

A nomogram model for predicting the risk of axillary lymph node metastasis in patients with early breast cancer and cN0 status

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Abstract. Axillary staging is commonly performed via sentinel lymph node biopsy for patients with early breast cancer (EBC) presenting with clinically negative axillary lymph nodes (cN0). The present study aimed to investigate the association between axillary lymph node metastasis (ALNM), clinicopathological characteristics of tumors and results from axillary ultrasound (US) scanning. Moreover, a nomogram model was developed to predict the risk for ALNM based on relevant factors. Data from 998 patients who met the inclusion criteria were retrospectively reviewed. These patients were then randomly divided into a training and validation group in a 7:3 ratio. In the training group, receiver operating characteristic curve analysis was used to identify the cutoff values for continuous measurement data. R software was used to identify independent ALNM risk variables in the training group using univariate and multivariate logistic regression analysis. The selected independent risk factors were incorporated into a nomogram. The model differentiation was assessed using the area under the curve (AUC), while calibration was evaluated

through calibration charts and the Hosmer-Lemeshow test. To assess clinical applicability, a decision curve analysis (DCA) was conducted. Internal verification was performed via 1000 rounds of bootstrap resampling. Among the 998 patients with EBC, 228 (22.84%) developed ALNM. Multivariate logistic analysis identified lymphovascular invasion, axillary US findings, maximum diameter and molecular subtype as independent risk factors for ALNM. The Akaike Information Criterion served as the basis for both nomogram development and model selection. Robust differentiation was shown by the AUC values of 0.855 (95% CI, 0.817-0.892) and 0.793 (95% CI, 0.725-0.857) for the training and validation groups, respectively. The Hosmer-Lemeshow test yielded P-values of 0.869 and 0.847 for the training and validation groups, respectively, and the calibration chart aligned closely with the ideal curve, affirming excellent calibration. DCA showed that the net benefit from the nomogram significantly outweighed both the 'no intervention' and the 'full intervention' approaches, falling within the threshold probability interval of 12-97% for the training group and 17-82% for the validation group. This underscores the robust clinical utility of the model. A nomogram model was successfully constructed and validated to predict the risk of ALNM in patients with EBC and cN0 status. The model demonstrated favorable differentiation, calibration and clinical applicability, offering valuable guidance for assessing axillary lymph node status in this population.

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Abbreviations: EBC, early breast cancer; cN0, clinical axillary lymph node negative; SLNB, sentinel lymph node biopsy; US, ultrasound; ALNM, axillary lymph node metastasis; ROC, receiver operating curve; AUC, area under the curve; DCA, decision curve analysis; AIC, Akaike Information Criterion; BC, breast cancer; ALN, axillary lymph nodes; MD, maximum diameter; LVI, lymphovascular invasion; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor-2; IHC, immunohistochemistry; OR, odds ratio; CI, confidence interval; CT, computed tomography; MRI, magnetic resonance imaging; PET-CT, positron emission tomography-computed tomography; TNBC, triple-negative breast cancer

Key words: early breast cancer, cN0, axillary lymph node metastasis, sentinel lymph node, nomogram

Introduction

Breast cancer (BC) has surpassed lung cancer as the most widespread malignant tumor worldwide, particularly among women. This poses a substantial risk to their physical and mental well-being and quality of life (1,2). With increased health awareness and the implementation of BC screening, more patients with early breast cancer (EBC) are being identified. Axillary lymph nodes (ALN) are the primary pathway for BC metastasis and dissemination. Identifying ALN metastasis (ALNM) is essential not only for accurately determining the tumor stage but also for determining the appropriate degree of axillary dissection to prevent tumor metastasis and spread (3).

Sentinel lymph node biopsy (SLNB) is the standard approach for axillary staging in patients with EBC and clinically negative axillary lymph nodes (cN0) who have not undergone neoadjuvant chemoradiotherapy (4). Nonetheless,

>70% of patients with EBC and cN0 do not exhibit ALNM (4,5). Moreover, SLNB is an invasive procedure and can result in complications, such as infections in the wound, hematomas and abnormalities in sensory perception (6,7). Liu *et al* have suggested that SLNB might be an overtreatment for most patients with EBC and cN0 (8). Recent studies have increasingly focused on the possibility of identifying patients with low risk of developing ALNM among those with EBC having cN0 to avoid unnecessary SLNB (9,10). Therefore, developing a convenient and effective method to predict the ALN status in patients with EBC and cN0 is necessary, which could greatly assist in devising individualized treatment strategies. Predicting the preoperative ALN status can help eliminate unnecessary SLNB and minimize surgical trauma.

Ultrasound (US) is preferred for assessing ALN status. ALNM prediction is based on morphological alterations of the size, cortical thickness, blood flow, lymphatic portal structure and boundary characteristics of the ALN (11-13). During the first phases of metastasis, there are minimal alterations in the size and structure of ALN. As a result, the US features of metastatic and reactive lymph nodes frequently exhibit similarities (13,14). Therefore, the sensitivity, specificity, and accuracy of US alone for ALNM diagnosis remain suboptimal (15,16).

In the era of precision medicine, constructing a more practical, reliable and accurate clinical decision-making tool for ALNM risk prediction carries great significance. Therefore, the present study aimed to develop a nomogram model for predicting risk of ALNM, utilizing readily available axillary US findings and clinicopathological features of tumors.

Patients and methods

Patients. The present study included data from a total of 1,799 patients with BC admitted to the Department of Breast Diseases of Jiaxing Maternity and Child Health Care Hospital (Jiaxing, China) between January 1st, 2014 and September 10th, 2023. The inclusion criteria were as follows: i) Having histologically confirmed early-stage (T1-T2) invasive ductal carcinoma; ii) in cases of SLN metastasis, the metastatic lesion was ≥ 2 mm with SLNB performed intraoperatively (17); iii) preoperative US examination was conducted; iv) preoperative clinical absence of ALN involvement; and v) availability of complete clinical data. The exclusion criteria were as follows: i) Male patients; ii) incomplete clinical data; iii) prior systemic neoadjuvant chemoradiotherapy; iv) non-invasive ductal carcinoma; v) recurrent or bilateral BC; vi) other concurrent malignant tumors; and vii) preoperative clinical positivity for ALN involvement. The present study was approved (approval no. KY-2023-132) by the Research Ethics Committee of Jiaxing Maternity and Child Health Care Hospital (Jiaxing, China).

Patient screening process. After applying the inclusion and exclusion criteria, a total of 998 patients, ranging from 21-87 years old were enrolled in the study and randomly divided into a training and validation group in a 7:3 ratio. The 7:3 split aims to balance between having enough training data and enough validation data to reliably estimate model performance on unseen data. The axillary US findings and

clinicopathological features of tumors of the enrolled patients were then retrospectively analyzed. Logistic regression analysis was performed to identify independent risk factors for ALNM. Based on the results, a nomogram model was constructed and was subsequently validated (Fig. 1).

Indicators. The evaluation indicators for the present study were categorized into two groups: i) Axillary US findings and ii) clinicopathological features of tumors. The morphological characteristics of ALN play a crucial role in determining ALNM via US. In healthy individuals, ALNs have an elliptical shape (18). However, when metastatic tumor cells infiltrate, the structure of ALNs becomes disrupted, leading to enlargement, thickening of the cortical layer, increased blood flow, expansion in the lateral direction and a decrease in the aspect ratio (19,20). A comprehensive review of the US findings for the enrolled patients was performed to assess ALN characteristics, including number, size, shape, aspect ratio, internal echogenicity, cortical thickness, lymphatic portal structure and blood flow patterns. Suspicious metastasis (positive) was considered when more than two metastatic features were present (21-23).

