

# Construction of a Nomogram Model to Predict The Risk of Hypothyroidism in Patients With Thyroid Nodule Caused by Environmental Iodine and Fluorine

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## Research

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# Abstract

**Background:** Patients with thyroid nodules may be complicated by hypothyroidism. However, effective means to predict thyroid-stimulating hormone (TSH) elevation in patients with thyroid nodules are currently lacking. Therefore, the research team recruited some patients with thyroid nodules to explore the relationship between TSH, environmental iodine, and fluoride and the development of thyroid nodules, and to draw a Nomogram in order to provide guidance for predicting hypothyroidism in patients with thyroid nodules.

**Methods:** The subjects were from 313 patients with thyroid nodules in different areas of iodine and fluoride, with 71 men and 242 women. The content of TSH in serum of thyroid nodule patients was determined by electrochemical luminescence method. The iodine content in drinking water and urine was determined by arsenic-cerium catalytic spectrophotometry. Fluoride in drinking water and urine was determined by fluoride ion selective electrode method. Univariate analysis, Lasso regression analysis and multiple factor Logistic regression analysis were used to screen the variables included in the Nomogram model. And the corresponding Nomogram model was constructed. ROC curve was drawn and repeated Bootstrap self-sampling method was used to test model differentiation.

**Results:** There were 53 patients with elevated serum TSH and 256 patients with normal thyroid nodule. Multivariate logistic regression analysis shows that urine iodine [Odds Ratio(OR)=1.001, 95% confidence interval [95%CI]:1.001-1.002,  $P=0.01$ ] and gender (OR=3.328, 95% CI:1.256-8.819,  $P=0.079$ ) are independent risk factors raised by serum TSH. And drinking water fluoride [OR=1.990, 95% CI:0.924-4.289,  $P=0.079$ ] is a critical factor. Based on these risk factors, the predictive model and nomogram of serum TSH elevation in patients with thyroid nodule were constructed. The area under the ROC curve was 0.678 ( $P<0.001$ ), confirming Nomogram's predictive potential. The calibration diagram of the Nomogram prediction model shows that the predicted values are in good agreement with the observed values.

**Conclusion:** Gender, urine iodine and drinking water fluoride of thyroid nodules are independent influencing factors for the rise of serum TSH. The Nomogram can become a predictive accuracy and differentiation.

## Introduction

Thyroid nodule is one of the most common thyroid diseases and it is a localized mass with one or more abnormal tissue structures caused by various reasons. In recent years, the prevalence has increased rapidly [1, 2] [3]. The etiology is complicated and related to gender, age[4], iodine[5] and fluorine[6, 7] intake, history of radiation exposure[8], and immune factors[9]. High or low iodine intake and high fluoride intake can cause thyroid nodules. At the same time, long-term stimulation of thyroid-stimulating hormone (TSH) may promote thyroid hyperplasia and form benign and malignant nodules. Studies have found that detecting serum TSH in patients with thyroid nodules is of great significance in assessing the properties of thyroid nodules [10, 11]

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Thyroid nodules can be complicated by hypothyroidism [3]. Hypothyroidism is a metabolic abnormality caused by reduced metabolism or insufficient secretion of thyroid hormones. It includes subclinical hypothyroidism (referred to as subclinical hypothyroidism) and thyroid. Hypofunction (abbreviated hypothyroidism). The survey shows[3] that the incidence of subclinical hypothyroidism is 16.7%, which is increasing year by year. Subclinical hypothyroidism is a high-risk factor for hypothyroidism And the incidence of subclinical hypothyroidism is increasing year by year. The prevalence of hypothyroidism among residents has also increased.

TSH is secreted by the pituitary gland, which can promote the proliferation of thyroid follicular epithelial cells, leading to thyroid hyperplasia, which is the main indicator for evaluating thyroid function. Elevated serum TSH levels can induce the occurrence of thyroid nodules and increase the incidence of thyroid cancer. Elevated serum TSH levels may also increase the risk of hypothyroidism [12].

Although there have been related reports, the relationship between thyroid nodules, iodine and fluorine nutrition status, and the change rule of TSH in thyroid nodule patients are not clear; The results of studies on the effects of iodine and fluorine intake on hypothyroidism are inconsistent [7, 13, 14] <sup>[15-21]</sup>. There is also a lack of an effective means to predict hypothyroidism based on changes in serum TSH. In view of this, we enrolled some patients with thyroid nodules in different water-derived iodine and fluorine regions to evaluate their iodine and fluorine nutrition status. The serum TSH level was detected to explore the relationship between TSH, environmental iodine and fluorine and the incidence of thyroid nodules. A Nomogram was drawn in order to provide a basis for the prevention of thyroid nodules in patients with thyroid nodules.

## 1. Object And Method

### 1.1 Subjects

The research team conducted a preliminary survey on the geographical distribution of iodine and fluorine in drinking water in Cangzhou City, Hebei Province [22]. According to the survey results, volunteers were recruited from Cangzhou City from October to December 2018 in four areas namely high iodine(drinking Water iodine  $\geq 100 \mu\text{g/L}$ , drinking water fluoride  $0.5 \sim < 1 \text{ mg/L}$ ), low iodine(drinking Water iodine  $\leq 10 \mu\text{g/L}$ , drinking water fluoride  $0.5 \sim < 1 \text{ mg/L}$ ), normal iodine fluoride(drinking Water iodine  $> 10 \sim < 100 \mu\text{g/L}$ , drinking water fluoride  $0.5 \sim < 1 \text{ mg/L}$ ) and high iodine and high fluorine(drinking Water iodine  $\geq 100 \mu\text{g/L}$ , drinking water fluoride  $\geq 1 \text{ mg/L}$ ).

