A model for the early identification of sentinel lymph node metastasis in patients with breast cancer based on contrast-enhanced ultrasound and clinical features

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Abstract. The present study was designed to establish a model for the early identification of sentinel lymph node (SLN) metastasis in patients with breast cancer (BC). The SLN metastasis predictive model was established with a retrospective training set of 365 patients with BC and was re-evaluated using a prospective validation set of 402 patients with BC. The multivariable analysis indicated that the tumor diameter [odds ratio (OR), 1.189; 95% confidence interval (CI), 1.124-1.257; P<0.001], menopause (OR, 1.011; 95% CI, 0.603-1.436; P<0.001), estrogen receptor (ER) expression (OR, 3.199; 95% CI, 1.077-6.567; P=0.043) and contrast-enhanced ultrasonography (CEUS) type (OR, 10.563; 95% CI, 6.890-28.372; P<0.001) were independent predictors of SLN status in patients with BC. The SLN metastasis predictive model was as follows: (0.173 x tumor diameter)-(4.490 x menopause) + (2.322 x ER) + (5.445 x CEUS type)-1.9521. In the training set, the model was highly sensitive (83.6%) and specific (94.3%) for the early identification of SLN metastasis. Similarly, in the validation set, the model was highly sensitive (70.4%) and specific (89.5%) for the early identification of SLN metastasis in patients with BC. Overall, in the present study, a model was successfully established to predict SLN metastasis in patients with BC that includes tumor diameter, menopausal status, ER expression and CEUS detection.

Introduction

Breast cancer (BC) is one of the most common malignant tumors. There are ~2.2 million new cases of BC and >680,000 deaths due to BC in the world every year (1). In China, 420,000 new cases of BC and 120,000 deaths from BC are registered per year (2,3). Recently, the survival rate of patients with BC has been significantly improved, with the cancer becoming one of the solid tumors with the best curative effect following the development of comprehensive BC treatments. However, there are still >100,000 BC-associated deaths in China annually, mainly due to recurrence and distant metastasis (4,5).

Axillary lymph nodes (ALNs) are an important prognostic factor for patients with BC, and ALN dissection (ALND) has been widely used in clinical practice as a diagnostic criterion to determine whether the ALNs are involved (6,7). However, its large surgical range can easily cause complications, such as lymphedema, hematoma formation, and restricted mobility (8,9). The sentinel lymph nodes (SLNs) are the first station or group of lymph nodes for drainage. As a barrier to prevent tumor cells from spreading from the lymphatic tract, the clinical significance of SLN has attracted increasing attention (10). Moreover, SLN biopsy (SLNB) is the standard procedure for axillary staging in patients with clinically node-negative (cN0) BC. However, the positive rate of cancer detection in SLNs in patients with cN0 stage BC receiving SLNB is between 20.5 and 25.5% (11,12). Nevertheless, identifying non-invasive and suitable SLNB candidates can be challenging. Although some studies have proposed non-invasive or minimally invasive methods to determine SLN metastasis in patients with BC, such as MRI (13,14), cytokeratin 19 mRNA detection in peripheral blood (15) and Ras association domain family 1 isoform A methylation detection in tissues (16), there is no consensus on the use or recommendation of these approaches in the National Comprehensive Cancer Network guidelines due to lack of evidence (17).

Contrast-enhanced ultrasound (CEUS) is a technology that enhances the echo of the backscatter using a contrast agent to improve the resolution, sensitivity and specificity of ultrasound diagnosis. CEUS can directly reflect the blood perfusion of diseased and normal tissues, show the new abnormal blood vessels that appear when the tumor rapidly progresses and play an important role in the qualitative diagnosis of tumors (18,19). Recently, a number of studies demonstrated that CEUS could be used to non-invasively predict SLN metastasis in patients with early stage BC (20,21), but it was rarely included in previous SLN metastasis prediction models (22). Hence, in the present study, a model was built to predict SLN metastasis based on CEUS and the basic clinical features of patients with BC.

