Nomogram for predicting axillary lymph node pathological response in node-positive breast cancer patients after neoadjuvant chemotherapy

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Abstract

Background: Pathological complete response (pCR) of axillary lymph nodes (ALNs) is frequently achieved in patients with clinically node-positive breast cancer after neoadjuvant chemotherapy (NAC), and ALN status is an important prognostic factor for breast cancer patients. This study aims to develop a new predictive clinical model to assess the ALN pCR rate after NAC.

Methods: This was a retrospective series of 467 patients who had biopsy-proven positive ALNs at diagnosis and underwent ALN dissection from 2007 to 2014 at the National Cancer Center/Cancer Hospital of the Chinese Academy of Medical Sciences. We analyzed the clinicopathologic features of the patients and developed a nomogram to predict the probability of ALN pCR. A multivariable logistic regression stepwise model was used to construct a nomogram to predict ALN pCR in node-positive patients. The adjusted area under the receiver operating characteristic curve (AUC) was calculated to quantify the ability to rank patients by risk. Internal validation was performed using the 50/50 hold-out validation method. The nomogram was externally validated with prospective cohorts of 167 patients from 2016 to 2018 at the Cancer Hospital of the Chinese Academy of Medical Sciences and 114 patients from 2018 to 2020 at Beijing Tiantan Hospital.

Results: In this retrospective study, 115 (24.6%) patients achieved ALN pCR after NAC. Multivariate analysis showed that clinical tumor stage (Odds ratio [OR]: 0.321, 95% confidence interval [CI]: 0.121–0.856; $P = 0.023$); primary tumor response (OR: 0.189; 95% CI: 0.123–0.292; $P < 0.001$), and estrogen receptor status (OR: 0.530, 95% CI: 0.304–0.925; $P = 0.025$) were independent predictors of ALN pCR. The nomogram was constructed based on the result of multivariate analysis. In the internal validation of performance of nomogram, the AUCs for the training and test sets were 0.719 and 0.753, respectively. The nomogram was validated in external cohorts with AUCs of 0.720, which demonstrated good discriminatory power in these data sets.

Conclusion: We developed a nomogram to predict the likelihood of axillary pCR in node-positive breast cancer patients after NAC. The predictive model performed well in multicenter prospective external validation. This practical tool could provide information to surgeons regarding whether to perform additional ALN dissection after NAC.

Trial registration: ChiCTR.org.cn, ChiCTR1800014968.

Keywords: Breast cancer; Neoadjuvant chemotherapy; Lymph node; Pathological response; Nomogram

Introduction

Neoadjuvant chemotherapy (NAC) reduces the tumor burden in breast cancer patients and has been increasingly used in patients with axillary lymph node (ALN) metastasis.[1,2] Currently, axillary lymph node dissection (ALND) is still recommended for most patients who are biopsy-proven to be ALN positive.[3] In patients with advanced and ALN-positive breast cancer, the pathological complete response (pCR) rate of the primary tumor is 24% to 46% and that of ALNs is 30% to 49%.[4,5] Hypothetically, ALND can be avoided in patients with axillary complete response (CR), and the number of patients afflicted with complications such as lymphedema and arm pain can be decreased.

Sentinel lymph node biopsy (SLNB) can be used to evaluate axillary staging.[6-9] However, performing SLNB in patients who have received NAC is still a controversial issue. ALND is the standard axillary management for patients after NAC. The ACOSOG Z1071 study reported a false negative rate

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(FNR) for SLNB of 12.6% when more than two sentinel lymph nodes (SLNs) were examined, which exceeded the acceptable cutoff value of 10%.[10] The SNFNAC study reported an identification rate (IR) of 87.6% and an FNR of 8.4% in patients with node-positive breast cancer after NAC.[7] The accurate prediction of achieving axillary response after NAC is important in establishing a treatment plan for patients with node-positive breast cancer. Therefore, in the present study, we sought to identify possible predictors and construct a nomogram for predicting pCR of ALNs after NAC in biopsy-proven node-positive breast cancer patients, which will increase the accuracy of SLNB after NAC. Combining SLNB and the nomogram prediction, patients with a high likelihood of ALN pCR can avoid ALND.

