



# Nomogram for predicting axillary lymph node status after neoadjuvant chemotherapy in breast cancer

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**Background:** Many breast cancer patients benefit from neoadjuvant chemotherapy (NAC). However, sentinel lymph node biopsy (SLNB) after NAC remains controversial, especially for patients with axillary lymph node metastasis (ALNM) at diagnosis. We developed a nomogram for predicting axillary lymph node (ALN) status after NAC to screen for patients for whom SLNB may be beneficial.

**Methods:** A total of 320 cT1–4N0–1M0 breast cancer patients receiving ALN dissection (ALND) after NAC were included. Univariate and multivariate logistic regression analyses determined significant factors for predicting ALN status. Efficacy of the resulting nomogram was assessed using receiver operating characteristic (ROC) and calibration curves, while decision curve analysis (DCA) was used to evaluate net clinical benefit. Our nomogram was validated using female patients grouped according to a diagnosis of node-positive (cN1) or node-negative (cN0) by ultrasound-guided needle biopsy of suspected lymph nodes before NAC.

**Results:** Logistic regression analyses indicated that estrogen receptor (ER), Ki67, degree of tumor regression, clinical tumor T stage after NAC, and ALN Breast Imaging-Reporting and Data System (BI-RADS) category after NAC, were associated with ALN status. The resulting nomogram had an area under the curve (AUC) of 0.802 [95% confidence interval (CI), 0.7485–0.8554], and the calibration plot showed strong uniformity between predicted and actual ALN status. DCA indicated a positive net benefit of nomogram predictions in our cohort. After internal validation, the cN1 and cN0 groups had an AUC of 0.7926 (95% CI, 0.7187–0.8665) and 0.8165 (95% CI, 0.7381–0.8949), respectively. The calibration plot indicated better performance in the cN0 group.

**Conclusions:** After NAC, some patients may benefit from SLNB. Our nomogram predicts ALN status after NAC and has great potential to assist in clinical decision-making.

**Keywords:** Breast cancer; neoadjuvant chemotherapy (NAC); nomogram; sentinel lymph node biopsy (SLNB)

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## Introduction

Breast cancer is the most common malignant tumor among females, and the leading cause of tumor-related death worldwide (1,2). In 2017 in the United States, 252,710 females were diagnosed with breast cancer, and breast cancer caused 40,610 deaths (14.4% of total tumor-related fatalities) (1). Neoadjuvant chemotherapy (NAC) is a treatment for patients with local advanced breast cancer. It is also useful for some early-stage breast cancer patients whose tumor size does not permit breast conservation. Several cycles of NAC can grant some patients a chance for breast-conserving surgery, and a subset of patients with axillary lymph nodes (ALNs) was reported achieving pathological complete response (pCR), indicating a good prognosis (3,4). The National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocols B-18 and B-27 assert that preoperative therapy is equivalent to adjuvant therapy for some patients (5). For local advanced breast cancer, mastectomy combined with ALN dissection (ALND) is a standard procedure. However, this can injury axillary lymph vessels and nerves, resulting in physical and psychological morbidities, and poor quality of life (6). The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology Version 1.2018 (NCCN Guidelines) (7) state that ALND should be done for clinically positive ALNs following NAC, while sentinel lymph node biopsy (SLNB) can be performed for clinically negative ALNs following NAC, avoiding possible ALND-related morbidities in these patients.

Until now, there has been no published nomogram that predicts ALN status after NAC in breast cancer patients regardless of their initial ALN condition. Therefore, we conducted this study to construct a nomogram to identify those patients suitable for receiving SLNB.

We present the following article in accordance with the TRIPOD reporting checklist (available at <http://dx.doi.org/10.21037/tcr-20-2377>).

## Methods

### Patients

This was a retrospective study of 320 females who received NAC for cT1–4N0–1M0 breast cancer at the First Hospital of China Medical University between 2013 and 2017. The inclusion criteria were as follows: (I) patients with invasive breast cancer confirmed by core needle biopsy before NAC; (II) patients who received at least one cycle of NAC; (III) patients with no anti-tumor treatments prior to NAC;

and (IV) patients who underwent mastectomy and ALND following NAC. The exclusion criteria were as follows: (I) patients with missing data; (II) patients who suffered distant metastasis prior to surgery; or (III) patients who had surgical histories of ipsilateral axilla. The study was conducted in accordance with the Declaration of Helsinki (as revised in 2013). The study was approved by the Ethical Committee of The First Hospital of China Medical University (2019-72-2), and informed consent was taken from all the patients.

