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Predicting the nature of thyroid nodules by nomogram modeling: A study of health checkup data in a Chinese region

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► ***Original article***

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Keywords: *Thyroid nodule, nomogram, physical examination, training set, validation set, ultrasonography.*

ABSTRACT

Background*:** Nomogram modeling of the nature of thyroid nodules (TNs) is useful in helping physical examiners to make early interventions for malignant nodules. To predict the nature of TNs (benign and malignant) in a Chinese population undergoing physical examination by using nomogram model. ***Materials and Methods: Basic information and ultrasound (US) images were collected from 4,144 examiners who were found to have TNs during their physical examinations between 2023 and 2024. Predictors of malignant thyroid nodules were assessed by univariate and multivariate logistic regression. The examiners' information was randomly categorized into the training set (n = 700) and the test set (n = 300) in a 7:3 ratios. The nomogram model was constructed based on the training set, and the ROCR and RMS program packages were used to plot the receiver operating characteristic (ROC) curve and calculate the area under curve (AUC) to evaluate the classification performance of the model. ***Results:*** The maximum diameter of TNs (P = 0.002), waist-to-hip ratio (P = 0.002), diastolic blood pressure (P < 0.001), TSH (P < 0.001), FT4 (P < 0.001), T4 (P = 0.013), Thyroglobulin (P ≤ 0.001), CEA (P = 0.007), Women (P = 0.012), Hypertension (P = 0.047), and multiple nodules (P < 0.001) were predictors of malignant thyroid nodules. The nomogram model constructed on the basis of waist-to-hip ratio, diastolic blood pressure, maximum diameter of TNs, and CEA values was able to better predict malignant thyroid nodules. ***Conclusions:*** Our nomogram model for the nature of TNs constructed on the basis of physical examination information has high accuracy, and can provide some decision support for patients with TNs.

INTRODUCTION

Thyroid nodules (TNs) are small lumps formed by the proliferation of abnormal tissues in the thyroid gland that can move up and down with swallowing movements [1,2]. Iodine deficiency, radioactive radiation exposure, family history of genetic disorders and thyroid verification are common causes of TNs [3-5]. TNs are categorized into benign and malignant nodules, of which the incidence of benign nodules can account for about 95% of the total incidence of TNs, and are characterized by a slower growth rate [6,7]. Malignant thyroid nodules are hazardous to human health and can easily lead to thyroid cancer and other thyroid-related symptoms, so early screening, characterization, and treatment of thyroid nodules is a key part of maintaining quality of life. The detection rate of TNs has been increasing in recent years with the increasing health awareness of the population and the popularization of physical examination screening techniques. Epidemiologic studies have shown that nodular thyroid disease is very common in the clinic, with a prevalence of 4% ~7% in adults in North America and a new incidence of 0.1% per year [8]. The detection rate of TNs in the Chinese regional medical examination population has increased from 4% to 19% [9]. Accurate and rapid determination of the nature of TNs is conducive to timely intervention to reduce the adverse effects of TNs on the human body.

The differentiation of benign and malignant thyroid nodules usually requires a combination of clinical manifestations, ultrasonography findings, fine needle aspiration (FNA) findings, laboratory findings, and imaging studies [10]. However, the interpretation of imaging results may be influenced by the subjective judgment of physicians [11]. A multi-country cohort study demonstrated that the widespread use of ultrasound-dominated imaging has led to over-treatment and over-diagnosis of TNs, and many patients with TNs underwent unnecessary biopsies and surgeries, resulting in unnecessary harm to the patients and a waste of social resources [12]. FNA is currently the gold standard for the

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determination of the nature of TNs, and this method has a high degree of sensitivity and specificity, but nodules smaller than 5 mm nodules have a false negative rate of puncture [13]. At the same time, the fine-needle puncture procedure may lead to local pain, bleeding, hematoma and other uncomfortable symptoms, and in rare cases may lead to infections and other complications. Most of the FNA test results define the nature of nodules as indeterminate nodules and clinical characterization of the nature of nodules still needs to be performed in conjunction with the results of immunocytochemistry analysis of candidate protein markers or differential microRNA expression patterns [14]. Abdullah *et al.* [15] conducted a retrospective study of 499 patients who underwent FNA in Jordan and found that in only 325 cases, the nature of the nodules could determine the nature of the nodule. Imaging and fine-needle aspiration biopsy, although they can provide information about the morphology, and cytologic features of TNs, still do not provide comprehensive information about the nodules, such as biomarkers at the molecular level.