Information regarding the clinicopathological characteristics of tumors was obtained from the electronic medical record system. The data included variables such as age, menopausal status, pathological type, maximum diameter (MD), tumor location, lymphovascular invasion (LVI), estrogen receptor (ER) status, progesterone receptor (PR) status, human epidermal growth factor receptor-2 (HER-2) status, Ki-67 expression, histological grade, molecular subtype and ALN status. Several lesions were observed, measurements were obtained for each lesion, and the largest MD was selected. The tumor location was categorized into upper outer and other quadrants. Histological grade was stratified into grades I/II and III. The positive threshold for ER and PR immunohistochemistry (IHC) was set at $\geq 1\%$, with an ER/PR expression of $\geq 1\%$ classified as hormone receptor (HR)-positive (24). Initially, the HER-2 status was evaluated via IHC, where an IHC score of 3+ indicated HER-2 positivity, while an IHC score of 0 or 1+ indicated HER-2 negativity. Subsequently, IHC 2+ was further verified through fluorescence *in situ* hybridization (25,26). The molecular subtype was divided into three categories based on the 2013 St. Gallen conference guidelines: i) Triple-negative BC (TNBC) [HR (-), HER-2 (-)]; ii) HER-2-positive BC [HR (-)/HR (+), HER-2 (+)] and luminal BC [HR (+), HER-2 (-)] (27).

Statistical analysis. Statistical Package for the Social Sciences (SPSS; version 26.0; IBM) and R (v.4.2.3; <https://www.r-project.org/>) software were used for data analysis. Receiver operating characteristic (ROC) curve analysis was used to convert continuous measurement data into binary classification countable data. These countable data were presented as frequencies (percentages) and analyzed using the chi-square test. To develop a nomogram model, logistic regression analysis was conducted using the 'glm' function (R v.4.2.3; <https://www.r-project.org/>). The findings were presented as odds ratios (OR) and 95% confidence intervals (CIs). The Akaike Information Criterion (AIC) was used to select the final model, that is, the model with the lowest AIC. To evaluate the presence of multicollinearity among the predictive factors, the variance inflation

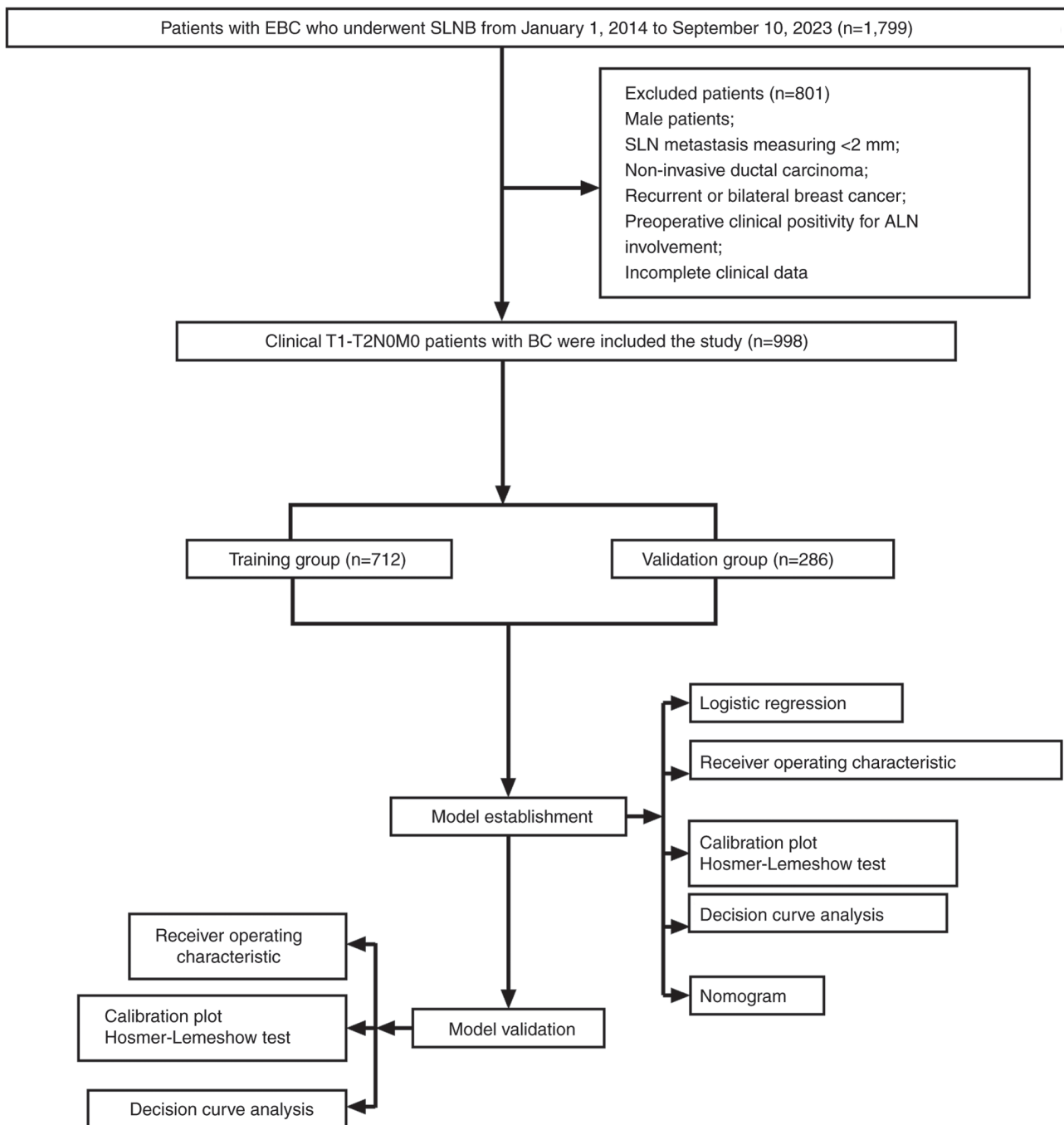


Figure 1. Flow chart of inclusion and exclusion criteria. EBC, early breast cancer; SLNB, sentinel lymph node biopsy; ALN, axillary lymph node.

factor (VIF) was computed for each variable. A VIF value <5 indicated the absence of significant multicollinearity. The ‘pROC’ package (R v.4.2.3; <https://www.r-project.org/>) was utilized to evaluate the performance of the model by generating the ROC curve and computing the corresponding area under the curve (AUC). Calibration curves were generated, and the nomogram was constructed using the ‘rms’ package (R v.4.2.3; <https://www.r-project.org/>). The calibration quality was evaluated using the Hosmer-Lemeshow test, which was applied using the ‘ResourceSelection’ package (R v.4.2.3; <https://www.r-project.org/>). The lower the P-values from this test, the poorer the calibration. The ‘rmda’ package (R v.4.2.3; <https://www.r-project.org/>) was used to conduct decision curve

analysis (DCA) to gauge the clinical utility of the model (28). Moreover, the internal validation was carried out using the Bootstrap resampling method with 1,000 iterations. P<0.05 was considered to indicate a statistically significant difference.

Results

Determination of cutoff thresholds for continuous data. The ROC curve for continuous data was based on the training group, and significant differences were observed in the ROC curve analysis for MD (P<0.05). Conversely, the ROC curve analysis for Ki-67 and age were not significantly different (P>0.05; Fig. 2). The continuous data with significant ROC

Table I. Baseline characteristics of the training and validation groups.

