Hospital.

The physical examination data were consisted of about 450 indicators, but many of these physical examination indicators had no strong relationship with T2DM. We manually selected some indicators that were more relevant to T2DM from the view of medicine, and the indicators we selected are shown in table 1^[23, 24]. The age of T2DM patients was from 32 to 104 years old, and that of non-T2DM people was 19 to 99 years old (fig. 1).

Table 1 The selected indicators

Indicators	Unit
Gender	Male/Female
Age	-
Body mass index	-
Systolic pressure	mmHg
Diastolic pressure	mmHg
Glycated hemoglobin (A1C)	%
Triglycerides	mmol/L
Total cholesterol	mmol/L
H-cholesterol	mmol/L
L-cholesterol	mmol/L
Glucose	mmol/L

Note: Considering that T2DM can cause some complications, we also take fewer common indicators which are highly relevant to T2DM complications that can help diagnose.

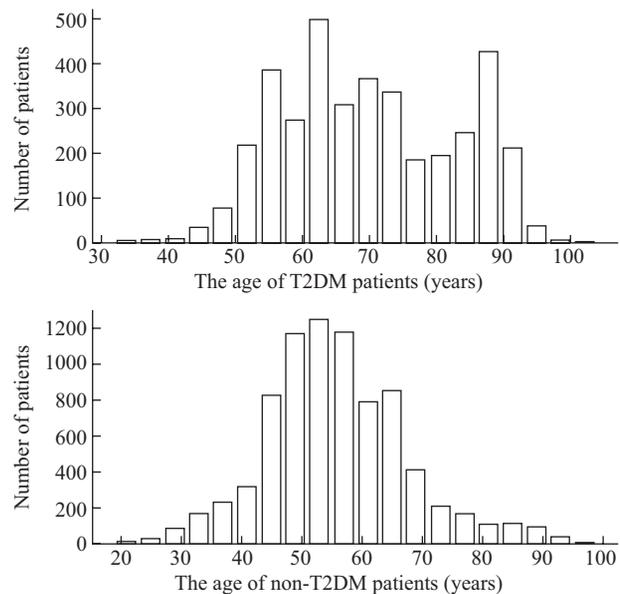


Fig. 1 The age distribution of T2DM (A) and non-T2DM (B) patients

1.2 Data Preprocessing

In this physical examination data set, most of the T2DM patients' data or non-T2DM people's data were complete, however, there were a fewer samples missing one or two feature values. The mean of the corresponding feature was used to fill the missing feature, which is a basic strategy. To make the filled values more representative, the mean of T2DM patients and non-T2DM patients was calculated separately.

Considering that the values of features have different intervals that can affect the results when building the machine learning model, we used the strategy which was called Min-Max Normalization to make sure the values were all between 0 and 1 in every feature.

$$v_{new} = \frac{v_{old} - \min_A}{\max_A - \min_A} (new_{\max_A} - new_{\min_A}) + new_{\min_A}$$

$$new_{\min_A} = 0 \quad new_{\max_A} = 1$$

1.3 Machine Learning Methods

We built a combination model which was based on five machine learning models to predict whether an unknown sample was a T2DM or not, and also output the probability he/she became T2DM patients. In this study, we used Multilayer Perceptron (MLP), Adaptive Boosting (AdaBoost), Random Forest, Support Vector Machine (SVM), and Gradient Boosting. The MLP consists of input layer, output layer and hidden layers. All the layers contain several simple interconnected neurons (also known as nodes). In each interconnected neuron this study used Relu function as activation function. The output of the node is calculated by the connection weight matrix and becomes the input value of the next layer. When training a multilayer perceptron,

back propagation algorithm is performed to update the weights matrix^[25].

By training some weak classifiers, AdaBoost combines these weak classifiers into a more complex classifier. Different from other traditional bagging strategy, this method pays more attention to the samples that are misclassified by the previous weak classifiers, which means the training instance who was misclassified by the previous weak classifiers will have greater weight to be selected^[4]. In Random Forests, each classifier is a decision tree which depends on independent sampling, and has the same distribution with other trees in the forest. Random forests can be constructed using a combination of bagging and random selection of features^[26]. SVM is a very popular machine learning algorithm. When the training data are linearly separable, SVM tries to maximize the marginal of hyperplanes so that as much as possible to separate the training data. But when the training data are non-linearly separable, SVM applies kernel function to transform the training data into high-dimensional space to separate the data effectively^[27]. Gradient Boosting is also by combining weak classifiers into a stronger classifier to make the final decisions. Every iteration aims to reduce the residual error of the previous iterations in the gradient direction^[28].