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Patients and methods

Patients. First, the data of 365 patients with BC (all female) hospitalized in the Cangzhou Central Hospital (Cangzhou, China) between January 2017 and December 2018 were retrospectively collected. These 365 patients comprised the training set (the population used to build the model; age range, 24-83 years; mean age, 52.07 years) and were divided into the SLN-negative (no-metastasis; n=255) and SLN-positive (metastasis; n=110) groups based on pathological results. Next, the data of 402 patients with BC (all female) hospitalized in the Cangzhou Central Hospital between January 2019 and April 2021 were prospectively collected (age range, 23-79 years; mean age, 51.43 years). These 402 patients were used as the prospective validation set to verify the SLN status predictive model established using the training set. Similarly, they were divided into SLN-negative (no-metastasis; n=287) and SLN-positive (metastasis; n=115) groups based on pathological results.

All recruited patients with BC (including patients in the validation and training sets) met the following criteria. The inclusion criteria were: i) Female sex; ii) no previous history of other malignancies; iii) a pathological diagnosis of BC; iv) cancer cells that have not metastasized to distant organs; v) the first diagnosis of BC; and vi) a clear SLN status. The exclusion criteria were: i) male sex; ii) radiotherapy and chemotherapy received before surgery; iii) allergy to ultrasound contrast agents; iv) pregnancy or breastfeeding; v) a previous history of axillary surgery; and vi) severe heart or lung disease. This study was approved by the Ethics Committee of the Cangzhou Central Hospital, and clinical diagnoses and treatments complied with the Helsinki Declaration.

Data collection. The age and menopause data of the patients with BC were extracted from electronic medical records. Laboratory tests included those for pathological type, tumor diameter, histological grade, CEUS detection, and expression of estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) and Ki-67. SLNB was used to identify SLN+/- status.

Establishment of CEUS scoring system. According to the CEUS performance, the patients with BC were divided into four categories: Complete uniform enhancement (type I), uniform enhancement of the periphery and medulla (type II), uneven enhancement (type III) and no enhancement of the periphery and/or medulla (type IV). In the training and prospective validation sets, most patients with SLN-negative BC were type I, followed by type II. By contrast, most patients with SLN-positive BC were type IV, followed by type III.

Statistical analysis. In the present study, SPSS19.0 software (IBM Corp.) was used for statistical analysis. Univariate binary regression analysis was used for univariate analysis of categorical data, and unconditional logistic regression was used for the multivariate analysis, and the relative risk is expressed as odds ratio (OR) and 95% confidence intervals (CIs). Additionally, receiver operating characteristic (ROC) curves were used to evaluate the predictive value of the SLN status predictive model in the patients with BC. The areas under the ROC curves (AUCs) were used to estimate the predictive accuracy. The cut-off value was defined at the maximum of the sum of sensitivity and specificity. P<0.05 was considered to indicate a statistically significant difference.

Results

Baseline characteristics of patients with BC in the training set. The baseline characteristics of the patients with BC in the training set are presented in Table I. Patients with SLN-negative and -positive BC significantly differed regarding the pathological type, tumor diameter, menopause, ER expression, PR expression and CEUS type. Namely, compared with the SLN-negative BC group, the SLN-positive BC group had a higher proportion of infiltration, a larger tumor diameter, a higher proportion of postmenopausal patients, a higher proportion of ER-positive patients and a higher proportion of PR-positive patients. Meanwhile, they did not differ in age, histological grade, HER2 expression and Ki-67 expression (P>0.05).