### Pathology

Data extracted from tumor samples included expression of estrogen receptor (ER), progesterone receptor (PR), human epithelial growth receptor 2 (HER2), and Ki67. These were measured by immunohistochemistry (IHC) performed on formalin-fixed, paraffin-embedded tissue sections by the Pathology Department of The First Hospital of China Medical University, using standard protocols. ER and PR positivity were defined as nuclear staining in >1% of tumor cells. HER2 positivity was defined as either scoring 3+ by IHC or amplification by fluorescent *in situ* hybridization (FISH) (8). Ki67 was divided into two groups, Ki67 <14% and ≥14%, with the latter considered high (9). Histology grade was assessed according to the Elston-Ellis system (10). ALN status after NAC was recorded after ALND. All samples were examined independently by at least two experienced pathologists.

All patients received breast and ALN ultrasound examinations prior to NAC, with the longest primary tumor diameter present recorded as the baseline. After the final cycle of NAC before surgery, all patients underwent another breast and ALN ultrasound examination, and the longest diameter after NAC was compared to the baseline.

### Neoadjuvant treatment regimens

Patients were classified into four groups according to NAC regimens. Group 1 received epirubicin or doxorubicin but no docetaxel. Group 2 received docetaxel but no epirubicin or doxorubicin. Group 3 received epirubicin or doxorubicin and docetaxel. Group 4 contained two subgroups, HER2+ with/without Herceptin treatment. Patients received four cycles of NAC on average.

### Statistical analysis

Statistical analyses for the comparisons included the

Student's *t*-test for continuous variables and the Chi-square test or Fisher's exact test for categorical variables. A *P* value <0.05 was considered significant. Data analyses were performed using SPSS version 22.0 (SPSS Inc, Chicago, IL, USA). R software was used in constructing the nomogram (Institute for Statistics and Mathematics, Vienna, Austria, Version 3.4.1, www.R-project.org).

## Results

### Description of enrolled patients

General characteristics of the 320 enrolled patients are shown in *Table 1*. Median age was 51 (ranging from 24 to 76) years. Of the patients with ALN metastasis (ALNM), 159 (71.3%) were ER positive and 64 (28.7%) were ER negative (*P*=0.001). Average Ki67 index was significantly higher in the ALN with no metastasis (ALNNM) cohort compared with the ALNM cohort (45.5% vs. 36.1%, respectively; *P*=0.008). More than half the patients in the ALNM cohort presented as ycT2-3, while the majority of patients in the ALNNM cohort were ycT1 (*P*<0.001). For ALN category based on Breast Imaging-Reporting and Data System (BI-RADS) under ultrasound after NAC, there were 68 (30.5%) ALNM patients and 72 (74.2%) ALNNM patients with ALN BI-RADS category ≤3, with the reverse outcome occurring for ALN BI-RADS category ≥4 (69.5% vs. 25.8%, *P*<0.001). Clinical tumor stage before NAC, PR status, HER2 status, NAC courses, and NAC regimens all

showed no significant difference between the ALNM and ALNNM groups.

### Construction of the nomogram

We constructed the nomogram based on statistically and clinically significant factors (*Table 1*). The following were evaluated by univariate analysis: clinical tumor stage before and after NAC (cT and ycT, respectively), patient age, ER, PR, HER2, Ki67, histological grades of core biopsy samples, NAC regimens, number of cycles, ALN BI-RADS category before and after NAC, and tumor regression degree (ratio between longest diameter of the primary tumor before and after NAC measured by ultrasound, with the cutoff value set at 1.0 such that a fold change >1 indicates that the primary tumor size is decreasing, and ≤1 indicates that the primary tumor has a limited response to the chemotherapy regimen). A multivariate logistic regression analysis was conducted on the meaningful variables, including ALN BI-RADS category before NAC (*P*=0.002), histologic grade (*P*=0.050), ER (*P*=0.001), Ki67 (*P*=0.491), tumor regression degree (*P*=0.087), ycT (*P*<0.001), and ALN BI-RADS category after NAC (*P*<0.001). We determined that ER (*P*=0.009), ycT (*P*=0.005) and ALN BI-RADS category after NAC (*P*<0.001) were significant factors. These five variables were used for the construction of our nomogram (*Table 2*). While primary tumor regression degree and Ki67 can reflect the response to NAC (11-14), these were not

