

A Simple Prediction Model of Hyperuricemia for use in a Rural Setting

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Abstract

Currently, the most widely used screening methods for hyperuricemia (HUA) involves invasive laboratory tests, which are lacking in many rural hospitals in China. This study explores the use of non-invasive physical examinations to construct a simple prediction model for HUA. Data of 9,252 adults from July to October 2019 in the Affiliated Hospital of Guilin Medical College were collected and divided randomly into a training set (n = 6,364) and a validation set (n = 2,888) at a ratio of 7:3. In the training set, non-invasive physical examination indicators of age, gender, body mass index (BMI) and prevalence of hypertension were included for logistic regression analysis, and a nomogram model was established. The classification and regression tree (CART) algorithm of the decision tree model was used to build a classification tree model. Receiver operating characteristic (ROC) curve, calibration curve and decision curve analyses (DCA) were used to test the distinction, accuracy and clinical applicability of the two models. The results showed age, gender, BMI and prevalence of hypertension were all related to the occurrence of HUA. The area under the ROC curve (AUC) of the nomogram model was 0.806 and 0.791 in training set and validation set, respectively. The AUC of the classification tree model was 0.802 and 0.794 in the two sets, respectively, but were not statistically different. The calibration curves and DCAs of the two models performed well on accuracy and clinical practicality, which suggested these models may be suitable to predict HUA for rural setting.

Introduction

Hyperuricemia (HUA) is a chronic metabolic disease caused by purine metabolic disorders, which can result from congenital purine metabolic abnormalities, systemic diseases or administration of certain drugs [REF]. Its clinical features include fluctuating or persistent increases in blood uric acid, gout and interstitial nephritis. In severe cases, joint deformities or uric acid urinary tract stones may occur [1]. With the continued improvement of China's economic level, the prevalence of diseases such as HUA is on the rise. A population study based on big data showed that from 2014 to 2017, the prevalence rate of HUA in Chinese adults increased from 18.29–23.06% [2]. At present, there were many studies to show that HUA is positively correlated with hypertension [3], acute myocardial infarction [4], coronary heart disease [5], acute kidney injury [6], chronic kidney disease [7], high incidence of cancer and mortality [8]. However, due to a lack of awareness regarding HUA in China the diagnosis and cure rate of patients of HUA is low. Therefore, early detection and prevention of this disease has become increasingly important goal.

In previous studies, genetic tests [9] and dietary information [10] were used in an attempt to predict the risk of HUA, but at present, these criteria have still been widely used to verify the incidence and risk factors of HUA by recording lifestyle characteristics and blood biochemical indicators [11]. Taking into account the large population base in China, the large proportion of the rural inhabitants, the imbalance of medical resources and the lack of corresponding facilities and equipment in many rural hospitals, coupled with the need to reduce the financial burden and avoid invasive procedures such as taking blood, we attempted to predict the risk of HUA based on some basic information of the patients and non-invasive examinations, including age, gender, body mass index (BMI) and the prevalence of hypertension.

Logistic regression is often used to look for risk factors associated with disease as well as to predict the probability of the occurrence of certain diseases. It is a specific and simple traditional prediction method, and it can visually present the results pictorially through the nomogram model. However, when dealing with complex relationships between multiple factors, the errors involved in analysis will tend to increase. The decision tree model is a simple and easy-to-use non-parametric classifier, among which the classification and regression tree (CART) algorithm is the most widely used algorithm for this model. When the dependent variable is the classification variable, the generated decision tree is the classification tree. The classification tree model is a tool to represent processing logic by using a binary tree diagram, which has no strict restrictions on the type of data and can make up for the shortcomings of traditional statistical methods [12]. Therefore, in this study, the nomogram and the classification tree models were combined to fully explore the physical examination database of a healthy population and construct a HUA prediction model suitable for people living in rural settings. It was anticipated that this procedure would produce a high accuracy, low cost and easy to use model which can provide assistance for the health management of rural community populations by helping in the prevention of HUA.

Materials And Methods

Study participants

The study population for this cross-sectional survey came from adults who underwent health examinations at the Physical Examination Center of the Affiliated Hospital of Guilin Medical College from July to October 2019. All participants underwent questionnaire surveys, physical examinations and laboratory examinations and patients with severe renal impairment (such as chronic renal insufficiency uremic periods), severe liver impairment (with ALT or AST > 120 U/L), malignant tumors and pregnant women were excluded. Finally, a total of 9,252 adults aged 18–90 years old were included in the study which was approved by the Ethics Committee of Guilin Medical College (approval number: GLMUIA2019064), and all participants gave written informed consent.