Characteristics	Training group (%)	Validation group (%)	P-value
ALNM			0.201
Non-ALNM	557 (78.2)	213 (74.5)	
ALNM	155 (21.8)	73 (25.5)	
Age at diagnosis (years)			0.191
<52	321 (45.1)	142 (49.7)	
≥52	391 (54.9)	144 (50.3)	
Menopausal status			0.336
Premenopausal	342 (48.0)	147 (51.4)	
Postmenopausal	370 (52.0)	139 (48.6)	
Lymphovascular invasion			0.696
Negative	568 (79.8)	225 (78.7)	
Positive	144 (20.2)	61 (21.3)	
Tumor location			0.922
Upper outer quadrant	341 (47.9)	136 (47.6)	
Others	371 (52.1)	150 (52.4)	
Ultrasound			0.542
Negative	586 (82.3)	240 (83.9)	
Positive	126 (17.7)	46 (16.1)	
Maximum diameter (cm)			0.747
<2.35	556 (78.1)	226 (79.0)	
≥2.35	156 (21.9)	60 (21.0)	
Histological grade			0.048
I/II	444 (62.4)	159 (55.6)	
III	268 (37.6)	127 (44.4)	
Ki-67(%)			0.114
<30	348 (48.9)	124 (43.4)	
≥30	364 (51.1)	162 (56.6)	
Molecular subtype			0.074
TNBC	101 (14.2)	57 (20.0)	
Luminal	462 (64.9)	170 (59.4)	
HER-2 positive	149 (20.9)	59 (20.6)	

ALNM, axillary lymph node metastasis; Others, Outer lower quadrant, Inner lower quadrant and/or Inner upper quadrant. TNBC, triple-negative breast cancer; HER-2, human epidermal growth factor receptor-2.

curve differences were categorized into high and low groups according to the maximum Youden index values (29), which were used to determine the cutoff values for the variables. MDs measuring <2.35 and ≥2.35 cm were divided into two groups. Furthermore, the continuous measurement data, which exhibited no significant differences in the ROC curve, were separated into two groups based on the median value. Ki-67 was categorized as <30 and ≥30%, while age was divided into <52 and ≥52, respectively.

Evaluating clinicopathological features of tumors and axillary US findings in the training and validation groups. The present study included a total of 998 patients ranging from 21-87 years old. They were randomly allocated into training and validation groups in a 7:3 ratio. Overall, the

distribution of variables between the two groups was fundamentally similar, with only slight differences observed in histological grading, making them suitable for constructing and validating a nomogram model. In the training group, the incidence rate of ALNM was 21.8%, whereas in the validation group, the rate was 25.5%. There was no significant difference in the incidence rate of ALNM (P=0.201; Table I). Significant statistical differences were observed within the training group in factors such as LVI, tumor location, US, MD and histological grading (P<0.05). These findings are essential for selecting variables when developing the nomogram model. Similarly, the validation group exhibited significant differences in LVI, tumor location, US and MD (P<0.05), confirming the significance of these variables in the model construction (Table II).

Table II. Comparison of axillary ultrasound findings and clinicopathological features of tumors between ALNM and non-ALNM in the training and validation groups.

Characteristics	Training group (%)		P-value	Validation group (%)		P-value
	Non-ALNM	ALNM		Non-ALNM	ALNM	
Age at diagnosis (years)			0.194			0.118
<52	244 (43.8)	77 (49.7)		100 (46.)	42 (57.5)	
≥52	313 (56.2)	78 (50.3)		113 (53.1)	31 (42.5)	
Menopausal status			0.234			0.042
Premenopausal	261 (46.9)	81 (52.3)		102 (47.9)	45 (61.6)	
Postmenopausal	296 (53.1)	74 (47.7)		111 (52.1)	28 (38.4)	
Lymphovascular invasion			<0.001			<0.001
Negative	513 (92.1)	55 (35.5)		194 (91.1)	31 (42.5)	
Positive	44 (7.9)	100 (64.5)		19 (8.9)	42 (57.5)	
Tumor location			0.012			0.002
Others	304 (54.6)	67 (43.2)		123 (57.7)	27 (37.0)	
Upper outer quadrant	253 (45.4)	88 (56.8)		90 (42.3)	46 (63.0)	
Ultrasound			<0.001			0.002
Negative	492 (88.3)	94 (60.6)		187 (87.8)	53 (72.6)	
Positive	65 (11.7)	61 (39.4)		26 (12.2)	20 (27.4)	
Maximum diameter (cm)			<0.001			0.004
<2.35	467 (83.8)	89 (57.4)		177 (83.1)	49 (67.1)	
≥2.35	90 (16.2)	66 (42.6)		36 (16.9)	24 (32.9)	
Histological grade			0.010			0.699
I/II	361 (64.8)	83 (53.5)		117 (54.9)	42 (57.5)	
III	196 (35.2)	72 (46.5)		96 (45.1)	31 (42.5)	
Ki-67(%)			0.965			0.359
<30	272 (48.8)	76 (49.0)		89 (41.8)	35 (47.9)	
≥30	285 (51.2)	79 (51.0)		124 (58.2)	38 (52.1)	
Molecular subtype			0.054			0.484
TNBC	88 (15.8)	13 (8.4)		46 (21.6)	11 (15.1)	
Luminal	352 (63.2)	110 (71.0)		124 (58.2)	46 (63.0)	
HER-2 positive	117 (21.0)	32 (20.6)		43 (20.2)	16 (21.9)	

ALNM, axillary lymph node metastasis; TNBC, triple-negative breast cancer; HER-2, human epidermal growth factor receptor-2.

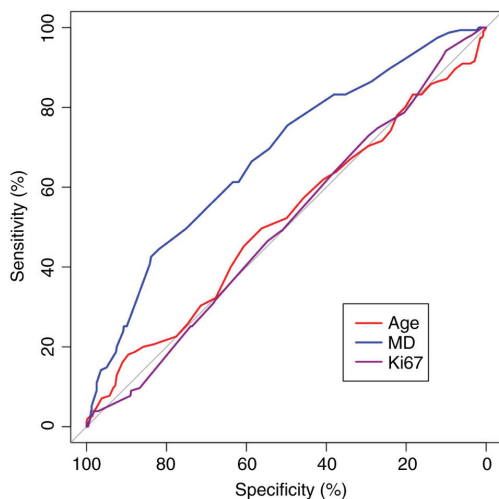


Figure 2. Receiver operating characteristic curve for continuous data. MD, maximum diameter.

Analysis of ALNM risk factors in the training group. Univariate logistic regression analysis revealed that LVI, tumor location, US, MD, histologic grading and molecular subtype exhibited statistically significant differences between the ALNM and non-ALNM groups ($P < 0.05$). Conversely, age, menopausal status and Ki-67 did not demonstrate significant differences ($P > 0.05$). Multivariate logistic regression analysis revealed that LVI, US, MD and molecular subtype remained independent risk factors for ALNM ($P < 0.05$) (Table III).

Multicollinearity test. A multicollinearity test performed on the four independent risk factors revealed that the tolerance values for LVI, US, MD and molecular subtype were 0.939, 0.942, 0.994 and 0.979, respectively, all of which were > 0.1 . Moreover, the tolerance values for VIF were 1.065, 1.061, 1.006 and 1.021, respectively, all of which were < 5 (30) (Table IV). Hence, it was concluded that there was no multicollinearity.

Table III. Univariate and multivariable logistic regression analyses for the prediction of axillary lymph node metastasis.