Methods

Ethical approval

This study was conducted in accordance with the *Declaration of Helsinki* and was approved by the Ethics Committee of Cancer Hospital, Chinese Academy of Medical Sciences (No. 2016-4-4026). The requirement for informed consent was waived due to the retrospective nature of the study. The patients recruited to the prospective cohort were required to sign the study consent form before the surgery date.

Participants and study design

Eligible patients who had biopsy-proven positive ALNs at diagnosis and underwent ALND at the National Cancer Center/Cancer Hospital of the Chinese Academy of Medical Sciences (CHCAMS) between January 1, 2007 and September 30, 2014 were included in the retrospective study. The inclusion criteria for retrospective series involved the following: (1) histologically confirmed primary invasive breast cancer; (2) ALN metastases diagnosed by fine-needle aspiration (FNA); (3) treatment with NAC before surgery; and (4) ALND after NAC. The exclusion criteria included (1) patients with distant metastases, (2) patients with negative ALNs before NAC, and (3) patients lack of clinicopathological information.

The nomogram was validated externally with two prospective cohorts: 167 patients at CHCAMS between May 1, 2016, and January 31, 2018, and 114 patients at Beijing Tiantan Hospital (BTH), Capital Medical University from January 1, 2018, to December 30, 2020. The inclusion criteria were as the following: (1) histologically confirmed primary invasive breast cancer; (2) ALN metastases confirmed by FNA or core needle biopsy (CNB); (3) treatment with NAC before surgery; (4) received ALND with at least ten nodes examined after NAC; and (5) received pathological assessment at our institution. The exclusion criteria included (1) patients with distant metastases; (2) patients with negative ALNs before NAC; (3) incomplete NAC treatment before surgery; and (4) patients received SLNB after NAC.

Treatment

Standard NAC regimens containing anthracyclines and taxanes were given according to the guidelines or ongoing protocols. Anthracycline-based and/or taxane-based NCT regimens were used every 3 weeks. Trastuzumab was added to taxane-based chemotherapy for patients with human epidermal growth factor receptor 2 (HER2)-overexpressing cancer. Pertuzumab was applied in patients with HER2-overexpressing cancer after January 1, 2020. Altered or interrupted treatment was recorded along with the reason for disruption. All patients underwent either breast-conserving surgery or mastectomy followed by a standard ALND of levels I and II.

Clinical staging, ultrasonography (US), and mammography before and after NAC were performed. Tumor node metastasis classification was based on the American Joint Committee on Cancer Cancer Staging Manual, 7th Edition.[11] Clinical response of primary tumor was assessed by US according to the Response Evaluation Criteria in Solid Tumors guidelines.[12] CR was defined as the absence of evidence of a palpable tumor in the breast and/or no visible tumor after NAC. Partial response was defined as at least a 30% decrease in the size of the lesion(s). Progressive disease (PD) was defined as a 20% increase in the size of the lesion(s). Stable disease was indicated when neither the PR nor PD criteria were met.

Pathologic evaluation

The original blocks of CNB and surgical specimens were stained for estrogen receptor (ER), progesterone receptor (PR), and HER2 antigens. Immunohistochemical staining positivity for ER and PR was defined as 1% or more nuclear staining. HER2 assessment was performed according to the guidelines of the American Society of Clinical Oncology (ASCO) and the College of American Pathologists (CAP). Pathologic response was assessed after the completion of NAC using the Miller-Payne grading system.[13] Surgical specimens with no histological evidence of invasive carcinoma in the breast or metastatic carcinoma cells in removed lymph nodes were classified as pCR.