Baseline characteristics of patients with BC in the prospective validation set. The baseline characteristics of patients with BC in the prospective validation set are shown in Table II. Similar to the training set, patients with SLN-negative and -positive BC were significantly different regarding the pathological type, tumor diameter, menopause, ER expression, PR expression, Ki-67 expression, and CEUS type (P<0.05). Namely, compared with the SLN-negative BC group, the SLN-positive BC group had a higher proportion of infiltration, a larger tumor diameter, a higher proportion of postmenopausal patients, a higher proportion of ER-positive patients, a higher proportion of PR-positive patients and a higher proportion of Ki-67-positive patients. Meanwhile, they did not differ in age, histological grade or HER2 expression (P>0.05).

Establishment of the SLN status predictive model. According to the results in Tables I and II, pathological type, tumor diameter (≤2, 2-3, and ≥3 were assigned as 1, 2, and 3, respectively), age (≤40, 40-50, 50-60 and ≥60 years were assigned as 1, 2, 3, and 4, respectively), ER (negative and positive were assigned as 1 and 2, respectively), PR (negative and positive were assigned as 1 and 2, respectively), Ki-67 (negative and positive were assigned as 1 and 2, respectively) and CEUS type (types I, II, III and IV were assigned as 1, 2, 3 and 4, respectively) were included into the multivariate analysis to establish the predictive model for SLN status. The model was as follows: (0.173 x tumor diameter)-(4.490 x menopause) + (2.322 x ER) + (5.445 x CEUS type). Moreover, the independent predictors of SLN status in patients with BC included tumor diameter (OR, 1.189; 95% CI, 1.124-1.257; P<0.001), menopause (OR, 1.011; 95% CI, 0.603-1.436; P<0.001), ER expression (OR, 3.199; 95% CI, 1.077-6.567; P=0.043) and CEUS type (OR, 10.563; 95% CI, 6.890-28.372; P<0.001) (Table III). Overall, the model could be used to predict the SLN status of patients with BC. According to SLN status using SLNB, the sensitivity and specificity of the model for diagnosing SLN status could then be calculated (Fig. 1). The clinical data (tumor diameter, menopause, ER and CEUS type) of one patient with BC were substituted into the aforementioned formula (model) to obtain a value, and if

Table I. Baseline characteristics of SLN-negative (n=255) and -positive (n=110) patients with breast cancer in the training set (n=365).

Characteristics	Total patients, n	SLN, n (%)		OR	95% CI	P-value[a]
		Negative	Positive			
Pathological type						
Non-infiltration	58	54 (93.10)	4 (6.90)	7.199	2.510-20.193	<0.001
Infiltration	307	201 (65.47)	106 (34.53)			
Tumor diameter, cm						
≤2	133	107 (80.45)	26 (19.55)	2.336	1.409-3.872	0.001
>2	232	148 (63.79)	84 (36.21)			
Age, years						
≤50	230	158 (68.70)	72 (31.30)	0.860	0.539-1.372	0.526
>50	135	97 (71.85)	38 (28.15)			
Menopause						
Yes	228	146 (64.03)	82 (35.97)	0.457	0.279-0.751	0.002
No	137	109 (79.56)	28 (20.44)			
Histological grade						
I+II	288	202 (70.14)	86 (29.86)	1.064	0.617-1.833	0.824
III	77	53 (68.83)	24 (31.17)			
ER						
Negative	113	92 (81.42)	21 (18.58)	2.009	1.167-3.458	0.012
Positive	252	163 (64.68)	89 (35.32)			
PR						
Negative	136	108 (79.41)	28 (20.59)	2.152	1.311-3.532	0.002
Positive	229	147 (64.19)	82 (35.81)			
HER2						
Negative	257	185 (71.98)	72 (28.02)	1.395	0.863-2.253	0.174
Positive	108	70 (64.81)	38 (35.19)			
Ki-67						
Negative	71	55 (77.46)	16 (22.54)	1.616	0.879-2.968	0.122
Positive	294	200 (68.03)	94 (31.97)			
CEUS type						
I+II	223	213 (95.52)	10 (4.48)	50.714	24.454-105.176	<0.001
III+IV	142	42 (29.58)	100 (70.42)			

