Original Article

Development and validation of an ultrasonography and clinicopathological features-based nomogram for non-sentinel lymph node metastasis

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Background: With the development of precise treatment for breast cancer, the current trend of clinical treatment aims to limit axillary surgery as much as possible. At present, there is an unmet need to predict the probability of patients with a low risk of non-sentinel lymph node (SLN) metastasis and determine whether the omission of axillary lymph node dissection (ALND) is appropriate.

Methods: We retrospectively analyzed the data of patients with breast cancer who underwent sentinel lymph node biopsy (SLNB) and ALND. The patients were randomly assigned to training and validation sets. The associations between non-SLN metastasis (NSLNM) and ultrasonography and clinicopathological characteristics were assessed by multivariate logistic regression. Then, a nomogram model was constructed and validated using the calibration curve and the receiver operating characteristic curve.

Results: Vascular infiltration, positive SLN number, negative SLN number, human epidermal growth factor receptor 2 (HER2) status, and lymph node shape were identified as independent predictive factors for positive NSLNM. The areas under the curve of the nomogram model to predict NSLNM were 0.793 and 0.780 in the training and validation sets, respectively, and P=0.161 and P=0.768 in the Hosmer-Lemeshow goodness of fit test, respectively.

Conclusions: A nomogram model based on ultrasonography and clinicopathological features predicting NSLNM was established in our study, which is helpful for accurately assessing the risk of NSLNM in invasive breast cancer and providing evidence for individual surgical procedures involving axillary lymph nodes.

Keywords: Breast cancer; non-sentinel lymph node; nomogram; predictive model

Submitted Feb 07, 2023. Accepted for publication Mar 17, 2023. Published online Mar 24, 2023.
doi: 10.21037/gs-23-58
View this article at: https://dx.doi.org/10.21037/gs-23-58

Introduction

The lymphatic metastasis of breast cancer (BC) mainly returns to the ipsilateral armpit through lymphatic vessels, so the management of the armpit is an important aspect of BC surgery. From the previous century, axillary lymph node dissection (ALND) has been the standard for the treatment of axillary lymph nodes (ALNs). However, the complications that are associated ALND, including limb lymphedema, local nerve injury, and shoulder joint dysfunction, negatively impact the patients' quality of life (1). Following the proposal of the Milan trial (2) in recent years, many prospective clinical trials (3-5) with large samples

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have confirmed the safety and clinical practicability of sentinel lymph node biopsy (SLNB) as a replacement for ALND in patients with negative sentinel lymph nodes (SLNs). CBCSG-01 (5) prospective clinical trials revealed that patients with negative SLNs have five-year overall survival rates and disease-free survival rates of 98.2% and 94.2%, respectively. NSABP B-32 (4) clinical trials showed that the overall accuracy of SLNB in patients was 97.1% and false negative (FN) rates was 9.8%. ALMANAC (3) clinical trials found that the overall accuracy of SLNB in patients was 97.6% and FN rates were 6.7%.

Some previous studies suggested that patients with positive SLNs could be exempted from ALND in certain conditions. In study IBCSG 23-01 (6) found that BC patients with primary tumor ≤5 cm and one or more SLNs with micrometastases (≤2 mm) are liable to an exemption from ALND. A 10-year follow-up of ACOSOG Z0011 (7) further confirmed that patients with cT1-2N0 and one or two SLNs BC can be exempted from ALND under the condition of breast-conserving surgery and whole breast radiotherapy. According to the AMAROS (8) study, axillary radiotherapy can be used as an alternative to ALND for BC patients who have more than two SLNs after a simple mastectomy. The same applies to those who currently have no postoperative radiation therapy plans or a history of breast-conserving surgery. Moreover, 40–70% of patients with positive SLNs were observed to have no extra ALN metastasis, so ALND seems to be an overtreatment in such cases. Although these studies confirmed the safety of SLNB in cases of limited tumor burden without ALND, many scholars still have serious concerns about the intervention. Positive lymph nodes beyond SLNs that are not removed will result in a residual tumor, which can cause axillary recurrence (9). Therefore, the establishment of a model that efficiently predicts axillary non-sentinel lymph node metastasis (NSLNM) could better manage patients with positive SLNs.

The first NSLNM risk prediction model that was developed by Memorial Sloan-Kettering Cancer Center (MSKCC) (10) is the most widely used. This model, which is currently the most verified, provides a percentage corresponding to the risk of NSLNM in SLN-positive patients. Due to the variations in in surgical methods, performer levels, pathological diagnostic criteria, and characteristics of BC patients in different countries and regions, there are discrepancies in the prediction results of the MSKCC model in different countries, with an area under the curve (AUC) ranging from 0.58 and 0.86 (10-15).