Statistical analysis and nomogram establishment

Descriptive analysis was performed for the clinicopathologic features of the patients. Groups were compared by Student's *t* test for continuous data, the Pearson chi-squared test for categorical variables, and the Mann-Whitney *U* test for grading variables. Univariable analysis was performed using a logistic regression model. A multivariable logistic regression stepwise model was used to generate a nomogram to predict ALN pCR in node-positive patients. The internal validation was performed by a calibration method, and the adjusted area under the receiver operating characteristic curve (AUC) was calculated to quantify the ability to rank patients by risk. Internal validation was estimated using the 50/50 hold-out validation method. The nomogram was validated externally with the prospective cohort. Statistical analysis was performed using SPSS, version 22.0 (SPSS Inc., Chicago, IL, USA) and R version 3.5.3 (R Foundation, Vienna, Austria). The related R packages used in the construction and assessment of the nomogram included the "rms," "glmnet," "Hmisc," "generalhoslem," "ggplot2," and "Dca.R" pack-

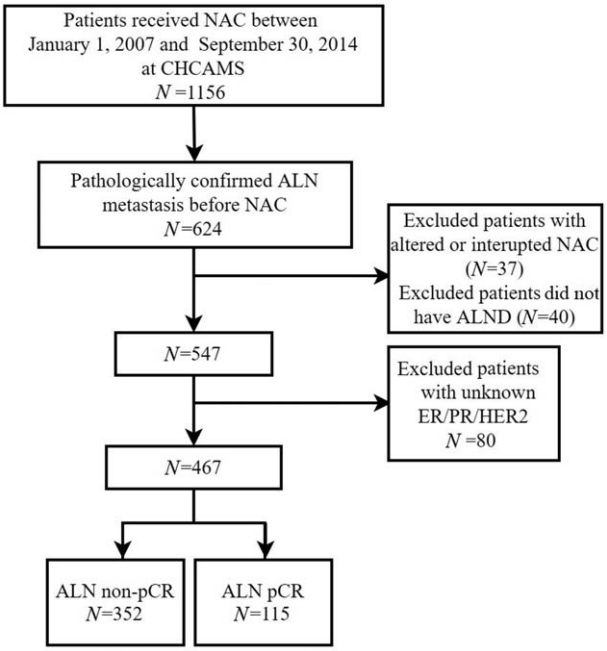

Figure 1: Flow diagram of the study design. ALN: Axillary lymph node; ALND: Axillary lymph node dissection; CHCAMS: Cancer Hospital of Chinese Academy of Medical Sciences; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; NAC: Neoadjuvant chemotherapy; PR: Partial response; pCR: Pathological complete response.

ages. All tests were two-sided, and $P \leq 0.05$ indicated statistical significance.

Results

Patient characteristics of retrospective series

A total number of 547 patients had positive ALNs and underwent ALND at CHCAMS between January 1, 2007, and September 30, 2014. Patients with missing data were excluded. Four hundred and sixty-seven patients were finally involved [Figure 1]. The median age of the patients was 52 years (range 24–75 years). A total of 115 (24.6%) patients achieved ALN pCR after NAC. The demographic and pathological features of the patients are summarized in Table 1.

Table 1: Demographic and clinicopathologic characteristics of the patients who had positive ALNs and underwent ALND.