Characteristics	Univariate analysis	P-value	Multivariate analysis	P-value
Age at diagnosis (years)		0.194		
<52	1			
≥52	0.789 (0.552-1.128)			
Menopausal status		0.234		
Premenopausal	1			
Postmenopausal	0.805 (0.563-1.150)			
Lymphovascular invasion		<0.001		<0.001
Negative	1		1	
Positive	21.198 (13.622-33.588)		17.741 (11.019-29.143)	
Tumor location		0.012		0.372
Others	1		1	
Upper outer quadrant	1.578 (1.103-2.264)		1.234 (0.775-1.961)	
Ultrasound		<0.001		<0.001
Negative	1		1	
Positive	4.911 (3.250-7.438)		3.744 (2.183-6.434)	
Multifocality		0.112		
No	1			
Yes	1.958 (0.819-4.387)			
Maximum diameter (cm)		<0.001		<0.001
<2.35	1		1	
≥2.35	3.847 (2.604-5.688)		3.110 (1.853-5.229)	
Histological grade		0.010		0.283
I/II	1	1		
III	1.597 (1.113-2.290)		1.308 (0.798-2.135)	
Ki-67 (%)		0.965		
<30	1			
≥30	0.992 (0.694-1.417)			
Molecular subtype				
TNBC	1		1	
Luminal	2.115 (1.174-4.101)	0.017	2.469 (1.141-5.732)	0.027
HER-2 positive	1.851 (0.936-3.846)	0.085	1.788 (0.757-4.434)	0.194

TNBC, triple-negative breast cancer; HER-2, human epidermal growth factor receptor-2.

Table IV. Multicollinearity test.

	Collinearity Statistics	
	Tolerance	VIF
Lymphovascular invasion	0.939	1.065
Ultrasound	0.942	1.061
Molecular subtype	0.979	1.021
Maximum diameter	0.994	1.006

VIF, variance inflation factor.

molecular subtype were predictors. These variables were then used to generate a visual nomogram representing their respective weights (Fig. 3). The variable values for each predictor are shown on the corresponding line segments, with the length of the line segment representing the variable's influence weight on ALNM. The higher the weight, the higher the score.

Assessment and verification of the nomogram model. Notably, two criteria, differentiation and calibration, were utilized to thoroughly evaluate and validate the nomogram model. Differentiation was quantified using the AUC. The AUCs for the training and validation groups were 0.855 (95% CI, 0.817-0.892; Fig. 4A) and 0.793 (95% CI, 0.725-0.857; Fig. 4B), respectively. Both AUC values exceeded 0.70, indicating a favorable degree of differentiation (31). Calibration was

Development of a nomogram model. The model with the lowest AIC was selected. The variables LVI, US, MD and

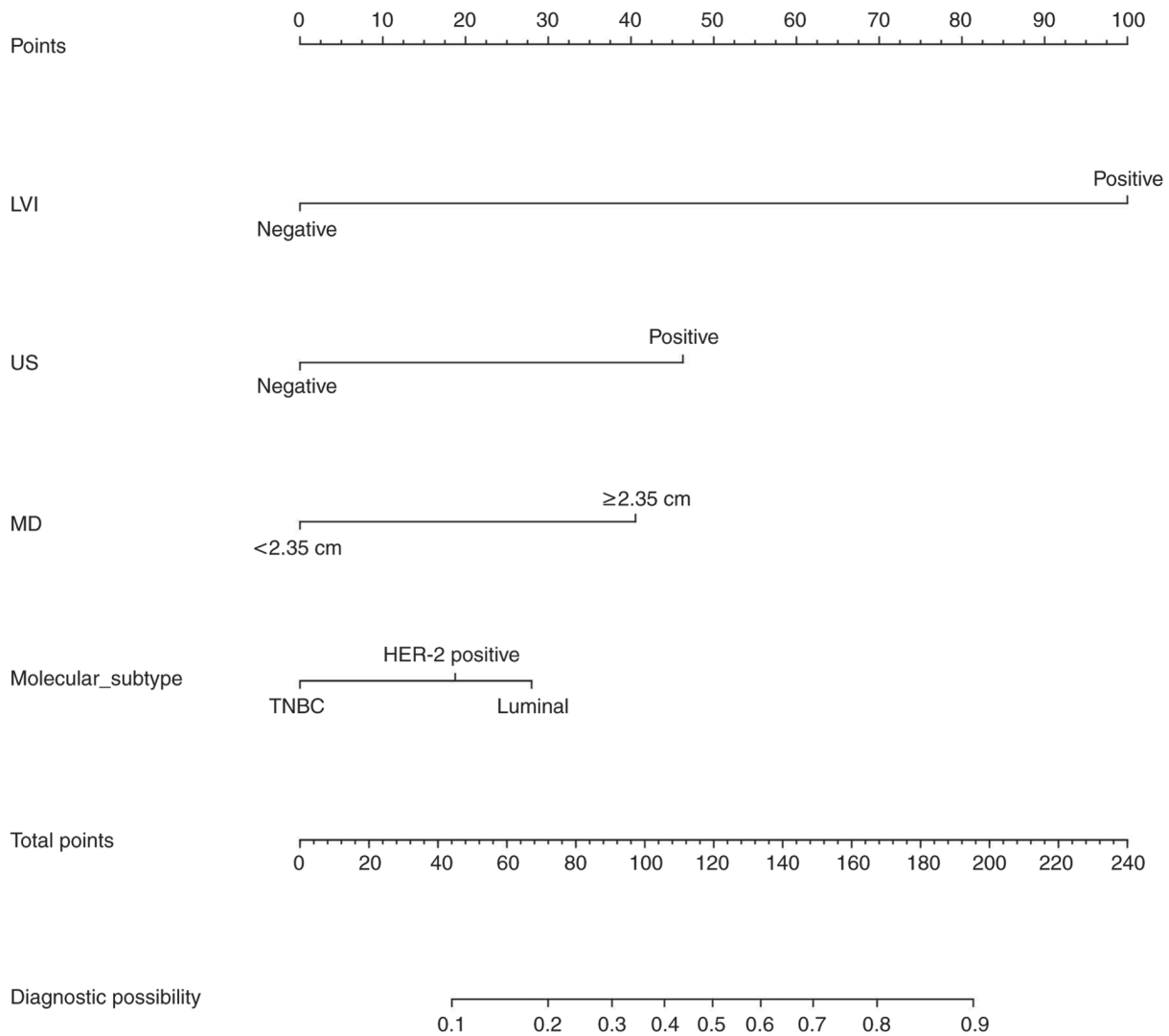


Figure 3. Nomogram prediction of the risk of axillary lymph node metastasis. LVI, lymphovascular invasion; US, ultrasound; MD, maximum diameter; HER-2, human epidermal growth factor receptor-2; TNBC, triple-negative breast cancer.

assessed by plotting the calibration curves and conducting the Hosmer-Lemeshow test. The calibration curves for this model exhibited a close fit between the true and ideal ALNM values, with an absolute error of <0.05 (Fig. 5A and B). Moreover, the P-values obtained from the Hosmer-Lemeshow tests were 0.869 and 0.943 for the training and validation groups, respectively ($P>0.05$), indicating strong alignment between the predicted and actual values. These analyses collectively demonstrated the robust differentiation and calibration of the nomogram, offering valuable insights into ALN status evaluation.

Assessment of clinical utility and applicability. ROC curves and their corresponding AUC values are frequently employed to evaluate the performance of prediction models. However, this approach primarily emphasizes sensitivity and specificity and provides limited insight into the clinical applicability of the model. Hence, DCA was also conducted to evaluate the practical utility of the model. The DCA plots have a black line at the bottom, which depicts a hypothetical situation where all patients neither developed ALNM nor underwent SLNB.

The presence of ALNM in all patients is indicated by the gray diagonal line, which necessitated SLNB for all. The greater the DCA curve deviation from the black and gray extreme lines, the higher the net clinical benefit rate. The red curve corresponds to the DCA curve generated from the nomogram model. By contrast, the remaining four curves represent the net benefit of four individual variable models: LVI, US, MD and molecular subtype. Within the training group, patients who treated using the nomogram model consistently experienced a net benefit, as opposed to those who did not, over a range of threshold probabilities from 12 to 97% (Fig. 6A). Similarly, in the validation group, patients treated with the nomogram model showed a more significant net benefit than those who did not while considering threshold probabilities ranging from 17 to 82% (Fig. 6B).