With the rapid development of deep learning technology, the prediction of thyroid nodule properties using machine learning models has become one of the hot topics of research. Compared with the traditional single diagnostic method, using the nomogram model to comprehensively consider multiple imaging features and patient information can improve the prediction accuracy of the nature of TNs and help doctors better identify high-risk patients for further diagnosis and treatment in a timely manner, thus avoiding unnecessary tests and treatments and reducing healthcare costs [16]. We were the first study to use a nomogram model to predict the nature of TNs in a population undergoing physical examination in Sichuan province based on imaging information, laboratory findings and basic information of the examiners. This study can reveal the factors associated with the occurrence and development of TNs, provide a scientific basis for further clinical studies, and promote the development of the field of diagnosis and treatment of TNs.

MATERIALS AND METHODS

Study subjects

The study subjects were 4,144 patients with detected TNS who underwent physical examinations at the Health Management Center of the Family Medicine Center of West China Hospital of Sichuan University between 2023.1 and 2024.1. All physical examiners signed an informed consent form. Anonymization measures were taken during data collection and processing. The entire study process complied with ethical principles and regulatory requirements, and the rights and interests of the subjects and the safety of the data were protected at all times.

Inclusion criteria: (1) the physical examination information was kept complete; (2) ≥ 2 experienced sonographers jointly determined the presence of thyroid nodules in the examiners; (3) the pathological examination was accepted to clarify the nature of nodules during the follow-up process. Exclusion criteria: (1) the combination of other tumors; (2) the combination of other endocrine abnormalities; (3) patients receiving I131 radiation therapy or other endocrine interventions. Information on the final 1,000 examiners (7:3 randomized into training and validation sets) who had the nature of thyroid nodules determined by follow-up information were included in this study.

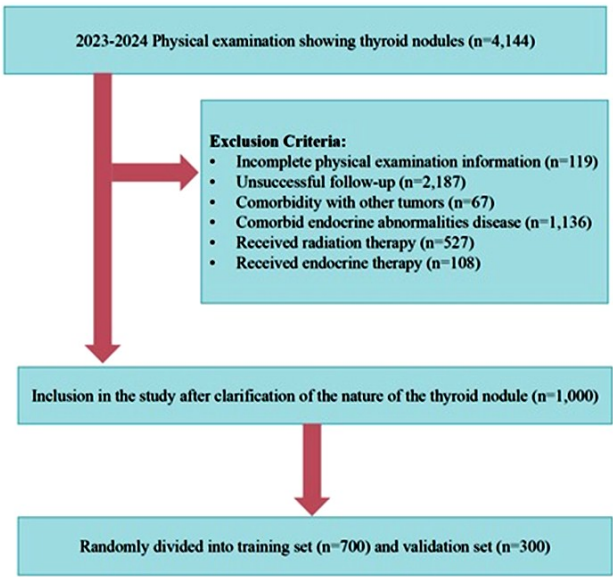

Figure 1. Screening process for patients participating in the study.

Data collection

The ultrasonic (US) examination instrument used is the Acuson Sequoia (C256, Siemens, USA). The physical examination data of the study subjects include general demographic characteristics, US results, and laboratory biochemical examination indicators. General demographic characteristics include age, gender, height, weight, BMI (Body Mass Index), waist circumference, hip circumference, waist -hip ratio, smoking history, alcohol consumption history, history of hypertension, history of diabetes mellitus, history of hyperlipidemia; Laboratory examination results include blood glucose, diastolic blood pressure, systolic blood pressure, Thyroid-Stimulating Hormone (TSH), Free Triiodothyronine (FT3), Triiodothyronine (T3), Free Thyroxine (FT4), Thyroxine (T4), Thyroglobulin Antibody (TGAb), Thyroid Peroxidase Antibody (TPO-Ab), Thyroglobulin (Tg), Carcinoembryonic Antigen (CEA); Imaging information includes nodule location, number of nodules, whether lymph nodes are enlarged, maximum diameter of TNs, and whether

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abnormal blood flow signals exist within the nodules. The data were entered by two physicians collaboratively and cross-checked.