In order to combine the five machine learning models' results, we used a strategy that simulated the doctor consultation in reality. Imagining that the five models are five experts, when the unknown sample comes, they diagnose the sample and have five probabilities whether the sample is T2DM patients or not. Then, we used weighted average probabilities to predict the probability that the sample becomes each class (In this study, the class is 0 or 1, 0 means the sample is non-T2DM person, while 1 represents T2DM patients).

1.4 Validation and Evaluation Strategy

We split all the data into three data sets (table 2): training set, cross-validation (CV) set, test set, and the ratio of the three sets was about 6:2:2. In the CV set, we use 10-fold CV, meaning that the CV set is randomly split into 10 subsets with no sample intersection, then we repeat the process 10 times, for each turn No. i , the subset of i is retained as the validation data, and the other data are used as training data. So, for each machine learning model, we can get 10 performance evaluation data in the end. Using CV data, we could evaluate the performance of each machine learning model, to choose which is better, also, adjust the model's parameter values.

Table 2 Three data sets

Groups	Training set	CV set	Test set	Total
T2DM	2307	769	769	3845
Non-T2DM	4800	1600	1600	8000
Total	7107	2369	2369	11845

The data were randomly distributed, although the original samples' order was originally randomized.

In order to assess the performance of the machine learning model, we calculate the confusion matrix. Suppose the positive and negative samples are P and N , in this study, the positive samples are T2DM patients, the negative samples are non-T2DM people, and the confusion matrix is shown in table 3.

Table 3 Confusion matrix model

Subjects		Predict class		
		T2DM patients	Non-T2DM people	
Real class	T2DM patients	TP	FN	P
	Non-T2DM people	FP	TN	N
		P'	N'	P+N

TP: true positive, meaning the T2DM patients are correctly classified by our model; TN: true negative, meaning the non-T2DM people are correctly classified by our model; FP: false positive, meaning the non-T2DM people are incorrectly classified as T2DM patients by our model; FN: true negative, meaning the T2DM patients are incorrectly classified as non-T2DM people by our model

To illustrate the diagnosis ability of our model, the ROC curve is drawn based on a series of different cut-off values to classify the samples. The horizontal axis is false positive ratio (also defined as $1 - \text{specificity}$), and the vertical axis is true positive ratio (also known as sensitivity).

2 RESULTS

2.1 Performance of Five Machine Learning Models in CV Set

Five machine learning models were tested in cross-validation set, and also, the hyper-parameters for each model were adjusted. The performance of each model in accuracy is shown in table 4. The results showed that these models had similar accuracy performance. Considering the low variance of each model, all the five models are stable and reliable.

For the model MLP, we built a three hidden layer artificial neural network, and the units for each hidden layer were 20, 10, and 2 respectively. We used Relu as our activation function, and Limited-memory BFGS as the solver for weight optimization. Those hyper-parameters could make the MLP model perform better.

For the model AdaBoost, we built a model whose maximum number of weak learners was 30. When

Table 4 The performance of each model in accuracy

Model name	Mean	Variance
MLP	0.87	0.0002
AdaBoost	0.86	0.0002
Random Forests	0.86	0.0003
SVM	0.86	0.0002
Gradient Boosting	0.86	0.0002

the learning rate was 0.5, the model had a better performance in CV data set.

For the model Random Forest, when we set the maximum number of weak learners to 50, the model had a satisfied performance.

For the model SVM, we created a model with a linear kernel for its great performance in CV data set after trying other kernels such as Polynomial kernel, Radial Basis Function kernel, Sigmoid Function kernel, etc. When we set 3.0 as the penalty parameter for error term and 5000 as the maximum number of iteration, this model could be performed better under the 10 CV methods.

