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Original article

Development and external validation of a nomogram to predict four or more positive nodes in breast cancer patients with one to three positive sentinel lymph nodes

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ABSTRACT

Objective: To develop a nomogram for predicting the possibility of four or more positive nodes in breast cancer patients with 1–3 positive sentinel lymph nodes (SLN).
Materials and methods: Retrospective analysis of data of patients from two institutions was conducted. The inclusion criteria were: invasive breast cancer; clinically node negative; received lumpectomy or mastectomy plus SLN biopsy followed by axillary lymph node dissection (ALND); and pathologically confirmed T1-2 tumor, with 1–3 positive SLNs. Patients from one institution formed the training group and patients from the other the validation group. Univariate and multivariate analyses were performed to identify the predictors of four or more positive nodes. These predictors were used to build the nomogram. The area under the receiver operating characteristic curve (AUC) was calculated to assess the accuracy of the model.
Results: Of the 1480 patients (966 patients in the training group, 514 in the validation group), 306 (20.7%) had four or more positive nodes. Multivariate stepwise logistic regression showed number of positive ($p < .001$) and negative SLN ($p < .001$), extracapsular extension ($p < .001$), pT stage ($p = .016$), and tumor location in outer upper quadrant ($p = .031$) to be independent predictors of four or more positive nodes. The nomogram was built using these five factors. The AUC was 0.845 in the training group and 0.804 in the validation group.
Conclusion: The proposed nomogram appears to accurately estimate the likelihood of four or more positive nodes and could help radiation oncologists to decide on use of regional nodal irradiation (RNI) for breast cancer patients with 1–3 positive nodes but no ALND.

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1. Introduction

Sentinel lymph node biopsy (SLNB) is currently the standard approach for clinically node-negative breast cancers. Axillary lymph node dissection (ALND) is reserved for patients with ≥3 positive lymph nodes on SLNB [1,2]. Women without sentinel lymph node (SLN) metastases should not receive ALND. In addition, ALND should be avoided in patients with 1–2 positive SLNs when whole-breast irradiation (WBI) therapy is planned [1,2]. Randomized trials have shown that SLNB is not inferior to ALND in patients with 1–2 positive SLNs. However, the radiation therapy volumes in these trials varied from standard WBI to high-tangential WBI and WBI plus regional nodal irradiation (RNI) [3–6]. Therefore, omitting ALND has created a new area of uncertainty for RNI in patients with positive SLNs.

Axillary nodal burden is one of the important indicators for RNI in breast cancer. It is well established that patients with ≥4 positive nodes benefit from RNI after axillary dissection, but whether patients with 1–3 positive nodes benefit from RNI is debated [7–9]. Recent data from the randomized NCIC MA.20 and EORTC 22922 trials showed that the addition of RNI to WBI in women with node-positive and high-risk node-negative breast cancer improves disease-free survival by lowering the risk of distant metastases, but does not improve overall survival. All patients in these two trials had undergone ALND, and majority had 1-3 positive nodes [10,11]. Currently, the indications of RNI for patients who received SLNB have to refer to those who received ALND. The aim of this study was to identify the predictors of four or more positive nodes in patients with 1–3 positive SLNs and to use these to create a nomogram that could help radiation oncologists decide on whether to deliver axillary plus supraclavicar and internal mammary nodal irradiation in SLN-positive patients who do not undergo ALND.

2. Patients and methods

2.1. Study population

The medical records of breast cancer patients who underwent surgery at two institutions—the Cancer Hospital of Chinese Academy of Medical Sciences and the Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University— in China between 2002 and 2018 were retrospectively reviewed. Patients were included in this study if they 1) had been diagnosed with invasive breast cancer; 2) were clinically node negative; 3) had undergone lumpectomy or mastectomy plus axillary SLNB and ALND; and 4) had pathologically confirmed T1-2 tumors and 1–3 positive SLNs. Patients were excluded if they had stage T3 or T4 disease or had undergone primary systemic therapy (PST).

The following clinicopathological data were collected: age; laterality, location and multifocality of the primary tumor; type of surgery; histology; tumor grade; tumor size; presence of lymphovascular invasion (LVI) and extracapsular extension (ECE); number of positive and negative SLNs; total number of positive nodes on final pathology; SLN micrometastasis or macrometastasis; estrogen receptor (ER), progesterone receptor (PR), human epidermal growth factor receptor 2 (HER2) status; and the Ki-67 index.

Patients from Cancer Hospital of Chinese Academy of Medical Sciences (n = 966; the training group) were used to develop a nomogram, and patients from Sun Yat-Sen Memorial Hospital of Sun Yat-Sen University (n = 514; validation group) were used for the external validation. The study protocol was approved by the institutional review board of Cancer Hospital of Chinese Academy of Medical Sciences (approval number 15–057/984), and waved the need for informed consent.

