

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

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Keywords: Breast cancer, Neoadjuvant chemotherapy, Lymph node, Pathology response, Nomogram

Posted Date: April 8th, 2021

DOI: <https://doi.org/10.21203/rs.3.rs-398841/v1>

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Version of Record: A version of this preprint was published at Journal of Clinical Oncology on May 20th, 2019. See the published version at https://doi.org/10.1200/JCO.2019.37.15_suppl.e12090.

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. Our goal is to develop a new predictive clinical model to assess the axillary lymph node pCR rate after NAC.

Methods

A retrospective series of 547 patients who had biopsy-proven positive ALNs at diagnosis and undergoing axillary lymph node dissection from 2007 to 2014 in National Cancer Center/Cancer Hospital of Chinese Academy of Medical Sciences. We analyzed the clinicopathologic features and developed a nomogram to predict the probability of ALN pCR. Univariate assessment was performed using a logistic regression model. A multivariate logistic regression stepwise model was used to generate a nomogram to predict ALN pCR in node positive patients. Variables with $P < 0.05$ on multivariable analysis were included in the nomogram. 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 50–50 hold out validation method. Nomogram was validated externally with the prospective cohorts of 167 patients from 2016 to 2018 of Cancer Hospital of Chinese Academy of Medical Sciences and 75 patients from 2018 to 2019 of Beijing Tiantan hospital.

Results

In retrospective study, there were 172 (31.4%) patients achieved axillary pCR after NAC. Multivariate analysis indicated that clinical nodal (N) stage, estrogen receptor (ER) status and clinical response of primary tumor after NAC were significant independent predictors for axillary pCR ($P < 0.05$). The NAC nomogram was based on these three variables. In the internal validation of performance, 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 0.862 and 0.766, respectively, which demonstrated good discriminatory power in the external validation 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 ALND after NAC.

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]. Nowadays, axillary lymph node dissection (ALND) has still been recommended for most patients with biopsy-proven ALD positive [3]. In patients with advanced and ALN-positive breast cancer, the pathological complete response (pCR) rate of the primary tumor is 24–46% and that of the ALNs is 30–49% [4, 5]. Hypothetically, ALND can be avoided in patients with axillary complete response, 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, SLNB for 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 of SLNB at 12.6% when more than two sentinel lymph nodes were examined, which exceeded the acceptable cut-off value of 10% [10]. The SNFNAC study reported an identification rate of 87.6% and a false negative rate of 8.4% in patients with node-positive breast cancer after NAC [7]. 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 ALN after NAC among biopsy proven node positive breast cancer patients, which will increase the accuracy of SLNB after NAC. Combining SLNB and nomogram prediction, patients with high likelihood of lymph nodes pCR can avoid ALN dissection.

Methods

We performed a retrospective review of 547 patients who had biopsy-proven positive ALNs at diagnosis and undergoing axillary lymph node dissection from January 1, 2007 to September 30, 2014 in National Cancer Center/Cancer Hospital of Chinese Academy of Medical Sciences (CHCAMS). Our study population involved the following criteria: (i) histologically confirmed primary invasive breast carcinoma; (ii) ALNs metastases diagnosed by fine needle aspiration (FNA); (iii) treated with NAC before surgery; (iv) underwent ALN dissection after NAC. Exclusion criteria included: (i) patients with distant metastases; (ii) patients with negative ALNs before NAC. The retrospective series was used to develop a predictive nomogram. The nomogram was then validated externally with two prospective cohorts, 167 patients from May 1, 2016 to January 31, 2018 in National Cancer Center/Cancer Hospital of Chinese Academy of Medical Sciences, and 75 patients in Beijing Tiantan Hospital affiliated to Capital Medical University (BTH) from Jan 1st, 2018 to April 30th, 2019. The prospective trial (<http://www.chictr.org/cn/>, identifier ChiCTR1800014968) was approved by the institutional review board (IRB) of Cancer Hospital, Chinese Academy of Medical Sciences and IRB of Beijing Tiantan Hospital affiliated to Capital Medical University. The informed consent was waived in the retrospective study. Patients accrued to the prospective cohort were required to sign the study consent before the surgery date.

Clinical staging, ultrasonography and magnetic resonance imaging before and after NAC were performed. TNM classification was based on the AJCC Cancer Staging Manual, Eighth Edition. We also evaluated the MRI and US after NAC to assess the clinical response of primary tumors and ALNs. All patients received NAC and standard chemotherapy regimens containing anthracyclines and taxanes that were given according to the guidelines or within ongoing protocols. Trastuzumab was added to taxane-based chemotherapy for patients with human epidermal receptor 2 (HER2)-overexpressing cancer. Altered or interrupted treatment was recorded with the reason for disruption. All patients underwent either breast-conserving surgery (BCS) or mastectomy followed by a standard ALND of levels I and II.