In addition to the MSKCC model, there are numerous other NSLNM risk prediction models worldwide, such as the MD Anderson (MDA), Mayo, Tenon, Cambridge and Stanford model. All these models were based on the analysis of the morbidity and pathological characteristics, as well as other factors that are associated with domestic patients. This was done to establish a prediction model that has high accuracy. However, none of these prediction model applied to the Chinese population, in addition to the fact that they do not include ultrasound image features. A metastatic ALN is commonly characterized by a cortical thickness of ≥2.5–3.0 mm (16), a lobulated cortex, loss of the hilum, a round shape, and an abnormal cortical blood flow (17). Moreover, Jiang *et al.* (18) found that shear-wave elastography and ultrasound image features were associated with ALN metastasis. Also, the experimental results that were reported by Fu *et al.* (19) indicated that magnetic resonance imaging (MRI) is worthy of clinical promotion and usage, based on its ability to diagnose the ALN metastasis of BC. However, MRI was limited by factors such as high sensitivity and costs, low specificity, and the long time for preliminary diagnosis (20), so its diagnostic value was not discussed in this study. Therefore, an NSLNM risk prediction model based on the Chinese population needs to be developed to further guide clinical treatment.

In this study, a nomogram model for predicting the axillary NSLNM risk was established based on the ultrasonographical and clinicopathological characteristics

Highlight box

Key findings

- We constructed a nomogram model of non-sentinel lymph node metastasis (NSLNM) based on ultrasonic and clinicopathological features to accurately assess the risk of invasive breast cancer with NSLNM.

What is known and what is new?

- It is now known that in order to accurately estimate the risk of NSLNM and omit excessive axillary treatment, many national medical institutions have established NSLNM prediction models.
- This manuscript incorporated ultrasonic image features into the prediction model.

What are the implications, and what should change now?

- In the future, subsequent clinical validation studies of multi-center large-scale samples should be conducted, and the prediction model should be adjusted more precisely.

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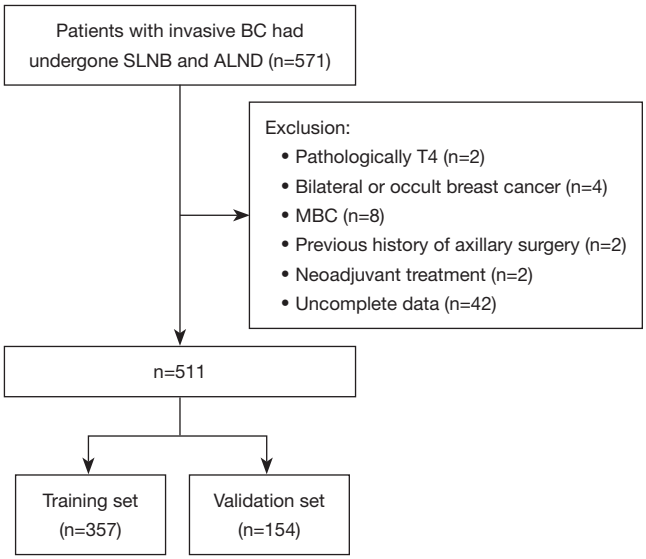

Figure 1 Flowchart of the study. BC, breast cancer; SLNB, sentinel lymph node biopsy; ALND, axillary lymph node dissection; MBC, metastatic breast cancer.

of female patients with invasive BC. This helps to provide a reference for clinicians regarding the management of ALNs. We present the following article in accordance with the TRIPOD reporting checklist (available at https://gs.amegroups.com/article/view/10.21037/gs-23-58/rc).

Methods

Patient selection

This study retrospectively collected the data of patients with invasive BC who underwent SLNB and ALND in Ningbo Medical Treatment Center Lihuili Hospital from January 1, 2012, to May 1, 2022. The exclusion criteria were as follows: (I) pathologically T4 BC; (II) bilateral or occult BC; (III) metastatic BC (MBC); (IV) previous history of axillary surgery; (V) neoadjuvant treatment; and (VI) incomplete data. *Figure 1* displays a flow chart of the study. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Ningbo Medical Treatment Center Lihuili Hospital (No. 2022-261), and the requirement for written informed consent to participate was waived due to the retrospective nature of the study. The patients included in the study were randomly assigned to training and validation sets at a ratio of 7:3 for the model establishment and internal validation.

Collection of the ultrasonography and clinicopathological characteristics

The following information was collected: (I) general information of patients: age at onset, menstruation, body mass index (BMI), and surgical procedures; (II) the characteristics of ultrasound imaging: tumor location, tumor quadrant, maximum tumor diameter, tumor margin, blood flow signal, posterior echo, aspect ratio, Breast Imaging Reporting and Data System (BI-RADS) classification, ALNs, lymph node shape, focal cortical status, cortex thickness, and lymphatic hilum state; and (III) clinicopathological characteristics: histological type, histological grading, number of lesions, vascular invasion, nerve invasion, positive SLN number, negative SLN number, SLN metastasis rate, non-SLN status, hormone receptors, human epidermal growth factor receptor 2 (HER2), Ki-67, and other clinical and pathological data.