2.2. SLN biopsy

Technetium-99 m (^{99m}Tc) colloid and/or nano-carbon dye were used to identify SLNs. ^{99m}Tc colloid was injected 1–3 h before surgery, and a gamma detection device was used to detect the radioactive hotspot. Nano-carbon dye was injected around the areola of breast before surgery. Lymph nodes that showed radioactivity or were dyed black were excised as SLNs for histopathological evaluation.

2.3. Pathological evaluation

The SLNs were dissected from adipose tissue and separately embedded and frozen within optimal cutting tissue media and cut on a standard (−20 °C) cryostat, creating 6- to 8-μm-thick sections, with a minimum of two levels per block. Frozen section analysis was performed after hematoxylin and eosin (H&E) staining of a portion of the frozen nodal tissue. The remaining tissue was fixed in formalin, embedded in paraffin, and stained with H&E for further evaluation. Routine H&E analysis was performed for all additional nodes identified by ALND.

2.4. Statistical analysis

The association of different clincopathological variables with final lymph node status (≥4 positive nodes) was analyzed in the training group. Univariate analysis was performed with Pearson chi-square test or Fisher exact test for categorical variables. Variables with p-value ≤ .25 in univariate analysis were assessed for multicollinearity by using variance inflation factor (VIF). A VIF of >10 was considered to have multicollinearity between variables [12]. Variables with p ≤ .25 entered into multivariate logistic regression analysis using backward stepwise analysis to identify the independent predictors of having ≥ 4 positive nodes. The interaction between the identified variables on predicting for having ≥4 positive nodes were tested. The variables in the final model with p-value < .05 were used to develop the nomogram using “rms” package for R. Receiver operating characteristic (ROC) analysis with area under the curve (AUC) was performed to assess the accuracy of the model using “pROC” package for R. Calibrate curve was plotted to show identity between observed and predicted outcomes. External validation of the nomogram was performed by an independent patient group.

Statistical analysis was performed using SPSS for Windows, version 24.0 (IBM Corp., Armonk, NY, USA, released in 2016) and package of “rms” and “pROC” in R 3.6.2 (https://www.r-project.org/, released in 2019).

3. Results

Table 1 lists the characteristics of the training group and the validation group. The median age was 48 years for both groups. The proportion of patients with ≥4 positive nodes was higher in the validation group than in the training group. The training group had higher proportions of patients treated with mastectomy; with ≥3 negative SLNs retrieved; and with N1, T1, grade 1–2, LVI negative, ECE, and triple negative disease.

Table 2 lists the variables associated with ≥4 positive nodes in the training group in univariate and multivariate analysis. Variables with p-value ≤ .25 in univariate analysis were assessed for multicollinearity (Supplementary Table 1). No variable with VIF >10 was found, indicating that there was no collinearity between the variables. The independent predictors of ≥4 positive nodes included the number of positive SLNs (p < .001), the number of negative SLNs (p < .001), ECE (p < .001), pT2 stage (p = .016), and tumor

Table 1
Clinical and pathological characteristics of the training group and the validation group. All figures are n (%), unless otherwise stated.