The ultrasound doctor used the color Doppler ultrasound of the Mindray Z5 and 75L 38EA probes to complete the thyroid examination .And according to the "China Guidelines for thyroid nodules and differentiated thyroid cancer (2012)[23], urine and blood samples were collected and tested in patients diagnosed with thyroid nodule by color ultrasound and those without obvious clinical symptoms. Inclusion criteria were as follow: 1) the age range was 25 to 80 years old. 2) the residents who were born and have lived continuously in the country for 25 years or more. 3) Thyroid nodule was diagnosed by

color Doppler ultrasonography and serum thyroid stimulating hormone (TSH) was detected for the first time. Exclusion criteria were as follow: the people who were taking iodine-containing drugs, suffering from thyroid cancer, thyroid surgery and person with serious diseases, or have incomplete urine or blood samples. or pregnant women. A total of 313 thyroid nodule patients, 71 male and 242 female, were recruited from seven administrative villages with different levels of iodine and fluoride in drinking water. (See Fig. 1)

## 1.2 Collection and inspection of water samples

Each administrative village where the volunteers were located had centralized water supply. Two terminal water samples were collected from each administrative village and the iodine fluoride content in the water samples was determined. The mean value of the detection results of the two water samples, namely, the iodine fluoride content in drinking water of the administrative village was determined by arsenic cerium catalytic spectrophotometry (GB/T5750.5-2006) (<http://down.foodmate.net/standard/sort/3/11211.html>). The iodine content in drinking water was determined by fluoride ion selective electrode method (GB/T5750.5-2006) (<http://down.foodmate.net/standard/sort/3/11211.html>).

## 1.3 Collection and inspection of urine samples

The subjects' morning urine was collected and the contents of urine iodine and fluorine were detected. Urine iodine was determined by arsenic-cerium catalytic spectrophotometry (WS/T107.1-2016) (<https://www.antpedia.com/standard/type.php?type=ccs&ino=C>). Urine fluoride was determined by fluoride ion selective electrode method (WS/T89-2015) (<https://max.book118.com/html/2018/1207/7003054064001163.shtm>).

## 1.4 Blood sample collection and inspection

Fasting venous blood of the subjects was collected in the morning. And the serum, TSH content was determined by electrochemical luminescence method using Roche CoBAS-E-602 electrochemical luminescence instrument (Roche Diagnostics Germany). Serum TSH kit is provided by Roche Diagnostics (Shanghai) Co. LTD. The test method is operated according to the instructions. Subjects were diagnosed as TSH increases[24], whose serum TSH is higher than 4.2uIU/ MI (Serum TSH reference range : 0.27 ~ 4.2uIU/ mL).

## 1.5 Statistical analysis

The measurement data should be tested for normality first. The Student's t-test was applied to text continuous and normal variables, and the results were expressed as the mean  $\pm$  standard deviation (SD). Skewed distribution data are given by M ( $Q_1, Q_3$ ), using Mann-Whitney U Test. Categorical variables are represented by number of cases or percentages, using two independent samples chi-squared test or Fisher's exact probability method.

Univariate analysis was performed on the collected predictors to assess the correlation with hypothyroidism. Predictors were included in the Lasso regression analysis to screen for important risk factors for hypothyroidism. Predictions of  $P \leq 0.05$  in the univariate logistic regression analysis were included. Variables were combined with predictive variables with non-zero coefficients in the Lasso regression analysis. And multivariate logistic regression analysis was performed to screen independent risk factors affecting hypothyroidism. Based on the results of multivariate logistic regression analysis, a Nomogram model was established. Bootstrap resampling the Nomogram model is used to verify the prediction performance. The consistency coefficient (C-index) is used to represent the prediction performance of the Nomogram model and a calibration chart is drawn to indicate its prediction compliance. The receiver operating characteristic curve (ROC curve) is plotted to obtain the area under the ROC curve (area under the curve (AUC) and its 95% CI, evaluating the prediction model.

Use R software to draw a line chart. In the application process, you can find the corresponding score value according to each predictor of the patient in the line chart. Adding the scores of each predictor variable is the total score, which corresponds to the total score.

All the analysis were completed with R3.4.2 software (<http://www.Rproject.org>).  $P < 0.05$  based on a two-tailed calculation was as the statistical significance.

## 2. Results

### 2.1 The characteristics of the patients with thyroid nodules

The characteristics of the selected population are shown in Table 1. Among 313 patients with thyroid nodules, 57 patients with abnormal serum TSH were found by serum TSH test (53 patients with elevated serum TSH and 4 patients with reduced TSH) and 256 patients with serum TSH within the reference value range (Table 1).

Table 1  
Main characteristics of 313 patients with thyroid nodules in  
Cangzhou, Hebei Province

Characteristics	Subjects (N = 313)
Age, Mean $\pm$ SD, years	56.96 $\pm$ 11.08
Gender, N (%)	
Male	71(22.68%)
Female	242(77.32%)
Urinary iodine, M (Q <sub>1</sub> ,Q <sub>3</sub> ), $\mu$ g/L	587.45(289.70, 1045.52)
Urinary fluoride, M (Q <sub>1</sub> ,Q <sub>3</sub> ), mg/L	3.88(2.38, 7.67)
Drinking water iodine, N (%)	
Low ( $\leq$ 10 $\mu$ g/L)	45(14.4%)
Normal (> 10 ~ < 100 $\mu$ g/L)	53(16.9%)
High ( $\geq$ 100 $\mu$ g/L)	215(68.7%)
Drinking water fluorine, N (%)	
Normal (0.5~1.0 mg/L)	142(45.4%)
High ( $\geq$ 1.0 mg/L)	171(54.6%)
Serum TSH, N (%)	
Low, ( $\geq$ 4.2 uIU/ mL)	4(1.3%)
Normal (0.27~4.2 uIU/ mL)	256(81.8%)
High, ( $\leq$ 0.27 uIU/ mL)	53(16.9%)

Urinary iodine and fluoride: The morning urine.

Drinking water iodine and fluorine: Peripheral water.

Serum TSH: Serum thyroid stimulating hormone.