Statistical analysis

IBM SPSS Statistics (version 25.0, SPSS Inc, Chicago, IL, USA) and R Software (version 3.5.3, http://www.r-project.org) were used for data analysis. The hypothesis test level was set at an alpha of 0.05 for all data. Continuous variables were tested for normality using the Kolmogorov-Smimov test; if the distribution was normal, the *t*-test was used, otherwise, the Mann-Whitney U test was employed. Categorical variables were analyzed using the chi-square test or Fisher's exact test. The related variables of NSLNM were selected by univariate and multivariate analyses. Then, a digital nomogram prediction model was established and a nomogram was drawn. The efficiency test of the model formula was assessed using a receiver operating characteristic (ROC) curve, correction curve, and Hosmer-Lemeshow (HL) goodness-of-fit test.

Results

Patients' characteristics

This study included 511 patients diagnosed with BC, with 357 in the training set and 154 in the validation set based on a ratio of 7:3 using R software. The age of the enrolled patients ranged from 26 to 88 years old, with a median age of 52 years. We compared the features of patients in the training and validation sets (see *Table 1*).

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Table 1 The characteristics of patients between the training and validation sets

Factors	Classification	Training set (n=357)	Validation set (n=154)	χ^2/Z	P
Age (years), median [range]	–	51 [26–88]	52 [27–82]	0.03	0.613
BMI (kg/m^2)	≤18.5	6 (1.7)	1 (0.6)	0.64	0.909
	18.5–24.9	116 (32.5)	47 (30.5)		
	25.0–29.9	96 (26.9)	48 (31.2)		
	>29.9	139 (38.9)	58 (37.7)		
Menstruation	Menopausal	212 (59.4)	87 (56.5)	0.37	0.558
	Pre-menopausal	145 (40.6)	67 (43.5)		
Procedures	BCT	121 (33.9)	43 (27.9)	1.76	0.185
	MRM	236 (66.1)	111 (72.1)		
Location	Left	188 (52.7)	81 (52.6)	0.00	1.000
	Right	169 (47.3)	73 (47.4)		
Quadrant	Outer up	159 (44.5)	53 (34.4)	6.18	0.102
	Outer down	70 (19.6)	29 (18.8)		
	Inner down	58 (16.2)	35 (22.7)		
	Inner up	70 (19.6)	37 (24.0)		
Diameter (cm)	≤2	204 (57.1)	85 (55.2)	5.81	0.052
	2–5	147 (41.2)	66 (42.9)		
	>5	6 (1.7)	3 (1.9)		
Histological type	IDC	341 (95.5)	144 (93.5)	0.90	0.342
	Other	16 (4.5)	10 (6.5)		
Grade	I	13 (3.6)	4 (2.6)	1.03	0.631
	II	234 (65.5)	108 (70.1)		
	III	110 (30.8)	42 (27.3)		
Lesions	Single	320 (89.6)	144 (93.5)	1.76	0.403
	Two	12 (3.4)	2 (1.3)		
	Multiple	25 (7.0)	8 (5.2)		
VI	No	75 (21.0)	39 (25.3)	1.16	0.298
	Infiltration	282 (79.0)	115 (74.7)		
NI	No	301 (84.3)	137 (89.0)	1.90	0.215
	Infiltration	56 (15.7)	17 (11.0)		
SLN+	1	247 (69.2)	108 (70.1)	3.36	0.340
	2	63 (17.6)	27 (17.5)		
	3	29 (8.1)	7 (4.5)		
	≥4	18 (5.0)	12 (7.8)		
SLN–	0	34 (9.5)	14 (9.1)	1.80	0.773
	1	64 (17.9)	29 (18.8)		
	2	88 (24.6)	30 (19.5)		
	3	70 (19.6)	33 (21.4)		
	≥4	101 (28.3)	48 (31.2)		

Table 1 (*continued*)

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Table 1 (*continued*)