**Table 1** Clinical and pathological features of the study population

Features	All patients, n (%)	ALNM, n (%)	ALNNM, n (%)	P value
Total no. of patients	320	223	97	
Age				0.940
Mean (SD)	50.8	51.6 (9.7)	48.9 (9.8)	
Range	24-76	26-76	24-66	
Clinical tumor stage before NAC (cT)				0.517
cT1-2	233 (72.8)	160 (71.7)	73 (75.3)	
cT3-4	87 (27.2)	63 (28.3)	24 (24.7)	
ALN BI-RADS category before NAC				0.002
≤3	44 (13.8)	22 (9.9)	22 (22.7)	
≥4	276 (86.2)	201 (90.1)	75 (77.3)	
Histologic grade				0.050

**Table 1** (continued)

Table 1 (continued)

Features	All patients, n (%)	ALNM, n (%)	ALNNM, n (%)	P value
≤2	284 (88.8)	203 (91.0)	81 (83.5)	
3	36 (11.2)	20 (9.0)	16 (16.5)	
ER				0.001
Positive	209 (65.3)	159 (71.3)	50 (51.5)	
Negative	111 (34.7)	64 (28.7)	47 (48.5)	
PR				0.136
Positive	201 (62.8)	146 (65.5)	55 (56.7)	
Negative	119 (37.2)	77 (34.5)	42 (43.3)	
HER2 status				0.497
Positive	123 (38.4)	83 (37.2)	40 (41.2)	
Negative	197 (61.6)	140 (62.8)	57 (58.8)	
Ki67				0.491
<14%	32 (10.0)	24 (10.7)	8 (8.2)	
≥14%	288 (90.0)	199 (89.3)	89 (91.8)	
NAC cycles				0.238
≤4	266 (83.1)	189 (84.8)	77 (79.4)	
≥5	54 (16.9)	34 (15.2)	20 (20.6)	
NAC regimens				0.910
Containing anthracycline only	231 (72.2)	160 (71.7)	71 (73.2)	
Containing docetaxel only	5 (1.6)	4 (1.8)	1 (1.0)	
Containing anthracycline and docetaxel	77 (24.1)	55 (24.7)	22 (22.7)	
HER2+ with Herceptin	7 (2.1)	4 (1.8)	3 (3.1)	
HER2+ without Herceptin	116 (36.3)	79 (35.4)	37 (38.1)	
Tumor regression degree (fold change)				0.087
≤1	46 (14.4)	37 (16.6)	9 (9.3)	
>1	274 (85.6)	186 (83.4)	88 (90.7)	
ycT				<0.001
1	119 (37.2)	67 (30.0)	52 (53.6)	
2	168 (52.5)	126 (56.5)	42 (43.3)	
3	33 (10.3)	30 (13.5)	3 (3.1)	
ALN BI-RADS category after NAC				<0.001
≤3	140 (43.8)	68 (30.5)	72 (74.2)	
≥4	180 (56.3)	155 (69.5)	25 (25.8)	

ALNM, axillary lymph node metastasis; ALNNM, axillary lymph node with no metastasis; NAC, neoadjuvant chemotherapy; ALN, axillary lymph node; BI-RADS, Breast Imaging-Reporting and Data System; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; ycT, clinical tumor T stage after NAC; ALN BI-RADS category before NAC, ALN category based on BI-RADS under ultrasound before NAC; ALN BI-RADS category after NAC, ALN category based on BI-RADS under ultrasound after NAC.

**Table 2** Multivariate analysis of ALNM factors of breast cancer patients after receiving NAC

Variables	OR	95% CI	P value
ALN BI-RADS category before NAC			0.216
≤3	–	–	
≥4	0.613	0.283–1.330	
Histological grade			0.313
≤2	–	–	
3	1.585	0.648–3.877	
ER			0.009
Negative	–	–	
Positive	0.427	0.226–0.805	
Ki67	0.989	0.976–1.002	0.110
Tumor regression degree (fold change)			0.672
≤1	–	–	
>1	1.218	0.490–3.026	
ycT			
1	–	–	
2	0.147	0.038–0.564	0.005
3	0.296	0.079–1.113	0.072
ALN BI-RADS category after NAC			<0.001
≤3	–	–	
≥4	0.172	0.094–0.315	

ALNM, axillary lymph node metastasis; NAC, neoadjuvant chemotherapy; CI, confidence interval; ALN, axillary lymph node; BI-RADS, Breast Imaging-Reporting and Data System; ER, estrogen receptor; ycT, clinical tumor T stage after NAC; ALN BI-RADS category before NAC, ALN category based on BI-RADS under ultrasound before NAC; ALN BI-RADS category after NAC, ALN category based on BI-RADS under ultrasound after NAC.

significant variables in our analysis. This may be due to the limited number of cases.