[a]P-values indicate differences between SLN-negative and SLN-positive patients with breast cancer. P<0.05 was considered to indicate a statistically significant difference. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CEUS, contrast-enhanced ultrasonography; OR, odds ratio; CI, confidence interval.

the value was >0, SLN positivity was predicted, otherwise an SLN-negative status was predicted. In the training set, the AUC, sensitivity and specificity were 0.899, 83.6 and 94.3%, respectively (Fig. 1A). In the prospective validation set, the AUC, sensitivity and specificity were 0.826, 70.4 and 89.5%, respectively (Fig. 1B).

Discussion

SLNB is a minimally invasive detection method that can accurately determine the pathological status of the ALNs in patients with early stage BC, preventing ALN-negative patients from undergoing ALND, thereby reducing the incidence of postoperative complications and improving the quality of life of patients after surgery (23,24). Nevertheless, SLNB still has postoperative complications, such as a 0-7% incidence of lymphedema and a 20% incidence of upper limb numbness (25,26). Furthermore, the radionuclide labeling, blue dye injection and fluorescent dye methods used in SLNB are not only invasive, but also have a low diagnostic accuracy rate due to the difficulty of lymph node puncture (27,28). Moreover, performing SLNB for all patients with wastes limited medical resources and increases the financial burden on the patients. By contrast, SLN status is not only necessary for the staging of patients with BC, but SLN burden also has a strong effect on the outcome of invasive patients with

Table II. Baseline characteristics of SLN-negative (n=287) and -positive (n=115) patients with breast cancer in the prospective validation set (n=402).

Characteristics	Total patients, n	SLN, n (%)		OR	95% CI	P-value[a]
		Negative	Positive			
Pathological type						
Non-infiltration	69	63 (91.30)	6 (8.70)	4.514	2.016-10.104	<0.001
Infiltration	333	224 (67.27)	109 (32.73)			
Tumor diameter, cm						
≤2	150	123 (82.00)	27 (18.00)	1.825	1.279-2.606	0.001
>2 to <3	165	108 (65.45)	57 (34.55)			
≥3	87	56 (64.37)	31 (35.63)			
Age, years						
≤40	80	58 (72.50)	22 (27.50)	1.084	0.910-1.291	0.804
40-50	172	126 (73.26)	46 (26.74)			
50-60	93	63 (67.74)	30 (32.26)			
≥60	57	40 (70.18)	17 (29.82)			
Menopause						
Yes	254	167 (65.75)	87 (34.25)	0.769	0.667-0.887	0.001
No	148	120 (81.08)	28 (18.92)			
Histological grade						
I	13	10 (76.92)	3 (23.08)	0.929	0.836-1.033	0.768
II	300	211 (70.33)	89 (29.67)			
III	89	66 (74.16)	23 (25.84)			
ER						
Negative	126	105 (83.33)	21 (16.67)	2.003	1.322-3.036	<0.001
Positive	276	182 (65.94)	94 (34.06)			
PR						
Negative	150	121 (80.67)	29 (19.33)	1.672	1.187-2.355	0.002
Positive	252	166 (65.87)	86 (34.13)			
HER2						
Negative	263	190 (72.24)	73 (27.76)	1.043	0.887-1.226	0.604
Positive	139	97 (69.78)	42 (30.22)			
Ki-67						
Negative	79	63 (79.75)	16 (20.25)	1.578	0.953-2.612	0.043
Positive	323	224 (69.35)	99 (30.65)			
CEUS type						
I	163	159 (97.55)	4 (2.45)	3.531	2.534-4.920	<0.001
II	82	68 (82.93)	14 (17.07)			
III	102	45 (44.12)	57 (55.88)			
IV	55	15 (27.27)	40 (72.73)			

[a]P-values indicate differences between SLN-negative and SLN-positive patients with breast cancer. P<0.05 was considered to indicate a statistically significant difference. ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CEUS, contrast-enhanced ultrasonography; OR, odds ratio; CI, confidence interval.

