ORIGINAL RESEARCH

Nomogram Model for Predicting Minimal Breast Cancer Based on Clinical and Ultrasonic Characteristics

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Purpose: To construct a nomogram prediction model on minimal breast cancer ($\leqq$ 10 mm) based on clinical and ultrasound parameters.

Methods: Clinical and ultrasound data of 433 patients with minimal breast lesions was conducted in this retrospective study. Patients were randomly divided into a training set and a validation set with a ratio of 7:3. Independent risk factors for minimal breast cancer were selected by the least absolute shrinkage and selection operator (LASSO) regression and multivariable logistic regression analysis to construct a nomogram prediction model. The calibration curve, the clinical decision curve analysis (DCA) and the area under the curve (AUC) of the receiver operating characteristic (ROC) curve were used to evaluate the diagnostic efficacy of the model.

Results: Age, margin, shape, and breast density were independent risk factors for malignant minimal breast lesions ($P < 0.05$). The AUC of the training set and validation set of the nomogram prediction model were 0.875, the sensitivity were 75.0% and 88.9%, the specificity were 83.8% and 77.7%, respectively. The mean absolute error (MAE) of the training set and validation set of the calibration curve were 0.01 and 0.024, respectively.

Conclusion: The nomogram prediction model has good discrimination, calibration and clinical practical value in the training set and validation set. The minimal breast cancer prediction model based on clinical and ultrasonic features possesses high clinical value, facilitating the early diagnosis of minimal breast cancer.

Keywords: predictive model, nomogram, minimal breast cancer, ultrasonography

Background

Breast cancer is the most common malignant tumor among women, with approximately 42,000 female fatalities annually.[1] According to data released by the International Agency for Research on Cancer (IARC) in 2020, breast cancer accounts for 11.7% of all cancers and has now become the second most common cancer worldwide.[2] The study suggests that early detection of breast cancer reduces the corresponding mortality by 40%.[3] Early detection and diagnosis, therefore, play an extremely important role in the choice of treatment and prognosis for breast cancer patients.

At present, there is still controversy about the definition of minimal breast cancer, and Chinese scholars refer to those with a diameter within 0.5 cm as microcarcinoma and those with a diameter of 0.5–1.0 cm as small carcinoma, collectively refer to as minimal breast cancer.[4,5] As an early lesion type of breast cancer, minimal breast cancer is difficult to diagnose due to its small size and atypical clinical symptoms. In recent years, medical imaging examination has been widely used in the diagnosis of breast diseases and could reflect the nature of the tumor and predict the pathological process of patients to some extent.[6] Compared with other examination methods, ultrasound has the advantages of easy operation, low cost, no radiation, and is of great value in the diagnosis and differential diagnosis

of breast cancer.[7,8] Comprehensive clinical and ultrasound features are helpful for the detection and diagnosis of minimal breast lesions.

In this study, a nomogram prediction model for the malignant risk of minimal breast cancer was established based on the clinical and ultrasonographic characteristics of minimal breast cancer patients, which may help to improve the understanding and diagnostic ability of minimal breast cancer, and improve the prognosis of patients. Meanwhile, clinical doctors can formulate more accurate screening and treatment plans based on the predictive results of the model, reducing unnecessary surgeries and biopsies, and improving the overall standard of care.

Methods
Patients Selection
All procedures of this study followed the Helsinki Convention, and this study has been approved by the Ethics Committee of Affiliated Hospital of Jiangnan University (Ethics No.LS2024232). A total of 477 patients with minimal breast lesions who underwent breast ultrasonography from December 2021 to January 2024 in the Affiliated Hospital of Jiangnan University were retrospectively analyzed. Inclusion criteria were as follows: (1) patients with confirmed minimal breast lesions ≤1 cm; (2) ultrasound images were clear; (3) complete clinical, surgical pathological, and radiological data. Exclusion criteria included: (1) patients who had undergone radiotherapy or endocrine treatment before the surgery; (2) poor quality of ultrasound images; (3) lack of pathological results or follow-up. A total of 433 patients met the inclusion criteria, with 329 benign cases and 104 malignant cases, ranging in age from 19 to 84 years, with an average age of 46.79 ± 12.14 years. Patients were randomly divided into a training set (n=303) and a validation set (n=130) in a 7:3 ratio. The research pathway is illustrated in Figure 1.

Data Collection
Evaluation of Clinical Data
The clinical medical records of the patients were retrieved by the picture archiving and communication system (PACS) system, and 14 indicators, including age, lesion side, pathological type, nipple discharge, history of breast cancer, family history of breast cancer, age of menarche, menopausal status, number of abortions, number of children, breastfeeding history, smoking, alcohol, and body mass index (BMI) were analyzed.