## 2.2 Univariate analysis

Univariate analysis was performed using serum TSH in patients with thyroid nodules as predicted variables, and six factors as age, gender, urinary iodine, urinary fluoride, drinking iodine and drinking water fluoride as predictors. The results showed that urine iodine and urine Fluorine and gender may be

the influencing factors of serum TSH elevation in patients with thyroid nodules ( $P < 0.05$ ), and iodine drinking water as the influencing factor is critically significant ( $P = 0.061$ ). (See Table 2)

Table 2  
Univariate analysis of elevated serum TSH in 309 patients with thyroid nodules in Cangzhou, Hebei Province

variable	TSH		<i>P</i>
	Ascent (53)	Normal (256)	
Age, Mean $\pm$ SD, years	56.6 $\pm$ 10.02	56.97 $\pm$ 11.36	0.828 <sup>a</sup>
Urinary iodine, M (Q <sub>1</sub> ,Q <sub>3</sub> ), $\mu$ g/L	286.95(145.44,620.50)	173.05(86.78,337.65)	0.002 <sup>b</sup>
Urinary fluoride, M (Q <sub>1</sub> ,Q <sub>3</sub> ), mg/L	2.96(1.57,4.40)	2.03(1.15,3.16)	0.008 <sup>b</sup>
Gender, N			
Male	5	66	0.010 <sup>c</sup>
Female	48	190	
Drinking water iodine, N			
Low ( $\leq 10 \mu$ g/L)	3	42	0.061 <sup>c</sup>
Normal (0.5~1.0 mg/L)	7	46	
High ( $\geq 100 \mu$ g/L)	43	168	
Drinking water fluoride (mg/L)			
Normal (0.5~1.0 mg/L)	19	122	0.116 <sup>c</sup>
High ( $\geq 1.0$ mg/L)	34	134	

*P* value is derived from the univariable analyses between each of the increased risk factors associated with serum TSH.

<sup>a</sup> t-test was used to compare values from both groups.;

<sup>b</sup> Mann-Whitney U Test was used to compare values from both groups,

<sup>c</sup> Chi-squared test was used to compare two or three positive rates.

Differences were considered significant when  $P < 0.05$  (2-tailed).

### 2.3 Lasso regression analysis

Through Lasso regression analysis, the relatively unimportant independent variable coefficients become 0 to exclude from modeling; those with non-zero variable coefficients are included as the most important

risk factors in the modeling. The dependent variable was whether the serum TSH in patients with thyroid nodules was increased, and the independent variables were age, gender, urine iodine, urine fluoride, iodine in drinking water and fluorine in drinking water. LASSO regression analysis was performed. The results showed that the coefficients of the two variables, age and water iodine, became 0. There were four variables with non-zero coefficient, namely, gender (coefficient = 0.857), urine iodine (coefficient = 0.0008), urine fluoride (coefficient = 0.050) and drinking water fluorine (coefficient = 0.470). ( See Table 3, Fig. 2 and Fig. 3)

Table 3  
Lasso regression analysis of elevated serum TSH in patients with thyroid nodules

Variables and intercept	coefficient
intercept	-3.932
Age,	0
gender	0.857
Urinary iodine( $\mu\text{g/L}$ )	0.0008
Urinary fluoride( $\text{mg/L}$ )	0.050
Drinking water iodine( $\mu\text{g/L}$ )	0
Drinking water fluoride( $\text{mg/L}$ )	0.470

In Lasso regression analysis, if the variable coefficient becomes zero, it will be excluded from modeling; if the variable coefficient is non-zero, it is included into the modeling as the most important risk factor.

#### 2.4 Multivariate logistic regression analysis

Based on the results of univariate analysis and lasso regression analysis, five factors including urinary iodine, urinary fluoride, gender, drinking water fluoride and drinking iodine were included in multivariate logistic regression analysis. The results showed that gender and urine iodine increased serum TSH in patients with thyroid nodules. Independent influencing factors, drinking water fluoride was the critical influencing factor. The risk of serum TSH in women with thyroid nodules is 3.328 times higher than that in men (95% CI:1.256 ~ 8.819,  $P < 0.05$ ). In patients with thyroid nodule, the risk of serum TSH increased by 1.001 times for each increase of urine iodine concentration unit (95%CI:1.001 ~ 1.002,  $P < 0.05$ ). The increased risk of serum TSH in thyroid nodule patients with high fluoride content in drinking water was 1.990 times that in normal drinking water (95%CI:0.924 ~ 4.289,  $P = 0.079$ ). (See Table 4)

Table 4  
Multivariate logistic regression analysis of elevated serum TSH in patients with thyroid nodules

Intercept and Variable	$\beta$	Odds Ratio (95% CI)	$p$
Intercept	-4.803		
gender	1.202	3.328(1.256 to 8.819)	0.016
Urine iodine	0.001	1.001(1.001 to 1.002)	0.001
Drinking wate fluoride	0.688	1.990(0.924 to 4.289)	0.079
C-index		0.678(0.604 to 0.753)	

$\beta$  is the regression coefficient.

95% CI indicates 95% confidence interval.

Correlation is significant at the 0.05 level (2-tailed).

### 2.5 Construction of Nomogram model

The multivariate logistic regression analysis results were used to establish a prediction model. The multivariate logistic regression coefficient ( $\beta$ ) was used to construct a model to estimate the risk of elevated serum TSH in patients with thyroid nodules caused by environmental iodine and fluorine. The scoring model was as follows:  $\text{Log}(p) = -4.803 + 1.202 \times \text{gender} + 0.001 \times \text{urine iodine} + 0.688 \times \text{drinking water fluoride}$  (See Table 4).

To more intuitively predict the risk of elevated serum TSH in patients with thyroid nodules, a Nomogram was drawn. The Nomogram includes: prediction index, score scale corresponding to single prediction index, total score scale, risk value line of serum TSH increase etc. Three predictors were included in this study: gender, urinary iodine, drinking water fluoride. The three predicted indicators were compared with the corresponding score scale to obtain the score. Sum of the scores of the above indicators to obtain a total score. The total score corresponds to the score on the predicted risk value line of serum TSH increase, that is, the predicted risk value of serum TSH increase. (See Fig. 4, Table S5 and Table S6)

### 2.6 Evaluation of Nomogram model prediction capabilities

The degree of discrimination of the model is evaluated by the consistency index (C-index). The initial C-index in this study is 0.678 (95% CI: 0.604 ~ 0.753). The receiver operating characteristic curve (ROC curve) is drawn to obtain the ROC. The area under the curve (AUC) is 0.678,  $P < 0.001$ . And the ROC analysis confirmed Nomogram's predictive potential. To see Fig. 5, a calibration diagram of a Nomogram prediction model is shown. There is good agreement between Nomogram's prediction and actual observation, indicating that the Nomogram model can be compared with Accurately predict the risk of elevated serum TSH in patients with thyroid nodules. (See Fig. 6)