Data selection and measurements

We adopted a questionnaire survey method to collect the general information and clinical data of the research population, including: (1) basic personal information (name, gender and age); (2) previous medical history (hypertension, diabetes, uremia stage of chronic kidney failure and tumor history) and (3) pregnancy history. The height, weight and blood pressure of the subjects were measured as part of the physical examination. The height was measured without a crown or shoes while standing upright (the value obtained was accurate to 0.01m). The weight was measured without shoes and an empty bladder (the value obtained was accurate to 0.1kg), and the BMI was calculated ($BMI = \text{weight (kg)} / \text{height}^2 (\text{m}^2)$). Before taking the blood pressure measurements, subjects were required to avoid drinking alcohol, smoking, drinking tea, coffee or performing vigorous exercise and resting for at least 5 minutes, and the blood pressure of the right arm brachial artery was measured twice at an interval of 1–2 minutes for each subject. If there was a big difference between the two measurements, the blood pressure of the right

brachial artery was measured for a third time, and the results were averaged for the three readings, with the value obtained being accurate to 1mmHg. During laboratory examination, subjects were asked to eat a low-purine diet at dinner the previous day with details of what they should not indulge in being given to them. The venous blood was drawn after the subjects had an empty stomach for more than 10 hours in order to detect serum uric acid (SUA), serum creatinine (SCr), blood urea nitrogen (BUN), alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels. All measurements were performed by well-trained doctors, nurses and researchers.

The diagnostic criteria of hypertension used was in accordance with the diagnostic criteria of the "2018 China Guidelines for the Prevention and Treatment of Hypertension" [13]: systolic blood pressure ≥ 140 mmHg and/or diastolic blood pressure ≥ 90 mmHg and/or a previous history of hypertension diagnosed as hypertension. The diagnosis of HUA was as stated in the "Guidelines for the Diagnosis and Treatment of Hyperuricemia and Gout in China (2019)" [14] and HUA was diagnosed when the SUA level was higher than 420 mmol/L for both men and women.

Statistical analysis

SPSS25.0 (IBM, USA), STATA (version 15.1) and R for Windows (version 4.0.0) statistical software were used for data processing and statistical analyses. The counts data were represented by n (%), and chi-squared test was used for comparison between groups. Measurement data were represented by $\bar{x} \pm SD$, and comparisons between groups were performed by Student's t -test. The model construction and analysis can be divided into three stages:

In the first stage, the method of pure random sampling was used to select 70% of the sample size to form a training set for calculating parameters and building the model, and the remaining 30% of the sample size was used to form a validation set for testing and evaluating the model.

In the second stage, two models were constructed. The establishment of a nomogram model: for the training set data, univariate logistic regression analysis was carried out first. Variables with $P < 0.05$ were further analyzed by multivariate logistic regression analysis. On this basis, the rms package, which offers a variety of tools to build and evaluate regression models in R, was used to establish a nomogram which could directly display the model. For establishment of the classification tree model, SPSS 25.0 was used for analysis and modeling in the training set, and debugging of the important parameters such maximum tree depth and minimum number of cases. After verification of the training set, when the maximum tree depth = 4, parent node = 200 and child node = 100, the model was deemed to have reached the optimal level.

The third stage was the evaluation of the models. The receiver operating characteristic (ROC) curves were drawn to analyze the sensitivity and specificity of the two models, and the discriminability of the two models was evaluated by comparing the area under ROC (AUC). Using the rms package and drawing a calibration curve, the accuracy of the prediction of the two models was further evaluated. Finally, in order to determine whether the two models could improve patient prognosis, decision curve analysis (DCA) was

drawn to evaluate the clinical practicality of the two models. All statistical tests were two-sided tests, and $P < 0.05$ was considered as statistically significant.

Results

Clinical characteristics of the subjects

The clinical characteristics of the population in this study are shown in Table 1. In this study, 2,023 HUA patients (1,861 males and 162 females) were identified, with an average SUA level of 482.41 ± 52.00 mmol/L, and 7,229 non-HUA patients (3,471 males and 3,758 females), with an average SUA level of 312.52 ± 61.55 mmol/L. There were 6,364 and 2,888 cases in the training and validation sets, respectively.

Table 1
Clinical characteristics of the population used in this study

Variable	Training set ($n = 6364$)		P value	Validation set ($n = 2888$)		P value
	Non-HUA ($n = 4960$)	HUA ($n = 1404$)		Non-HUA ($n = 2269$)	HUA ($n = 619$)	
Age (years)	42.71 ± 12.59	44.30 ± 13.17	< 0.001	42.75 ± 12.79	44.11 ± 13.36	0.021
Gender			< 0.001			
Male	2399	1295		1072	566	
Female	2561	109		1197	53	
BMI (kg/m^2)	23.65 ± 3.29	26.25 ± 3.35	< 0.001	23.58 ± 3.17	25.98 ± 3.38	< 0.001
Hypertension			< 0.001			< 0.001
No	4064	954		1848	423	
Yes	896	450		421	196	

Participants in the training and validation sets had similar clinical characteristics, with no statistical difference in age, gender, BMI, prevalence of hypertension and prevalence of SUA ($P > 0.05$). In the training set, the age, gender, BMI and prevalence of hypertension of HUA patients were statistically different from those of non-HUA patients ($P < 0.05$). The comparison of clinical characteristics between the two groups in the validation set was consistent with the training set (Table 1).