Assessment of Ultrasound Data
This retrospective study was conducted on minimal breast lesions diagnosed using color Doppler ultrasound devices from the Mindray, Kaili, GE, and others, following the fifth edition of the Breast Imaging Reporting and Data System (BI-RADS),[9] in which the lesion shape included round, oval, and irregular; orientation was divided into parallel and non-parallel; the margin was circumscribed and non-circumscribed; echogenicity included anechoic, hypoechoic, isoechoic, hyperechoic, liquid-mixed solid echo, and uneven echo; calcifications included no calcification, microcalcification, and macrocalcification; blood flow was divided into grades 0, I, II, and III; and posterior characteristics included enhancement, shadow, mixed change, and no change. All breast ultrasound images were evaluated by two physicians with more than 10 years of experience in ultrasound diagnosis but without knowledge of pathological findings, and when opinions were inconsistent, by a senior physician.

Evaluation of X-Ray Data
The imaging data of the patients were obtained by the PACS system to analyze their breast density, and they were divided into four types according to the fifth edition of BI-RADS [9], including ACR a (almost fatty entirely, glandular tissue less than 25%), ACR b (scattered fibroglandular density, glandular tissue accounts for 25–50%), ACR c (heterogeneously fibroglandular density, glandular tissue accounts for 50–75%), and ACR d (extreme fibroglandular tissue, glandular tissue more than 75%).

Statistical Analysis
Statistical analysis was performed using SPSS software (v.26.0) and R software (v.4.2.0). Continuous variables conforming to the normal distribution were presented as mean ± standard deviation and analyzed by independent sample *t*-test; those not
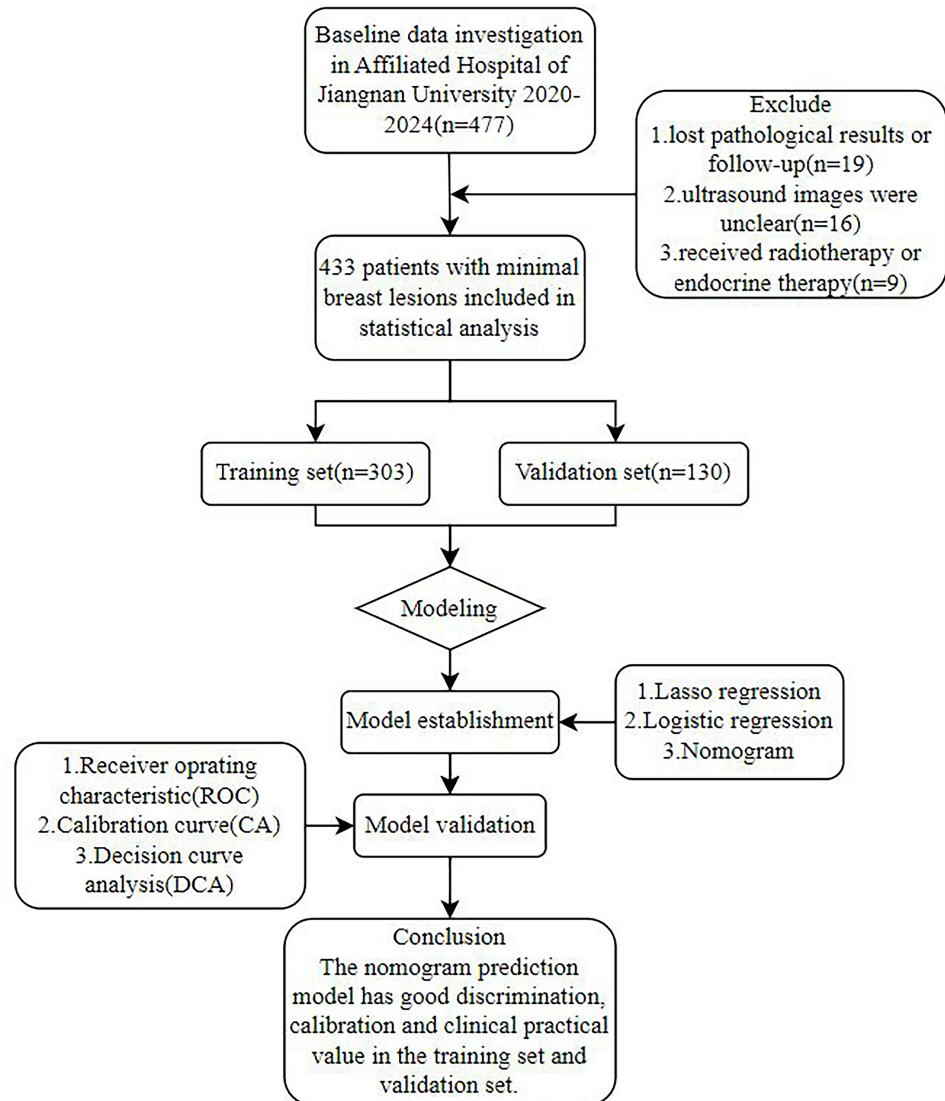
Figure 1 Research pathway diagram.