Discussion

Evaluating the ALN status is crucial for performing the pathological staging and deciding on treatment options for EBC. It also substantially impacts the locoregional recurrence

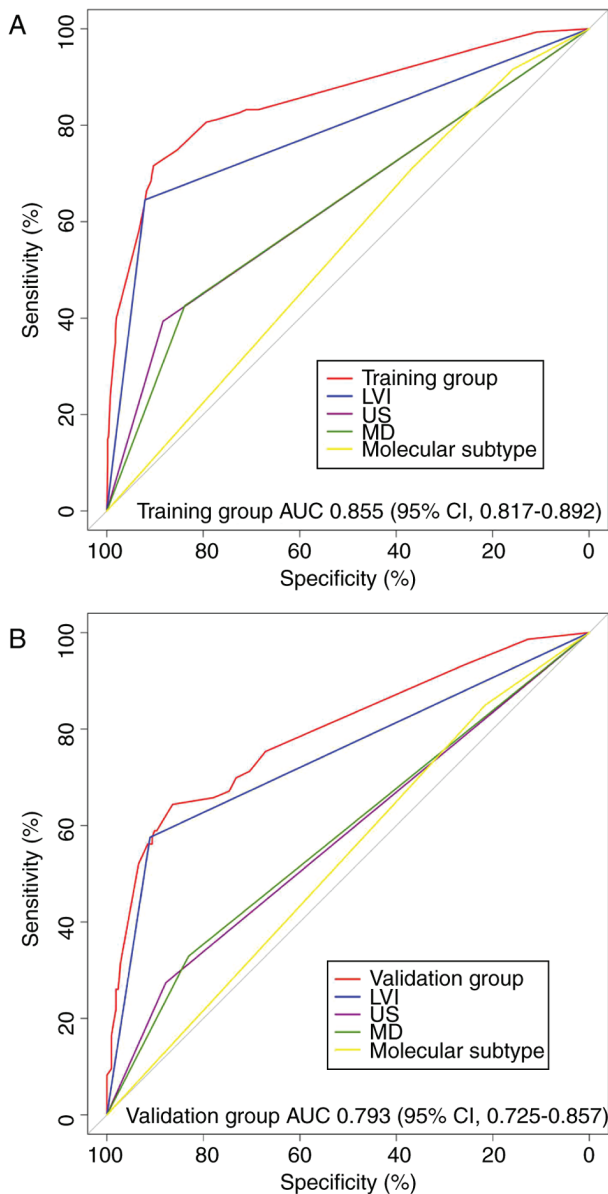


Figure 4. Receiver operating characteristic curves for five different models in the (A) training and (B) validation groups. LVI, lymphovascular invasion; US, ultrasound; MD, maximum diameter.

rates (32). With the latest developments in precise-oriented BC surgery, axillary treatments have transitioned from extensive ALN dissection to the less invasive strategy of SLNB (4). As EBC screening becomes more widespread, it is now possible to detect smaller tumors in patients at the time of diagnosis. This leads to a reduced probability of having ALNM. Thus, performing SLNB on all patients with EBC and cN0 is no longer justifiable. Accurate assessment and treatment of ALN and reduction of unnecessary trauma pose significant clinical challenges at this stage. Consequently, there has been a rise in research on alternatives for SLNB in patients with EBC and cN0 status. Therefore, finding other methods to detect the status of the ALNs is essential. While US-guided needle biopsy is one option, performing biopsies on non-enlarged ALNs can be challenging and carries a risk of vascular injury.

With advancements in imaging technology, imaging modalities such as X-ray, computed tomography (CT), US,

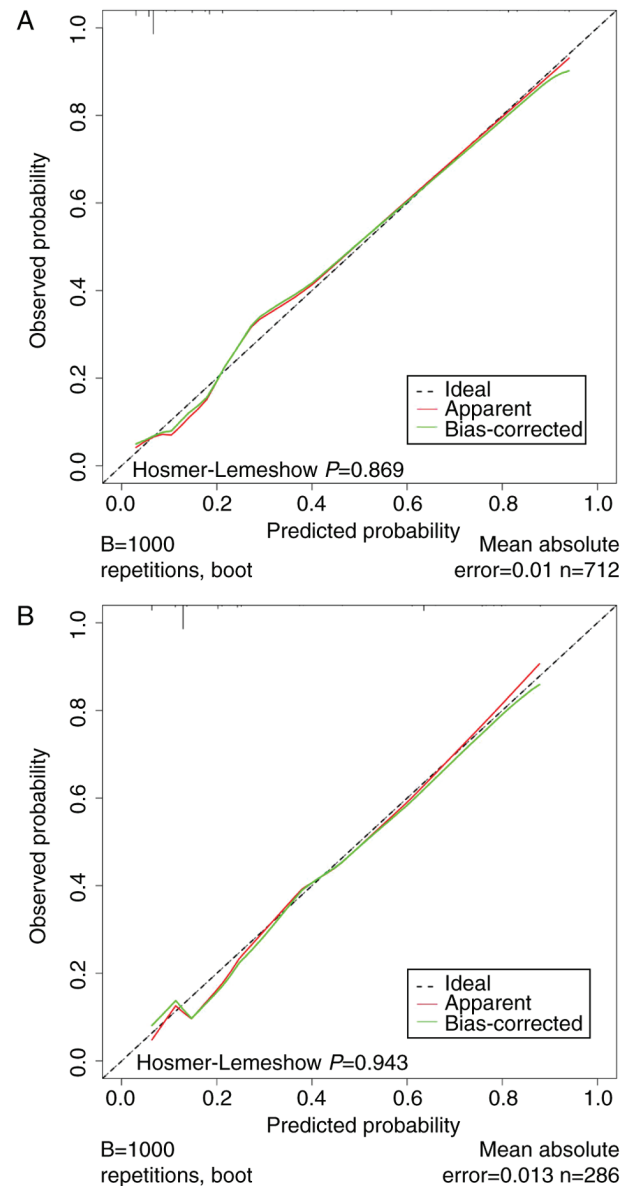


Figure 5. Calibration curves for the (A) training and (B) validation groups.

magnetic resonance imaging (MRI) and positron emission tomography-computed tomography (PET-CT) have emerged as the preferred methods for preoperative assessment of ALN status. There are limitations to the diagnostic utility of X-ray and CT in determining ALN status (33). Despite their potential to yield important information, MRIs and PET-CT scans are not frequently performed due to their high cost and limited practicality for routine usage in all patients (34,35). Conversely, US scanning is a straightforward, affordable, and non-invasive imaging technique that does not require radiation or intravenous contrast agents, and it is commonly used to determine the ALN status (11,12). It is important to mention that ALNM usually does not cause major alterations in the size and structure of ALN during the initial stages of metastasis.