For the model Gradient Boosting, we set 150 as the maximum number of weak learners, for each tree, we set 3 as the maximum depth of the individual regression estimators.

So, on the whole, the performance of the five models in the CV set under the 10 CV methods was similar, no matter from the view of the average accuracy or the variance of accuracy. From another aspect, the results also showed that we could integrate the five models to build our final decision model.

2.2 Combination of Five Models

After observing the performance of five machine learning models in CV data set, all the five models were used to generate the final decision model, considering they have very similar performance in CV data set. When voting the unknown sample, we gave the five models the same voting weight, so, the last computing method is as follows (table 5).

Table 5 The voting weight of five models

Classifier	T2DM patients	Non-T2DM people
MLP	$1 \times p_1^1$	$1 \times p_0^1$
AdaBoost	$1 \times p_1^2$	$1 \times p_0^2$
Random Forest	$1 \times p_1^3$	$1 \times p_0^3$
SVM	$1 \times p_1^4$	$1 \times p_0^4$
Gradient Boosting	$1 \times p_1^5$	$1 \times p_0^5$
<i>P</i> average	$\sum_{i=1}^5 p_i^1/5$	$\sum_{i=1}^5 p_i^0/5$

We can get two useful results when we predict the unknown sample. One is the class of the unknown sample, and the other is the probability of the unknown sample as the predicted class.

The p_j means the probability of an unknown sample becomes class j , the value of j is 1 or 0, and i represents the number of the five models. The p_i^j means that the probability of model i predicts the sample as class j .

2.3 Evaluation of Model

We trained the combination model using the training data set, and then we used the test data set to evaluate the performance of the combination model.

The accuracy of our combination model in the test

data set was 0.91, and the confusion matrix is shown in table 6.

Table 6 The confusion matrix

Subjects		Predict class	
		T2DM patients	Non-T2DM people
Real class	T2DM patients	641	128
	Non-T2DM people	87	1513

The sensitivity was equal to 0.83, and the specificity was equal to 0.95. The relationship between sensitivity and specificity was inversely proportional. Also, the precision was 0.88, and the recall was 0.83.

The AUC value was 0.97, and the ROC curve is shown in fig. 2.

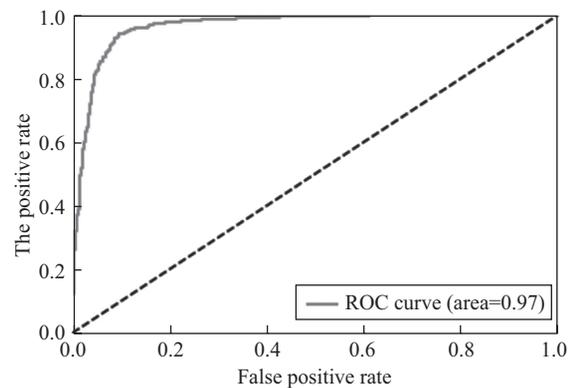


Fig. 2 The combined model's ROC curve

3 DISCUSSION

T2DM accounts for more than 90% of patients with diabetes and leads to microvascular and macrovascular complications that cause profound psychological and physical distress to both patients and carriers and put a huge burden on health-care systems. However, it tends to be undiagnosed as a result of a lack of specific symptoms and limited interest in the public health care sector. Early diagnosis and detection might help in preventing its complications^[29] and delaying its progression^[5]. Furthermore, it is also beneficial for both public health and clinical practice in general^[29]. Until now, diabetes prevention trials included people with impaired glucose tolerance, who can be identified only by conducting an oral glucose tolerance test^[12]. However, screening by oral glucose tolerance test would probably increase the yield and economic efficiency of screening^[30]. Thus, finding simpler methods to identify individuals of diabetes and who might benefit from targeted prevention is an important goal.