Figure 1 shows the nomogram for predicting the probability of ALN with metastasis after NAC. For each covariate, we drew a vertical line upwards from its respective axis to the “points” bar on top to calculate its individual point value. After summing all the covariate points, we drew a vertical line downwards from the “total points” line to evaluate ALNM risk. The figure clearly shows that ALN BI-RADS category after NAC makes the greatest

contribution to the total score, while ER, Ki67, ycT, and tumor regression degree have moderate influences.

### Quantifying the performance of the nomogram

We constructed the receiver operating characteristic (ROC) to validate the nomogram internally. The area under the curve (AUC) was 0.802 [95% confidence interval (CI), 0.7485–0.8554], indicating a fairly accurate predictive ability (Figure 2).

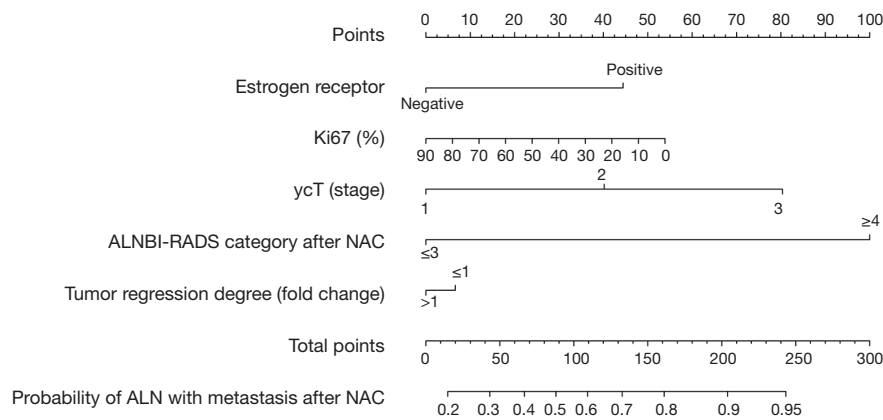
Bootstrapping is a form of internal validation which involves repeatedly applying the model to randomly selected sample sets from the original cohort. By using a calibration plot with bootstrap sampling (n=1,000), we internally calibrated the performance of the nomogram (Figure 3) and found good agreement between the bias-corrected prediction and the ideal reference line. This indicated that the nomogram performed well.

Decision curve analysis (DCA) (15) was used to determine the clinical validity of the nomogram in our cohort. Because the range of threshold probabilities were wide, the results indicated a good clinical applicability of the model in predicting the probability of ALN with metastasis after NAC (Figure 4).

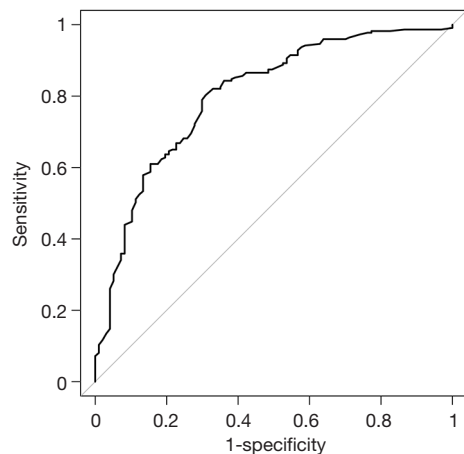
The enrolled population had varying ALN status before NAC. To explore the value of the nomogram in different groups, the population was divided into two groups: cN1 and cN0. The ROC curve for the cN1 group was illustrated in Figure 5A with an AUC of 0.7926 (95% CI, 0.7187–0.8665) and calibration plots for the cN1 was shown in Figure 5B. Figure 6A shows the ROC curve for the cN0 group, with an AUC of 0.8165 (95% CI, 0.7381–0.8949), and Figure 6B describes calibration plots for the cN0. These results indicate substantial predictive power of the nomogram as well as good agreement between the actual and expected outcomes.

