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Risk factors and a predictive nomogram for non-sentinel lymph node metastases in Chinese breast cancer patients with one or two sentinel lymph node macrometastases and mastectomy

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ABSTRACT

Background Two ongoing prospective randomized trials are evaluating whether omitting axillary lymph node dissection (ALND) in patients with breast cancer (BCA) and sentinel lymph node (SLN) macrometastases undergoing mastectomy is safe. Determining predictive risk factors for non-SLN metastases and developing a model to predict the probability of those patients having non-SLN metastases is also important.

Methods This retrospective study enrolled 396 patients with BCA and 1–2 SLNs with macrometastases who underwent ALND and mastectomy between January 2012 and December 2016. Factors influencing the non-SLN metastases were determined, and a predictive nomogram was formulated. Performance of the nomogram was evaluated by its area under the curve (AUC).

Results We developed a predictive nomogram with an AUC of 0.81 (cross-validation 95% confidence interval: 0.75 to 0.86) that included 4 factors (tumour size, histologic grade, and number of negative SLNs and axillary lymph nodes on imaging).

Conclusions Our predictive nomogram assesses the risk of non-SLN metastases in patients with BCA and 1–2 SLN macrometastases undergoing mastectomy.

Key Words Breast cancer, predictive nomograms, non-sentinel lymph nodes, macrometastases

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INTRODUCTION

Breast cancer (BCA) is one of the most commonly diagnosed malignancies and the primary cause of cancer-related morbidity and mortality in women all over the world. In patients with BCA, one of the most critical prognostic factors is axillary lymph node (ALN) status. Traditionally, ALN dissection (ALND) in breast surgery has been used for staging and surgical treatment. However, since the late 1990s, sentinel lymph node biopsy (SLNB) has replaced ALND in the treatment of patients with early-stage BCA, and patients with positive sentinel lymph nodes (SLNs) undergo ALND. Compared with patients undergoing ALND, those with negative SLNs who undergo SLNB have similar overall survival and disease-free survival, fewer postoperative complications, and better quality of life[1,2].

During in-depth study of SLNs, some research has indicated that only approximately 40% of patients with positive SLNs have metastatic disease in non-SLNs. The other 60% of patients do not benefit from subsequent ALND[3–5]. Several clinical trials have reported that results are similar after ALND or SLNB in patients with early-stage BCA who have 1–2

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positive SLNs and who undergo breast-conserving surgery and systemic therapy[5–7]. Guidelines for BCa from the U.S. National Comprehensive Cancer Network recommend that patients who meet certain criteria (1 or 2 positive SLNs, breast-conserving surgery, and planned whole-breast radiotherapy) can avoid ALND. At the same time, several predictive models have been developed to estimate the risk of non-SLN metastases based on clinicopathologic features[8]. The most popular nomograms, which are based on Western populations in developed countries, are the Memorial Sloan Kettering Cancer Center nomogram, the Stanford online calculator for metastasis, the Mayo Clinic model, and the MD Anderson Cancer Center score[9–12]. Numerous studies have reported that, despite performing well in one population, those models might not be reliable in another population[9–14]. Few studies have focused on safety for patients with BCa and 1–2 positive SLN macrometastases who undergo mastectomy.

In developing countries such as China, most BCa patients undergo mastectomy[15]; even in the best cancer hospital in China, the proportion of patients undergoing breast-conserving treatment was less than 35% in 2017 (Fang Y. Chinese Academy of Medical Sciences Cancer Hospital, unpublished data). Studying the possibility of omitting ALND for patients with early-stage disease and 1–2 SLNs who undergo mastectomy is therefore of great importance. In the present study, we retrospectively analyzed potential predictive risk factors for non-SLN metastases and developed a model to predict the probability of non-SLN metastases in patients with 1–2 SLN macrometastases who undergo mastectomy.