Variable	ALN non-pCR ($n = 352$)	ALN pCR ($n = 115$)	χ^2	*P* value
Age, years	52.31 ± 0.49	52.13 ± 0.66	–	0.834
Pathological type			0.022	0.969
IDC	349 (99.1)	114 (99.1)		
Others*	3 (0.9)	1 (0.9)		
Clinical T stage			1.053	0.778
T1	8 (2.3)	1 (0.9)		
T2	150 (42.6)	50 (43.4)		
T3	118 (33.5)	38 (33.4)		
T4	76 (21.5)	26 (22.6)		
Primary tumor response			18.150	<0.001
PR and SD	309 (87.8)	83 (72.2)		
CR	43 (12.2)	32 (27.8)		
Histological grade			4.236	0.360
I	5 (1.4)	3 (2.6)		
II	239 (67.9)	90 (78.3)		
III	108 (30.7)	22 (19.1)		
ER			9.829	0.002
Negative	119 (33.8)	58 (50.4)		
Positive	233 (66.2)	57 (49.6)		
PR			4.152	0.042
Negative	131 (37.2)	56 (48.7)		
Positive	221 (62.8)	59 (51.3)		
HER2			0.656	0.418
Negative	243 (69.0)	90 (78.2)		
Positive	109 (30.9)	25 (21.7)		

Data are presented as mean ± standard deviation and *n* (%). *Others, invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma. ALN: Axillary lymph node; CR: Complete response; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; Clinical T stage: Clinical tumor stage; PR: Partial response; PR: Progesterone receptor; pCR: Pathological complete response; SD: Stable disease.

Factors associated with ALN pCR

In univariable analysis, clinical T stage, primary tumor response, ER, and PR status were significantly associated with the likelihood of ALN pCR (all $P < 0.05$) [Table 2]. In multivariable stepwise logistic regression analysis, clinical T stage (odds ratio [OR]:0.321, 95% confidence interval [CI]: 0.121–0.856; $P = 0.023$); primary tumor response (OR: 0.189; 95% CI: 0.123–0.292; $P < 0.001$); and ER status (OR: 0.530, 95% CI: 0.304–0.925; $P < 0.001$) were independent predictors of ALN pCR [Table 3].

Nomogram

A multivariable logistic regression nomogram was developed using variables including age, clinical T stage, pathological type, histological grade, primary tumor response, ER, PR, and HER2 status [Figure 2]. The total sum for each variable is located on the "total points" line, and a line can be drawn downward to calculate the probability of axillary pCR. The *P* value for the Hosmer and Lemeshow test was 0.693, indicting a good fit to the model. The calibration of the nomogram was performed internally by a calibration plot with bootstrap sampling, which indicated that the nomogram was well calibrated [Figure 3].

A total of 467 patients were randomly divided into training set and test set. The clinicopathologic characteristics of training set and test set are shown in Supplementary Table 1, http://links.lww.com/CM9/A834. The receiver operating characteristic was performed to validate the nomogram internally in the training set. In the internal validation of the model performance, the AUCs for the training and test sets were 0.719 (95% CI: 0.638–0.771) and 0.753 (95% CI: 0.704–0.791), respectively, demonstrating that the nomogram provides precise predictions of ALN pathological response after NAC [Figure 4].

Table 2: Univariable analysis of ALN pCR in the retrospective patient series.

Variable	OR	95% CI	*P* value
Age*	0.39	0.203–1.996	0.867
Pathological type			
IDC	1		
Others†	1.184	0.105–13.33	0.891
Clinical T stage			
T1	1		
T2	0.449	0.180–1.119	0.085
T3	0.552	0.220–1.384	0.205
T4	0.321	0.120–0.854	0.023
Primary tumor response			
PR and SD	1		
CR	1.082	1.011–1.158	0.023
Histological grade			
I	1		
II	1.216	0.704–1.747	0.801
III	1.585	0.523–2.027	0.665
ER			
Negative	1		
Positive	0.554	0.287–0.807	<0.001
PR			
Negative	1		
Positive	0.568	0.296–0.890	0.039
HER2			
Negative	1		
Positive	1.215	0.649–2.410	0.052

*Continuous variables. †Others, invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma. ALN: Axillary lymph node; CR: Complete response; CI: Confidence interval; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; Clinical T stage: Clinical tumor stage; OR: Odds ratio; PR: Partial response; PR: Progesterone receptor; pCR: Pathological complete response; SD: Stable disease.