### Discussion

NAC is commonly used for breast cancer patients with local advanced cancer or patients with larger primary tumors who desire breast-conserving surgery. After several cycles of NAC, some patients experience tumor reduction with positive lymph nodes becoming negative. NAC also acts as a chemo-sensitivity test *in vivo*, guiding doctors in choosing appropriate therapy regimens. Patients whose tumors are unresponsive to NAC should have their chemotherapy



**Figure 1** Nomogram for predicting the probability of ALN with metastasis after NAC. ALN, axillary lymph node; NAC, neoadjuvant chemotherapy; BI-RADS, Breast Imaging-Reporting and Data System.

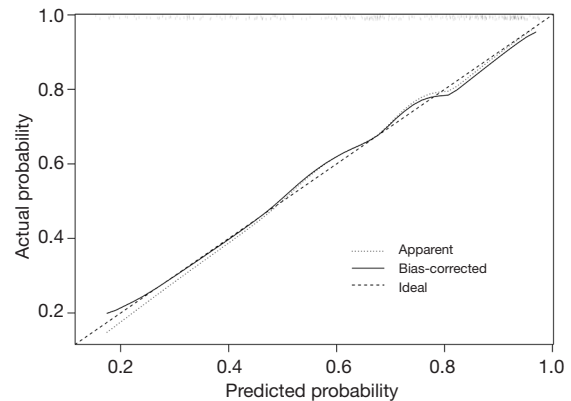


**Figure 2** Discrimination plot. The AUC for the ROC was 0.802 (95% CI, 0.7485–0.8554). AUC, area under the curve; ROC, receiver operating characteristic; CI, confidence interval.

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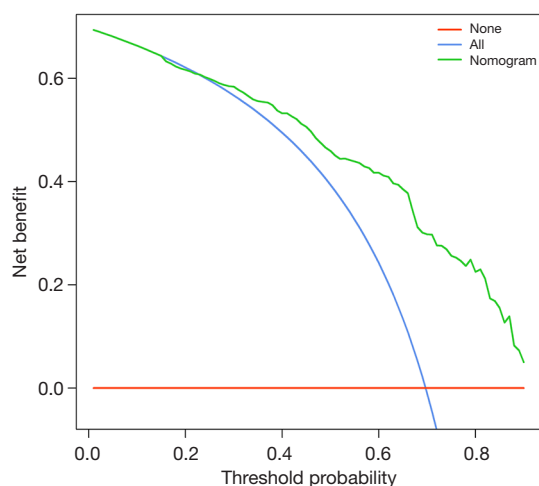
According to the NCCN guidelines, SLNB can be performed in cN0 patients after neoadjuvant systemic therapy. In cN1 patients, axilla may be restaged after neoadjuvant systemic therapy. When ALNs are clinically positive, ALND should be performed. When ALN are clinically negative, ALND or SLNB can be performed. However, SLNB remains controversial.

Some patients with initial ALNM confirmed by core needle biopsy may progress to metastasis-free lymph nodes following NAC. A meta-analysis revealed a pCR rate of 36.8% (95% CI, 34.2–39.5%) (16). ALN pCR is



**Figure 3** Calibration plot of the nomogram predicting the probability of ALN with metastasis after NAC. The X-axis and Y-axis indicate the predicted and actual probability of ALN with metastasis after NAC, respectively. A perfect prediction would correspond to a slope of 1. ALN, axillary lymph node; NAC, neoadjuvant chemotherapy.