Despite difficulties and challenges, substantial efforts have been made to explore the feasibility of exempting patients with EBC and cN0 status from SLNB. The SOUND study, for instance, reported that there was no significant difference in results between SLNB and the absence of axillary surgery

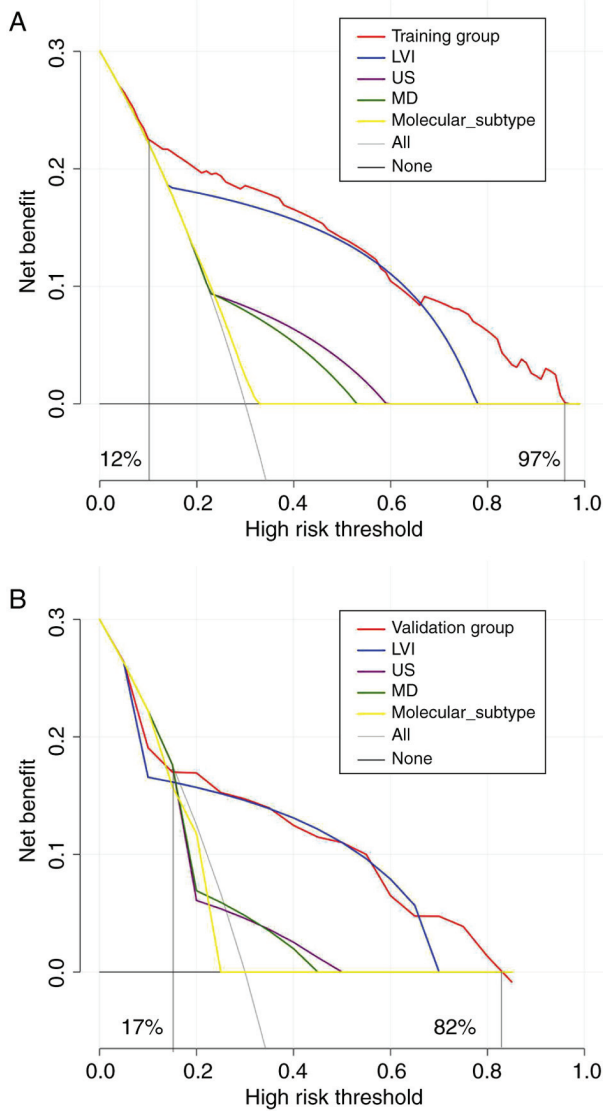


Figure 6. Decision curve analysis of the nomogram in the (A) training and (B) validation groups. LVI, lymphovascular invasion; US, ultrasound; MD, maximum diameter.

in patients with BC with negative preoperative axillary US findings and an MD of ≤ 2 cm. For such patients, SLNB can be safely omitted (9). The findings of the SOUND trial established the potential for safely avoiding SLNB based on preoperative axillary US findings. Notably, the SOUND trial employed relatively stringent selection criteria, with a majority (87.8%) of cases classified as luminal BC.

A number of studies have established a close association between clinicopathological features of tumors and ALNM (36-38). In the present study, a nomogram model was developed to predict the risk of ALNM in patients with EBC and cN0. The model considers the results of axillary US examinations and the clinicopathological characteristics of the tumors. The model aimed to reduce surgical trauma and associated consequences in low-risk patients. All included indicators were systematically grouped in this investigation, and univariate and multivariate logistic regression analyses were conducted. The results indicated that LVI emerged as an independent risk factor for ALNM. LVI refers to the

process by which tumor cells infiltrate the lymphatic or blood arteries, acting as the main pathway for BC to metastasize to lymph nodes or distant organs. This finding aligns with the conclusions drawn in numerous previous studies as well (39,40). Furthermore, a positive axillary US also emerged as an independent risk factor for ALNM, underscoring the need for vigilance when encountering suspicious axillary US findings (8,41). Ding *et al* (42) and Orsaria *et al* (43) have previously reported that a larger MD and increasingly irregular tumor boundaries are associated with a heightened risk of developing ALNM. The results of the present study were consistent with these observations. Out of the molecular subtypes of EBC, there were 632 instances of luminal BC, 208 cases of HER-2 positive BC and 158 cases of TNBC. Luminal BC constituted approximately two-thirds of the EBC molecular subtypes. Consistent with previous studies, the present study also identified that TNBC had the lowest likelihood of ALNM (44,45). Prior research has consistently found that luminal BC is more susceptible to ALNM than TNBC and HER-2-positive BC (46-48), which aligns with the findings of the present study. The difference in risk of ALNM may be due to the higher vulnerability of TNBC to distant metastasis rather than local axillary metastasis (47,49). The limited sample size of TNBC could have influenced this result in the present study. Furthermore, Houvenaeghel *et al* (44) reported that HER-2-positive patients exhibited a higher probability of ALNM than HER-2-negative patients (31.9 vs. 22.9%). However, the present study did not find a significant difference (23.07 vs. 22.78%; Table II). Age, tumor location, histological grade and Ki-67 have also been found to be independent risk factors for ALNM in earlier research. Nevertheless, due to variances in sample size and population selection, these parameters did not show significant differences in the logistic regression analysis of the present study (37,38,50-52).

The nomogram was constructed by selecting four independent risk factors (LVI, US, MD and molecular subtype) based on the AIC. The feasibility of the model was cross-verified using both the training and the validation groups. The AUCs for the training and the validation groups were 0.855 (95% CI, 0.817-0.892) and 0.793 (95% CI, 0.725-0.857), respectively. The Hosmer-Lemeshow test yielded P-values of 0.869 and 0.943 for the training and validation groups, respectively ($P > 0.05$), indicating the best fit. Additionally, there was exceptional alignment between the three curves on the calibration chart. These metrics collectively suggested that the nomogram model offers robust differentiation and calibration, highlighting its predictive efficacy. The clinical practicality of the prediction model was assessed by analyzing the DCA curves. According to the DCA, the nomogram model offered a superior net clinical benefit to patients in both the training group and the validation group.

Previous reports have detailed the construction of ALNM prediction models for patients with EBC and cN0 (8,36,38,53-55). By contrast, the current study utilized four independent risk variables, namely LVI, MD, US and molecular subtypes, which may be acquired by either mass puncture or resection. The US is a relatively straightforward examination method also used in less developed regions. Based on axillary US results and clinicopathological characteristics of tumors, the nomogram model developed in the

present study is now the most pragmatic and well-aligned with clinical practice.

Although the model adequately demonstrated the importance of each predictor variable, it has certain limitations. First, this was a single-center, retrospective study with a limited sample size, potentially introducing inherent selection bias that could impact the validity and reliability of the study. Second, using a relatively small sample size, the model only underwent internal validation. Further validation within a multi-center, independent cohort is imperative to assess its predictive capacity more comprehensively. Additionally, the present study solely relied on the review of US reports, which could introduce some errors. Therefore, in subsequent validation studies, the US characteristics related to ALNM should be refined, additional risk factors should be incorporated, and the predictive performance of the model should be further enhanced.

In conclusion, the present study constructed a nomogram model using LVI, US, MD and molecular subtypes. The ROC, calibration and DCA curves of both the training and validation groups demonstrated strong predictive performance of the model. The predictive indicators used in this model were easily accessible clinically. The nomogram effectively and explicitly depicted the magnitude of the weight of each predictor variable, which can be graphically represented using a line segment image. By calculating the weights of the different predictive variables, the magnitude of the risk for ALNM can be obtained to improve the ability to clinically predict the outcomes in patients with ALN metastasis under limited conditions. Combined with clinical experience, the nomogram model can improve the accuracy of predicting the occurrence of ALNM in patients with EBC and cN0 to a certain extent and has a specific application prospect in practical clinical diagnosis and treatment.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

QJ and ZZ contributed to the conception and design of the study. JW and XY prepared the materials, collected the data and performed the analysis. ZZ drafted the manuscript. QJ and ZZ confirm the authenticity of all the raw data. All authors revised the manuscript. All authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

This study was conducted in accordance with the ethical standards of the institutional research committee and with

the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. The study was approved (approval no. KY-2023-132) by the Research Ethics Committee of Jiaxing Maternity and Child Health Care Hospital (Jiaxing, China).