METHODS

Study Population

The study enrolled 396 consecutive patients with primary BCa who were treated at the National Cancer Center (Cancer Hospital of the Chinese Academy of Medical Sciences and Peking Union Medical College) between January 2012 and December 2016. Patients were eligible for the study if they met all the following conditions: 1–2 SLNs with macrometastases (metastases > 2 mm), successful SLNB and ALND, first-time BCa diagnosis, no neoadjuvant systemic therapy, and mastectomy.

The study was approved by the Institutional Ethics Review Board of the National Cancer Center, National Clinical Research Center for Cancer, and Cancer Hospital, Chinese Academy of Medical Sciences and Peking Union Medical College.

SLNB Procedure

Sentinel nodes were located using a combined technique of radiocolloid and blue dye injection. First, 2 mCi of ^{99m}Tc–dextran was injected into the subareolar region 2–6 hours before surgery. Subsequently, 5–10 minutes before surgery, 1 mL methylene blue was injected into the subareolar plane. A handheld gamma probe was used to guide the incision and dissection sites in the axilla. Nodes with isotope counts greater than 10% of the count at the injection site were considered "hot" nodes. All hot, blue, hot and blue, and palpably suspicious lymph nodes were dissected and submitted for frozen sectioning. If SLNs were found to be positive for metastases, ALND was performed at the same time. Nodes obtained from SLNB and ALND were submitted for routine histopathology. If a positive SLN was diagnosed by postoperative pathology examination, affected patients underwent ALND within 3 weeks after the primary surgery.

Data Collection

Table I shows the data collected from patients. Histologic grade, estrogen receptor status, progesterone receptor status, HER2 (human epidermal growth factor receptor 2) status, and Ki-67 index were classified as documented in the U.S. National Comprehensive Cancer Network guideline[16].

Statistical Analysis

The IBM SPSS Statistics software application (version 19.0: IBM, Armonk, NY, U.S.A.) was used to perform a backward stepwise binary logistic regression analysis to determine risk factors. We used the rms package in the R software application (version 3.3.3: The R Foundation, Vienna, Austria) with 5-fold cross-validation to formulate the predictive nomogram. The performance of the predictive nomogram was determined by the area under the receiver operating characteristic curve (AUC). The AUC represents the probability that the nomogram predicts greater risk for a randomly selected patient with the outcome (non-SLN metastases) than for a randomly selected patient without the outcome[17].

RESULTS

Clinical Characteristics

The 396 enrolled patients with SLN-positive BCa ranged in age from 25 to 80 years. In this cohort, 90 patients (22.7%) had non-SLN metastases and 367 (92.7%) had invasive ductal carcinoma. The mean number of identified SLNs was 4.4, and the mean number of negative SLNs was 3.3. Table I presents other descriptive characteristics of the study cohort.

Predictive Model and Nomogram

Tumour size, histologic grade, and the numbers of negative SLNs and ALNs on imaging were selected to formulate the predictive model (Table II). The final model is presented as a nomogram that visually presents the individual risk. In the predictive nomogram, values for the individual patient are located along the variable axes, and a line is drawn upward to the Points axis to determine the number of points assigned for each variable. The sum of the points is located on the Total Points axis, and a line is then drawn downward to the Risk axis to determine the risk of non-SLN metastases. Considering a sample patient with a T2 tumour of histologic grade 2, 1 negative SLN, and abnormal ALNs on imaging, the Total Points score reaches approximately 223 (Figure 1), which translates to a risk ratio between 0.4 and 0.5 for non-SLN metastases.