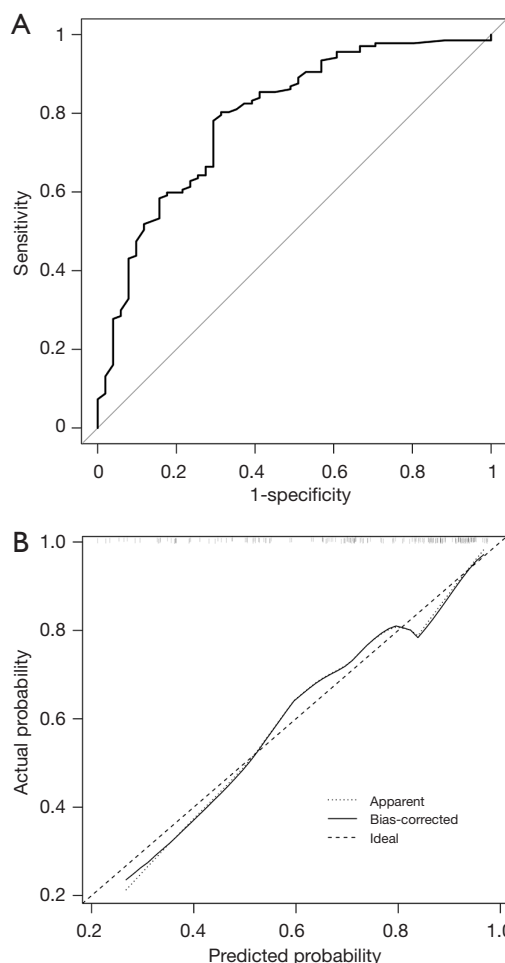
a well-known predictor of disease-free survival, allowing patients to safely avoid ALND (17). The traditional surgery method is ALND, which may result in side effects such as lymphedema, upper limb numbness, arm pain, limited arm movement, and difficulty handling liquid gathering in the armpit. There is insufficient evidence to recommend SLNB for patients following NAC treatment (18), as lymphatic drainage could be disturbed, making the sentinel lymph node difficult to find. Importantly, tumor cells throughout the axilla may react to NAC differently, with some ALNs responding well and reaching pCR, and others remaining



**Figure 4** DCA for nomogram-predicted probabilities of ALNM in our cohort. Theoretical results for all patients with negative ALN or with positive ALN after NAC are represented by red and blue lines, respectively. The green line indicates the net benefit of using the nomogram. DCA, decision curve analysis; ALNM, axillary lymph node metastasis; ALN, axillary lymph node; NAC, neoadjuvant chemotherapy; ycT, clinical T stage after NAC.

positive for tumor cells (19-22), leading to unacceptable false-negative rates (FNRs). In several studies assessing the identification rate (IR) and FNR of SLNB after NAC, the FNR range was 9–33%, while the IR range was 86.7–100% (23-27). In a meta-analysis, IR range was 78–95%, while the FNR range was 5–25% for breast cancer patients with clinically positive nodes after NAC (19). Although some authors have suggested the use of clipping the nodes at the point of initial biopsy for identification after NAC and before surgery. However, modeling with limited data to predict lymph node status after NAC may not only improve accuracy but also minimize patient suffering. In view of the high pCR rate of lymph nodes after NAC, and the inevitable FNR of SLNB, we combined clinical pathological factors and other predictors into a nomogram to evaluate the status of ALN after NAC, and then filtered a group of patients receiving SLNB to show its confidence.

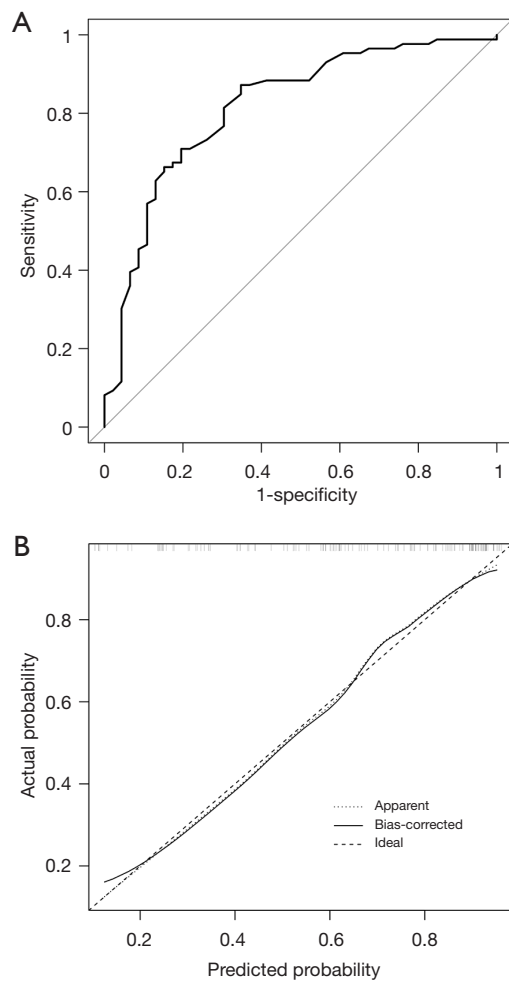
We developed a nomogram based on the clinical and pathological parameters of primary tumors to evaluate ALN status in breast cancer patients following NAC treatment. Tumor characteristics of 320 patients who underwent NAC were analyzed. Only ER, ycT, and ALN BI-RADS category after NAC were identified as independent predictors of ALNM through multivariate logistic regression analysis.