Clinical response was assessed according to response evaluation criteria in solid tumors guidelines [11]. Complete response (CR) was defined as the absence of evidence of a palpable tumor in breast and/or no visible tumor on MRI or US after NAC. Partial response (PR) stands for at least 30% decrease in lesion(s). Progressive disease (PD) stands for 20% increase of lesions. Stable disease (SD) indicated that neither PR nor PD criteria were met. Pathologic response was assessed after completion of NAC using Miller-Payne Grading system [12]. Surgical specimens with no histological evidence of invasive carcinoma in the breast and of metastatic carcinoma cells in removed lymph nodes were classified as pCR.

The original blocks were stained for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) antigen. Immunohistochemical staining positivity for ER and PR was defined as 1% or more nuclear staining. The HER2 assessment was performed as per the guidelines of the American Society of Clinical Oncology and the College of American Pathologists. Samples were considered positive if they scored 3+ and negative if they scored 1+. For patients with a score of 2+, the samples were further assayed using fluorescence in situ hybridization and considered positive if the ratio of HER2 signal to centromeric probe for chromosome 17 (CEP17) was greater than 2.2 [13].

Descriptive analysis was performed for clinicopathological features of patients. Univariate assessment was performed using a logistic regression model. A multivariate logistic regression stepwise model was used to generate a nomogram to predict ALN pCR in node positive patients. Variables with $P < 0.05$ on multivariable analysis were included in the nomogram. 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 50–50 hold out validation method. Nomogram was validated externally with the prospective cohort of 167 patients. All tests were two-sided, and $P \leq 0.05$ indicated statistical significance. Statistical analysis was performed using SPSS, version 22.0 (SPSS Inc., Chicago, IL, U.S.) and R version 3.5.3 (R Foundation, Vienna, Austria). The related R packages were applied in construction and assessment of the nomogram, including 'rms', 'glmnet', 'Hmisc', 'generalhoslem', 'ggplot2' and 'Dca.R'.

Results

Patient characteristics

The baseline characteristics showed 547 patients had positive ALNs and underwent ALND (Table 1). The median age was 52 years (range 24–75 years). 172 (31.4%) patients achieved axillary lymph node pCR after NAC.

Table 1
Demographic and clinicopathologic characteristics of patients in the retrospective series

Variable	LNs non-pCR n = 375 (%)	LNs pCR n = 172 (%)	P value
Age			0.092
≤ 50	150 (40.0)	82 (47.7)	
> 50	225 (60.0)	90 (52.3)	
Pathological type			0.969
IDC	360 (96.0)	165 (95.9)	
Others*	15 (4.0)	7 (4.1)	
Clinical T stage			0.728
T1	8 (2.1)	6 (3.5)	
T2	165 (44.0)	72 (41.9)	
T3	122 (32.5)	60 (34.9)	
T4	80 (21.3)	34 (19.7)	
Clinical N stage			0.013
N1	291 (77.6)	149 (86.6)	
N2	84 (22.1)	23 (13.4)	
Primary tumor response			< 0.001
CR	60 (16.0)	83 (48.3)	
PR and SD	315 (84.0)	89 (51.7)	
Histological grade			0.865
I	13 (3.5)	6 (3.5)	
II	257 (68.5)	104 (60.5)	
III	105 (28.0)	62 (36.0)	
ER			0.002
Negative	119 (31.7)	58 (33.7)	
Positive	233 (62.1)	59 (34.3)	

*Others, invasive lobular carcinoma, papillary carcinoma, adenoid cystic carcinoma, mucinous carcinoma;

Variable	LNs non-pCR n = 375 (%)	LNs pCR n = 172 (%)	P value
Unknown	23 (6.2)	55 (32.0)	
PR			0.042
Negative	131 (34.9)	56 (32.5)	
Positive	221 (58.9)	61 (35.5)	
Unknown	23 (6.2)	55 (32.0)	
HER2			0.738
Negative	270 (72.0)	92 (53.5)	
Positive	80 (21.3)	25 (14.5)	
Unknown	25 (6.7)	55 (32.0)	

*Others, invasive lobular carcinoma, papillary carcinoma, adenoid cystic carcinoma, mucinous carcinoma;

On univariate analysis, clinical T stage, N stage, primary tumor response and estrogen receptor status were significantly associated with the likelihood of axillary lymph node pCR ($P < 0.05$, Table 2). On multivariate stepwise logistic regression analysis, clinical N stage ($P = 0.002$; odds ratio [OR], 2.408; 95% confidence interval [CI], 1.383–4.194), primary tumor response ($P < 0.001$; OR, 0.189; 95% CI, 0.123–0.292), and estrogen receptor status ($P = 0.025$; OR, 0.530, 95% CI, 0.304–0.925) were independent predictors of ALN pCR (Table 3).