Factors	Classification	Training set (n=357)	Validation set (n=154)	χ^2/Z	P
SLN%	0–25%	121 (33.9)	58 (37.7)	0.24	0.462
	26–50%	157 (44.0)	60 (39.0)		
	51–75%	32 (9.0)	16 (10.4)		
	76–100%	47 (13.2)	20 (13.0)		
ER	Positive	273 (76.5)	112 (72.7)	0.81	0.373
	Negative	84 (23.5)	42 (27.3)		
PR	Positive	236 (66.1)	104 (67.5)	0.10	0.761
	Negative	121 (33.9)	50 (32.5)		
HER2	Positive	87 (24.4)	28 (18.2)	2.36	0.135
	Negative	270 (75.6)	126 (81.8)		
Ki-67	≤15%	107 (30.0)	47 (30.5)	0.45	0.801
	15–30%	126 (35.3)	58 (37.7)		
	>30%	124 (34.7)	49 (31.8)		
Margins	Irregular	336 (94.1)	151 (98.1)	4.44	0.067
	Regular	21 (5.9)	3 (1.9)		
Flow signal	Detected	185 (51.8)	79 (51.3)	0.01	0.923
	No	172 (48.2)	75 (48.7)		
Posterior echo	Attenuation	171 (47.9)	80 (51.9)	0.71	0.441
	No	186 (52.1)	74 (48.1)		
Aspect ratio	>1	134 (37.5)	71 (46.1)	3.29	0.077
	≤1	223 (62.5)	83 (53.9)		
BI-RADS	3	17 (4.8)	6 (3.9)	2.272	0.686
	4A	63 (17.4)	33 (21.4)		
	4B	116 (32.5)	55 (35.7)		
	4C	124 (34.7)	46 (29.9)		
	5	37 (10.4)	14 (9.1)		
NSLN	Positive	113 (31.7)	49 (31.8)	0.00	0.971
	Negative	244 (68.3)	105 (68.2)		
ALN	Detected	49 (13.7)	19 (12.3)	0.18	0.672
	No	308 (86.3)	135 (87.7)		
LN shape	Blurred	15 (4.2)	3 (1.9)	1.61	0.205
	Clear	342 (95.8)	151 (98.1)		
Focal cortical status	Lobulation	3 (0.8)	1 (0.6)	0.05	1.000
	No	354 (99.2)	153 (99.4)		
Cortex thickness	Incrassated	21 (5.9)	5 (3.2)	1.55	0.275
	No	336 (94.1)	149 (96.8)		
Hilum	Disappeared	16 (4.5)	7 (4.5)	0.00	1.000
	No	341 (95.5)	147 (95.5)		

Except for age presented as median, all the others were presented as No. (%). BMI, body mass index; BCT, breast-conserving therapy; MRM, modified radical mastectomy; IDC, invasive ductal breast cancer; VI, vascular invasion; NI, neural invasion; SLN+, positive SLN number; SLN–, negative SLN number; SLN%, sentinel lymph node metastasis rate; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BI-RADS, breast imaging reporting and data system; NSLN, non-sentinel lymph node; ALN, axillary lymph node; LN, lymph node.

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Establishment of the prediction model

Univariate analysis of NSLNM

Univariate analysis showed that the following variables were significantly associated with the incidence of NSLNM: vascular invasion, positive SLN number, negative SLN number, SLN metastasis rate, BI-RADS classification, ALN status, lymph node shape, focal cortical status, cortex thickness, lymphatic hilum state, HER2 status (P<0.05), and the relationships between NSLNM and clinicopathological characteristics (*Table 2*).

Multivariate analysis of NSLNM

Multivariate analysis showed that vascular infiltration (P=0.009), positive SLN number (P=0.004), HER2 overexpression (P<0.001), and lymph node shape (P=0.002) are independent statistically significant predictors of NSLNM, while negative SLN number (P=0.002) was an independent protective factor of NSLNM. The details are presented in *Table 3*.

Preliminary establishment of the nomogram prediction model

R software was used to develop a nomogram prediction model (*Figure 2*) consisting of five variables: vascular invasion, positive SLN number, negative SLN number, HER2 status, and lymph node shape. A ROC of the subjects was drawn, which showed an AUC of 0.793 (*Figure 3A*).

Evaluation of the prediction model

The data of 154 patients in the validation set were used to validate the predictive effect of the nomogram model, and the ROC curve was drawn. The AUC was 0.780, indicating that the differentiation ability of the model was good (*Figure 3B*). The calibration curves of training and validation sets were drawn (*Figure 3C,3D*). Meanwhile, the calibration of the model was assessed by the HL test (training set: χ^2=11.79, P=0.161; validation set: χ^2=4.904, P=0.768). At the same time, decision curve analysis (DCA) curve was drawn for all patients (*Figure 4*), and it was found that the curve threshold was 0–0.96, which proved that this model had high clinical application value. The P values were greater than 0.05 and the prediction model showed good calibration ability. At the cut-off points of 10% and 15% for NSLNM, the FN rates of the nomogram were 1.85% and 8.64%, and the negative predictive values (NPVs) of the nomogram were 96.59% and 89.89%, respectively (*Table 4*).