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

- Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 71: 209-249, 2021.
- Torre LA, Siegel RL, Ward EM and Jemal A: Global cancer incidence and mortality rates and trends-an update. *Cancer Epidemiol Biomarkers Prev* 25: 16-27, 2016.
- Malter W, Hellmich M, Badian M, Kirn V, Mallmann P and Kraemer S: Factors predictive of sentinel lymph node involvement in primary breast cancer. *Anticancer Res* 38: 3657-3662, 2018.
- Krag DN, Anderson SJ, Julian TB, Brown AM, Harlow SP, Costantino JP, Ashikaga T, Weaver DL, Mamounas EP, Jalovec LM, *et al*: Sentinel-lymph-node resection compared with conventional axillary-lymph-node dissection in clinically node-negative patients with breast cancer: Overall survival findings from the NSABP B-32 randomised phase 3 trial. *Lancet Oncol* 11: 927-933, 2010.
- Reimer T, Engel J, Schmidt M, Offersen BV, Smidt ML and Gentilini OD: Is axillary sentinel lymph node biopsy required in patients who undergo primary breast surgery? *Breast Care (Basel)* 13: 324-330, 2018.
- Langer I, Guller U, Berclaz G, Koechli OR, Schaer G, Fehr MK, Hess T, Oertli D, Bronz L, Schnarwyler B, *et al*: Morbidity of sentinel lymph node biopsy (SLN) alone versus SLN and completion axillary lymph node dissection after breast cancer surgery: A prospective Swiss multicenter study on 659 patients. *Ann Surg* 245: 452-461, 2007.
- McLaughlin S: A longitudinal comparison of arm morbidity in stage I-II breast cancer patients treated with sentinel lymph node biopsy, sentinel lymph node biopsy followed by completion lymph node dissection, or axillary lymph node dissection. *Breast Diseases* 22: 68-70, 2011.
- Liu D, Lan Y, Zhang L, Wu T, Cui H, Li Z, Sun P, Tian P, Tian J and Li X: Nomograms for predicting axillary lymph node status reconciled with preoperative breast ultrasound images. *Front Oncol* 11: 567648, 2021.
- Gentilini OD, Botteri E, Sangalli C, Galimberti V, Porpiglia M, Agresti R, Luini A, Viale G, Cassano E, Peradze N, *et al*: Sentinel lymph node biopsy vs no axillary surgery in patients with small breast cancer and negative results on ultrasonography of axillary lymph nodes: The SOUND randomized clinical trial. *JAMA Oncol* 9: 1557-1564, 2023.
- Jung JG, Ahn SH, Lee S, Kim EK, Ryu JM, Park S, Lim W, Jung YS, Chung IY, Jeong J, *et al*: No axillary surgical treatment for lymph node-negative patients after ultra-sonography [NAUTILUS]: Protocol of a prospective randomized clinical trial. *BMC Cancer* 22: 189, 2022.
- Cools-Lartigue J and Meterissian S: Accuracy of axillary ultrasound in the diagnosis of nodal metastasis in invasive breast cancer: A review. *World J Surg* 36: 46-54, 2012.