Nomogram Performance

The AUC of our model was 0.81 (cross-validation 95% confidence interval: 0.75 to 0.86; Figure 2). A useless prediction model, such as a coin flip, would result in an AUC of 0.5, and a model that discriminates perfectly would result in

TABLE I Patient and tumour characteristics

Characteristic	Patient group [*n* (%)]	
	Overall	Non-SLN metastases
Age group at diagnosis		
≤50 Years	189 (47.7)	40 (21.2)
>50 Years	207 (52.3)	50 (24.2)
Tumour size		
T1ab	33 (8.3)	2 (6.1)
T1c	177 (44.7)	39 (22.0)
T2	186 (47.0)	49 (26.3)
Histologic type		
Invasive ductal carcinoma	367 (92.7)	83 (22.6)
Invasive lobular carcinoma	22 (5.6)	6 (27.3)
Others	7 (1.8)	1 (14.3)
Histologic grade		
I	32 (38)	1 (9.6)
II	237 (59.8)	51 (21.5)
III	89 (22.5)	31 (34.8)
Others	32 (8.1)	7 (21.9)
Lymphovascular invasion		
Positive	135 (34.1)	32 (23.7)
Negative	261 (65.9)	58 (22.2)
Multifocality		
Yes	56 (14.1)	13 (23.2)
No	340 (85.9)	77 (22.6)
Negative SLNs		
0–2	148 (37.4)	61 (41.2)
>2	248 (62.6)	29 (11.7)
Extranodal extension		
Positive	19 (4.8)	6 (31.6)
Negative	377 (95.2)	84 (22.3)
Estrogen receptor status		
Positive	335 (84.6)	78 (23.3)
Negative	61 (15.4)	12 (19.7)
Progesterone receptor status		
Positive	317 (80.1)	75 (23.7)
Negative	79 (19.9)	15 (19.0)
HER2 status		
Positive	89 (22.5)	24 (27)
Negative	287 (72.5)	62 (21.6)
Unknown	20 (5.1)	4 (20.0)
Ki-67 index		
≤14	98 (24.7)	19 (19.4)
>14	298 (75.3)	71 (23.8)
Axillary lymph nodes on imaging		
Normal	322 (81.3)	51 (15.8)
Abnormal	74 (18.7)	39 (51.7)

SLN = sentinel lymph node; HER2 = human epidermal growth factor receptor.

an AUC of 1. We therefore achieved a satisfying model. As shown in Table III, patients with a predictive risk of non-SLN metastases less than 0.1 accounted for 49.0% of all patients.

TABLE II Multivariable analysis of risk factors for non–sentinel lymph node metastases

Factor	OR	95% CI	*p* Value
Tumour size	1.80	1.13 to 2.86	0.013
Histologic grade	1.73	1.19 to 2.50	0.004
Negative SLNs	6.58	3.68 to 11.77	<0.001
Axillary lymph nodes on imaging	8.77	4.56 to 16.87	<0.001

SLNs = sentinel lymph nodes; HER2 = human epidermal growth factor receptor.

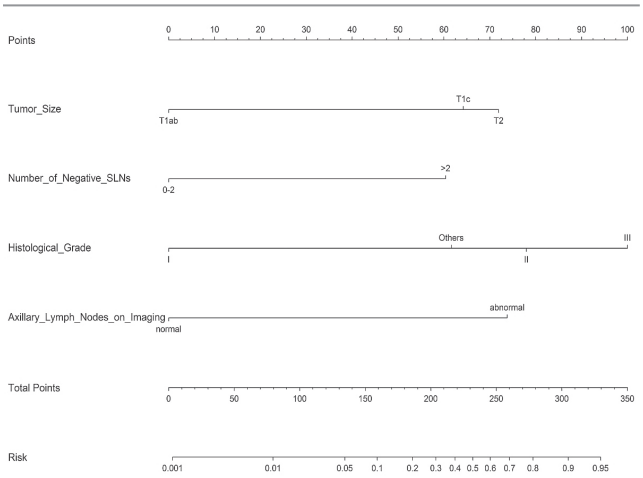

FIGURE 1 The predictive nomogram.