Discussion

After decades of clinical practice, SLNB has become the standard of axillary staging for early BC and clinical node-negative patients (21). Trials such as IBCSG 23-01 (6), ACOSOG Z0011 (7), and AMAROS (8) have coherently shown that ALND should not be performed on patients with positive SLNs under specific predetermined circumstances. On the other hand, there is ongoing debate regarding the safety and dangers that are associated with exempting patients with positive SLNs from receiving ALND. To accurately estimate the risk of NSLNM, medical institutions in various countries have established NSLNM prediction models [MDA (22), Mayo (23), Tenon (24), Cambridge (13), and Stanford (25)]. For patients with a low risk of metastasis, excessive axillary treatment can be omitted. It is important to note that, the indicators included in each prediction model are not identical, and factors such as poor repeatability ad well as stability and regional differences are a cause for concern.

Vascular infiltration is regarded as an independent predictor of NSLNM in patients with positive SLNs in the MSKCC (10), MDA (22), and Stanford (25) models, as is the case with some researchers' own models (26,27). In this study, multivariate analysis in the training set showed that vascular infiltration was a risk factor of NSLNM [odds ratio (OR) =2.91; 95% confidence interval (CI): 1.356–6.725; P=0.009].

In previous studies, the number of positive SLNs was found to be associated with NSLNM in the MSKCC (10) and MDA (22) models, while the number of negative SLNs was found to be an independent protective factor for NSLNM. Similar conclusions were also made in this study (OR =1.80; 95% CI: 1.310–2.516; P=0.004). The SLN metastasis rates of patients with only one positive SLN and more than three positive SLNs were 20.6% and 77.7%, respectively. The risk of metastasis increased with the rise in the number of positive SLNs. Apparently, the number of negative SLN is an important factor for predicting NSLNM, and this has also been confirmed by a previous study (28).

The overexpression of HER2 is related to the occurrence and invasion of tumors. Although the MSKCC (10), MDA (22), Stanford (25), and Shanghai Cancer Hospital (SCH) (15) models did not include this factor in their studies, many subsequent domestic studies have

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Table 2 Univariate analysis results of NSLNM in the training set

Factors	Classification	Case	NSLN+	NSLN–	χ^2/Z	P
Age (years), median [range]	–	–	51 [28–88]	51 [28–88]	–1.22	0.221
BMI (kg/m^2)	≤18.5	6	1	5	2.27	0.518
	18.5–24.9	116	32	84		
	25.0–29.9	96	34	62		
	>29.9	139	46	93		
Menstruation	Menopausal	212	69	143	0.19	0.660
	Pre-menopausal	145	44	101		
Method	BCT	121	35	86	0.63	0.428
	MRM	236	78	158		
Location	Left	188	66	122	2.19	0.139
	Right	169	47	122		
Quadrant	Outer up	159	51	108	3.49	0.322
	Outer down	70	22	48		
	Inner down	58	23	35		
	Inner up	70	17	53		
Diameter (cm)	≤2	204	60	144	1.11	0.574
	2–5	147	51	96		
	>5	6	2	4		
Histological type	IDC	341	109	232	0.34	0.558
	Other	16	4	12		
Grade	I	13	4	9	2.34	0.311
	II	234	68	166		
	III	110	41	69		
Lesions	Single	320	99	221	0.85	0.654
	Two	12	5	7		
	Multiple	25	9	16		
VI	No	75	13	62	9.00	0.003
	Infiltration	282	100	182		
NI	No	301	93	208	0.51	0.477
	Infiltration	56	20	36		
SLN+	1	247	51	196	102.36	0.000
	2	63	32	31		
	3	29	16	13		
	≥4	18	14	4		
SLN–	0	34	23	11	33.14	0.000
	1	64	27	37		
	2	88	27	61		
	3	70	17	53		
	≥4	101	19	82		

Table 2 (*continued*)

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Table 2 (*continued*)

Factors	Classification	Case	NSLN+	NSLN–	χ^2/Z	P
SLN%	0–25%	121	20	101	47.70	0.000
	26–50%	157	45	112		
	51–75%	32	19	13		
	76–100%	47	29	18		
ER	Positive	274	88	186	0.12	0.732
	Negative	83	25	58		
PR	Positive	235	76	159	0.15	0.698
	Negative	122	37	85		
HER2	Positive	87	45	42	21.42	0.000
	Negative	270	68	202		
Ki-67	≤15%	108	33	75	0.34	0.845
	15–30%	125	42	83		
	>30%	124	38	86		
Margins	Irregular	335	108	227	0.86	0.353
	Regular	22	5	17		
Flow signal	Detected	185	57	128	0.13	0.723
	No	172	56	116		
Posterior echo	Attenuation	172	59	113	1.08	0.299
	No	185	54	131		
Aspect ratio	>1	134	44	90	0.14	0.709
	≤1	223	69	154		
BI-RADS	3	17	0	17	31.66	0.000
	4A	63	7	56		
	4B	116	38	78		
	4C	124	48	76		
	5	37	20	17		
ALN	Positive	49	31	18	26.24	0.000
	Negative	308	82	226		
LN shape	Blurred	15	14	1	27.54	0.000
	Clear	342	99	243		
Focal cortical status	Lobulation	3	3	0	6.53	0.008
	No	354	110	244		
Cortex thickness	Incrassated	21	15	6	16.63	0.000
	No	336	98	238		
Hilum	Disappeared	16	13	3	19.05	0.000
	No	341	100	241		

SLN+, positive SLN number; SLN–, negative SLN number; BMI, body mass index; BCT, breast-conserving therapy; MRM, modified radical mastectomy; IDC, invasive ductal breast cancer; VI, vascular invasion; NI, neural invasion; SLN%, sentinel lymph node metastasis rate; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; BI-RADS, breast imaging reporting and data system; NSLN, non-sentinel lymph node; ALN, axillary lymph node; LN, lymph node.