conforming to the normal distribution were presented as median and quartiles and analyzed by Man-Whitney U-test. Categorical variables were presented as frequency (%), the comparison were used χ^2 test or Fisher's exact test. The patients were randomly divided into a training set and a validation set with a ratio of 7:3. All variables in the training set were selected by the least absolute shrinkage and selection operator (LASSO) regression using the "glmnet" package of R software, and the variables corresponding to Lambda.min were selected to construct the optimal LASSO regression model. Predictive variables screened by LASSO regression analysis were subjected to multivariable logistic regression analysis, and independent risk factors were gradually selected. Then the nomogram prediction model was constructed by the "rms" package of R software, and receiver operating characteristic curve (ROC) was further plotted to assess the prediction efficacy of the model; clinical decision curve analysis (DCA) was plotted to assess the clinical applicability; and calibration curve was plotted to assess the consistency between the prediction probability of the model and the actual results. $P < 0.05$ indicates a statistical difference.

Results

Pathological Results

A total of 433 female patients with minimal breast lesions were included in this study, with a mean age of 46.79 years. According to the pathological types of breast tumors specified in World Health Organization (WHO),[10] 104 cases (24.0%) were malignant and 329 (76.0%) were benign. Pathological types are shown in Table 1.

Patient Characteristics

433 patients were randomly divided into training set (n = 303) and validation set (n = 130) with a ratio of 7:3. There were no statistical differences in the clinical data (including age, lesion side, pathological type, nipple discharge, history of breast cancer, family history of breast cancer, age of menarche, menopausal status, number of abortions, number of children, breastfeeding history, smoking, alcohol, and BMI), ultrasound data (including maximum diameter, shape, orientation, margin, echogenicity, calcification, blood flow, posterior characteristics of the lesion) and breast density ($P > 0.05$, Table 2).

Independent Risk Factors Selection

The training set was included in LASSO regression analysis to screen out independent risk factors for malignancy in minimal breast cancer, and the results showed that there were significant differences in seven variables including age, maximum diameter, shape, margin, posterior characteristics, blood flow, and breast density (Figure 2). Advanced age, irregular shape, non-circumscribed margin, shadow, rich blood flow, and low breast density are independent risk factors for minimal breast cancer.

Pathological types of minimal breast lesions were used as the dependent variable (assignment: benign=0, malignant=1), and statistically significant variables selected by LASSO regression analyses (age, maximum diameter, shape (assignment: regular=0, irregular=1), margin (assignment: circumscribed=1, non-circumscribed=2), posterior (assignment: enhancement=1, shadow=2, mixed change=3, no change=4), blood, breast density (assignment: ACR a=1, ACR b=2, ACR c=3, ACR d=4)) as independent variables were subjected to multivariable logistics regression analysis, and the

Table 1 Pathological Results of 433 minimal Breast Lesions

Pathology	Number (%)
Malignant	104 (24.02)
Infiltrating duct carcinoma	71 (16.40)
Ductal carcinoma in situ	19 (4.39)
Lobular carcinoma	7 (1.62)
Solid papillary carcinoma	5 (1.15)
Invasive solid papillary carcinoma	1 (0.23)
Mucinous adenocarcinoma	1 (0.23)
Benign	329 (75.98)
Adenopathy and sclerosing lesions	147 (33.95)
Fibroadenoma	116 (26.79)
Intraductal papilloma	55 (12.70)
Tubular adenoma	1 (0.23)
Others	10 (2.31)

Table 2 Comparison of Baseline Data in Training Set and Validation Set n (%)

Characteristics	All (n = 433)	Train (n = 303)	Validation (n = 130)	P
Age (year)	46.00 (38.00, 55.00)	46.00 (37.00, 54.00)	48.00 (40.00, 57.00)	0.055
Side				0.809
Left	217 (50.1)	153 (50.5)	64 (49.2)	
Right	216 (49.9)	150 (49.5)	66 (50.8)	
Maximum diameter	8.00 (7.00, 10.00)	8.70 (7.00, 10.00)	8.00 (7.00, 9.80)	0.459
Shape				0.289
Regular	276 (63.8)	198 (65.4)	78 (60.0)	
Irregular	157 (36.3)	105 (34.7)	52 (40.0)	
Orientation				0.524
Parallel	367 (84.8)	259 (85.5)	108 (83.1)	
Not Parallel	66 (15.2)	44 (14.5)	22 (16.9)	
Margin				0.240
Circumscribed	185 (42.7)	135 (44.6)	50 (38.5)	
Non-circumscribed	248 (57.3)	168 (55.4)	80 (61.5)	
Echogenicity				0.801
Anechoic	6 (1.4)	5 (1.7)	1 (0.8)	
Hypoechoic	389 (89.8)	268 (88.4)	121 (93.1)	
Isoechoic	3 (0.7)	2 (0.7)	1 (0.8)	
Hyperechoic	6 (1.4)	5 (1.7)	1 (0.8)	
Liquid-mixed solid echo	18 (4.2)	15 (5.0)	3 (2.3)	
Uneven echo	11 (2.5)	8 (2.6)	3 (2.3)	
Posterior				0.598
Enhancement	14 (3.2)	12 (4.0)	2 (1.5)	
Shadow	46 (10.6)	33 (10.9)	13 (10.0)	
Mixed change	5 (1.2)	3 (1.0)	2 (1.5)	
No change	368 (85.0)	255 (84.2)	113 (86.9)	
Calcification				0.831
No calcification	342 (79.0)	237 (78.2)	105 (80.8)	
Microcalcification	61 (14.1)	44 (14.5)	17 (13.1)	
Macrocalcification	30 (6.9)	22 (7.3)	8 (6.2)	
Blood				0.695
0	333 (76.9)	237 (78.2)	96 (73.8)	
I	81 (18.7)	54 (17.8)	27 (20.8)	