External validation

The prospective series included 281 patients with positive LNs before NAC who were enrolled for the external validation of the nomogram. Of these patients, 167 were from CHCAMS, and 114 were from BTH; the age were 45.7 ± 4.76 and 53.7 ± 3.92 years, respectively. In the CHCAMS series, 71 patients (42.5%) had breast tumor CR, and 62 patients (37.1%) had ALN pCR. In the BTH validation group, 42 patients (36.8%) had breast tumor CR, and 46 patients (40.3%) had ALN pCR [Table 4]. When the nomogram was applied to the prospective series, the AUCs were 0.720 (95% CI: 0.684–0.731) [Figure 5], which showed that the nomogram had good discriminatory power in the external validation data sets.

Discussion

The surgical management of axillary tissue after NAC is closely related to the pathological response. With the development of chemotherapy regimens and targeted anti-HER2 treatment, the primary tumor and axillary pCR rates have increased substantially.[14] Since the application of SLNB after NAC for assessing axillary status, the standard treatment of ALND may be omitted in axillary pCR patients after accurate identification. Building on the present research, we constructed a nomogram to predict ALN pCR in node-positive patients after NAC. To avoid bias, we used cohorts from separate comprehensive institutions. In this study, we established a registered prospective database and used the data collected in that database to construct a nomogram for predicting axillary pCR after NAC. We also enrolled two prospective series from different centers to validate the accuracy of the nomogram.

We retrospectively analyzed 467 patients with biopsy-proven ALN positive breast cancer. Among them, 115 (24.6%) patients achieved axillary pCR, which is slightly lower than the results reported in the studies of Gonzalez-Angulo *et al*[15]and Kida *et al*[16]. Based on the multivari-

Table 3: Multivariate logistic regression analysis of factors for ALN pCR in the retrospective series.

Variable	Coefficient	SE	Wald	OR (95% CI)	*P* value
Age*	−0.391	0.205	3.647	0.677 (0.453–1.010)	0.056
Clinical T stage					
T2	−0.804	0.466	2.975	0.447 (0.179–1.116)	0.085
T3	−0.598	0.470	1.622	0.550 (0.219–1.381)	0.203
T4	−1.135	0.500	5.153	0.321 (0.121–0.856)	0.023
Pathological type Others†	−0.292	0.515	0.322	0.747 (0.272–2.049)	0.570
Histologic grade					
II	−0.180	0.629	0.082	1.106 (0.444–1.174)	0.775
III	0.029	0.244	1.302	1.114 (0.658–1.710)	0.254
Primary tumor response CR	−1.762	0.231	58.150	0.189 (0.123–0.292)	<0.001
ER positive	−0.635	0.284	4.991	0.530 (0.304–0.925)	0.025
PR positive	−0.031	0.284	0.012	0.970 (0.555–1.694)	0.915
HER2 positive	0.331	0.231	2.047	1.392 (0.885–2.189)	0.153

*Continuous variables. †Others, invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma. CR: Complete response; CI: Confidence interval; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; OR: Odds ratio; Clinical T stage: Clinical tumor stage; PR: Progesterone receptor; pCR: Pathological complete response; SE: Standard error.