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Table 3 Multivariate factor logistic regression analysis in the training set

Variables	B	STD	Wald	P	OR	95% CI
VI	1.07	0.406	6.91	0.009	2.91	1.356 to 6.725
SLN+	0.59	0.167	12.69	0.004	1.80	1.310 to 2.516
SLN–	–0.42	0.114	13.59	0.002	0.66	0.524 to 0.819
HER2	1.23	0.321	14.72	<0.001	3.42	1.836 to 6.483
LN shape	4.28	1.355	9.99	0.002	72.40	6.661 to 1,924.124

STD, standard deviation; OR, odds ratio; CI, confidence interval; VI, vascular invasion; SLN+, positive sentinel lymph node number; SLN–, negative sentinel lymph node number; HER2, human epidermal growth factor receptor 2; LN, lymph node.

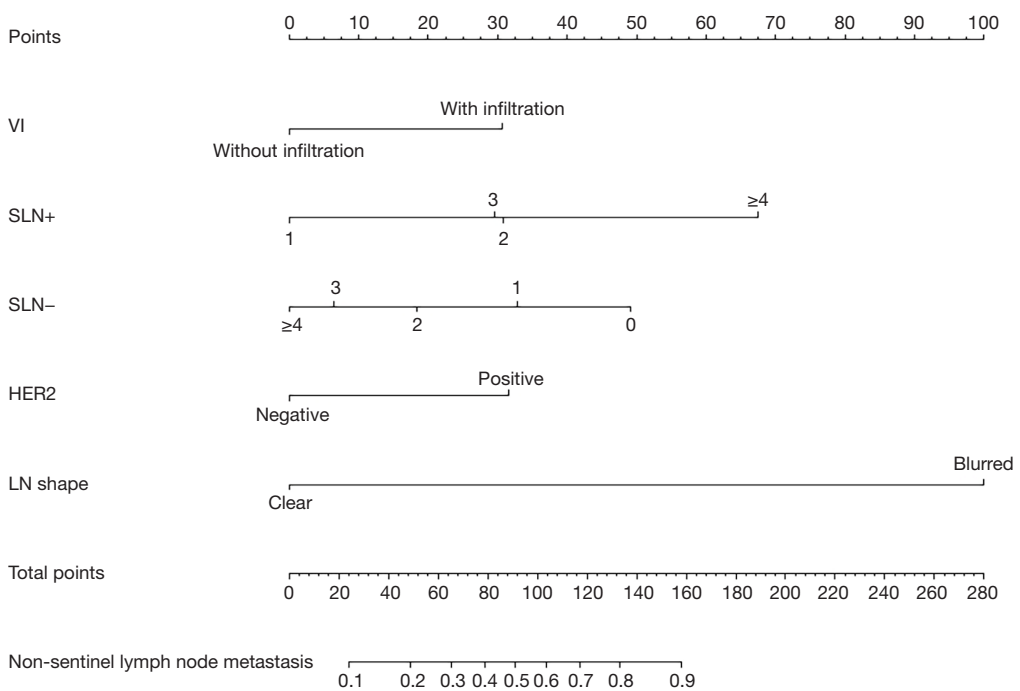

Figure 2 NSLNM nomogram prediction model. VI, vascular invasion; SLN+, positive SLN number; SLN–, negative SLN number; HER2, human epidermal growth factor receptor 2; LN, lymph node; NSLNM, non-sentinel lymph node metastasis.

demonstrated that HER2 overexpression is an independent risk factor for NSLNM (29,30). These findings are consistent with the results of the present study (OR =3.42; 95% CI: 1.836–6.482; P<0.001).