Establishment and exhibition of nomogram model

The results of univariate logistic regression analysis showed that the risk factors for HUA included age, gender, BMI and hypertension, and the results were statistically significant ($P < 0.05$). Age (assigned to four groups: 18–29 years old = 1, 30–49 years old = 2, 50–69 years old = 3, ≥ 70 years old = 4), gender (assigned to two groups: female = 0, male = 1), hypertension (assigned to two groups: no = 0, yes = 1) and BMI were taken as independent variables, and hyperuricemia (assigned to two groups: no = 0, yes = 1) as a dependent variable, and then further multivariate unconditional logistic regression analysis was performed. The results suggest that old age (OR = 3.382, 95%CI 1.707–6.701), male (OR = 10.039, 95%CI 8.146–12.372), high BMI (OR = 1.199, 95%CI 1.174–1.225) and hypertension (OR = 1.478, 95%CI 1.260–1.733) were independent risk factors for HUA (Table 2). Based on these results, a nomogram model was established by using R4.0.0 and a rms package to predict HUA occurrence (Fig. 1).

Table 2

The results of multivariate logistic regression analysis on the occurrence of hyperuricemia

Variables	β	SE	Wald value	P value	OR	95%CI
Gender	2.307	0.107	468.163	0.000	10.039	8.146 ~ 12.372
Age						
18 ~ 29			23.267	0.000	1	Reference
30 ~ 49	-0.216	0.096	5.026	0.025	0.805	0.667 ~ 0.973
50 ~ 69	-0.242	0.104	5.378	0.020	0.785	0.640 ~ 0.963
≥ 70	1.219	0.349	12.202	0.000	3.382	1.707 ~ 6.701
Hypertension	0.390	0.081	23.083	0.000	1.478	1.260 ~ 1.733
BMI	0.182	0.011	274.227	0.000	1.199	1.174 ~ 1.225

Establishment of the classification tree model

Age, gender, BMI and hypertension were taken as influencing factors of HUA patients and used to construct a classification tree model. Based on the growth and pruning of the minimum sample sizes of root and child nodes, the classification tree model was concluded to include 4 layers, 18 ordinary nodes and 6 terminal nodes (Fig. 2). The results of the classification tree model showed that the importance of HUA factors ranged from high to low in terms of gender, BMI, hypertension and age, respectively.

Validation and evaluation of the model

The ROC curve was used to evaluate the discriminability of the two models. The AUC of the nomogram model constructed in this study was 0.806 and 0.791, the specificity was 63.83% and 64.20% and the sensitivity was 84.40% and 83.52% in the training and verification sets, respectively. The AUC of the classification tree model was 0.802 and 0.794, the specificity was 58.29% and 58.82% and the sensitivity was 88.60% and 87.11% in the training and verification sets, respectively (Fig. 3). The AUC difference of

the two models in the training and verification sets were not statistically significant ($P \geq 0.05$). The ROC curve parameters of the two models are shown in Table 3.

Table 3
The ROC curve parameters of the two models

Parameters	Training set			Validation set		
	Nomogram model	Classification tree model	<i>P</i> value	Nomogram model	Classification tree model	<i>P</i> value
Specificity (%)	63.83	58.29		64.20	58.82	
Sensitivity (%)	84.40	88.60		83.52	87.11	
Youden index (%)	48.23	46.89		47.73	0.45.93	
AUC (95%CI)	0.806 (0.796 ~ 0.815)	0.802 (0.792 ~ 0.812)	0.1691	0.791 (0.775 ~ 0.806)	0.794 (0.778 ~ 0.809)	0.5537
Cut-off	0.23	0.17		0.22	0.17	

In the calibration curve, the predicted incidence curve of the nomogram and the classification tree models in this study fitted well with the optimal curves of the actual incidence, and the difference was not statistically significant ($P \geq 0.05$; Fig. 4). The results showed that the average absolute error between the predicted risk of HUA occurrence and the actual risk in the training and verification sets of the nomogram model were 0.006 and 0.017, respectively; the average absolute error between the predicted risk of HUA occurrence and the actual risk of HUA occurrence in the training and verification sets of the classification tree model was 0.002 and 0.018, respectively, indicating that the accuracy of the two models was good.