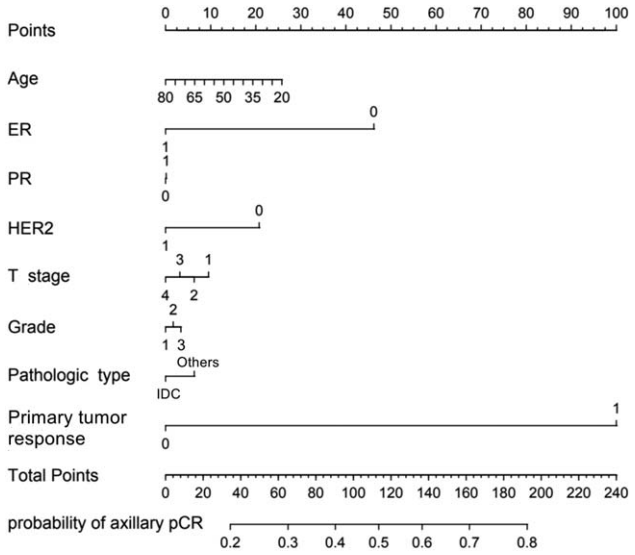

Figure 2: Nomogram to predict ALN pCR in patients with positive lymph nodes before NAC. ALN: Axillary lymph node; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; NAC: Neoadjuvant chemotherapy; PR: Partial response; pCR: Pathological complete response.

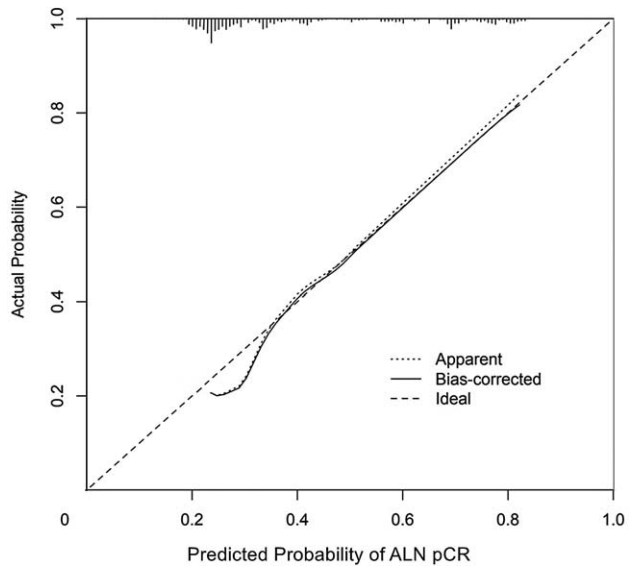

Figure 3: Calibration plot of the nomogram for the probability of ALN pCR. ALN: Axillary lymph node; pCR: Pathological complete response.

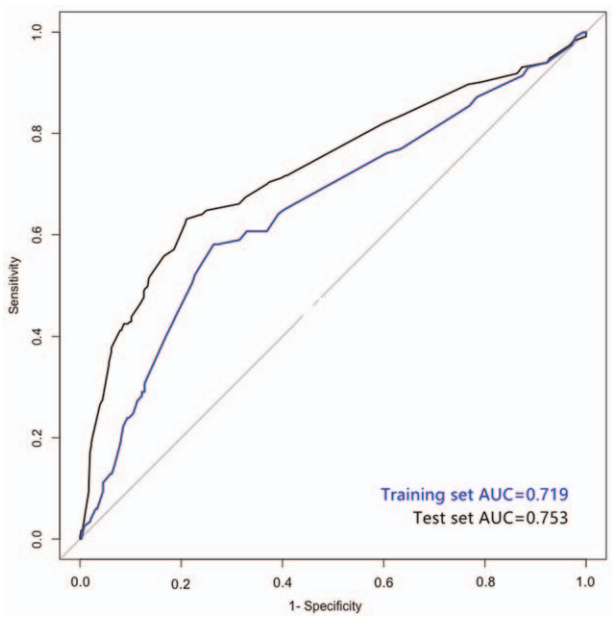

Figure 4: ROC curve for the nomogram in the training and testing sets; the AUCs were 0.719 and 0.753, respectively. AUCs: Area under the receiver operating characteristic curve; ROC: Receiver operating characteristic.