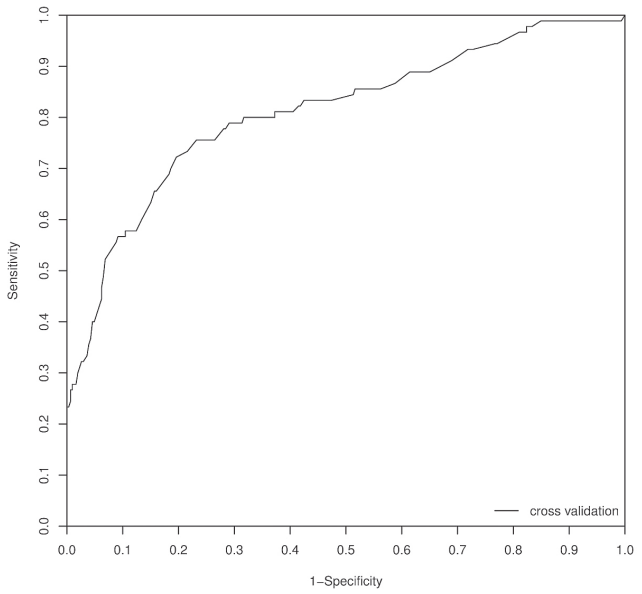

FIGURE 2 Receiver operating characteristic curve for the predictive nomogram. The area under the curve is 0.81 (cross-validation 95% confidence interval: 0.75 to 0.86).

TABLE III Patient distribution by level of risk for non–sentinel lymph node (SLN) metastases and patients found to have non-SLN metastases

Risk level	Patient risk level distribution [*n* (%)]	Patients with non-SLN metastases (*n*)
0–0.10	194 (49.0)	16
0.11–0.20	38 (9.6)	3
0.21–0.30	32 (8.1)	5
0.31–0.40	53 (13.4)	15
0.41–0.50	38 (9.6)	21
0.51–0.60	11 (2.8)	5
0.61–0.70	4 (1.0)	1
0.71–0.80	11 (2.8)	9
0.81–0.90	11 (2.8)	11
0.91–1.00	4 (1.0)	4

DISCUSSION

The importance of ALN metastases in patients with BCA has been recognized by doctors for a long time, and ALN metastases are associated with poor prognosis. The effect of omitting ALND in patients with positive SLNs has been studied for more than 10 years. The 10-year follow-ups reported for the American College of Surgeons Oncology Group Z0011 trial[7,18] and the International Breast Cancer Study Group 23-01 trial[19] showed no statistically significant differences in the incidences of regional recurrence and distant metastases between the ALND and SLNB-only groups. The European Organisation for Research and Treatment of Cancer AMAROS trial[3] also reported similar rates of regional recurrence and overall survival in an ALND group and a SLNB-only group. However, patients who underwent mastectomy accounted for only 9.2% of the patients (86 of 931) in the International Breast Cancer Study Group 23-01 trial, and the patients who underwent breast-conserving surgery received at least whole-breast irradiation. More patients in the AMAROS trial underwent mastectomy, but patients with a positive SLNB in the SLNB-only group received adjuvant axillary radiotherapy. Furthermore, in the International Breast Cancer Study Group 23-01 trial, overall survival was poorer for the patients who underwent mastectomy than for those who underwent breast-conserving surgery (82.1% vs. 90.4%, $p = 0.038$). We believe that the radiotherapy contributed to the low recurrence rate in patients undergoing SLNB only and that distant metastases are influenced by metastases in the ALNs, as shown in the mouse model reported by Pereira *et al.*[20] and Brown *et al.*[21].

The ongoing prospective randomized Swedish SENOMAC and U.K. POSNOC trials are focusing on evaluating whether ALND can be safely omitted in patients with BCA and SLN macrometastases who are undergoing mastectomy[22,23]. Our retrospective study set out to discover the risk factors for non-SLN metastases and to develop a predictive model adapted for patients with BCA and 1–2 SLN macrometastases undergoing mastectomy. Previous predictive models have usually included various sizes of SLN metastases—that is, isolated tumour cells, micrometastases, and macrometastases—and a low proportion of patients undergoing mastectomy[24–26].