12. Ibrahim-Zada I, Grant CS, Glazebrook KN and Boughey JC: Preoperative axillary ultrasound in breast cancer: Safely avoiding frozen section of sentinel lymph nodes in breast-conserving surgery. *J Am Coll Surg* 217: 7-15; discussion 15-16, 2013.
13. Zhang H, Sui X, Zhou S, Hu L and Huang X: Correlation of conventional ultrasound characteristics of breast tumors with axillary lymph node metastasis and Ki-67 expression in patients with breast cancer. *J Ultrasound Med* 38: 1833-1840, 2019.
14. Marino MA, Avendano D, Zapata P, Riedl CC and Pinker K: Lymph node imaging in patients with primary breast cancer: Concurrent diagnostic tools. *Oncologist* 25: e231-e242, 2020.
15. Diepstraten SC, Sever AR, Buckens CF, Veldhuis WB, van Dalen T, van den Bosch MA, Mali WP and Verkooijen HM: Value of preoperative ultrasound-guided axillary lymph node biopsy for preventing completion axillary lymph node dissection in breast cancer: A systematic review and meta-analysis. *Ann Surg Oncol* 21: 51-59, 2014.
16. Koehler KE and Ohlinger R: Sensitivity and specificity of preoperative ultrasonography for diagnosing nodal metastases in patients with breast cancer. *Ultraschall Med* 32: 393-399, 2011.
17. Vohra LM, Gulzar R and Saleem O: Intra operative frozen examination of sentinel lymph node in breast cancer. *J Ayub Med Coll Abbottabad* 27: 40-44, 2015.
18. Andersson Y, Bergkvist L, Frisell J and de Boniface J: Long-term breast cancer survival in relation to the metastatic tumor burden in axillary lymph nodes. *Breast Cancer Res Treat* 171: 359-369, 2018.
19. Feu J, Tresserra F, Fábregas R, Navarro B, Grases PJ, Suris JC, Fernández-Cid A and Alegret X: Metastatic breast carcinoma in axillary lymph nodes: In vitro US detection. *Radiology* 205: 831-835, 1997.
20. Yang WT, Chang J and Metreweli C: Patients with breast cancer: differences in color Doppler flow and gray-scale US features of benign and malignant axillary lymph nodes. *Radiology* 215: 568-573, 2000.
21. Bedi DG, Krishnamurthy R, Krishnamurthy S, Edeiken BS, Le-Petross H, Fornage BD, Bassett RL Jr and Hunt KK: Cortical morphologic features of axillary lymph nodes as a predictor of metastasis in breast cancer: In vitro sonographic study. *AJR Am J Roentgenol* 191: 646-652, 2008.
22. Elmore LC, Appleton CM, Zhou G and Margenthaler JA: Axillary ultrasound in patients with clinically node-negative breast cancer: which features are predictive of disease? *J Surg Res* 184: 234-240, 2013.
23. Liu Q, Xing P, Dong H, Zhao T and Jin F: Preoperative assessment of axillary lymph node status in breast cancer patients by ultrasonography combined with mammography: A STROBE compliant article. *Medicine (Baltimore)* 97: e11441, 2018.
24. Allison KH, Hammond MEH, Dowsett M, McKernin SE, Carey LA, Fitzgibbons PL, Hayes DF, Lakhani SR, Chavez-MacGregor M, Perlmutter J, *et al*: Estrogen and progesterone receptor testing in breast cancer: American society of clinical oncology/College of American pathologists guideline update. *Arch Pathol Lab Med* 144: 545-563, 2020.
25. Wolff AC, Hammond ME, Hicks DG, Dowsett M, McShane LM, Allison KH, Allred DC, Bartlett JM, Bilous M, Fitzgibbons P, *et al*: Recommendations for human epidermal growth factor receptor 2 testing in breast cancer: American society of clinical oncology/College of American Pathologists clinical practice guideline update. *J Clin Oncol* 31: 3997-4013, 2013.
26. Wolff AC, Hammond MEH, Allison KH, Harvey BE, McShane LM and Dowsett M: HER2 testing in breast cancer: American society of clinical oncology/College of American pathologists clinical practice guideline focused update summary. *J Oncol Pract* 14: 437-441, 2018.
27. Goldhirsch A, Winer EP, Coates AS, Gelber RD, Piccart-Gebhart M, Thürlimann B and Senn HJ; Panel members: Personalizing the treatment of women with early breast cancer: Highlights of the St Gallen International expert consensus on the primary therapy of early breast cancer 2013. *Ann Oncol* 24: 2206-2223, 2013.
28. Kerr KF, Brown MD, Zhu K and Janes H: Assessing the clinical impact of risk prediction models with decision curves: Guidance for correct interpretation and appropriate use. *J Clin Oncol* 34: 2534-2540, 2016.
29. Schisterman EF, Perkins NJ, Liu A and Bondell H: Optimal cut-point and its corresponding Youden Index to discriminate individuals using pooled blood samples. *Epidemiology* 16: 73-81, 2005.
30. Lan A, Chen J, Li C, Jin Y, Wu Y, Dai Y, Jiang L, Li H, Peng Y and Liu S: Development and assessment of a novel core biopsy-based prediction model for pathological complete response to neoadjuvant chemotherapy in women with breast cancer. *Int J Environ Res Public Health* 20: 1617, 2023.
31. Franken R, den Hartog AW, de Waard V, Engele L, Radonic T, Lutter R, Timmermans J, Scholte AJ, van den Berg MP, Zwinderman AH, *et al*: Circulating transforming growth factor-beta as a prognostic biomarker in Marfan syndrome. *Int J Cardiol* 168: 2441-2446, 2013.
32. Canavese G, Bruzzi P, Catturich A, Tomei D, Carli F, Garrone E, Spinaci S, Lacofo F, Tinterri C and Dozin B: Sentinel lymph node biopsy versus axillary dissection in node-negative early-stage breast cancer: 15-year follow-up update of a randomized clinical trial. *Ann Surg Oncol* 23: 2494-2500, 2016.
33. Uematsu T, Sano M and Homma K: In vitro high-resolution helical CT of small axillary lymph nodes in patients with breast cancer: Correlation of CT and histology. *AJR Am J Roentgenol* 176: 1069-1074, 2001.
34. García Vicente AM, Soriano Castrejón Á, León Martín A, Relea Calatayud F, Muñoz Sánchez Mdel M, Cruz Mora MA, Jiménez Londoño GA and Espinosa Aunión R: Early and delayed prediction of axillary lymph node neoadjuvant response by (18) F-FDG PET/CT in patients with locally advanced breast cancer. *Eur J Nucl Med Mol Imaging* 41: 1309-1318, 2014.
35. Memarsadeghi M, Riedl CC, Kaneider A, Galid A, Rudas M, Matzek W and Helbich TH: Axillary lymph node metastases in patients with breast carcinomas: Assessment with nonenhanced versus uspio-enhanced MR imaging. *Radiology* 241: 367-377, 2006.
36. Fong W, Tan L, Tan C, Wang H, Liu F, Tian H, Shen S, Gu R, Hu Y, Jiang X, *et al*: Predicting the risk of axillary lymph node metastasis in early breast cancer patients based on ultrasonographic-clinicopathologic features and the use of nomograms: A prospective single-center observational study. *Eur Radiol* 32: 8200-8212, 2022.
37. Wang Q, Li B, Liu Z, Shang H, Jing H, Shao H, Chen K, Liang X and Cheng W: Prediction model of axillary lymph node status using automated breast ultrasound (ABUS) and ki-67 status in early-stage breast cancer. *BMC Cancer* 22: 929, 2022.
38. Xiong J, Zuo W, Wu Y, Wang X, Li W, Wang Q, Zhou H, Xie M and Qin X: Ultrasonography and clinicopathological features of breast cancer in predicting axillary lymph node metastases. *BMC Cancer* 22: 1155, 2022.
39. Fujii T, Yajima R, Hirakata T, Miyamoto T, Fujisawa T, Tsutsumi S, Ynagita Y, Iijima M and Kuwano H: Impact of the prognostic value of vascular invasion, but not lymphatic invasion, of the primary tumor in patients with breast cancer. *Anticancer Res* 34: 1255-1259, 2014.
40. Karahallı Ö, Acar T, Atahan MK, Acar N, Hacıyanlı M and Kamer KE: Clinical and pathological factors affecting the sentinel lymph node metastasis in patients with breast cancer. *Indian J Surg* 79: 418-422, 2017.
41. Yu FH, Wang JX, Ye XH, Deng J, Hang J and Yang B: Ultrasound-based radiomics nomogram: A potential biomarker to predict axillary lymph node metastasis in early-stage invasive breast cancer. *Eur J Radiol* 119: 108658, 2019.
42. Ding J, Jiang L and Wu W: Predictive value of clinicopathological characteristics for sentinel lymph node metastasis in early breast cancer. *Med Sci Monit* 23: 4102-4108, 2017.
43. Orsaria P, Caredda E, Genova F, Materazzo M, Capuano I, Vanni G, Granai AV, DE Majo A, Portarena I, Sileri P, *et al*: Additional nodal disease prediction in breast cancer with sentinel lymph node metastasis based on clinicopathological features. *Anticancer Res* 38: 2109-2117, 2018.
44. Houvenaeghel G, Lambaudie E, Classe JM, Mazouni C, Giard S, Cohen M, Faure C, Charitansky H, Rouzier R, Daraï E, *et al*: Lymph node positivity in different early breast carcinoma phenotypes: A predictive model. *BMC Cancer* 19: 45, 2019.
45. Lu X, Lu X, Wang ZC, Iglehart JD, Zhang X and Richardson AL: Predicting features of breast cancer with gene expression patterns. *Breast Cancer Res Treat* 108: 191-201, 2008.
46. Gangi A, Mirocha J, Leong T and Giuliano AE: Triple-negative breast cancer is not associated with increased likelihood of nodal metastases. *Ann Surg Oncol* 21: 4098-4103, 2014.
47. Mattes MD, Bhatia JK, Metzger D, Ashamalla H and Katsoulakis E: Breast cancer subtype as a predictor of lymph node metastasis according to the SEER Registry. *J Breast Cancer* 18: 143-148, 2015.

48. Zhou W, He Z, Xue J, Wang M, Zha X, Ling L, Chen L, Wang S and Liu X: Molecular subtype classification is a determinant of non-sentinel lymph node metastasis in breast cancer patients with positive sentinel lymph nodes. *PLoS One* 7: e35881, 2012.
49. Holm-Rasmussen EV, Jensen MB, Balslev E, Kroman N and Tvedskov TF: Reduced risk of axillary lymphatic spread in triple-negative breast cancer. *Breast Cancer Res Treat* 149: 229-236, 2015.
50. Abdel-Razeq H, Iweir S, Abdel-Razeq R, Rahman FA, Almasri H, Bater R, Taqash A and Abdelkhaleq H: Differences in clinicopathological characteristics, treatment, and survival outcomes between older and younger breast cancer patients. *Sci Rep* 11: 14340, 2021.
51. Andea AA, Bouwman D, Wallis T and Visscher DW: Correlation of tumor volume and surface area with lymph node status in patients with multifocal/multicentric breast carcinoma. *Cancer* 100: 20-27, 2004.
52. Wu JL, Tseng HS, Yang LH, Wu HK, Kuo SJ, Chen ST and Chen DR: Prediction of axillary lymph node metastases in breast cancer patients based on pathologic information of the primary tumor. *Med Sci Monit* 20: 577-581, 2014.
53. Li J, Ma W, Jiang X, Cui C, Wang H, Chen J, Nie R, Wu Y and Li L: Development and validation of nomograms predictive of axillary nodal status to guide surgical decision-making in early-stage breast cancer. *J Cancer* 10: 1263-1274, 2019.
54. Qiu SQ, Zeng HC, Zhang F, Chen C, Huang WH, Pleijhuis RG, Wu JD, van Dam GM and Zhang GJ: A nomogram to predict the probability of axillary lymph node metastasis in early breast cancer patients with positive axillary ultrasound. *Sci Rep* 6: 21196, 2016.
55. Xie X, Tan W, Chen B, Huang X, Peng C, Yan S, Yang L, Song C, Wang J, Zheng W, *et al*: Preoperative prediction nomogram based on primary tumor miRNAs signature and clinical-related features for axillary lymph node metastasis in early-stage invasive breast cancer. *Int J Cancer* 142: 1901-1910, 2018.



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