able analysis, we found that clinical T stage, primary tumor response, and ER status were significant independent predictors for axillary pCR ($P < 0.05$). Recent studies indicated that biological subtype was also associated with pCR. Based on the data from the Z1071 trial, Boughey *et al*[17] found that the pCR rate was 21.1% in hormone receptor (HR)+/HER2− patients, but in HR−/HER2− patients, it was 49.4% ($P < 0.0001$). In our study, ER-negative patients were the most likely to achieve pCR, which was consistent with the finding of a previous study. However, we found that HER2 was not a significant factor for predicting ALN pCR, which may be different with other studies.[9] We suggested that it might be associated with the changing guideline of HER2 testing recommendation released in 2007, 2013, and 2018 by ASCO/CAP.[18,19] Previous studies indicated that the positive and equivocal cases increased under the 2013 and 2018 guidelines.[20,21] In our study, the proportion of HER2 overexpressing in internal group was lower than external group (28.7% *vs*. 41.3%). In our study, the proportion of primary tumor response and axillary pCR in external cohort was higher than in retrospective series (34.5% *vs*. 24.5% and 29.9% *vs*. 16.1%, respectively). This result indicated that the improvement of NAC efficacy in recent years.

Nomograms are used as a prediction tool to provide individualized estimates of risk.[22,23] Nomograms are concise and powerful for predicting ALN pCR, which could help to assess the actual ALN status and increase the accuracy of SLNB. Building on the present research, we constructed a nomogram to predict ALN pCR in node-positive patients after NAC. To avoid bias, we used separate comprehensive institutions. Some researchers have also evaluated nomograms for predicting axillary status in patients with breast cancer.[9,24] The result of SENTINA showed that in patients whose axillaries were downstaged to cN0 after NAC, the IR was 80.1%, and the FNR was 14.2%.[25] The ACOSOG Z1071 study reported an FNR for SLNB of 12.6% when more than two SLNs were examined, which exceeded the acceptable cutoff value of 10%.[26,27] Based on our nomogram, patients with high scores were more likely to show ALN pCR. Combined with imaging tests, patients could safely avoid undergoing ALN dissection.[28] The evaluation of ALNs offers prognostic information about breast cancer. Recent studies have shown that no residual invasive cancer in the breast and ALN can indicate a better outcome.[29-31] Among patients with cytologically proven ALN metasta-

Table 4: Characteristics of the patients in internal and external validation groups.

Variable	Internal validation group ($N = 467$)	Patients from CHCAMS ($n = 167$)	Patients from BTH ($n = 114$)	χ^2	*P* value
Age, years	51.2 ± 0.39	56.4 ± 0.38	47.2 ± 0.82		
Clinical T stage				34.200	0.002
T1	9 (1.9)	7 (4.2)	10 (8.7)		
T2	200 (42.8)	69 (41.3)	64 (56.1)		
T3	156 (33.8)	74 (44.3)	29 (25.4)		
T4	102 (21.8)	17 (10.2)	11 (9.6)		
Pathological type				0.519	0.771
IDC	449 (96.0)	161 (96.4)	111 (97.4)		
Others*	18 (4.0)	6 (3.6)	3 (2.6)		
Histologic grade				9.304	0.050
I	7 (1.5)	9 (5.7)	10 (8.7)		
II	329 (70.5)	98 (58.8)	65 (57.1)		
III	131 (28.1)	60 (35.5)	39 (34.2)		
Primary tumor response				20.160	<0.001
PR + SD	392 (83.9)	116 (69.5)	81 (71.1)		
CR	75 (16.1)	51 (30.5)	33 (28.9)		
Axillary response				10.130	0.006
Non-pCR	352 (75.4)	105 (62.9)	79 (69.3)		
pCR	115 (24.6)	62 (37.1)	35 (30.7)		
ER				0.023	0.981
Negative	177 (37.9)	63 (37.7)	42 (36.8)		
Positive	290 (62.1)	104 (62.3)	72 (63.2)		
PR				0.089	0.965
Negative	187 (40.0)	65 (38.9)	44 (38.6)		
Positive	280 (60.0)	102 (61.1)	70 (61.4)		
HER2				7.064	0.030
Negative	333 (71.3)	100 (59.9)	65 (57.0)		
Positive	134 (28.7)	67 (40.1)	49 (43.0)		