### 3. Discussion

Studies have shown that the prevalence of thyroid disease is on the rise [1-3]. Thyroid nodules are one of the common diseases of thyroid disease and patients do not have obvious clinical symptoms in the early stage. They are mostly accidentally found during physical examination. The detection rate of color Doppler ultrasound can reach 19% ~ 68%, of which 7% ~ 15% are thyroid cancer [25, 26]. And it may also be accompanied by changes in thyroid function and thyroiditis. Our previous work found that the prevalence of thyroid nodules in people over 30 years of age in Cangzhou City, Hebei, China ranges from 25.1% to 43.3% [22]. The etiology of thyroid nodules is complex. And it is related to gender [4], age [4], iodine nutrition level [4, 5], high fluoride [16, 20, 27] as well as history of radiation exposure [8]. and immune factors [9] etc. But it is not fully explored at present. There are reports that environmental iodine and fluorine may be one of the risk factors [20, 25]. Most of the subjects in this study came from water-source areas with high iodine content and low iodine content and high iodine content and high fluorine content. Through more Logistic regression analysis of factors found that gender and urinary iodine were independent factors influencing serum TSH elevation in patients with thyroid nodules, and drinking water fluorine was the critical factor. Therefore, the study of the etiology of thyroid nodules can help to explore the effects of hypothyroidism and thyroid cancer risk factors.

The Nomogram is based on multivariate analysis and integrates multiple forecasting indicators, which can transform complex formulas into intuitive graphs. As a reliable statistical model, the Nomogram has been widely used in industrial and atmospheric research. In the medical field, researchers [28-30] have established a Nomogram of the survival probability of different cancers. Clinicians can predict the survival probability of cancer patients after surgery based on the Nomogram, reduce the occurrence of overtreatment, rationally use medical resources, and reduce patients' pain. The established Nomogram can effectively predict the overall survival of patients with hepatocellular carcinoma after hepatectomy [31]. But there is no report about the prediction model of serum TSH increase in patients with thyroid nodules. The Nomogram C-index established in this study was 0.678 (95% CI: 0.604-0.753). The ROC curve AUC of the Nomogram prediction model is 0.678, indicating that Nomogram has certain practical value for predicting the risk of serum elevation in patients with thyroid nodules. The calibration chart of Nomogram shows that using Nomogram to predict the risk of elevated serum TSH in patients with thyroid nodules is more accurate. In clinical work, it is also expected that it can provide clinicians with an intuitive and personalized prediction tool.

Serum TSH is the most sensitive indicator reflecting thyroid function. With the continuous improvement of measurement technology, it has become the first-line screening index for subclinical thyroid dysfunction [32]. TSH is secreted by the adenohypophysis and can promote the growth and differentiation of thyroid tissue and the synthesis and release of thyroid hormones. The TSH level is affected by various factors such as age, gender, genetics, geographic area, day-night cycle and measurement methods. Serum TSH level is not only an important factor in the development of thyroid nodules but TSH can also be used as an important indicator to judge the benign and malignant tumors of

Loading [MathJax]/jax/output/CommonHTML/jax.js also the best indicator for screening and diagnosing

hypothyroidism [31-33]. Most patients with thyroid nodules have normal thyroid function. Studies have shown [12] that elevated serum TSH levels are one of the risk factors for clinical hypothyroidism in patients with thyroid nodules within 20 years. In patients with thyroid nodules, as the serum TSH increases, the risk of thyroid malignant tumors also increases [34-37].

In recent years, with the increasing number of patients with hypothyroidism in the population, the impact of iodine and fluoride on thyroid function has become a hot issue of common concern but the research results are different [7, 13, 14] [15-21, 38, 39]. This study found that gender and urinary iodine are influencing factors of TSH increase, which is consistent with the results of studies such as Vanderpump MP [12], Danchen Wang[40], and Wang D [41] Drinking water fluoride is a critical influencing factor. Some studies have found that [6, 15, 16, 42, 43] high fluoride and high iodine and high fluoride are related to elevated serum TSH. Malin AJ et al [14] found that there is a correlation between serum fluoride and urine fluoride and drinking water fluoride-serum fluoride, serum fluoride and TSH. Therefore, we also regard drinking water as one of the influencing factors.

Studies have shown that although some patients with elevated TSH can return to normal on their own [12, 44] There are still some patients who will develop hypothyroidism [12], so early individualized prediction and treatment are very important. Of the 313 patients with thyroid nodules in this survey, 53 patients had serum TSH higher than the reference value and 4 patients had lower reference values. Therefore, this study only explored the predictive model of TSH elevation in patients with thyroid nodules. According to the urinary iodine, gender, and drinking water fluoride are the independent factors influencing the increase of serum TSH concentration A Nomogram model with a predictive efficacy of 0.678 was established. The Nomogram model is intuitive and visual and can realize individualized prediction according to the value of each individual factor.

Due to the small sample content, this study only constructed the Nomogram and failed to carry out external verification. Due to the lack of data of water-source low iodine and high fluorine population, this prediction model is not suitable for the prediction of serum TSH increase in water-source low iodine and high fluorine population. In the future, further data should be collected to improve the prediction model.

In summary, the Nomogram prediction model established in this study allows doctors to assess the risk of elevated serum TSH in patients with asymptomatic thyroid nodules based on gender, urine iodine content and fluoride content in drinking water. On the one hand, it can be determined whether the patient has a thyroid function test. On the other hand, high-risk groups with hypothyroidism can be detected early and corresponding measures can be taken to reduce the progression of thyroid nodules to hypothyroidism. It has high clinical application value and is worth promoting.

## 4. Conclusion

Gender, urine iodine and drinking water fluoride of thyroid nodules are independent influencing factors for the rise of serum TSH. The Nomogram can become a predictive accuracy and differentiation.

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# Abbreviations

TSH: thyroid-stimulating hormone

# Declarations

## *Ethics approval and consent to participate*

This project was approved by the school's ethics committee and all respondents signed informed consent, which is in line with medical ethics Academic regulations.

## *Consent for publication*

Not applicable.

## *Availability of data and materials*

The datasets used and/or analysed during the current study are available from the corresponding author on reasonable request.

## *Competing interests*

The authors declare that they have no competing interests.

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## *Authors' contributions*

All of the authors contributed to the design of the study. Ruixia Yan: Writing - original draft, Funding acquisition, Conceptualization. Dongliang Yang: Writing - original draft, Methodology. Yanguo Li: Data curation, Investigation. Yuan Zhou: Data curation. Yaxian Pang: Participate in manuscript writing. Shuzhen Li and Guiran Yang: Investigation. Ruoqi Xu: Participate in manuscript writing. Mingqing Liu: Supervision. Fengyan Yang and Chunhe Zhang: Resources Caihong Hu and Juan zhang and Tong Zhang: Investigation. Qiuyu zhang: Project administration. Mingqing Liu: Writing -review & editing Conceptualization, Methodology.