(*Continued*)

Table 2 (Continued).

Characteristics	All (n = 433)	Train (n = 303)	Validation (n = 130)	P
II	16 (3.7)	10 (3.3)	6 (4.6)	
III	3 (0.7)	2 (0.8)	1 (0.7)	
Breast Density				0.446
ACR a	4 (0.9)	2 (0.7)	2 (1.5)	
ACR b	86 (19.9)	65 (21.5)	21 (16.2)	
ACR c	305 (70.4)	209 (69.0)	96 (73.8)	
ACR d	38 (8.8)	27 (8.9)	11 (8.5)	
Discharge				0.412
No	406 (93.8)	286 (94.4)	120 (92.3)	
Yes	27 (6.2)	17 (5.6)	10 (7.7)	
Family history				0.776
No	418 (96.5)	293 (96.7)	125 (96.2)	
Yes	15 (3.5)	10 (3.3)	5 (3.8)	
History of breast cancer				0.408
No	412 (95.2)	290 (95.7)	122 (93.8)	
Yes	21 (4.8)	13 (4.3)	8 (6.2)	
The age of menarche (year)	14.00 (14.00, 14.00)	14.00 (14.00, 14.00)	14.00 (14.00, 14.00)	0.539
Menopausal				0.094
No	285 (65.8)	207 (68.3)	78 (60.0)	
Yes	148 (34.2)	96 (31.7)	52 (40.0)	
Breastfeeding				0.861
No	45 (10.4)	32 (10.6)	13 (10.0)	
Yes	388 (89.6)	271 (89.4)	117 (90.0)	
Number of children	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 2.00)	0.124
Abortions	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 1.00)	0.104
Smoking				0.300
No	432 (99.8)	303 (100.0)	129 (99.2)	
Yes	1 (0.2)	0 (0.0)	1 (0.8)	
Alcohol				0.300
No	432 (99.8)	303 (100.0)	129 (99.2)	
Yes	1 (0.2)	0 (0.0)	1 (0.8)	
BMI (kg (m2)	22.83 (20.76, 25.23)	22.77 (20.70, 25.15)	23.09 (20.96, 25.39)	0.421

(*Continued*)

Table 2 (Continued).

Characteristics	All (n = 433)	Train (n = 303)	Validation (n = 130)	P
Pathology				0.241
Benign	329 (76.0)	235 (77.6)	94 (72.3)	
Malignant	104 (24.0)	68 (22.4)	36 (27.7)	

results showed that age, margin, shape, and breast density were independent risk factors for minimal breast cancer (*P* < 0.05, Figure 3).