Characteristics	Training group N = 966	Validation group N = 514	p
Positive nodes			<.001
1–3	820 (84.9)	354 (68.9)	
≥4	146 (15.1)	160 (31.1)	
Age, years			.343
Median (range)	48 (21–86)	48 (25–83)	
≤50 years	563 (58.3)	306 (59.5)	
>50 years	403 (41.7)	207 (40.3)	
Unknown	0 (0)	1 (0.2)	
Laterality			.019
Left	483 (50.0)	274 (53.3)	
Right	470 (48.7)	240 (46.7)	
Unknown	13 (1.3)	0 (0)	
Surgery			.011
MRM	529 (54.8)	246 (47.9)	
BCS	437 (45.2)	268 (52.1)	
Quadrant			.826
OUQ	419 (43.4)	226 (44.0)	
Others	547 (56.6)	288 (56.0)	
Multifocal			.136
No	856 (88.6)	445 (86.6)	
Yes	106 (11.0)	69 (13.4)	
Unknown	4 (0.4)	0 (0)	
Tumor type and nuclear grade			<.001
IDC I	86 (8.9)	17 (3.3)	
IDC II	598 (61.9)	216 (42.0)	
IDC III	225 (23.3)	206 (40.1)	
ILC	18 (1.9)	9 (1.8)	
Unknown	39 (4.0)	66 (12.8)	
pT Stage			<.001
pT1	594 (61.5)	258 (50.2)	
pT2	372 (38.5)	256 (49.8)	
LVI			<.001
Positive	298 (30.8)	215 (41.8)	
Negative	660 (68.3)	170 (33.1)	
Unknown	8 (0.8)	129 (25.1)	
ECE			.001
Positive	92 (9.5)	23 (4.5)	
Negative	871 (90.2)	491 (95.5)	
Unknown	3 (0.3)	0 (0)	
Number of positive SLN			.823
1	637 (65.9)	343 (66.7)	
2	231 (23.9)	116 (22.6)	
3	98 (10.1)	55 (10.7)	
Number of negative SLN			<.001
0	73 (7.6)	176 (34.2)	
1	138 (14.3)	143 (27.8)	
2	227 (23.5)	98 (19.1)	
≥3	528 (54.7)	97 (18.9)	
No. of SLN removed			<.001
1–2	130 (13.5)	255 (49.6)	
3–5	603 (62.4)	218 (42.4)	
>5	233 (24.1)	41 (8.0)	
Positive/removed SLN ratio			<.001
≤20%	261 (27.0)	33 (6.4)	
20%–35%	331 (34.3)	113 (22.0)	
35%–50%	216 (22.4)	136 (26.5)	
>50%	158 (16.4)	232 (45.1)	
HER2			.064
Positive	194 (20.1)	118 (23.0)	
Negative	737 (76.3)	350 (68.1)	
Unknown	35 (3.6)	46 (8.9)	
Molecular subtype			<.001
Luminal A	150 (15.5)	74 (14.4)	
Luminal B	487 (50.4)	232 (45.1)	
Luminal B-HER2 positive	126 (13.0)	96 (18.7)	
HER2 overexpression	61 (6.3)	21 (4.1)	
TNBC	93 (9.6)	22 (4.3)	
Unknown	49 (5.1)	69 (13.4)	

MRM modified radical mastectomy; BCS breast-conserving surgery; OUQ outer upper quadrant; SLN sentinel lymph node; IDC infiltrating ductal carcinoma; ILC infiltrating lobular carcinoma; LVI lymphovascular invasion; ECE extracapsular extension; HER2 human epidermal growth factor receptor 2; TNBC triple-negative breast cancer.

Table 2
Univariate and multivariate analyses of predictors of four or more positive nodes in the training group.

Characteristics	Training Group N = 966			Univariable Analysis	Multivariable Analysis	
		N1	N2 or N3	P	OR (95% CI)	p
Age, n (%)				.868		
≤50 years	563 (58.3)	477 (58.2)	86 (58.9)			
>50 years	403 (41.7)	343 (41.8)	60 (41.1)			
Laterality, n (%)				.242		.673
Left	483 (50.0)	416 (51.5)	67 (46.2)		1	
Right	470 (48.7)	392 (48.5)	78 (53.8)		1.097 (0.715–1.682)	
Surgery, n (%)				.725		
MRM	529 (54.8)	451 (55.0)	78 (53.4)			
BCS	437 (45.2)	369 (45.0)	68 (46.6)			
Quadrant, n (%)				.008		.031
Others	547 (56.6)	479 (58.4)	68 (46.6)		1	
OUQ	419 (43.4)	341 (41.6)	78 (53.4)		1.605 (1.043–2.469)	
Multifocal, n (%)				.384		
No	856 (88.6)	730 (89.4)	126 (86.9)			
Yes	106 (11.0)	87 (10.6)	19 (13.1)			
Tumor type and nuclear grade, n (%)				.266		
IDC I	86 (8.9)	79 (10.1)	7 (4.9)			
IDC II	598 (61.9)	501 (64.0)	97 (67.4)			
IDC III	225 (23.3)	188 (24.0)	37 (25.7)			
ILC	18 (1.9)	15 (1.9)	3 (2.1)			
pT Stage, n (%)				<.001		.016
pT1	594 (61.5)	526 (64.1)	68 (46.6)		1	
pT2	372 (38.5)	294 (35.9)	78 (53.4)		1.694 (1.102–2.605)	
LVI, n (%)				.001		.202
Negative	660 (68.3)	578 (71.0)	82 (56.9)		1	
Positive	298 (30.8)	236 (29.0)	62 (43.1)		1.338 (0.856–2.092)	
ECE, n (%)				<.001		<.001
Negative	871 (90.2)	760 (92.9)	111 (76.6)		1	
Positive	92 (9.5)	58 (7.1)	34 (23.4)		3.883 (2.195–6.868)	
Number of positive SLN, n (%)				<.001		<.001
1	637 (65.9)	597 (72.8)	40 (27.4)		1	
2	231 (23.9)	180 (22.0)	51 (34.9)		3.238 (1.996–5.252)	
3	98 (10.1)	43 (5.2)	55 (37.7)		12.813 (7.257–22.623)	
Number of negative SLN, n (%)				<.001		<.001
≥3	528 (54.7)	484 (59.0)	44 (30.1)		1	
2	227 (23.5)	190 (23.2)	37 (25.3)		1.954 (1.137–3.356)	
1	138 (14.3)	107 (13.0)	31 (21.2)		2.537 (1.406–4.577)	
0	73 (7.6)	39 (4.8)	34 (23.3)		7.427 (3.888–14.188)	
SLN macrometastasis, n (%)				.010		.998
Yes	930 (96.3)	784 (95.6)	146 (100)			
No	36 (3.7)	36 (4.4)	0 (0)			
HER2, n (%)				.136		.755
Negative	737 (79.2)	632 (80.0)	105 (74.5)		1	
Positive	194 (20.1)	158 (20.0)	36 (25.5)		1.082 (0.659–1.778)	
Molecular subtype, n (%)				.314		
Luminal A	150 (15.5)	130 (15.9)	20 (13.7)			
Luminal B	487 (50.4)	414 (50.5)	73 (50.0)			
Luminal B-HER2 positive	126 (13.0)	99 (12.1)	27 (18.5)			
HER2 overexpression	61 (6.3)	53 (6.5)	8 (5.5)			
TNBC	93 (9.6)	83 (10.1)	10 (6.8)			