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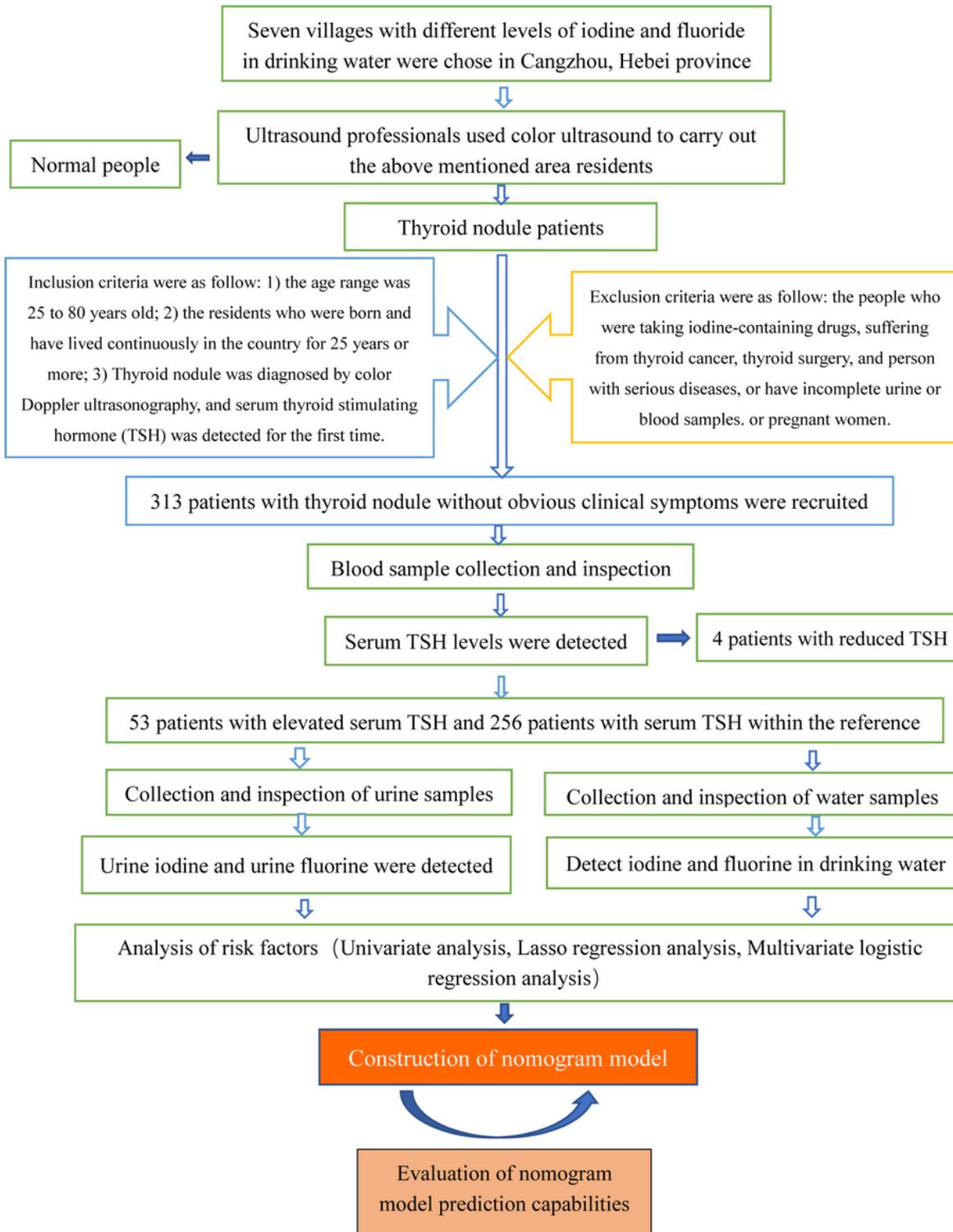
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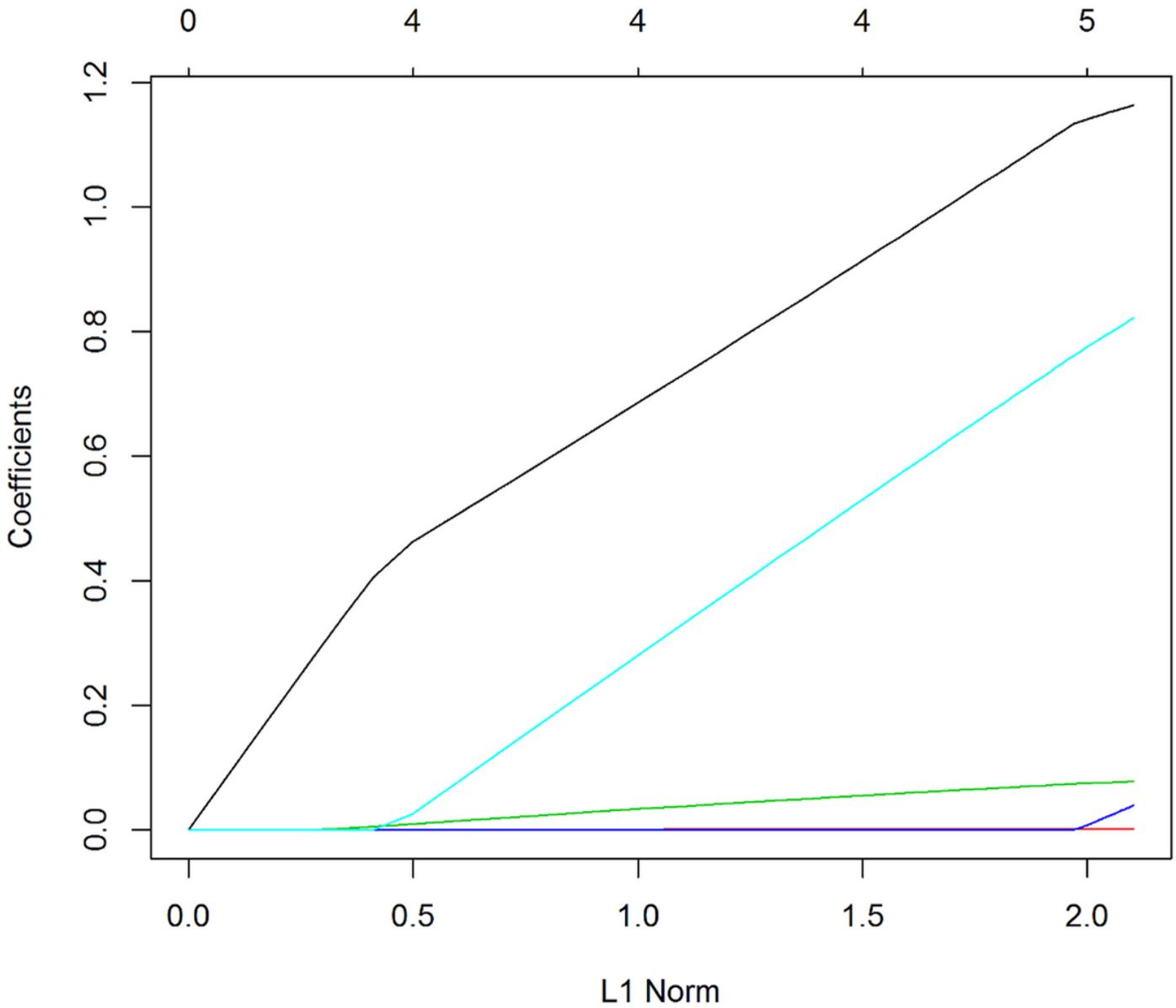
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## Figures