Statistical analysis

Statistical analysis was conducted using IBM SPSS Statistics version 26.0 software (IBM Corporation, Armonk, NY, USA) and R software version 3.5.3 (The R Foundation for Statistical Computing, Vienna, Austria). A two-tailed $P < 0.05$ was considered statistically significant. For normally distributed continuous data, descriptive statistics are presented as mean ± standard deviation; otherwise, median with interquartile range (Q1, Q3) was used. Independent sample t-tests or Mann-Whitney U tests were employed for between-group comparisons of continuous variables. Group comparisons of categorical data were performed using chi-square tests or Fisher's exact tests. Variables with statistical significance ($P < 0.05$) in univariate analysis were included in multivariate analysis, and predictive factors selected were used to construct a logistic regression model. The predictive ability of the model was evaluated using receiver operating characteristic (ROC) curves, and further assessment was conducted through calibration curves. Decision curve analysis (DCA) was performed to evaluate the clinical net benefit of the model.

RESULTS

General Information

Information of 1000 examiners with definite nature of TNs were included in the present study. During the follow-up 830 (83.00%) examiners had nodules of benign nature (including benign neoplastic nodules and benign non-neoplastic nodules) and 170 (17.00%) examiners had nodules of malignant nature. Benign and malignant nodule groups were characterized by height, age, gender, waist to hip ratio, FT4, Systolic blood pressure, TSH, T3, T4, TGAb, CEA, Lymph Node Enlargement, Hypertension, Hyperlipidaemia, Number of nodes, and Blood Signal were statistically different ($P < 0.05$), (table 1).

Univariate and multifactorial analysis

The results of univariate analysis (table 2) showed that age, height, waist to hip ratio, blood glucose, blood pressure, TSH, FT4, T3, T4, Thyroglobulin, Maximum diameter of the nodule, CEA, gender, smoking history, hypertension, TPO-Ab, number of nodules, and lymph node enlargement may be the influencing factors for the nature of TNs ($P < 0.05$). Step forward method of analysis concluded that waist to hip ratio, Diastolic blood pressure, TSH, FT4, T4, Thyroglobulin, Maximum diameter of the nodule, CEA, Female, Hypertension, Number of nodules, Lymph node enlargement were the influencing factors for the nature of TNs nodules ($P < 0.05$).

Modeling and validation

A nomogram prediction model was constructed based on the results of multifactorial analysis, and the factors that contributed less to the model were removed, and waist-to-hip ratio, blood pressure, maximum diameter of the nodule and CEA were finally included in the prediction model (figure 2a).The results of ROC curve analysis showed an AUC of 0.973 (0.961 - 0.984) for the training set (figure 2b), and an AUC of 0.968 (0.949 - 0.987) (figure 2c), suggesting that the model has a strong ability to distinguish between different endings.

The results of the calibration curves for the training set (figure 3a) and the validation set (figure 3b) show a high degree of closeness between the models' actual and predicted probabilities. The training set DCA decision curve (figure 3c) shows that the net clinical benefit of intervening according to the model's predicted probabilities is higher than intervening with no intervention for all (None) and intervening with all (All). The validation set DCA decision curve (figure 3d) shows that the net clinical benefit of intervening according to the model's predicted probability is higher than that of no intervention for all (None) and intervention for all (All) over the range of threshold probabilities 0.00 - 0.91.

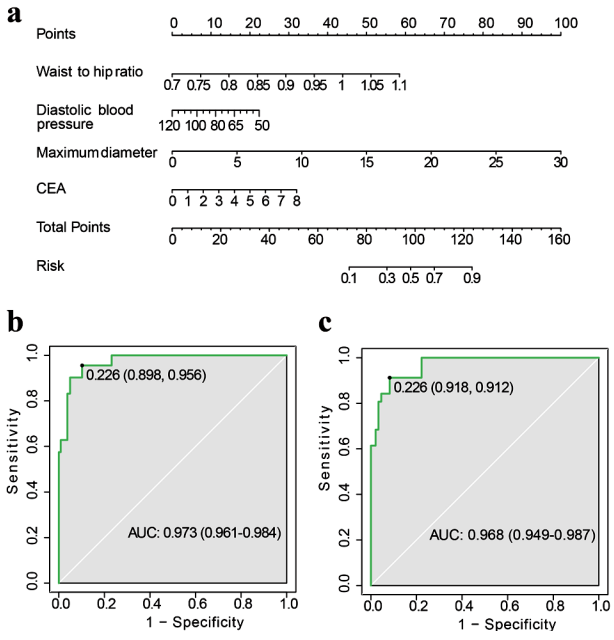

Figure 2. Nomogram modeling and ROC validation (**a.** nomogram; **b.** ROC curve for training set; **c.** ROC curve for validation set).