location in the outer upper quadrant (OUQ; p = .031). The possible interactions among the variables were tested, and no significant interaction between variables was found (Supplementary Table 2). These five predictors were used to create the predictive nomogram (Supplementary Table 3, Fig. 1). Bootstrap-corrected ROC analysis showed the AUC to be 0.845 (95% confidence interval [CI]: 0.811–0.879) (Fig. 2A). In the external validation group, the AUC was 0.804 (95% CI: 0.762–0.847) (Fig. 2B). In addition, the calibrate curves showed a well match between observed and predicted outcomes in the training group (Fig. 3A) and validation group (Fig. 3B).

Table 3 presents the sensitivity, specificity, positive predictive value, and negative predictive value of this model at different cutoff points for the entire cohort.

4. Discussion

This study presents a simple nomogram that can be used to predict which patients with 1–3 positive SLNs will have ≥4 positive nodes on final pathology. The model was developed according to the principles of transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD) [13], and the checklist is provided in Supplementary Table 4. Traditionally, radiation oncologists relied on the ALND results to design the radiation treatment fields. In contrast to patients with ≥4 positive nodes, the role of RNI in those with 1–3 positive nodes after ALND is controversial. The Early Breast Cancer Trialists' Collaborative Group (EBCTCG) meta-analysis showed that postmastectomy chest wall and comprehensive RNI significantly reduced locoregional recurrence (LRR) and breast cancer–related mortality in T1-2N1 breast cancer [14]. However, most trials included in this meta-