Finally, in order to determine whether the two models had clinical practicality, this study evaluated whether the two models can bring net benefits through DCA. As shown in Fig. 5, in the training and validation sets, both models could bring net benefits within the appropriate threshold probability (Pt) range, and these were deemed to be similar.

Discussion

The focus of this study was to explore the construction of simple model tools for predicting HUA. We have developed and verified two new and simple HUA prediction models. The nomogram model was selected as a parametric class model, and the classification tree model was selected as a non-parametric class model. We included four non-invasive physical examination indicators that were easy to obtain clinically, such as age, gender, BMI and hypertension, and the results indicated that they were all risk factors of HUA ($P \geq 0.05$) and were included in the model. The final AUC of the nomogram model obtained was 0.806 and the AUC of the classification tree model was 0.802. The specificity of the

nomogram model was higher at 63.68% and the sensitivity of the classification tree model was higher at 88.60%. Each model had its own advantages and disadvantages.

In previous studies, Lee *et al.* [9] used gender, BMI and PPAR γ genes to establish a model to predict the potential risk of HUA. The final model had a sensitivity of 69.3% and a specificity of 83.7% and although its sensitivity was better than those of the two models in this study, the cost of HUA prediction through genetic testing methods was high, and they were not suitable for rural hospitals with outdated medical equipment and widespread population distribution. Zeng *et al.* [10] built a HUA prediction model based on dietary information such as the frequency of eating vegetables, meat and eggs, and obtained a neural network model with an AUC of 0.827, a sensitivity of 75% and a specificity of 86%. Its AUC and sensitivity were both better than those of the two models in this study, but the model structure was more complex and it required a higher statistical background knowledge from the operators, and more variables needed inclusion. This model was also time consuming and the subjects were prone to recall bias when it was applied to the clinic.

The nomogram model is based on logistic regression analysis. It is a traditional medical model with a certain amount of accuracy, repeatability, visualization and it does not require computer software intervention. It is often used to explore the risk factors that cause diseases and predict the incidence of diseases through these risk factors. But it is difficult to fully reflect the coupling relationship between variables, and cannot effectively deal with the problem of collinearity [15]. The classification tree model is a non-parametric regression model with no special requirements for the variables included in the model, and continuous variables can also be used as independent variables into the model. It is a type of machine learning model that can effectively deal with the problem of missing independent variables in the data. Not only can the missing values be classified into the category of a mode, but it can also be set as a separate category, so that the result is not affected by the collinearity of the variables. It can also effectively, intuitively and hierarchically display the risk factors and the interactions between them [16].

In recent years, some scholars have successfully applied the classification tree model to predict myocardial infarction [17], multi-drug resistant tuberculosis [18], portal vein thrombosis in patients with acute pancreatitis [19] and other internal or surgical diseases, and its application in medical-related fields has proven its effectiveness. However, classification trees also have some shortcomings. First, the quantitative explanation of the individual effects of the classification tree on each factor is not as clear as the nomogram model. In this study, logistic regression analysis was used to obtain the OR value, which can clearly determine the specific risk factors that affect the risk of HUA. But the classification tree model can only obtain the importance of ranking for different variables and cannot allocate a specific degree of importance for a particular variable. Second, the classification tree model has poor stability when a small sample size is available. Fortunately, the large amount of data in this study allows the classification tree model to have good stability in its prediction capability.

In this study, the ROC and calibration curves as well as DCA of the nomogram and classification tree models in both the training and validation sets achieved satisfactory results, and they were relatively

similar. However, some scholars have used machine learning algorithms such as support vector machines, decision trees and random forests to build HUA prediction models with traditional logistic algorithms. They found that the machine learning model was superior to the logistic model for HUA prediction, which is different from the results of our research. The reasons may be related to the large number of dependent variables in these models and the existence of collinearity [20]. In this study the number of variables included was small and therefore the possibility of collinearity was small, and they were confirmed to be closely related to HUA, so the performance of the nomogram model was relatively stable. In previous studies, it was shown that the prediction accuracy and performance of the nomogram model was better than those of machine learning models such as artificial neural networks and classification tree models [21, 22]. Therefore, the quality of a certain model cannot be judged unilaterally, and the accuracy and stability of a single algorithm prediction model are relatively low, which cannot always meet the clinical decision-making needs of multi-sourced, high-dimensional medical data. In future applications, we should pay more attention to the combination of multiple models in order to provide support for the improvement of disease prediction methods.