Machine learning models are increasingly used in the field of science^[31-36]. These models can be used for prediction and estimation^[34, 37]. Machine learning models can be defined as a process to design a model

that is learned through experience and to improve its performance. In medical science, machine learning techniques are widely used for the diagnosis of T2DM^[16-19]. Using those tools as a diagnostic tool can reduce the workload of doctors. To date, most existing prediction models for risk of developing diabetes have been derived from white populations^[35-42], and few models are based on Asian ethnic groups^[40-44]. It has been shown that the models developed in white populations tended to poorly predict high-risk subjects for diabetes in Asian populations^[43], because each ethnic group has different and distinctive genetic and environmental characteristics. Therefore, considering the high incidence of diabetes in Chinese urban population, there is need for developing different models for different populations to screen individuals for diabetes, especially for Chinese urban residents. We created predictive models for detecting undiagnosed diabetes using the data from Nanjing Drum Hospital with different machine-learning methods. We collected physical examination data from 8000 people with non-T2DM and 3845 patients with T2DM. The classifiers used in this study included MLP, AdaBoost, Random Forest, SVM and Gradient Boosting. These methods were evaluated based on the criteria of sensitivity, specificity, accuracy, ROC curve and precision. The result of comparison shows that the performance of each model in accuracy is similar, no matter from the view of the average accuracy or the variance of accuracy. Considering the stability and reliability of each model, we integrated the five models to build our final decision model. The combination of five models achieved a high accuracy prediction (AUC=0.97). Generally, most of the algorithms used achieved mean AUCs greater than 70%. Since these test dataset values are superior to the AUCs of several other scores that were previously validated in other populations, this score shows potential for use in practice.

Zou *et al* randomly selected the data from 68 994 healthy people and diabetic patients in Luzhou, China. In this study, decision tree, random forest and neural network were used to predict T2DM. The results showed that prediction with random forest could reach the highest accuracy (ACC=0.8084) when all the attributes were used. The prediction model developed by Habibi *et al*^[44] used decision tree for screening T2DM, which did not require laboratory tests for T2DM diagnosis. The model was built based on diagnosis variables defined by other studies as main predictor variables [age, body mass index (BMI)]. It does not require any blood assays or mathematical calculations to derive a model and seems to be a simple and easy way to use. Although collecting data from a questionnaire is likely less costly and more acceptable than methods of screening involving biochemical measures such as blood glucose, difficulties in distributing questionnaires,

the time required to complete them, the complexity of computing the results, issues related to misreporting (reporting bias), and unavailability of some required information may hamper their population-wide application. Questionnaires may also create anxiety or false reassurance. Furthermore, these risk scores focus mainly on non-modifiable risk factors such as age and family history or on the consequences of adverse health behaviors such as high BMI and medication use. In addition, available risk factor information might differ between health services. This study used 11 features that are closely related to the occurrence of T2DM, including gender, age, BMI, systolic pressure, diastolic pressure, HbA1c, triglycerides, total cholesterol, H-cholesterol, L-cholesterol and fasting blood glucose. Of importance, validation tests confirmed that our risk score performed well in the prediction of diabetes in the independent sample, but additional external validation would be warranted.

The current study has some limitations, which could be addressed by additional investigations. Firstly, the model might be unable to precisely predict the risk of future development of diabetes because the data were derived from a cross-sectional study. Although cross-sectional studies are well suited for prevalent but undiagnosed disease, additional verification based on prospective studies could be needed for the Chinese population. Second, the number of samples needs to be enlarged in future. Although currently selected 8000 people with non-T2DM and 3845 patients with T2DM achieve high accuracy on detecting T2DM, we still need more samples from our hospitals to confirm scalability of our models. This process will require more reviewing efforts from humans and will be considered as our next plan. Thirdly, our model is not confirmed on other institutes such as western data and does not include potentially important risk factors such as diet/nutrition or family history because of the lack of data. The included people in this study was the physical examination population in our hospital. Diabetes was diagnosed based on fasting blood glucose. The proportion of diabetic patients in this article is slightly biased, which is another one of the limitations. Although the combined models achieve a high performance on Chinese data, we believe it is also fit for identifying T2DM subjects on western people and we will test such hypothesis in our next step.

In summary, use of machine-learning techniques proves to be a viable alternative for building predictive diabetes models with good results. Our results significantly outperform the results which are reported in other reports of the literature in general. In our future work, we will validate our results with other related cohorts. Our combined model can be proposed for identifying people who are at high risk of developing T2DM. This method can be used for feature selection

and in application. This approach needs to be tested and validated in other studies.

Conflict of Interest Statement

The authors declare that they have no conflicts of interest.

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