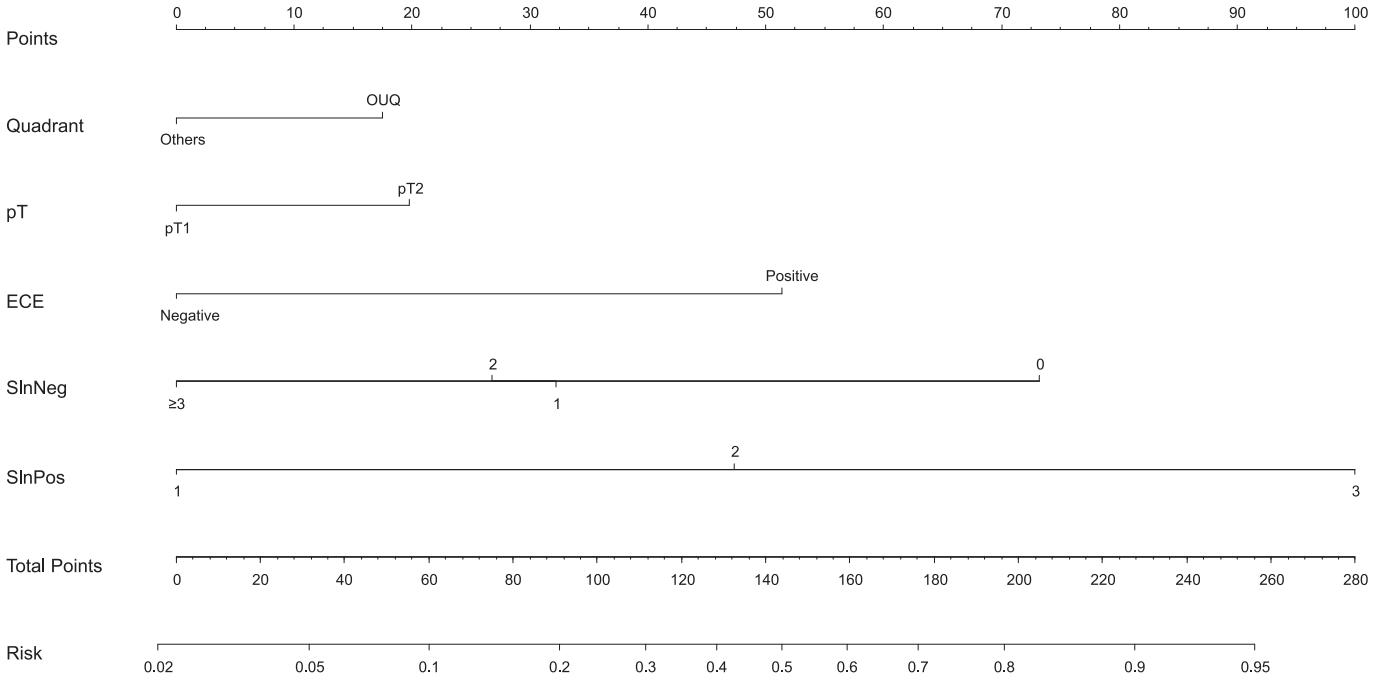

Fig. 1. Nomogram for predicting four or more positive nodes in breast cancer patient.

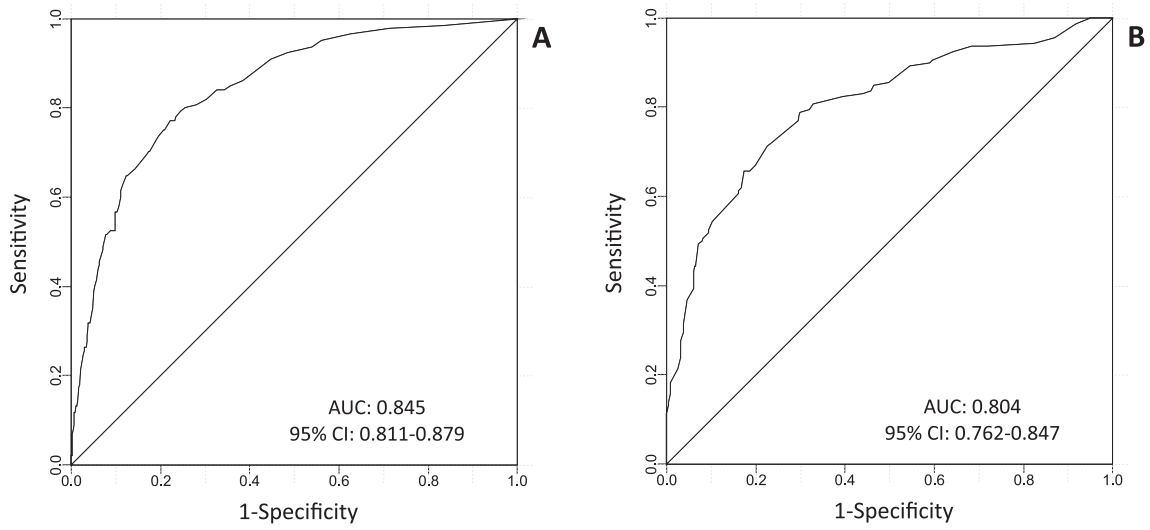

Fig. 2. The area under curve of receiver operating characteristic graph in training group (A) and validation group (B).

analysis were conducted 20 years ago, when the LRR rate for patients not receiving radiation therapy was as high as 30% [15–17]. With modern surgery and contemporary systemic therapies, the LRR rate for patients with 1–3 positive nodes is now approximately 10% [18–20]. Therefore, not all patients are likely to benefit sufficiently from RNI to justify its routine use. When SNLB is preferred for clinically node-negative patients, the radiation fields has increased despite low to intermediate pathological features [21,22], RNI is likely overused. In a survey examining the patterns of RNI practice in European Organization for Research and Treatment of Cancer (EORTC) affiliated centers, approximately 60% of centers recommended RNI for pN1 disease when ALND was not performed [23]. A survey conducted in the US found that 28.2% of radiation oncologists used a nomogram to aid decision making on delivery of RNI in patients with 1–3 positive SLNs [21].