In this study, the overall prevalence rate of HUA was 21.9% of which 34.9 and 4.1% were seen in male and female populations, respectively. The prevalence rate of HUA in male population was much higher than in females, which agreed with previous reports [23]. However, the lower prevalence of HUA in the female population in this study was considered to be related partly to the latest Chinese guidelines for the diagnosis and treatment of HUA [14]. In this study, the multivariate logistic regression analysis and classification tree model both showed that male gender male accounts for the largest proportion of all risk factors, as was shown previously [24, 25].

The risk of HUA in males is high, and this may be partly due to capacity of estrogen to regulate the levels of uric acid transporter in the kidney through gene expression and thus promoting the excretion of uric acid and reducing its production [26, 27]. Therefore, after menopause, the difference in prevalence rates of HUA between males and females gradually decreases [28]. In the classification tree model in this study, the node of female age classification was 49.5 years old, and the prevalence of HUA increased after 49.5 years old, which was roughly consistent with the age of menopausal women. On the other hand, due to work demands and life pressures, men are often associated with unhealthy living habits (such as the consumption of high-purine diets and alcohol), and previous literature has reported that alcohol consumption was a risk factor for HUA [29]. In the nomogram model, the score corresponding to the ages between 18 and 29 years was higher. In the classification tree model, the prevalence of HUA for men younger than 28.5 years was higher than that for men in an older age group, which was the same as that reported by Jin *et al.* [30].

In this study, the classification tree model suggested that there was an interaction between gender and BMI. For both men and women, the prevalence of HUA in people with high BMI was higher than that in people with low BMI, and this parameter was the second most important influencing factor in the classification tree. Previous epidemiological evidence has shown that obesity was closely related to HUA, and BMI and waist circumference were positively correlated with HUA[31, 32], especially visceral fat

obesity, which could accelerate ribose-5-phosphate *de novo* synthesis of phospho-ribose pyrophosphate through the NADP-NADPH metabolic pathway, and eventually lead to an increase of uric acid and trigger HUA[33]. Therefore, the results of this study suggested that obese young men and postmenopausal women are key health management subjects in attempting to prevention HUA.

There are several advantages attributed to this study. First, the predictive variables required in this model were non-invasive and easy to evaluate. In addition to saving medical expenses, limited information could be used to screen undetected and unsuspected high-risk groups of HUA, which ideal for large populations with limited health resources, especially in poorer areas. At the same time, not only China, Africa and India have poor sanitary conditions, they may also benefit from this model. In addition, we combined parametric and non-parametric methods to build two prediction models. For practical applications, this method allows the possibility to select different algorithms for comprehensive comparisons and complementary advantages based on the available data characteristics and sample size, so as to improve the reliability of prediction results obtained and expand the scope of application of the model.

However, this study also had several limitations. Our sample size originated from the database of the same medical examination center, and hence there was selection bias. Therefore, it may not be possible to determine whether it is applicable to populations in other regions, and further external verification is required. As a cross-sectional survey, this study was unable to confirm the causal and temporal relationships between age, gender, BMI, hypertension and HUA, which needs to be confirmed by a large number of further multi-center, prospective studies.

Conclusions

In summary, this study developed and validated two simple HUA prediction models suitable for Chinese and general rural populations by using simple and non-invasive physical examination indexes of a healthy population. The two models have high resolution, good accuracy and some encouraging clinical practicalities, which can potentially help to identify high-risk groups and reduce the prevalence of HUA and gout and the adverse health consequences caused by cardiovascular diseases.

Declarations

Authorship

JCS and XHC analyzed the data, drew the diagrams and wrote the manuscript. QH and YMS conducted data analysis and graph generation. QY and CMW obtained the clinical data and revised the manuscript. JY contributed to the design of the research, and helped to wrote the manuscript. All authors read and approved the final manuscript.

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Conflict of Interest Statement

All authors have no relevant conflicts of interest to disclose.

Ethical approval information

This study was approved by Ethical Committee of Guilin Medical University in China (approval number: GLMUIA2019064). All research was performed in accordance with relevant guidelines. Informed consent was obtained from all participants and/or their legal guardians.

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Data Availability Statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