Establishment of Nomogram Prediction Models

After including the above independent risk factors into the model, a minimal breast cancer nomogram prediction model was established (Figure 4), and the scores of each independent risk factor could be obtained from the scale of the model, and the total score could be calculated by adding them, and the prediction probability corresponding to the total score was the risk of minimal breast cancer.
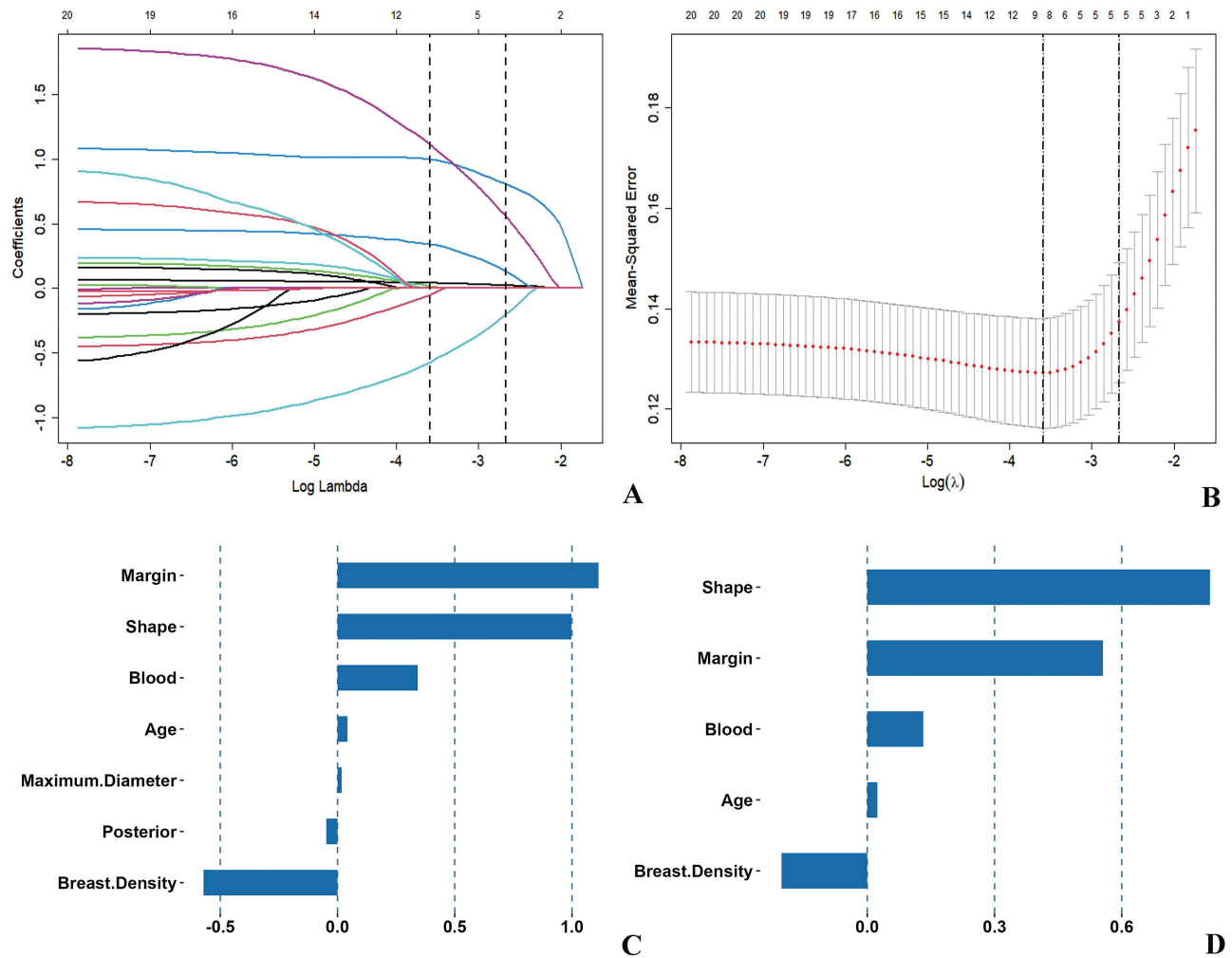