This study incorporated detailed ultrasound imaging, including primary tumors and lymph nodes. At present, ultrasonography is the preferred screening method for BC. Preoperative ultrasound is helpful in screening patients with a low risk of metastasis (31). Some studies showed that the ratio of the length to the diameter of the lymph node, cortical thickness, focal cortical lobulation, lymphatic hilum state, lymph node shape, and abnormal cortical blood flow were independent predictors of lymph node metastasis (17,32). In addition to these parameters, Qiu *et al.* (33) reported that the transverse diameter of the lymph node is associated with ALN metastasis. Additionally, Xiong *et al.* (34) showed that a spiculated margin and distance from the skin were also found to be associated with ALN metastasis. However, there is currently no prediction model for NSLNM that includes ultrasonic imaging characteristics, especially for more detailed analyses of lymph node characteristics. The present study analyzed the following four aspects: lymph node shape, focal cortical lobulation, cortical state, and lymphatic hilum state. These

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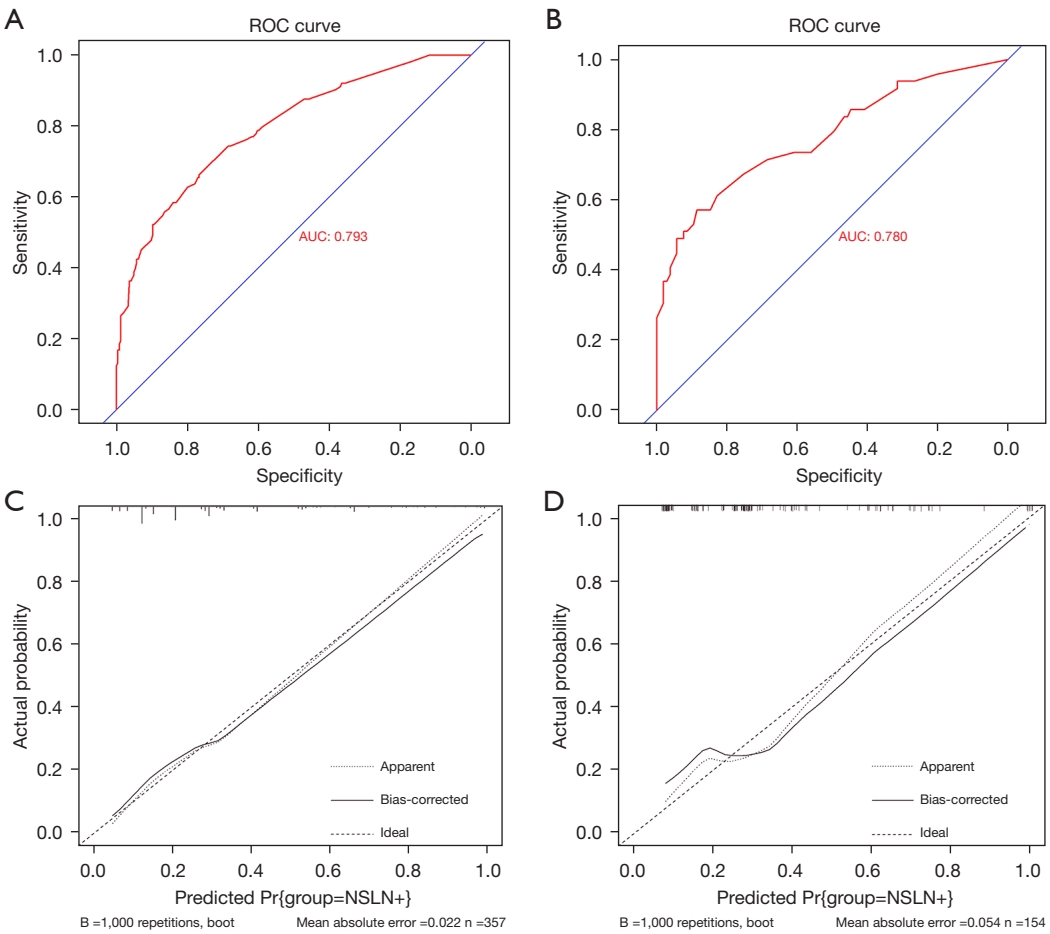

Figure 3 ROC and correction curves. (A) ROC curve in the training set (AUC =0.793); (B) ROC curve in the validation set (AUC =0.780); (C) correction curve in the training set; (D) calibration curve in the validation set. ROC, receiver operating characteristic; AUC, area under the curve; NSLN, non-sentinel lymph node.

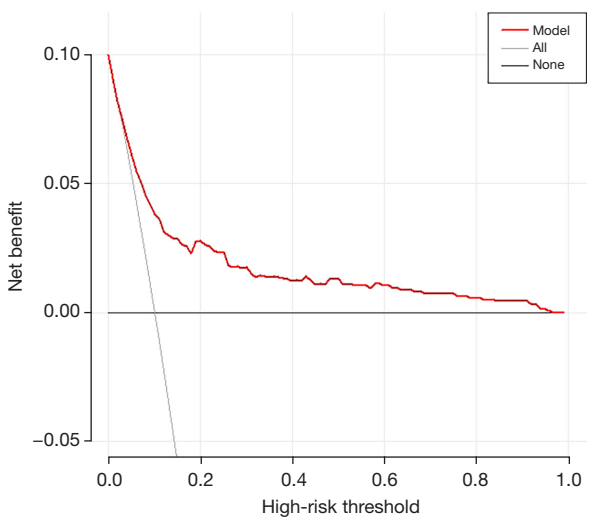

Figure 4 Decision curve analysis.

ultrasound features that were incorporated into our model were easily obtained in all BC patients, which guarantees the application of the model. In our study, the univariate analysis results suggested that the P values of the four ultrasonic parameters were all less than 0.05, suggesting that they were related to NSLNM. However, the multivariate analysis showed that only the blurred shape of the lymph node was an independent risk factor for NSLNM (P=0.002).