Table 2
Univariates analysis of axillary lymph node pCR in the retrospective patient series

Variable	OR	95%CI	P value
Age			
≤ 50	1		
> 50	0.592	0.442 ~ 0.998	0.442
Pathological type			
IDC	1		
Others*	1.184	0.105 ~ 13.33	0.891
Clinical T stage			
T1	1		
T2	1.839	1.414~2.392	< 0.001
T3	3.437	2.674~4.417	< 0.001
T4	9.221	9.197~11.81	< 0.001
Clinical N stage			
N1	1		
N2	3.462	1.792 ~ 6.668	< 0.001
Primary tumor response			
CR	1		
PR and SD	1.082	1.011~1.158	0.023
Histological grade			
I	1		0.801
II	1.216	0.704 ~ 1.747	
III	1.585	0.52~2.03	
ER			
Negative	1		
Positive	0.554	0.287 ~ 0.807	< 0.001
PR			
Note: IDC, invasive ductal carcinoma; Clinical T stage, clinical tumor stage; Clinical N stage, clinical nodal stage; CR, complete response; PR, partial response; SD, stable disease; ER, estrogen receptor; PR, progesterone receptor; HER2, human epithelia growth factor receptor 2.			

Variable	OR	95%CI	P value
Negative	1		
Positive	0.568	0.296 ~ 0.890	0.039
Unknown	0.844	0.516 ~ 1.090	0.089
HER2			
Negative	1		
Positive	1.215	0.649 ~ 2.410	0.504
Unknown	0.347	0.125 ~ 1.442	0.81

Note: IDC, invasive ductal carcinoma; Clinical T stage, clinical tumor stage; Clinical N stage, clinical nodal stage; CR, complete response; PR, partial response; SD, stable disease; ER, estrogen receptor; PR, progesterone receptor; HER2, human epithelia growth factor receptor 2.

Table 3

Logistic regression analysis using backward stepwise likelihood ratio method in the retrospective patient 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					0.420
T1	0.533	0.658	0.655	1.704 (0.469–6.189)	
T2	-0.260	0.280	0.858	0.771 (0.445–1.336)	
T3	0.033	0.288	0.013	1.033 (0.587–1.819)	
Clinical N stage	0.879	0.283	9.639	2.408 (1.383–4.194)	0.002
Tumor type	-0.292	0.515	0.322	0.747 (0.272–2.049)	0.570
Histologic grade	-0.180	0.629	0.082	0.835 (0.444–1.174)	0.775
Primary tumor response	-1.762	0.231	58.15	0.189 (0.123–0.292)	< 0.001
ER	-0.635	0.284	4.991	0.530 (0.304–0.925)	0.025
PR	-0.031	0.284	0.012	0.970 (0.555–1.694)	0.915
HER2	0.331	0.231	2.047	1.392 (0.885–2.189)	0.153

Note: SE, standard error; CI, confidence interval; Clinical T stage, clinical tumor stage; Clinical N stage, clinical nodal stage; ER, estrogen receptor; PR, progesterone receptor; HER2, human epithelia growth factor receptor 2.

Table 4
Patients characteristics in External Validation Group

Variable	Patients of CHCAMS n = 167 (%)	Patients of BTB n = 74 (%)	Chi-square	P value
Age	45.7 ± 4.76	53.7 ± 3.92		
Tumor stage			15.46	0.002
cT1	7 (4.2)	8 (10.8)		
cT2	69 (41.3)	45 (60.8)		
cT3	74 (44.3)	16 (21.6)		
cT4	17 (10.2)	5 (6.8)		
N stage			0.11	0.916
cN1	105 (62.9)	46 (62.2)		
cN2	62 (37.1)	28 (37.8)		
Tumor Grade			2.05	0.359
I	9 (5.7)	2 (2.7)		
II	98 (58.8)	50 (67.6)		
III	60 (35.5)	22 (29.7)		
HR			0.284	0.594
Negative	63 (37.7)	31 (41.3)		
Positive	104 (62.3)	44 (58.7)		
HER2			9.000	0.003
Negative	100 (59.9)	59 (79.7)		
Positive	67 (40.1)	15 (20.3)		

Note: CHCAMS, Cancer Hospital of Chinese Academy of Medical Sciences; BTB, Beijing Tiantan Hospital affiliated to Capital Medical University; N stage, clinical nodal stage; HR, hormone receptor; HER2, human epidermal receptor 2.

Nomogram

A nomogram was developed using 4 variables: clinical T stage, clinical nodal stage, primary tumor response and HR (Figure 1). The total sum for each variable was located on a “total points” line, and a line was drawn downward to calculate the probability of axillary pCR. In the internal validation of 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 fairly precise predictions of ALN pathological response after NAC (Figure 2).