Figure 2 Best matching factor screening match by LASSO regression. (**A**) is the LASSO regression path diagram; (**B**) shows the plot of the best matching factors screened by the best fold matching validation method, and the best cross fold regression factors selected using Lambda.min as the criterion; (**C**) shows the factors of Lambda.min; (**D**) shows the factors of Lambda.1se.
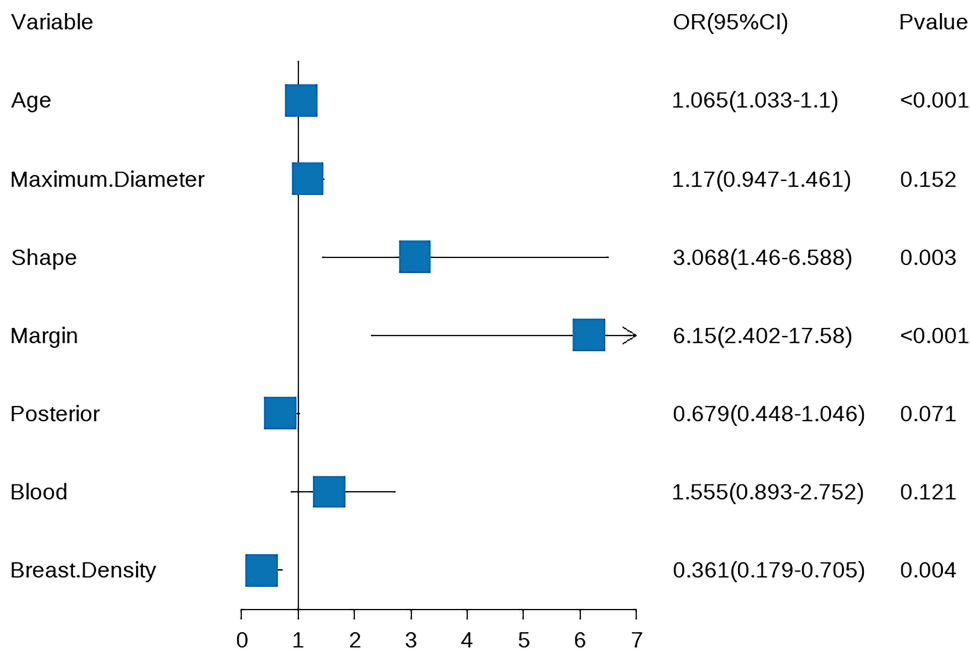
Figure 3 Forest plots of independent influencing factors for minimal breast cancer by multivariable analysis. OR (odds ratio) values represent estimates of the effects observed in the study. The parentheses next to each OR values contain the corresponding 95% CI (confidence interval), and the two values in parentheses indicate the lower and upper bounds of the OR values, reflecting the uncertainty of the estimate.The smaller the 95% CI, the less uncertain about the parameters (eg, the OR value), and the more reliable the results.
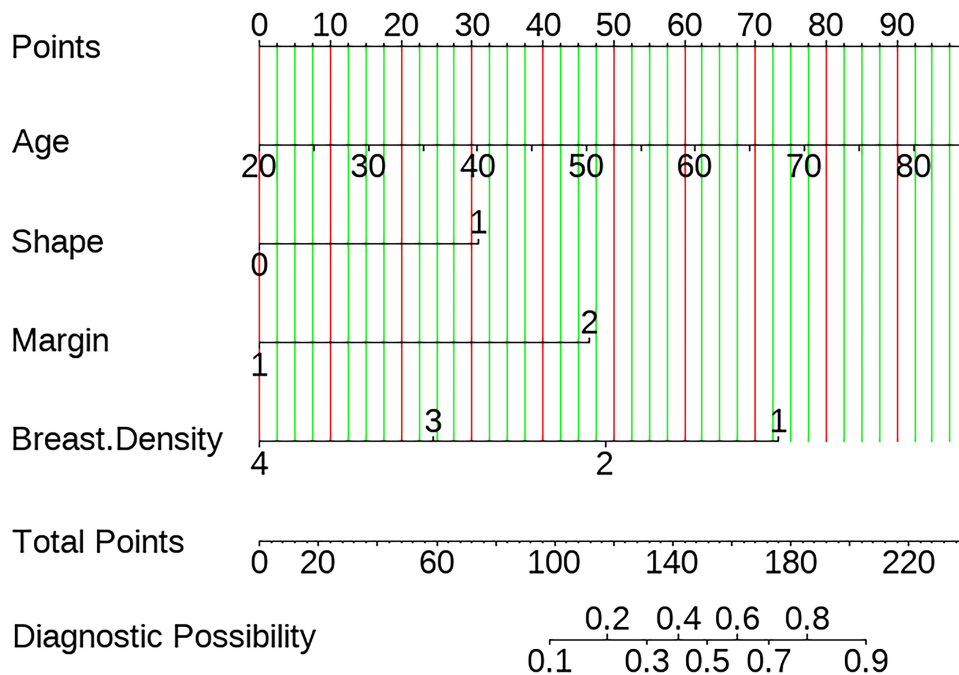

Figure 4 Nomogram of the prediction model for minimal breast cancer (shape (assignment: regular=0, irregular=1), margin (assignment: circumscribed=1, non-circumscribed=2), breast density (assignment: ACR a=1, ACR b=2, ACR c=3, ACR d=4)).