BC (29). Therefore, the establishment of a model that can predict SLN metastasis is of great significance to patients with BC. However, the clinicopathological characteristics of SLN-positive patients are similar to those of SLN-negative patients, which limits the ability to predict lymph node metastasis before surgery (30).

In the present study, besides the clinicopathological characteristics of BC patients, CEUS was introduced to establish an SLN metastasis prediction model for patients with BC. In CEUS detection, the contrast agent is percutaneously injected and can conveniently pass through the lymphatic endothelial cell space and enter lymphatic vessels

Table III. Multivariate analysis of CEUS, clinical features and sentinel lymph node status.

Variables	Coefficient	S.E.	Wals	P-value	OR	95% CI
Pathological type	1.048	0.568	3.402	0.065	2.851	0.936-8.677
Tumor diameter	0.173	0.028	36.805	<0.001	1.189	1.124-1.257
Age	-0.062	0.022	2.650	0.056	0.940	0.900-0.982
Menopause	-4.490	0.599	56.287	<0.001	1.011	0.603-1.436
ER	2.322	1.147	4.099	0.043	3.199	1.077-6.567
PR	-4.845	1.545	3.838	0.062	0.008	0.000-0.162
Ki-67	-1.289	1.093	1.390	0.238	0.276	0.032-2.348
CEUS type	5.445	0.619	77.484	<0.001	10.563	6.890-28.372
Constant value	-1.952	0.948	1.009	0.315	0.386	

ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; CEUS, contrast-enhanced ultrasonography; OR, odds ratio; CI, confidence interval; S.E. standard error; Wals, a χ^2 value.
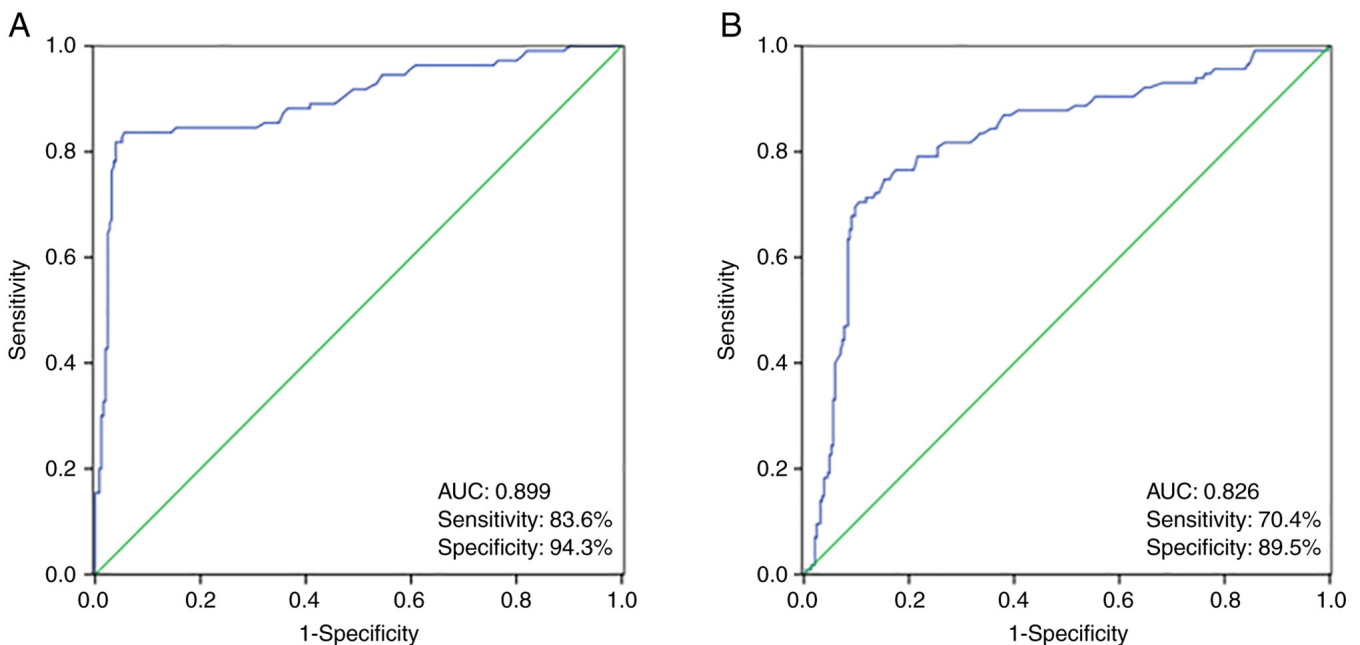