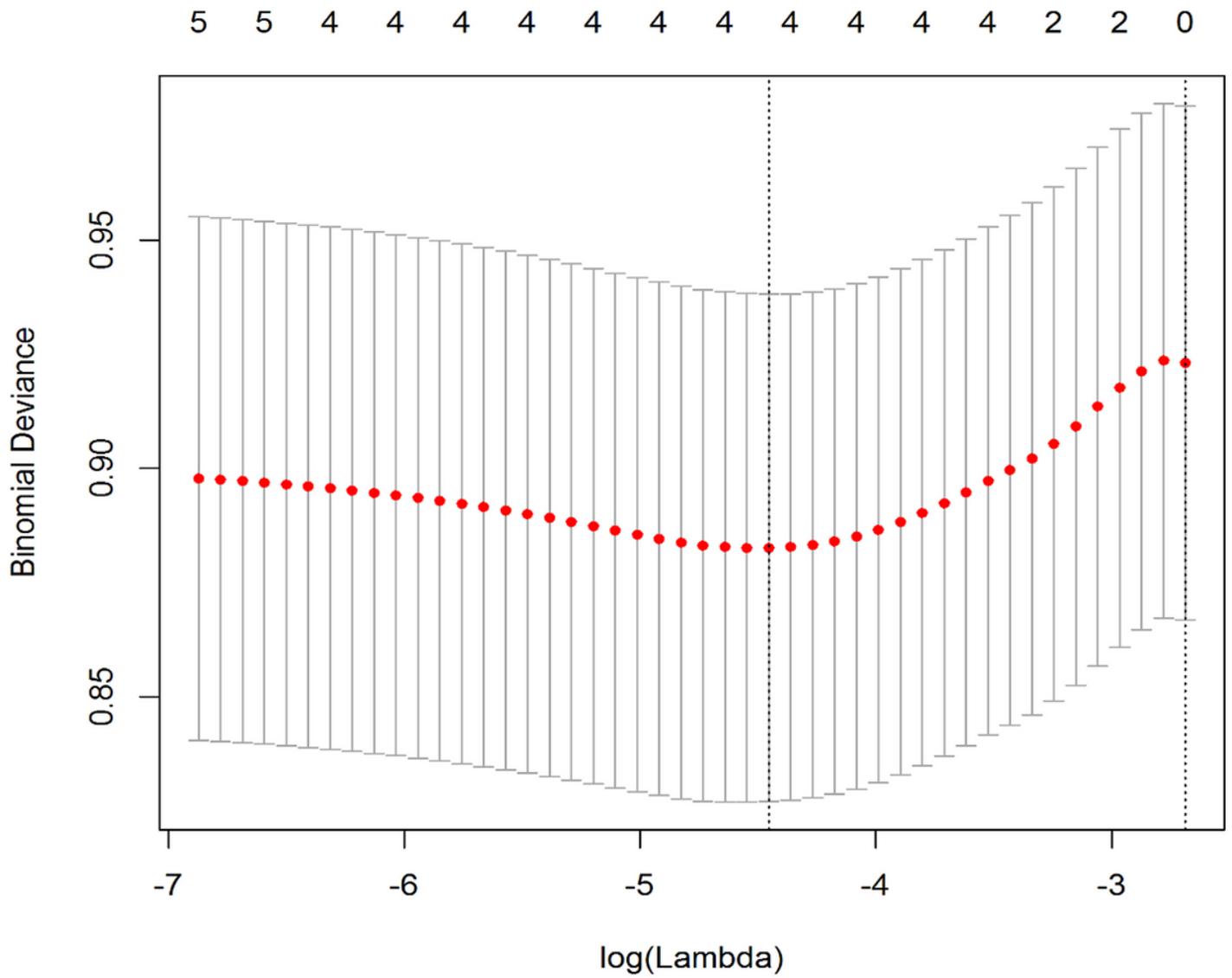
**Figure 1**

The flow chart of the selected subjects.