Models for predicting the risk of non-SLN involvement in a positive SLN situation are available that are based on clinicopathologic factors, or primary tumor miRNAs signature, or total tumor load determined by the amount of CK19 mRNA copies in all positive SLNs [24–26]. When making decisions on whether to deliver RNI, radiation oncologists consider not only the risk of further axillary nodal involvement but also the risk of supraclavicular/internal mammary nodal involvement, how the radiation field design might affect the risk of recurrence, and the risk of normal tissue complications. There is high risk of supraclavicular/internal mammary nodal involvement in patients with ≥4 positive axillary nodes [27,28]. While RNI may improve disease-free survival, the risk of lymphedema and lung fibrosis is higher than with WBI alone [10,11].

Table 4 summarizes previous nomograms that have been

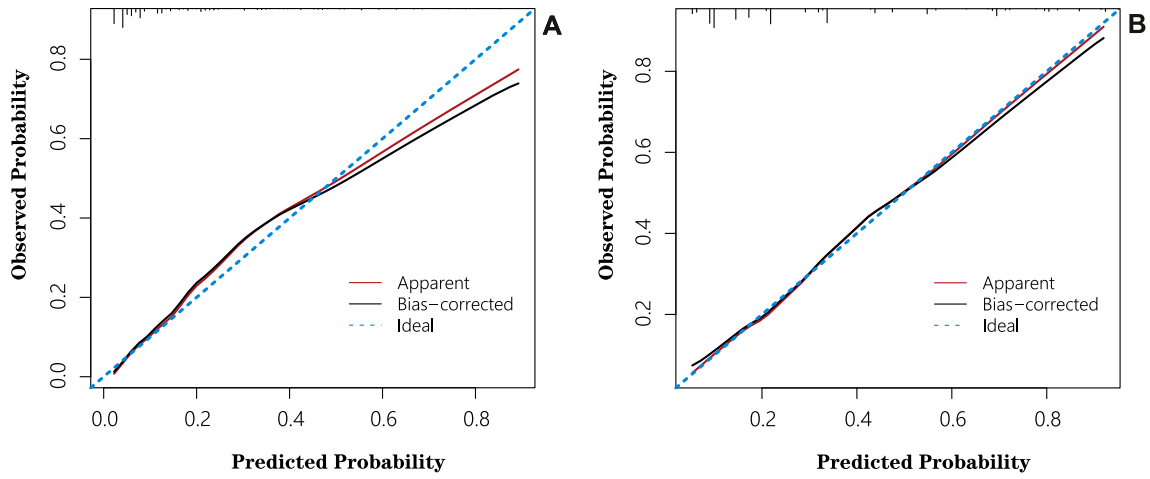

Fig. 3. Calibration curves for nomogram in training group (A) and validation group (B). The red line presents actual performance of nomogram with apparent accuracy; black line shows bootstrap corrected performance of nomogram. The diagonal line represents the performance of an ideal nomogram. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

Table 3
The sensitivity, specificity, positive predictive value, and negative predictive value of this nomogram at different cutoff points in the entire cohort.

Predicted probability	Sensitivity (%)	Specificity (%)	Positive predictive value (%)	Negative predictive value (%)
≥5%	94.8 (289/305)	36.0 (422/1172)	27.8 (289/1039)	96.3 (422/438)
≥10%	84.9 (259/305)	62.2 (729/1172)	36.9 (259/702)	94.1 (729/775)
≥15%	77.4 (236/305)	75.9 (890/1172)	45.6 (236/518)	92.8 (890/959)
≥20%	73.8 (225/305)	79.1 (927/1172)	47.9 (225/470)	92.1 (927/1007)
≥25%	58.7 (179/305)	88.2 (1034/1172)	56.5 (179/317)	89.1 (1034/1160)
≥30%	52.5 (160/305)	91.1 (1068/1172)	60.6 (160/264)	88.0 (1068/1213)

Table 4
Comparison of nomograms proposed for prediction of ≥4 positive nodes on final pathology.