Data are presented as mean ± standard deviation and *n* (%). * Others, invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma. ALN: Axillary lymph node; BTH: Beijing Tiantan Hospital Affiliated to Capital Medical University; CHCAMS: Cancer Hospital of Chinese Academy of Medical Sciences; CR: Complete response; ER: Estrogen receptor; HER2: Human epidermal growth factor receptor 2; IDC: Invasive ductal carcinoma; Clinical T stage: Clinical tumor stage; PR: Partial response; pCR: Pathological complete response; PR: Progesterone receptor; SD: Stable disease.

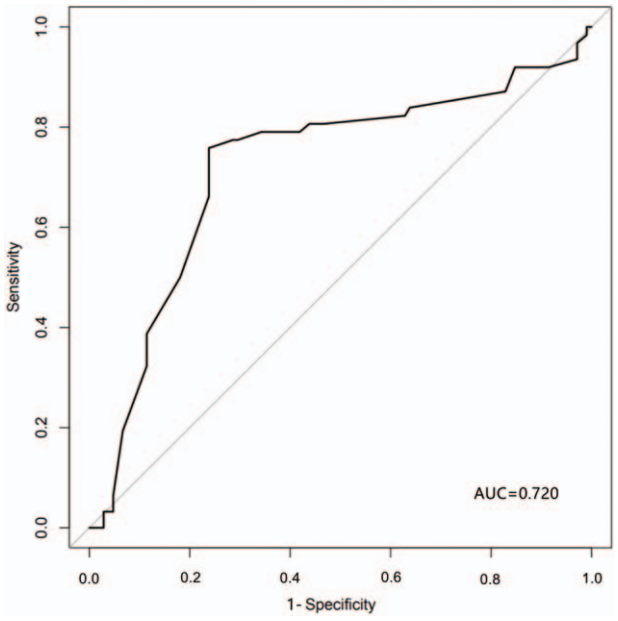

Figure 5: ROC curves for the discrimination of the external validation sets. The AUCs were the AUCs were 0.720 (95% CI: 0.674–0.731). AUCs: Area under the receiver operating characteristic curve; CI: Confidence interval; ROC; Receiver operating characteristic.

ses, survival was improved in patients who achieved ALN pCR.[29,32] The nomogram may also be helpful in communications between patients and oncologists.

Our study has some limitations. The retrospective data may have selection bias since patients who were monitored until 2007 were included. Additionally, chemotherapy might be a confounding factor because patients from different hospitals were not given homogeneous NAC, and baseline characteristics of patients from two different centers also had bias. The improvement of NAC regimens also influences the efficacy. Before 2020, trastuzumab was added to anti-HER2 regiments in this study while pertuzumab has not been applied in retrospective series, the LN pCR rate of HER2 overexpressing patients was not significantly higher than HER2 negative groups. Also, previous studies indicated that Ki67 index and tumor-infiltrating lymphocytes were relevant to pCR.[33,34] However, we did not include Ki67 index as an indicator because there were missing values for Ki67 staining in retrospective study. And in external valid cohort, the laboratory of each center establishes its own optimal value. In addition, the National Comprehensive Cancer Network guidelines have incorporated the comment that marking biopsied lymph nodes to document their removal can

decrease the FNR of SLNs after NAC. However, removing ALNs at initial percutaneous biopsy is still a challenge, and this procedure has not been established in China.

In conclusion, we constructed a nomogram, which included eight comprehensive predictors, with high discrimination and calibration for predicting post-NAC ALN pCR. With the nomogram, the post-NAC ALN status of a patient can be predicted accurately and precise surgery can be conducted for patients with a high probability of achieving axillary pCR.

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Conflicts of interest

The abstract of this manuscript was presented as part at 2019 ESMO BREAST conference. This conference was held by European Society Medical Oncology, and was held in Berlin, Germany, during May 2–4, 2019.

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