According to the findings from this study, the AUC of the nomogram prediction model was 0.793. Previous researchers investigated the application value of the MSKCC prediction model in Chinese BC patients, with an AUC of 0.688 (35). Liu *et al.* (36) verified the MSKCC and SOC models with AUC values of 0.624 and 0.679, respectively, in Chinese populations. The new model that is presented by this study had higher accuracy and

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Table 4 The NSLNM nomogram applied to datasets at 10% and 15% predicted probability cut-off values

Cut-off values	No. of patients	FN rate (%)	FN patients	NPV (%)	Sensitivity (%)	Specificity (%)
10%	88	1.85	3	96.59	98.15	24.36
15%	178	8.64	18	89.89	88.89	45.85

Specificity: the percentage of the truly negative patients labeled as "negative" by the model; Sensitivity: the percentage of the truly positive patients labeled as "positive". NSLNM, non-sentinel lymph node metastasis; FN, false-negative; NPV, negative predictive value.

discriminating ability. According to a previous study, AUC values between 0.5 and 0.7, 0.7 and 0.9, and equal or above 0.9 showed that the predictive effect was poor, generally accurate, and very good, respectively (37). Therefore, the predictive ability of our model is within acceptable ranges. In this study, the NSLNM rates in the training and validation sets were 31.7% and 31.8%, respectively, and this was consistent with previous literature (4,38,39). In our study, NSLNM was not found in patients with a metastatic probability of less than 6% when the predictive model was applied. According to a study by Poirier *et al.* (40), most surgeons omitted ALND in patients with positive SLNs if the predicted probability of NSLNM was 10% or less. When the predicted cut-off point was 10%, the FN rate of our model was only 1.85% and the NPV, sensitivity, and specificity were 96.59%, 98.15%, and 24.36%, respectively. When the cut-off point was 15%, the FN rate of the nomogram was 8.64%, and the NPV, sensitivity, and specificity were 89.89%, 88.89%, and 45.85%, respectively. Therefore, when the risk of metastasis that is obtained by applying our study model is less than 10%, omitting the ALND seems relatively acceptable, following discussion with patients.

However, our study also has some limitations that should be noted. Firstly, since our study is a single-center retrospective study with a relatively small sample size, external validation is needed to improve the applicability of the model. Secondly, multiple models have included the size of SLN metastasis among the predictive factors; however, data related to the size of SLN metastasis was lacking in this study. Moreover, the imaging data collected in the study are relatively simple, and mammography and breast MRI could have also been included. Finally, this study did not collect the comprehensive follow-up treatment and prognostic data of patients, which should be considered in future studies. In the future, subsequent clinical validation multi-center studies with large samples should be conducted, and the prediction model should be adjusted more precisely.

Conclusions

In conclusion, based on the samples collected from our center, an NSLNM risk prediction model was established and verified to provide a quantitative way for clinicians who exempt patients with positive SLNs due to ALND concerns to judge the NSLNM risk and make treatment decisions after integrating the risk and patient prognosis.

Acknowledgments

The authors thank the patients included in this study.
Funding: This study was supported by the Medical Scientific Research Foundation of Zhejiang Province, China (Nos. 2022KY1078 and 2023KY1030).

Footnote

Reporting Checklist: The authors have completed the TRIPOD reporting checklist. Available at https://gs.amegroups.com/article/view/10.21037/gs-23-58/rc

Data Sharing Statement: Available at https://gs.amegroups.com/article/view/10.21037/gs-23-58/dss

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://gs.amegroups.com/article/view/10.21037/gs-23-58/coif). The authors have no conflicts of interest to declare.

Ethical Statement: 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 conducted in accordance with the Declaration of Helsinki (as revised in 2013). This study was approved by the Ethics Committee of Ningbo Medical Treatment Center Lihuili Hospital (No. 2022-261). The requirement for written informed consent to participate was waived due to the retrospective nature of the study.

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(English Language Editor: A. Kassem)

Cite this article as: Chen Y, Dai Y, Chen Y, Xu Z, Ding J. Development and validation of an ultrasonography and clinicopathological features-based nomogram for non-sentinel lymph node metastasis. Gland Surg 2023;12(3):402-414. doi: 10.21037/gs-23-58

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