Study	Number of Patients	T1-2 (%)	1-2 positive SLNs (%)	≥4 positive nodes on final pathology (%)	Predictive factors	AUC	
						Training group	Validation group
Chagpar et al. [29] 2006	1133	100	91.9	18.7	Tumor size, Number of positive SLNs, Proportion of positive SLNs, Hematoxylin-eosin detection	0.882	0.895
Katz et al. [30] 2008	402	97.3	95.5	21.6	Tumor size, Invasive lobular histology, LVI, ECE, Number of positive SLNs, Macroscopic size of largest SLN metastasis, Number of negative SLNs	0.83	0.81
Unal et al. [31] 2009	309	94.2	94.5	25.9	Tumor size, ECE, Number of positive SLNs, Overall metastasis size	–	0.801 (validate Katz's model)
Kim et al. [32] 2017	1437	100	100	5.7	Tumor size, Proportion of positive SLNs, LVI, ECE	0.805	0.825
Shimazu et al. [33] 2018	623	97.4	95.2	11[a]	Clinical tumor size, Number of macrometastatic SLNs, Total tumor load of SLNs	0.79	0.70
Our study	1480	100	89.7	20.7	Tumor size, Upper outer quadrant, ECE, Number of positive SLNs, Number of negative SLNs	0.845	0.804

SLN = sentinel lymph node, AUC = area under the curve, LVI = lymphovascular invasion, ECE = extracapsular extension.
[a] In training group.

proposed for predicting the risk of ≥4 positive nodes [29–33]. The majority of patients in these studies had T1-2 tumor with 1–2 positive SLNs; the proportion with ≥4 positive nodes in the final pathology varied from 5.7% to 25.9%. Consistently, the main predictors were primary tumor size, tumor burden of SLNs (characterized by the number of positive SLNs), proportion of positive SLNs, macroscopic size of the largest SLN metastasis, H&E detection, ECE, overall metastasis size, and total tumor load. Only the model devised by Katz et al. was validated in an external population [30].

In our study, in addition to the predictive factors mentioned above (i.e., primary tumor size, number of positive SLNs, number of negative SLNs, and ECE), tumor location in the OUQ was identified as an independent predictor of having ≥ 4 positive nodes. Previous studies on large populations have shown OUQ to be a predictor of axillary nodal metastases [34,35].

A major strength of our model is that it is based on pathological features available in common clinical practice. Our model showed high accuracy for predicting the likelihood of having ≥4 positive nodes (AUC = 0.845). Although imbalances exist in the two cohorts used for nomogram construction and validation, our model performed well in the validation group (AUC = 0.804), suggesting the robustness of the model. To our knowledge, this is the first nomogram with an external validation in a large cohort of patients. Of the 305 patients with ≥4 positive nodes, 289 had a nomogram-calculated probability of ≥5%; thus, the sensitivity was 94.8%. Of the 438 patients with a nomogram-calculated probability of <5%, 422 did not have ≥4 positive nodes; thus, the negative predictive value was 96.3%. If we hypothesize that patients with <5% chance of having ≥4 positive nodes do not need RNI, then 31.8% (438/1377) of patients in the entire cohort could have been spared the morbidity of comprehensive nodal irradiation. A cutoff point of 10% results in a sensitivity of 84.9%, a negative predictive value of 94.1% and 56.3% (775/1377) of patients sparing nodal irradiating morbidity.

Some limitations of our study must be acknowledged. First, the nodes retrieved were examined only by routine pathological analysis and H&E staining alone. Serial sectioning and immunohistochemistry may have identified more nodal metastases. Second, we did not have data on the size of nodal metastases. However, as shown in Table 4, the performance of our model is comparable with other models, and so the method of detection of the nodal metastasis used in our study is practical and reproducible. Third, almost 90% of the patients in the training group had more than one SNL removed, the nomogram might be applicable only if more than one node was removed.

In conclusion, there is a growing tendency to omit ALND in early-stage breast cancer patients. The nomogram that we propose uses commonly available information to estimate the likelihood of having ≥4 positive nodes in final pathology. The model shows good accuracy, and can help the radiation oncologist to decide on whether to deliver RNI for breast cancer patients with 1–3 positive SLNs but no ALND.

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Ethical approval

The study protocol was approved by the institutional review board of Cancer Hospital of Chinese Academy of Medical Sciences (approval number 15–057/984), and waved the need for informed consent.

Declaration of competing interest

None of the authors have conflicts of interest or financial disclosure.

Supplementary Table 1
The evaluation of multi-collinearity for variables with p-value ≤ .25 in univariate analysis.

Variables	VIF
Laterality	1.006
Quadrant	1.015
pT Stage	1.036
LVI	1.044
ECE	1.024
No. of Positive SLN	1.098
No. of Negative SLN	1.055
SLN macrometastasis	1.015

VIF variance inflation factor; LVI lymphovascular invasion; ECE extracapsular extension; SLN sentinel lymph node.

Supplementary Table 2
Evaluation of interactions between the predictive variables in the main effects model to predict four or more positive nodes.