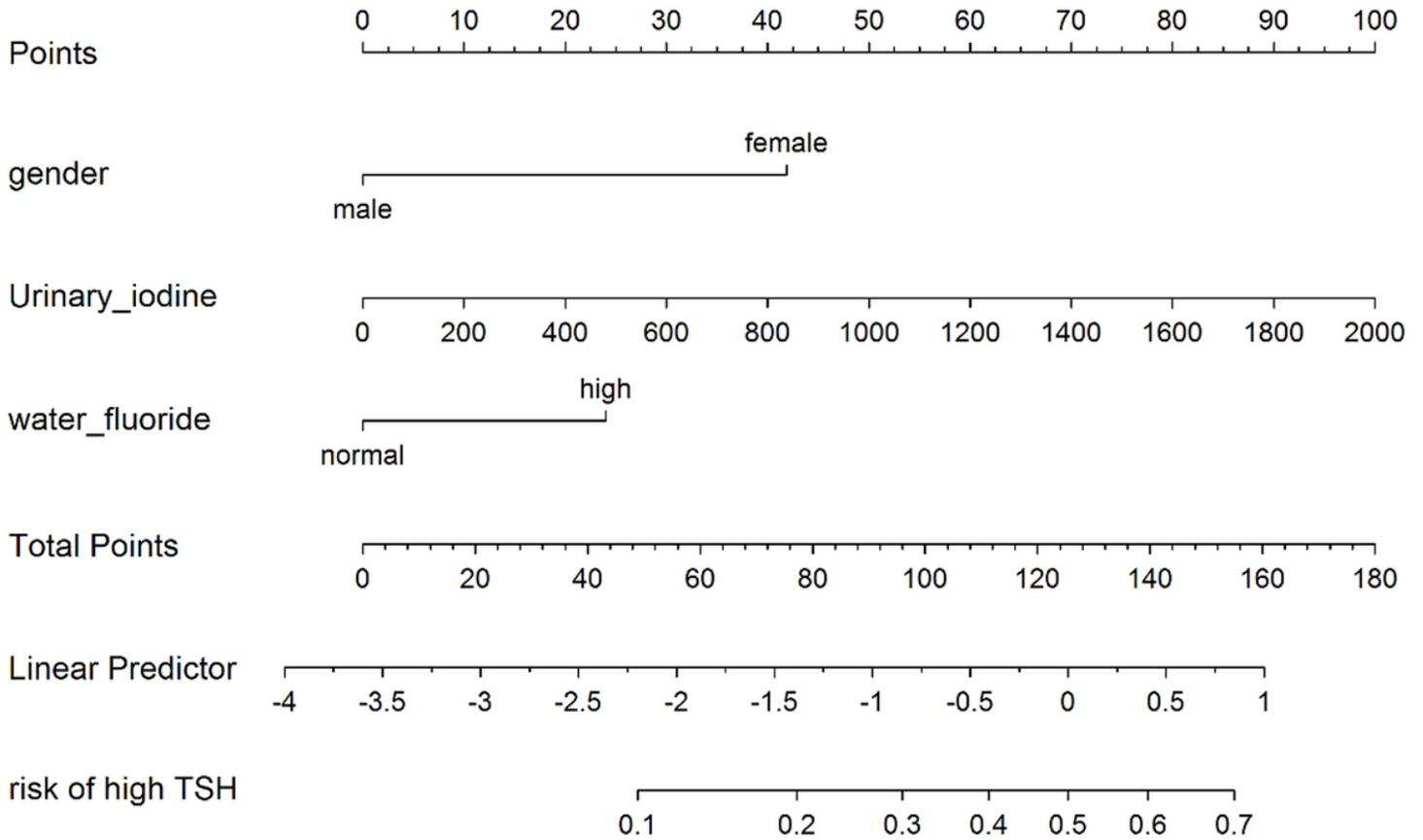
**Figure 2**

Lasso coefficient profiles of the 6 features. A coefficient profiles plot was produced against the log ( $\lambda$ ) sequence. Vertical line was drawn at the value selected using 10-fold cross-validation, where optimal  $\lambda$  resulted in 4 nonzero coefficients.