Evaluation of the Nomogram Prediction Model

By plotting the ROC curves for the training and validation sets, their area under the curves (AUC) were 0.875 (95% CI: 0.832–0.918) and 0.875 (95% CI: 0.803–0.947), respectively, suggesting better discrimination of the nomogram model. The sensitivity of this nomogram were 75.0% and 88.9%, and the specificity were 83.8% and 77.7%, respectively. The
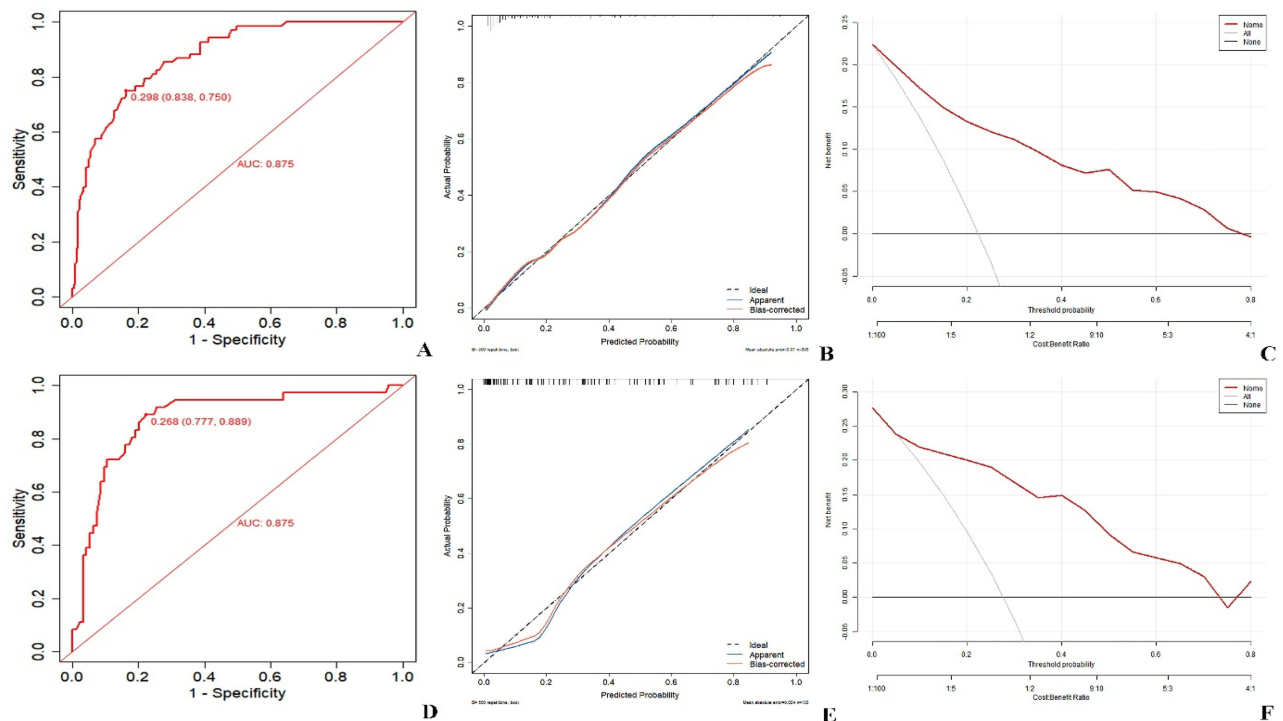
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Figure 5 The receiver operating curve of the nomogram in the training set (**A**) and validation set (**D**), the numbers on the ROC curve represent the cut-off values, and the numbers inside the brackets represent the specificity and sensitivity, respectively. The calibration curves of the nomogram in the training set (**B**) and in the validation set (**E**). The clinical decision curves of the nomogram in the training set (**C**) and validation set (**F**), the "all" line (the gray solid line) indicates intervention for anyone, indicating the maximum net benefit regardless of the model's predictions. The "none" line (the black solid line) indicates no intervention for anyone, representing the minimum net benefit. The red solid line indicates intervention for the nomogram. The area enclosed by the three lines presents the clinical utility of the nomogram.

results of the calibration curves showed that the mean absolute error (MAE) of the training and validation sets were 0.01 and 0.024, respectively (the smaller the MAE value, the higher the degree of calibration), and the table showed good agreement between the probability of predicting minimal breast cancer obtained by this nomogram model and the actual results. The DCA suggested that the nomogram prediction model had a high net benefit over a large threshold, illustrating the good clinical utility of the nomogram prediction model. (Figure 5)

Discussion

A nomogram is a practical tool that helps clinicians assess clinical risk and identify the appropriate treatment for patients by integrating comprehensive data, and is now widely used in clinical studies.[11,12] In this study, a nomogram prediction model for minimal breast cancer was constructed based on the clinical data and ultrasound characteristics of patients, each variable was quantified, and the corresponding degree of malignant risk was analyzed, and the results showed that this model had good clinical prediction value.

Twenty-two clinical and ultrasound parameters were included in our study, and seven diagnostic indicators were selected by LASSO regression, including age, maximum diameter, shape, margin, posterior characteristics, blood flow, and breast density, which have been mentioned in previous studies on breast cancer. Among them, clinical indicators only include age, which is an important risk factor for breast cancer and has been mentioned in relevant literature. According to statistics released in 2022,[13] the overall median age at onset of breast cancer is approximately 62 years. Breast cancer in Chinese women is younger than in Europe and the United States.[14] The median age of disease in the 433 patients in this study was approximately 46 years, which is similar to the peak incidence of breast cancer in Chinese women of 45–55 years, according to related studies.[15,16] However, there are many other risk factors associated with breast cancer, including obesity, family history of breast cancer, smoking and alcohol, but our findings do not include these factors,

which may be related to the small sample size included in this study, and the lower incidence of patients with family history of breast cancer, smoking, and alcohol.