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Table 1. Baseline data of examiners.

Variables	Total (n = 1000)	Benign Nodules (n = 830)	Malignant nodules (n = 170)	P
Age	48.49 ± 12.67	47.71 ± 12.74	52.29 ± 11.67	<.001
Height (m)	1.64 ± 0.07	1.64 ± 0.07	1.65 ± 0.06	0.008
Weight (kg)	64.87 ± 12.64	64.58 ± 13.06	66.29 ± 10.23	0.059
BMI	24.00 ± 3.63	23.93 ± 3.64	24.33 ± 3.59	0.188
Waist (cm)	81.70 ± 10.47	81.48 ± 10.82	82.76 ± 8.53	0.090
Hip (cm)	94.81 ± 7.10	95.00 ± 7.09	93.88 ± 7.10	0.062
Waist to hip ratio	0.86 ± 0.09	0.86 ± 0.09	0.88 ± 0.07	<.001
FT3	4.86 ± 0.88	4.85 ± 0.82	4.90 ± 1.10	0.478
FT4	16.22 ± 2.06	16.15 ± 1.99	16.59 ± 2.35	0.011
Blood Sugar (mmol/L)	5.87 (5.18, 6.93)	5.98 (5.21, 6.89)	5.30 (5.02, 8.27)	0.308
Systolic blood pressure (mmHg)	122.00 (115.00, 135.00)	121.00 (114.00, 133.00)	127.00 (115.00, 148.00)	<.001
Diastolic blood pressure (mmHg)	75.00 (66.00, 84.25)	75.00 (64.00, 82.00)	84.00 (68.00, 93.00)	<.001
TSH	2.25 (1.34, 2.82)	2.23 (1.31, 2.82)	2.42 (1.82, 2.72)	<.001
T3	1.75 (1.54, 1.97)	1.74 (1.52, 1.91)	1.95 (1.83, 2.01)	<.001
T4	93.40 (83.95, 103.00)	92.70 (83.80, 98.10)	98.34 (89.40, 114.00)	<.001
TGAb	13.95 (12.70, 15.65)	13.70 (12.70, 15.40)	15.00 (13.40, 15.90)	<.001
Thyroglobulin	5.45 (4.68, 8.17)	5.27 (4.47, 7.38)	8.42 (6.89, 9.09)	<.001
Maximum diameter of the nodule (mm)	6.00 (4.00, 10.00)	6.00 (3.00, 9.00)	14.00 (9.00, 18.00)	<.001
CEA	1.23 (0.68, 1.73)	1.15 (0.67, 1.58)	1.67 (1.42, 1.87)	<.001
Gender				<.001
Male	531 (53.10)	477 (57.47)	54 (31.76)	
Female	469 (46.90)	353 (42.53)	116 (68.24)	
Smoking history				<.001
No	774 (77.40)	664 (80.00)	110 (64.71)	
Yes	226 (22.60)	166 (20.00)	60 (35.29)	
Drinking history				0.613
No	634 (63.40)	509 (61.33)	125 (73.53)	
Yes	366 (36.60)	321 (38.67)	45 (26.47)	
Hypertension				0.002
No	742 (74.20)	631 (76.02)	111 (65.29)	
Yes	258(25.80)	199 (23.98)	60 (34.71)	
Hyperglycaemia				0.098
No	818 (81.80)	688 (82.89)	130 (76.47)	
Yes	182 (18.20)	143 (17.11)	40 (23.53)	
Hyperlipidaemia				0.007
No	877 (87.70)	721 (86.87)	156 (91.76)	
Yes	123 (12.30)	109 (13.13)	14 (8.24)	
TPO-Ab				<.001
<9	421 (42.10)	381 (45.90)	40 (23.53)	
≤9 and <19	502 (50.20)	408 (49.16)	94 (55.29)	
≤19 and <29	33 (3.30)	15 (1.81)	18 (10.59)	
≥29	44 (4.40)	26 (3.13)	18 (10.59)	
Nodule location				0.102
Left	244 (24.40)	207 (24.94)	37 (21.76)	
Right	321 (32.10)	266 (32.05)	55 (32.35)	
Both	435 (43.50)	357 (43.01)	78 (45.89)	
Number of nodes				<.001
1	384 (38.40)	366 (44.10)	18 (10.59)	
>1	616 (61.60)	454 (55.90)	152 (89.41)	
Lymph Node Enlargement				<.001
No	355 (35.50)	277(33.37)	78 (45.88)	
Yes	105 (10.50)	33 (3.98)	72 (42.35)	
Blood Signal				<.001
No	872 (87.20)	819 (98.67)	53 (31.18)	
Yes	128 (12.80)	11 (1.33)	117 (68.82)	

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Table 2. Univariate and multifactorial analysis.