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Figures

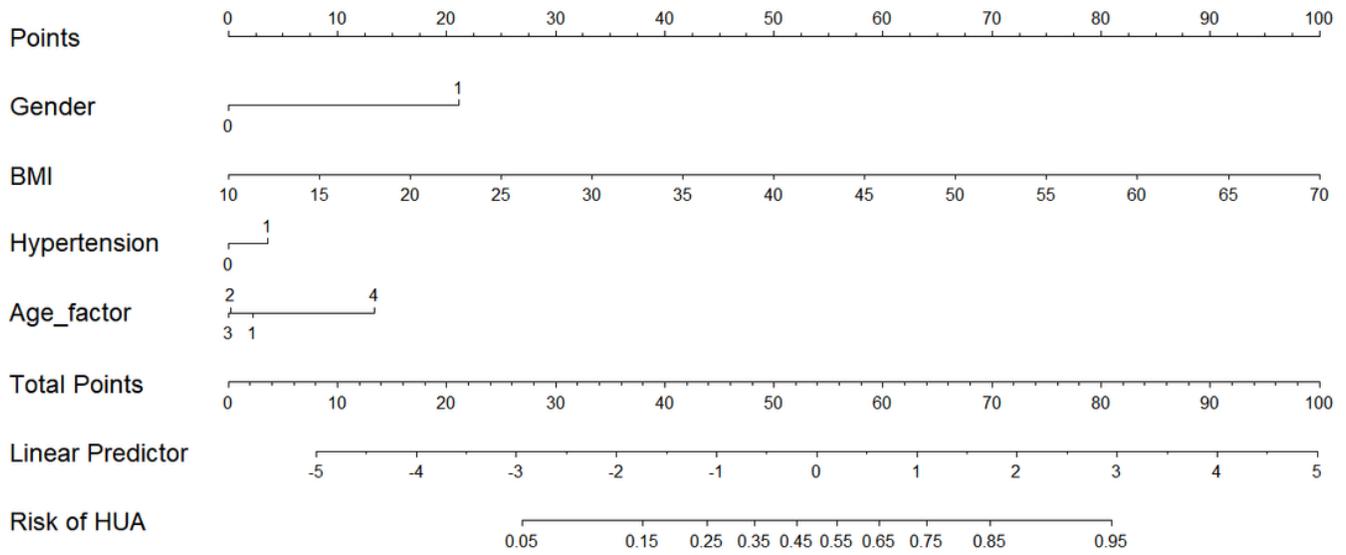


Figure 1

The usage method of nomogram to predict the risk of HUA. The scores were calculated according to the following factors (gender, BMI, hypertension and age) of the enrolled patients, and sum the total scores was used to calculate the risk of HUA.

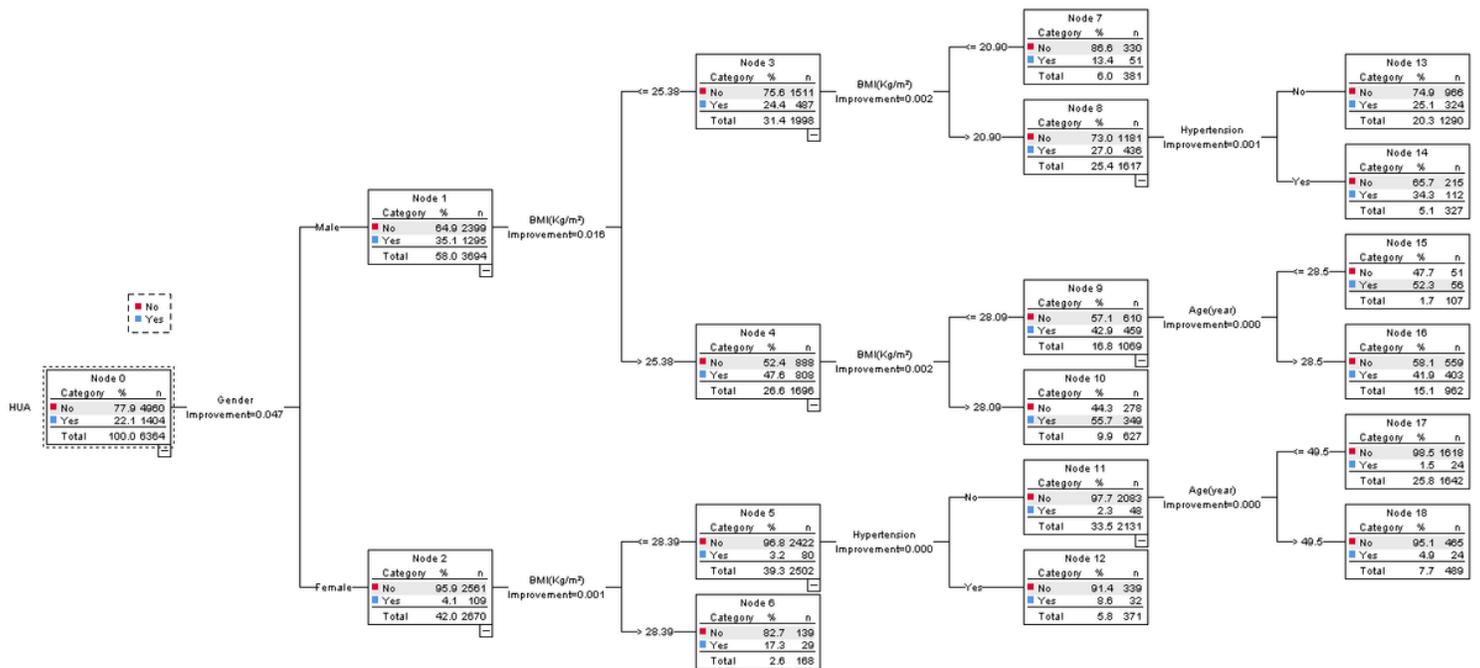
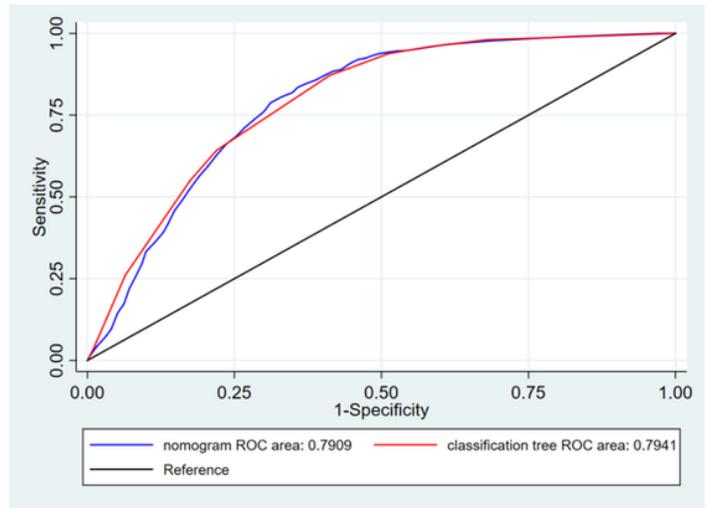
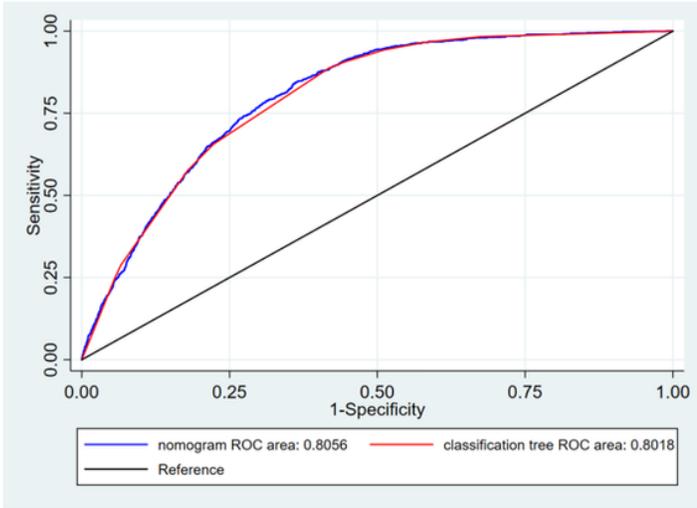