Interaction	P
Main effects model	
Quadrant* pT Stage	0.122
Quadrant* ECE	0.067
Quadrant* No. of positive SLN	0.306
Quadrant*No. of negative SLN	0.114
pT Stage * ECE	0.427
pT Stage * No. of positive SLN	0.089
pT Stage * No. of negative SLN	0.634
ECE * No. of positive SLN	0.669
ECE * No. of negative SLN	0.938
No. of positive SLN * No. of negative SLN	0.063

Supplementary Table 3
Multivariate analyses of the five variables in the main effects model.

Varibles.	OR	P
Quadrant	1.583	0.017
pT Stage	1.680	0.002
ECE	3.847	<.001
No. of Positive SLN		<.001
1	1	
2	3.463	
3	13.807	
No. of Negative SLN		<.001
≥3	1	
2	2.019	
1	2.329	
0	6.830	

Supplement table 4
Checklist of a nomogram predicting the likelihood of having four or more positive nodes in early stage breast cancer patients according to TRIPOD statement.

Section/topic	Item	Checklist item	page
Title and abstract			
Title	1	Identify the study as developing and/or validating a multivariable prediction model, the target population, and the outcome to be predicted	1
Abstract	2	Provide a summary of objectives, study design, setting, participants, sample size, predictors, outcome, statistical analysis, results, and conclusions.	1
Introduction			
Background and objectives	3a	Explain the medical context (including whether diagnostic or prognostic) and rationale for developing or validating the multivariable prediction model, including references to existing models.	2
	3b	Specify the objectives, including whether the study describes the development or validation of the model or both.	2
Methods			
Source of data	4a	Describe the study design or source of data (e.g., randomized trial, cohort, or registry data), separately for the development and validation data sets, if applicable.	2
	4b	Specify the key study dates, including start of accrual; end of accrual; and, if applicable, end of follow-up.	2
Participants	5a	Specify key elements of the study setting (e.g., primary care, secondary care, general population) including number and location of centers.	2
	5b	Describe eligibility criteria for participants.	2
	5c	Give details of treatments received, if relevant.	2
Outcome	6a	Clearly define the outcome that is predicted by the prediction model, including how and when assessed.	2
	6b	Report any actions to blind assessment of the outcome to be predicted.	Not applicable
Predictors	7a	Clearly define all predictors used in developing or validating the multivariable prediction model, including how and when they were measured.	2
	7b	Report any actions to blind assessment of predictors for the outcome and other predictors.	Not applicable
Sample size	8	Explain how the study size was arrived at.	Not applicable
Missing data	9	Describe how missing data were handled (e.g., complete-case analysis, single imputation, multiple imputation) with details of any imputation method.	Not applicable
Statistical analysis methods	10a	Describe how predictors were handled in the analyses.	2
	10b	Specify type of model, all model-building procedures (including any predictor selection), and method for internal validation.	2
	10c	For validation, describe how the predictions were calculated.	2
	10d	Specify all measures used to assess model performance and, if relevant, to compare multiple models.	2
Risk groups	11	Provide details on how risk groups were created, if done.	Not applicable
Development v validation	12	For validation, identify any differences from the development data in setting, eligibility criteria, outcome, and predictiors.	Table 1 & Table 2
Results			
Participants	13a	Describe the flow of participants through the study, including the number of participants with and without the outcome and, if applicable, a summary of the follow-up time. A diagram may be helpful.	2
	13b	Describe the characteristics of the participants (basic demographics, clinical features, available predictors), including the number of participants with missing data for predictors and outcome.	Table 1
	13c	For validation, show a comparison with the development data of the distribution of important variables (demographics, predictors and outcome).	Table 1
Model development	14a	Specify the number of participants and outcome events in each analysis.	Table 1 & Table 2
	14b	If done, report the unadjusted association between each candidate predictor and outcome.	Table 2
Model specification	15a	Present the full prediction model to allow predictions for individuals (i.e., all regression coefficients, and model intercept or baseline survival at a given time point).	Fig. 1
	15b	Explain how to the use the prediction model.	Fig. 1
Model performance	16	Report performance measures (with CIs) for the prediction model.	Fig. 2
Model updating	17	If done, report the results from any model updating (that is, model specification, model performance).	Not applicable
Discussion			
Limitations	18	Discuss any limitations of the study (such as nonrepresentative sample, few events per predictor, missing data).	4-6
Interpretation	19a	For validation, discuss the results with reference to performance in the development data, and any other validation data.	3-4
	19b	Give an overall interpretation of the results, considering objectives, limitations, and results from similar studies, and other relevant evidence.	3-4
Implications	20	Discuss the potential clinical use of the model and implications for future research	6
Other information			
Supplementary information	21	Provide information about the availability of supplementary resources, such as study protocol, Web calculator, and data sets.	Not applicable
Funding	22	Give the source of funding and the role of the funders for the present study.	6

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