**Figure 5** Validation of the nomogram in the cN1 group. (A) Internal validation in the cN1 group. The AUC of the ROC was 0.7926 (95% CI, 0.7187–0.8665); (B) calibration plot in the cN1 group. AUC, area under the curve; ROC, receiver operating characteristic; CI, confidence interval.

Interestingly, Ki67 was a meaningful factor in univariate analysis, but not after multivariate analysis. Tumor regression degree of primary tumors and Ki67 reflect the response to NAC (11-14); therefore, we included these in our nomogram. The resulting nomogram showed a discriminative ability for AUC of 0.802 (95% CI, 0.7485–0.8554). DCA also showed a favorable predictive profile for evaluating ALN status after NAC, providing a more precise and individualized prediction.

Several previous nomograms have been developed for breast cancer patients receiving NAC (28-31), including ER, PR, HER2, Ki67, age, histology grade, initial clinical



**Figure 6** Validation of the nomogram in the cN0 group. (A) Internal validation in the cN0 group. The AUC for the ROC was 0.8165 (95% CI, 0.7381–0.8949); (B) calibration plot in the cN0 group. AUC, area under the curve; ROC, receiver operating characteristic; CI, confidence interval.

T stage, and number of courses as covariates. For our nomogram, we considered ER and Ki67, as well as the less frequently considered ycT, tumor regression degree, and ALN BI-RADS category after NAC. In our statistical analysis, ycT ( $P=0.005$ ) and ALN BI-RADS category after NAC ( $P<0.001$ ) showed strong significance, and our nomogram had an AUC of 0.802, which is higher than most existing models. Additionally, the subgroup internal validation of our model in both the cN1 group and cN0 group showed good results.

Despite the good performance of our model, additional steps are needed to enhance the predictive ability. According

to the NCCN guidelines, the FNR for SLNB is reduced by using dual tracer or by removing two or more sentinel nodes for patients confirmed to be node-positive before NAC (7). Previous studies have subdivided their population into two groups, comparing those with only one sentinel lymph node removed versus those patients with two or more sentinel lymph nodes removed during the operation (32-35). Subgroup analysis showed that the FNR was significantly improved if two or more sentinel nodes were removed versus only one, with a pooled FNR of 10.4% and 23.9%, respectively ( $P=0.026$ ) (16). After enrolling 756 patients who received NAC, Boughey *et al.* reported that mapping techniques were the only factors influencing SLN identification. By comparing blue dye alone with blue dye plus radio-labelled colloid, the SLN IR improved from 78.6% to 93.8% ( $P=0.006$ ), indicating that optimal tracer use is important for enhancing the IR (36). Our nomogram could be used in addition to this, by classifying patients into several groups with different probabilities of ALNM. For patients suitable for SLNB, future work should focus on screening for patients with different risks of ALNM to receive diverse tracer agents.

There are several limitations in our study. First, it was a single-center analysis, and validation by an external database may improve the model's performance. We searched several existing public databases but were unable to find a suitable database that included all our target predictors (ER, ycT, ALN BI-RADS category after NAC, Ki67, tumor regression degree). Second, due to the limited data of patients treated with NAC in the single institution, there may be other significant factors related to ALNM that were not included in our nomogram. Third, for HER2+ patients in our cohort, only a small portion received anti-HER2-therapy. Whether NAC regimen affects the status of ALN after NAC is worthy of further discussion, and more patients who received anti-HER2-therapy should be included in future studies. Finally, obtaining all our data from a single institution might have led to selection bias. Consequently, we need to assemble a multicenter database of patient data to optimize and validate the nomogram in the future.

## Conclusions

In conclusion, the present study identified five predictors to construct a nomogram which predicts ALN status after receiving NAC, regardless of the initial status of ALN in



breast cancer patients. This may assist in determining the best option for patients in relation to axillary surgery after NAC.

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### Footnote

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*Conflicts of Interest:* All authors have completed the ICMJE uniform disclosure form (available at <http://dx.doi.org/10.21037/tcr-20-2377>). 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). The study was approved by the Ethical Committee of The First Hospital of China Medical University (2019-72-2), and informed consent was taken from all the patients.

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