Figure 2

The classification tree model of HUA patients HUA: hyperuricemia; BMI: body mass index.

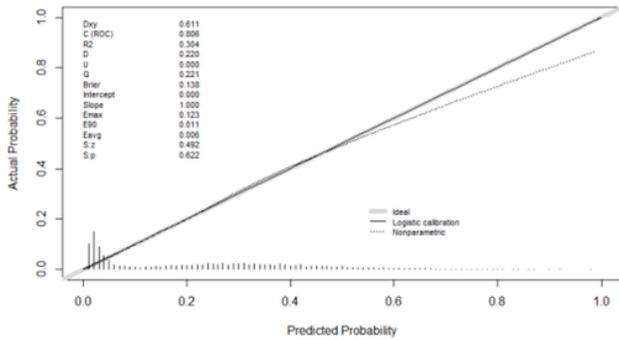


(A) ROC of two models in the training set

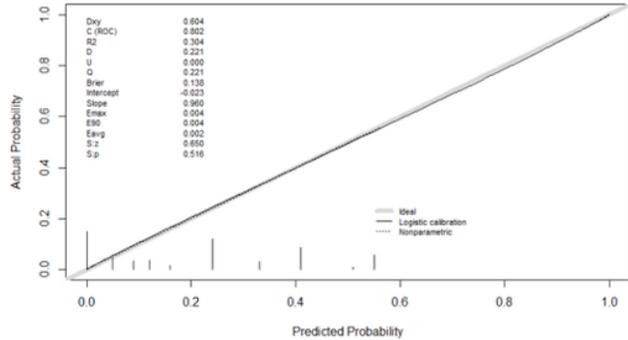
(B) ROC of two models in the validation set