Variables	OR (95%CI)	P	aOR (95%CI)	aP
Age	1.03 (1.01 - 1.04)	0.001	1.04 (0.99 - 1.09)	0.100
Height	18.26(1.66 - 200.27)	0.017	17.65(1.75 - 416.79)	0.075
Weight	1.02 (1.00 - 1.03)	0.064		
BMI	1.04 (0.99 - 1.10)	0.136		
Waist	1.02 (1.00 - 1.04)	0.059		
Hip	0.99 (0.96 - 1.01)	0.341		
Waist to hip ratio	22.81 (3.50 ~ 148.61)	0.001	29.26 (3.40 ~ 251.65)	0.002
Blood Sugar	1.13 (1.06 - 1.20)	< 0.001	1.08 (0.73 - 1.60)	0.696
Systolic blood pressure	1.03 (1.02 - 1.04)	< 0.001	1.02 (0.96 - 1.08)	0.558
Diastolic blood pressure	1.03 (1.02 - 1.05)	< 0.001	0.82 (0.74 - 0.90)	<.001
TSH	1.20 (1.08 - 1.33)	< 0.001	2.01 (1.42 - 2.85)	<.001
FT3	1.06 (0.84 - 1.33)	0.624		
T3	2.45 (1.50 - 4.01)	< 0.001	0.22 (0.05 - 1.05)	0.057
FT4	1.12 (1.02 - 1.23)	0.021	1.91 (1.36 - 2.66)	<.001
T4	1.04 (1.03 - 1.05)	< 0.001	0.96 (0.93 - 0.99)	0.013
TGAb	1.01 (0.96 - 1.06)	0.762		
Thyroglobulin	1.54 (1.40 - 1.69)	< 0.001	2.74 (1.94 - 3.87)	<.001
Maximum diameter	1.23 (1.18 - 1.28)	< 0.001	1.93 (1.59 - 2.33)	<.001
CEA	1.23 (1.05 - 1.45)	0.010	3.93 (2.28 - 6.77)	0.007
Gender				
Male	1.00 (Reference)		1.00 (Reference)	
Female	0.48 (0.32 - 0.73)	< 0.001	11.39 (1.73 - 75.17)	0.012
Smoking history				
No	1.00 (Reference)		1.00 (Reference)	
Yes	2.23 (1.45 - 3.43)	< 0.001	2.30 (0.76 - 6.95)	0.140
Drinking history				
No	1.00 (Reference)			
Yes	0.96 (0.63 - 1.47)	0.857		
Hypertension				
No	1.00 (Reference)		1.00 (Reference)	
Yes	1.80 (1.17 - 2.77)	0.007	4.18 (1.02 - 17.23)	0.047
Hyperglycaemia				
No	1.00 (Reference)			
Yes	1.57 (0.98 - 2.50)	0.059		
Hyperlipidaemia				
No	1.00 (Reference)			
Yes	0.57 (0.27 - 1.22)	0.150		
TPO Ab grade				
<9	1.00 (Reference)		1.00 (Reference)	
≤9 and <19	2.68 (1.82 ~ 3.95)	< 0.001	1.62 (1.02 ~ 2.58)	0.040
≤19 and <29	19.00 (8.32 ~ 43.40)	< 0.001	4.99 (1.97 ~ 12.60)	<0.001
≥29	0.00 (0.00 ~ Inf)	0.978	0.00 (0.00 ~ Inf)	0.976
Nodule location				
Left	0.76 (0.44 - 1.34)	0.351		
Right	1.21 (0.77 - 1.89)	0.408		
Both	1.00 (Reference)			
Number of nodes				
1	1.00 (Reference)		1.00 (Reference)	
>1	12.87 (6.70 - 24.74)	< 0.001	16.00 (8.20 - 31.22)	<0.001
Blood signal				
Yes	1.00 (Reference)			
No	0.00 (0.00 - Inf)	0.984		
Lymph Node Enlargement				
No	1.00 (Reference)		1.00 (Reference)	
Yes	5.91 (3.72 ~ 9.37)	< 0.001	7.13 (4.20 ~ 12.11)	<0.001