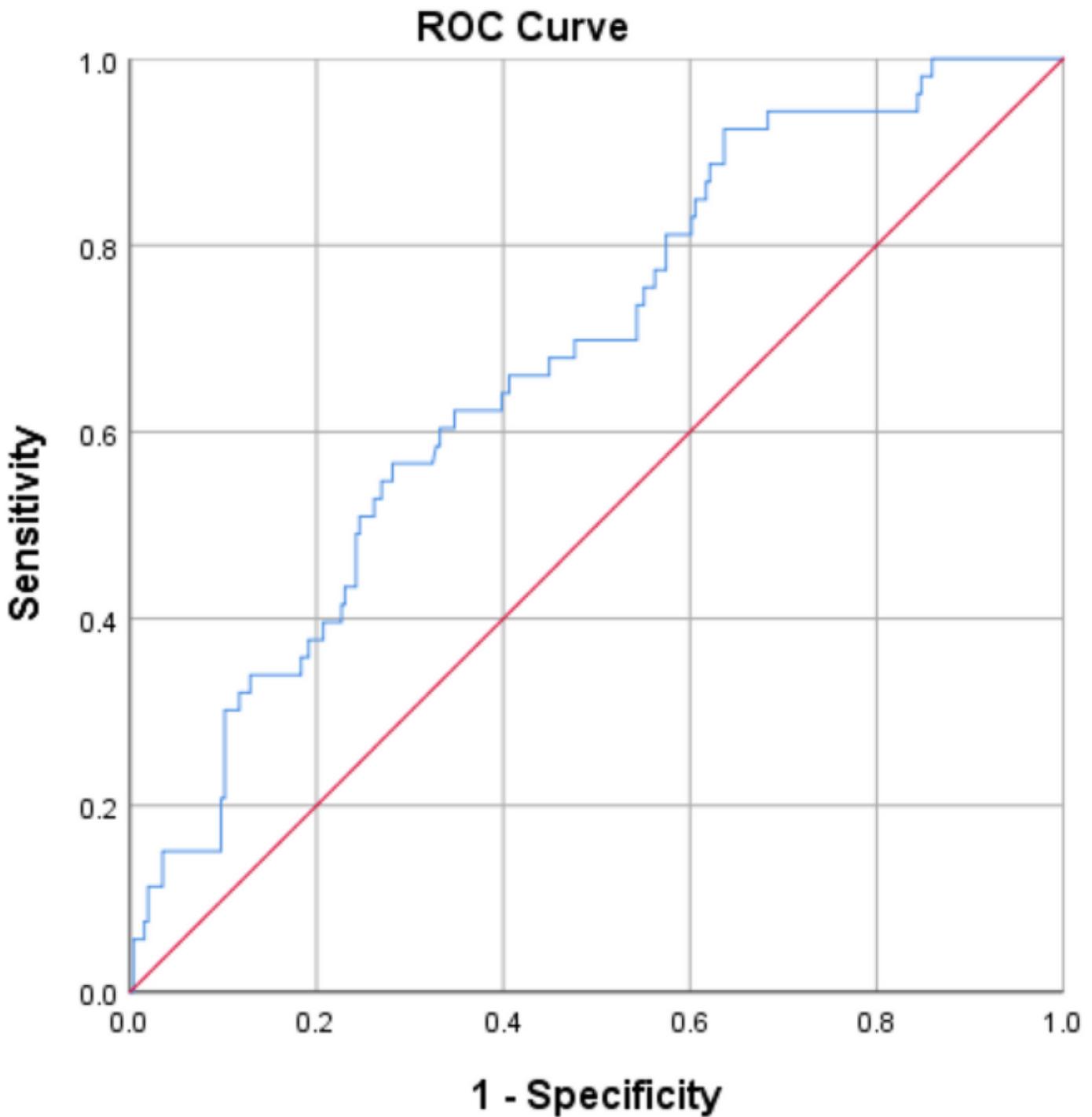
**Figure 3**

Risk factors of lasso regression detection. By using the minimum error criterion, the final zero coefficient selected by lasso regression is 4.



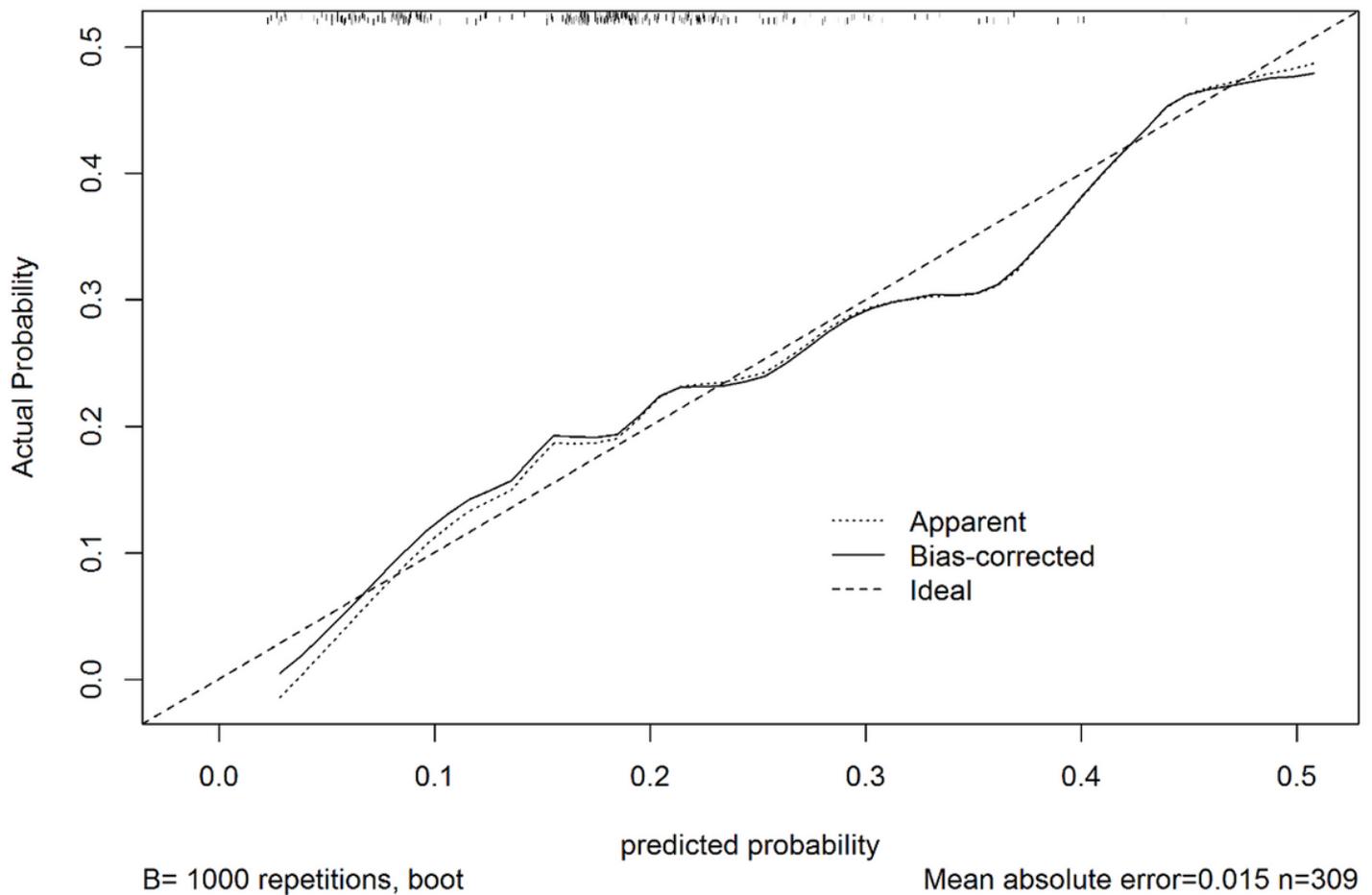
**Figure 4**

A Nomogram model that predicts that environmental iodine and fluorine will increase serum TSH in patients with thyroid nodules. The Nomogram includes three indicators: gender, urine iodine, and drinking water fluoride. Points is gender score scale, gender is gender grade, urinary iodine is urinary iodine fractional scale and water fluoride is drinking water fluoride fractional mark, total points is total score scale mark, linear predictor is linear predictive value line, risk of high serum TSH is predictive risk value line of serum TSH.



**Figure 5**

ROC curve of the Nomogram prediction model. The ROC curve takes the true positive rate (sensitivity) as the ordinate and the diagonal of the curve drawn with false positive rate (1-specificity) as the horizontal coordinate as the reference line. The closer the ROC curve is to the upper left corner, the more accurate the prediction model will be. Similarly, the area under the ROC curve (AUC) is between 0.0 and 1. The closer the AUC is to 1, the greater the predicted value of the model is.



**Figure 6**

Calibration diagram of the Nomogram prediction model. The calibration curve describes the calibration of each model based on the consistency of the predicted risk of serum TSH elevation in patients with thyroid nodules and the observed increase in serum TSH. The y-axis represents the actual serum TSH elevation rate. The x-axis represents the predicted risk of elevated serum TSH. The diagonal dashed line represents a perfect prediction of an ideal model. The solid line represents the performance of the Nomogram where the dashed line closer to the diagonal represents a better prediction.

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