The present study included 1–2 SLN metastases in patients with BCA who underwent mastectomy. It showed that tumour size and histologic grade were risk factors for non-SLN metastases and that larger tumour size and higher histologic grade were associated with a higher risk for non-SLN metastases. Other investigators have also reported that those two factors influence non-SLN metastasis[27–30].

We found that the number of negative SLNs was also associated with non-SLN metastases. The risk of non-SLN metastases was higher in patients with fewer negative SLNs. As the National Surgical Adjuvant Breast and Bowel Project B-32 study demonstrated, the false-negative rate was directly related to the number of resected SLNs[31]. Hence, all nodes that qualify as sentinel nodes should be removed, not just the bluest or hottest nodes. If more ALNs had been removed during the SLNB when the surgeon sent palpably suspicious lymph nodes to pathology, the possibility of metastases in the remaining ALNs would be lower. Our study suggests that it is better to use a number of more than 2 for negative SLNs. Compared with patients having only a single ALN metastasis, patients with more than 1 metastatic ALN are more likely to be preoperatively detected with axillary ultrasonography[26]. In China, few patients undergo core or ultrasound-guided fine-needle aspiration biopsy when axillary ultrasonography finds abnormal lymph nodes that are impalpable. Most patients undergo SLNB or, alternatively, ALND directly. Our results show that abnormal and normal lymph nodes on imaging were associated with 51.7% and 15.8% rates of non-SLN metastasis respectively. Abnormal lymph nodes on imaging were significantly associated with an increased risk of non-SLN involvement in patients with SLN metastases. In a meta-analysis, van Wely *et al.*[32] also found that patients with abnormal ALNs on imaging had a higher risk of having multiple metastatic lymph nodes. Patients with multiple metastatic lymph nodes might need post-mastectomy radiotherapy to lower the recurrence rate[33,34].

Patients less than 50 years of age accounted for 47.7% of our study cohort, which shows that the incident population of patients with BCA in China is young. According to data published by the Chinese Cancer Center, Chinese patients less than 59 years of age accounted for 70.2% of new BCA cases in 2015—an estimate based on previous population data[35]. Compared with the population of patients with BCA in the United States, the population of such patients in China is nearly 10 years younger.

As has been reported previously, lymphovascular invasion is one of the main factors influencing SLN metastases[36], and so the proportion of patients with lymphovascular invasion in our study was higher than the proportion in the general BCA population.

In the end, we established a predictive nomogram with a good AUC in the 0.75–0.86 range, based on 4 risk factors. As Table III shows, almost half the patients in our cohort had a predictive risk for non-SLN metastases of no more than 10%, and so those patients could avoid ALND. In the future, the two ongoing trials on this topic might reveal that omitting ALND for patients with early-stage BCA and 1–2 macrometastases undergoing mastectomy is also safe. However, it is also important that doctors assess the individual risk of

non-SLN metastases. Our nomogram could be regarded as an ancillary tool in a multidisciplinary decision process for breast oncologists in clinical practice when a patient with early-stage BCa and 1–2 SLN macrometastases comes to consult about whether ALND is advisable.

Our study has several limitations in. First, the patient cohort came from a single cancer centre, which might result in selection bias. Second, our test cohort did not provide sufficient data for an external validation, and so we used the 5-fold cross-validation method to formulate and validate the nomogram in the test cohort, which might partly counter that deficiency. Furthermore, a prospective randomized clinical trial is better than a retrospective study, and so a prospective trial should be conducted in Chinese patients in the near future.

CONCLUSIONS

We developed a predictive nomogram with satisfactory predictive ability to assess the risk of non-SLN metastases in patients with BCa and 1–2 SLN macrometastases undergoing mastectomy. The nomogram could be regarded as an ancillary tool in a multidisciplinary decision-making process for breast oncologists in clinical practice.

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CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare that we have none.

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