Figure 1. ROC curves of the sentinel lymph node status predictive model in (A) the training set and (B) the prospective validation set. AUC, area under the ROC curve; ROC, receiver operating characteristic.

through a series of related processes, such as endocytosis and exocytosis, and finally gathers in the lymph nodes of the drainage area. Moreover, CEUS has proved to be helpful for the diagnosis of SLN metastasis (31,32). Previous studies have divided the mode of SLN transcutaneous CEUS enhancement into uniform, uneven and no enhancement (32,33). The uniform enhancement is characterized as benign, and the uneven and non-enhancement as malignant. However, this classification method has very low specificity in the diagnosis of SLN metastasis (52-78%) (32,33). This might be related to the fact that some benign lymph nodes can also show uneven enhancement. Therefore, uneven enhancement cannot be simply diagnosed as a metastatic lymph node. The present study first established the CEUS classification standard based on the CEUS performance of 365 patients with BC in the training set: Completely uniform enhancement (type I), uniform enhancement of the periphery and medulla (type II), uneven enhancement (type III), and no enhancement of the periphery and (or) medulla (type IV).

In both the retrospective training and prospective validation sets, it was found that most patients with SLN-negative BC were classified as type I, followed by type II, and that most patients with SLN-positive BC were classified as type IV, followed by type III. Considering the associations between SLN metastasis and clinical characteristics, pathological type, tumor diameter, age, ER expression, PR expression, Ki-67 expression and CEUS type were included into the multiple regression analysis. Hence, a simple model was established to predict SLN metastasis in patients with BC, including tumor diameter, menopause, ER expression and CEUS type. In the training and validation sets, the AUCs were 0.899 and 0.826,

respectively, which suggested that this model had high accuracy in predicting SLN metastasis in patients with BC (34,35). At the same time, the model also had high sensitivity and specificity in diagnosing SLN metastasis in training and validation sets.

However, since the clinical data of the training set was retrospectively analyzed when building the model, invasive tests (CEUS) were included, indicating that the model can not work under non-invasive conditions. Meanwhile, in the retrospective and prospective validation sets, the sensitivity of the model was not high (83.6 and 70.4%, respectively). Nevertheless, a predictive model can be gradually revised as the sample size increases in the future. Overall, in the present study, a model was established to predict SLN metastasis in patients with BC based on tumor diameter, menopausal status, ER expression and CEUS detection. However, one limitation of the present study was that it did not have a test set. In the future, larger scale clinical data in patients with BC, including tumor diameter, menopausal status, ER expression and CEUS detection, could be applied from other studies to evaluate the model. In addition, a nomogram was not constructed for relapse in the patients with BC (36), which makes the results of this study difficult to understand for non-specialists.

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Availability of data and materials

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

Authors' contributions

JX was responsible for the conception and design of the study. JX and JL performed the experiments, analyzed the data and confirm the authenticity of all the raw data. Both authors have read and approved the final version of the manuscript.

Ethics approval and consent to participate

The present study was approved by the Cangzhou Central Hospital Ethics Committee (Cangzhou, China). All patients provided written informed consent.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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