Among ultrasound indicators, previous studies have shown that breast cancer has an irregular shape, non-circumscribed margin, microcalcification, non-parallel position, shadow, rich blood flow, and other characteristics, however, in this study, only shape, margin, posterior characteristics, and blood flow four indicators were selected by LASSO regression. This may be related to the fact that this study focused on minimal breast lesions, which have mostly atypical ultrasonographic features and clearly crossed benign and malignant features. At the same time, although the results of this study showed that the maximum diameter of lesions was related to the evaluation of benign and malignant nodules, this was not mentioned in the relevant studies, and the author concluded that this may be due to chance factors.

In addition, breast density was also included in this study, which was determined by the proportion of fibrous and glandular tissue compared to adipose tissue in the breast and assessed by X-ray.[17] Breast cancer is usually epithelial in origin, and dense breasts have a more abundant epithelial component, which increases the risk of breast cancer.[18] Some studies have shown that women with dense breasts have a higher risk of breast cancer than women with breast hypertrophy, and this phenomenon is widespread in patients of different age groups and menopausal status.[19–21] Some scholars incorporate breast density into risk prediction models, such as the Tyrer-Cuzick and Gail breast cancer risk models, which can more accurately distinguish between high-risk and low-risk groups for breast cancer.[22,23] Dense breasts have been confirmed as one of the high-risk factors for breast cancer in Western countries, however, our findings show that the risk of minimal breast cancer decreases with increasing breast density, which the author believes may be related to racial differences. For Asian women, a small number of studies have shown that the incidence of breast cancer also gradually increases with the decrease in breast density,[24] which may also have a certain relationship with age. Most of the young Chinese women have dense breasts. With the increase of age, the glands in the breast are gradually replaced by adipose tissue, and the breast density gradually decreases.[25] At the same time, age is the greatest risk factor for breast cancer, which will lead to a certain degree of inconsistency between our study and European and American studies.

The results of multivariable regression analysis showed that age, margin, shape, and breast density were independent risk factors for minimal breast cancer, which were also mentioned in previous studies on breast cancer. However, in contrast to studies on breast cancer, factors such as obesity, menopause, family history of breast cancer, orientation, microcalcification, and blood flow were not mentioned in our findings, which may be related to the fact that patients included in our study had minimal breast lesions less than 1 cm. Breast density, a risk factor, is also different in our results from previous studies, mainly because the patients selected in our study were Chinese women, and breast density in Chinese women is denser compared with Europe and the United States.

Based on clinical and ultrasound risk factors of minimal breast cancer, a nomogram prediction model was developed to quantitatively express the risk of minimal breast cancer development. Our study developed a nomogram model to identify four independent risk factors predictive of minimal breast cancer using LASSO regression as well as logistic regression analysis. According to the respective score of each factor, the total score was calculated, and the probability of minimal breast cancer occurrence could be obtained from the total score. Further validation of the prediction model showed that the AUC were 0.875, the sensitivity were 75.0% and 88.9%, and the specificity were 83.8% and 77.7% in the training set and validation set, respectively, and they had good discrimination in the training set validation set. The calibration curve shows that the predicted probability of minimal breast cancer is in good agreement with the actual probability and can be tried for clinical application. The DCA suggests good clinical utility. Therefore, the nomogram model developed in this study can improve the early prediction and recognition ability of minimal breast cancer, facilitate the development of corresponding clinical management strategies based on different malignant risks in clinical practice, reduce some unnecessary biopsies, and have high clinical application value.

This study has the following limitations: First, our study is a retrospective study, and the results may have some selection bias. Second, our study failed to include cases from outside hospitals for validation, and a multicenter retrospective study was planned in the future to further strengthen the model. Third, the sample size is still small. So data from different healthcare organizations and more sample size is needed, in order to assess the performance of the model in various clinical settings, thus providing a diagnostic basis for the clinical assessment of minimal breast cancers. To make it easier for others to use this model, we can also develop a Web APP based on the nomogram model in the future.

Conclusion

In summary, age, margin, shape, and breast density are independent risk factors for minimal breast cancer, and constructed nomogram prediction model has high clinical application value and is conducive for early diagnosis of breast cancer.

Data Sharing Statement

The original contributions presented in the study are included in the article. Further inquiries can be directed to the corresponding author.

Ethical Approval and Consent to Participate

The authors are accountable for all aspects of this work, ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. All procedures involving human participants were performed in accordance with the Declaration of Helsinki (revised 2013). The ethics committee of Affiliated Hospital of Jiangnan University approved this retrospective study, and waived the requirement for informed consent. Patient information, such as name, age, sex, occupation, address, ID card, related diseases, and treatment plan, was provided by the Affiliated Hospital of Jiangnan University during the treatment period due to illness. Owing to the privacy of patients, the Affiliated Hospital of Jiangnan University kept the above information confidential.

Consent for Publication

All authors declare the final manuscript and the submission to this journal.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

Disclosure

No conflict of interest.

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