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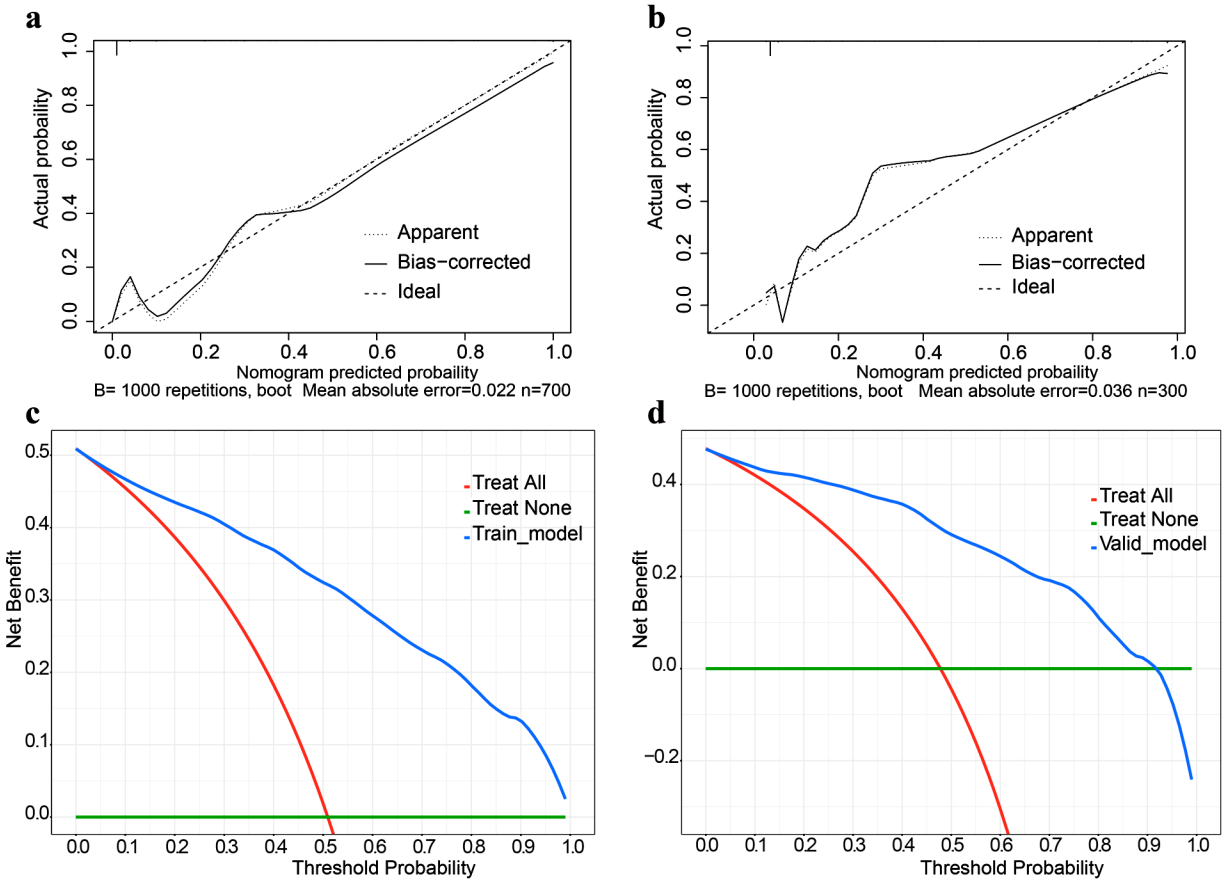

Figure 3. Calibration curves and DCA decision curves (**a.** Training set calibration curve; **b.** Validation set calibration curve; **c.** Training set DCA decision curve; d. Validation set DCA decision curve).

DISCUSSION

The results of our study on the physical examination population in Chengdu showed that waist-to-hip ratio, blood pressure, maximum diameter of the nodule and CEA value may be the key indicators for constructing a prediction model for the nature of TNs. The accuracy and discrimination of the nomogram model in the training and validation sets were better, and the results of the DCA decision curve showed that the prediction model had a better net clinical benefit.