Figure 3

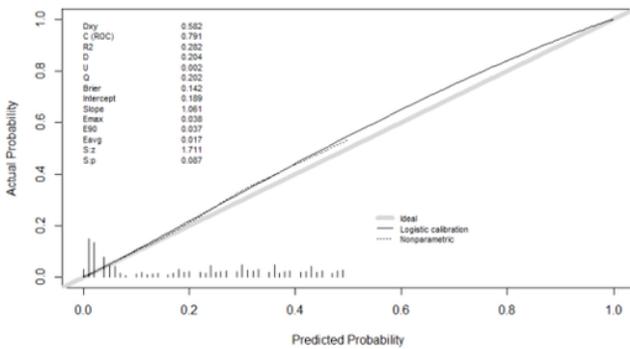
ROC curves of the two models in the training and validation sets



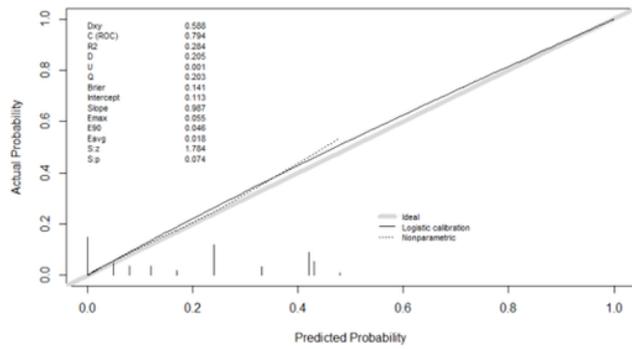
A



B



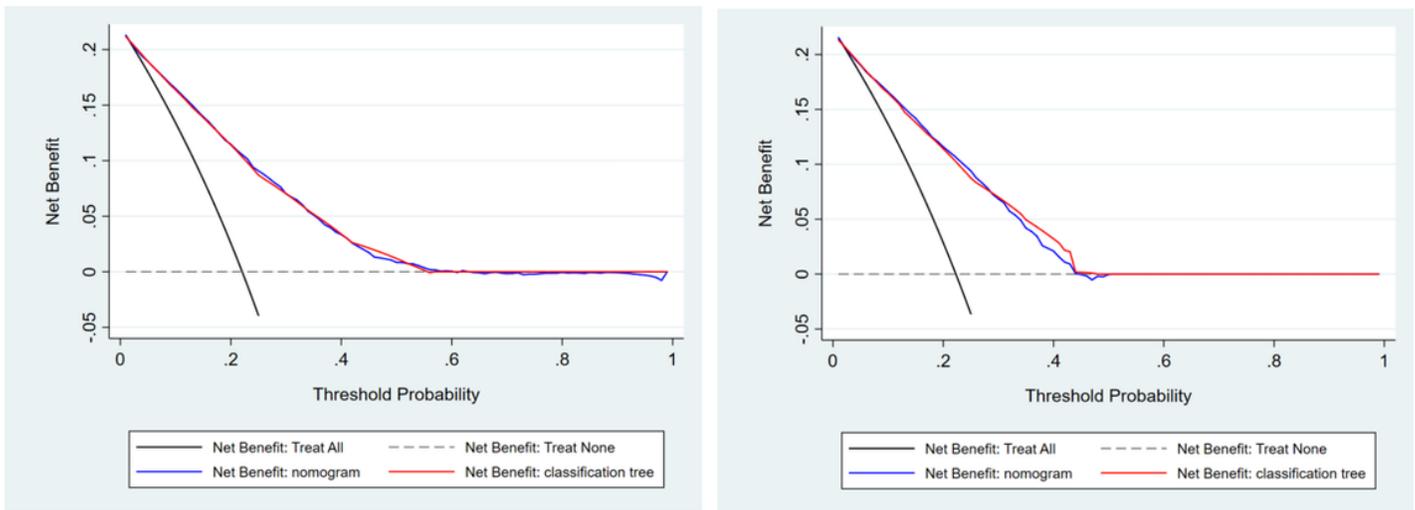
C



D

Figure 4

Calibration curves of the two models in the training and validation sets. The dashed line represents the predicted incidence curve, the black solid line represents the actual incidence curve and the gray line represents the ideal reference curve at 450. $P > 0.05$ in the 4 graphs indicates that the difference between the predicted incidence curve and the actual incidence curve is not statistically significant.



(A) DCA of two models in training set

(B) DCA of two models in validation set

Figure 5

DCA curves of the two models in the training and validation sets. The abscissa represents the threshold probability, and the ordinate represents the net benefit after the benefit (the perceived benefit after treatment for the real patient) minus the disadvantage (the perceived harm after treatment for the fake patient). The dotted reference line indicates that all the samples were free of disease with none of them receiving any intervention, and the net benefit was 0; the black reference line indicates that all of the samples were treated for the disease, and the net benefit is represented by the backslash of the slope. The further the model curve is away from the two reference lines, the better the clinical utility of the graph.