More studies are trying to find out the key indicators for predicting the nature of thyroid nodules, but most of them are retrospective studies with well-defined target factors. Bestepe *et al.* [17] studied 5561 intraoperatively resected thyroid nodules in 2463 patients in Turkey and found that well-defined nodule diameters and volumes play a weak role in the prediction of malignant TNs, which has an inconsistency and we believe that the reason for the inconsistency in results may be racial differences. Shayganfar *et al.* [18] conducted a cross-sectional study of 239 patients with TNs and found that TIRADS and thyroid nodule diameter were predictors of malignant nodules, which is consistent with our study. Zhao *et al.* [19] conducted a cross-sectional study of 15,283 TNs from 10,944 patients and found that TIRADS was a weak predictor of malignant nodules. Mao L *et al.* [19] performed a study of 10,944 patients with 15,283 thyroid nodules that were statistically analyzed and found that thyroid nodule size was negatively correlated with the risk of malignancy, which is consistent with the findings of Cavallo *et al.* [20] Guo *et al.* [21] constructed a predictive model for 1675 histologically confirmed TNs and found that ultrasound-based nomograms could be used to quantify the probability of malignant TNs, however, it was not possible to exclude the subjective influence of physicians, so they called for an objective diagnostic model. Only the maximum diameter of the nodule is imaging information in our predictive model, and measurements may be influenced by subjective factors. Waist-to-hip ratio, blood pressure and CEA values are less subjectively influenced, which we believe can improve the stability and accuracy of the model. Xu *et al.* [22] constructed a prediction model based on 1016 thyroid nodules from 1016 patients and found that BMI was one of the factors predicting malignant TNs, which is also inconsistent with the results of our study, and further data are still needed to validate the results.

There were also studies constructing prediction models for TN risk from other perspectives. For example, the prediction of the nature of thyroid

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nodules based on the Thyroid Imaging Reporting and Data System (TI-RADS) found that age, tumour characteristics, and ACR score were the key factors in distinguishing TR5 nodules, and the AUC of the nomogram was higher than that of the American College of Radiology (ACR) scoring model (0.786 vs. 0.626, p < 0.001) [23]. Ruan *et a*l. assessed the malignancy risk of 801 TNs in 756 patients and found that CEUS-based assessment of the nature of the nodules had a high degree of accuracy [24]. Our study covered all patients with TNs with TI-RADS classification and we will stratify the study based on TI-RADS classification in our next study. In addition to this multicenter clinical studies are constructing models to predict the nature of TNs based on clinical data. Yi *et al*. [25] evaluated multimodal ultrasonographic data from 447 patients with TNs from more than 20 hospitals and found that nodule shape, elastography score (≥ 3), acyclic enhancement, and ill-defined margins on enhancement were predictive factors for malignant TNs. With China's large population base, routine physical examinations need to fulfil the requirements of a simple, easy-to-perform and economically convenient population, as well as to ensure that the results serve as an early warning for individual health. Our study is based on simple data commonly found in physical examinations, and the natural prediction of TNs at the time of detection through nomograms can help medical examiners intervene in the early stage of malignant nodules to a greater extent.

This study has some limitations. First, the imaging information in the physical examination data was simple and did not accurately describe the relevant ultrasound parameters, such as the nodule aspect ratio and the regularity of nodule margins. Secondly, the collection of physical examination data only from a group in a fixed city led to conclusions that may have overlooked geographic and racial differences. However, we increased the accuracy of the study conclusions by increasing the amount of included data, processing the data accurately, and selecting reasonable and effective prediction models. We will increase the accuracy and generalizability of the model for predicting the nature of TNs by adding medical examination data from different regions in our next study.

CONCLUSION

We constructed a model for predicting the nature of racked TNs based on physical examination data with a high degree of accuracy, simplicity, and non-invasiveness of the nomogram. This is beneficial in helping physicians and medical examiners to intervene in the early stage of malignant nodules and to reduce the adverse effects of malignant nodules on patients' health.

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Conflicts of interest: The authors declare that the study was conducted in the absence of any business or financial relationship that could be interpreted as a potential conflict of interest.

Ethical Considerations: This study posed a low risk to the study participants and no formal ethical approval was given, but the entire study process followed ethical principles and the data were anonymized.

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