External Validation

The prospective series included 242 patients with positive LNs before NAC were obtained for external validation of the nomogram, 167 patients from Cancer Hospital, Chinese Academy of Medical Sciences (CHCAMS) and 75 patients from Beijing Tiantan Hospital (BTH). The median age was 45.7 ± 4.76 years and 53.7 ± 3.92 years, respectively. In CHCAMS series, 71 patients (42.5%) had breast tumor complete response and 62 patients (37.1%) had ALNs pathology complete response. While in BTH validation group, 19 patients (25.3%) had breast complete response and 42 patients (56.0%) had ALNs pathology complete response (Table 3). When the nomogram applied to the prospective series, the AUCs were 0.862 (95% CI 0.793-0.911) and 0.766 (95% CI 0.616-0.826), respectively (Figure 3), which demonstrated good discriminatory power in the external validation data sets.

Discussion

Surgical management of axillary after NAC is closely related to pathological response. With the development of chemotherapy regimen and targeted anti-HER2 treatment, the primary tumor and axillary pCR rates have increased substantially. Since the application of SLNB after NAC for assessing axillary status, the standard treatment ALND may be omitted in axillary pCR patients after accurately identified. Built on the present researches, we constructed a nomogram to predict ALN pCR in node positive patients after NAC. To avoid bias, we performed it in separate comprehensive institutions. In this study we performed a registered prospectively database to demonstrate a nomogram to predict axillary pCR after NAC and we performed two prospective series from different centers to validate the probability of nomogram.

In this study we performed a registered prospectively database to demonstrate a nomogram to predict axillary pCR after NAC. Two prospective series from different centers were then carried out to validate the accuracy of the nomogram. We analyzed 547 patients with biopsy-proven ALN positive breast cancer. Among them, 172 (31.4%) patients achieved axillary pCR, which is slightly higher than the results reported in the studies of Gonzalez-Angulo et al [14] and Kida K et al [15]. Based on the multivariate analysis, we identified that clinical nodal (N) stage, estrogen receptor (ER) status and clinical response of the primary tumor after NAC were significant independent predictors for axillary pCR ($P < 0.05$). Histologic grade and HER2 status did not show statistically significant in the multivariate logistic regression analysis. In addition, biological subtype was also associated with pCR. Based on the data from Z1071 trial, Boughey et al found that the pCR rate was 21.1% in HR+/HER2- patients, but in patients with HR-/HER2-, it was 49.4% ($P < 0.0001$) [16]. In our study, ER negative patients were the most likely to achieve pCR, which was consistent with the previous study.

The nomogram is used as prediction tool to provide individualized estimates of risk [17, 18]. It is concise and powerful for predicting ALN pCR, which could help to assess the actual ALN status and increase the

accuracy of SLNB. Built on the present researches, we constructed a nomogram to predict ALN pCR in node positive patients after NAC. To avoid bias, we performed it in separate comprehensive institutions. Some researchers also have evaluated nomograms for predicting axillary status in patients with breast cancer [9, 19]. The result of SENTINA showed that in patients whose axillary have downstage to cN0 after NAC, the identification rate (IR) was 80.1% and false negative rate (FNR) was 14.2% [20]. The ACOSOG Z1071 study reported a FNR of SLNB at 12.6% when more than two SLNs were examined, which exceeded the acceptable cut-off value of 10% [21, 22]. Based on our nomogram, patients with high points were more likely to show ALN pCR. Combination of imaging tests, patients could safely avoid receiving ALN dissection [23]. The evaluation of axillary offering prognostic information about breast cancer. Recent studies have showed no residual invasive cancer in breast and axillary was used to provide a better outcome [24–26]. Among patients with cytologically proven axillary lymph node (ALN) metastases, survival was improved in which achieving ALN pCR [26]. While the nomogram may also be helpful in the communications between patients and oncologists.

Our study has some limitations. The retrospective data may have selection bias since it included patients who have been monitored up until 2007. Additionally, chemotherapy might be a confounding factor, for patients from different hospitals did not receive homogeneous NCT. In addition, the National Comprehensive Cancer Network (NCCN) guidelines have incorporated a comment that marking biopsied lymph nodes to document their removal can decrease the FNR of SLN after NAC. However, clipping of ALNs at initial percutaneous biopsy is still a challenge and this procedure has not been established in China. Our study was conducted only in the Chinese population and the result still needs to be validated in larger population in different regions.

In conclusion, we constructed a high discrimination and calibration ability nomogram for predicting post-NAC axillary lymph node pCR, which included five comprehensive predictors. With the nomogram, we can predict post-NAC lymph node status accurately and conduct precise surgery for patients with a high probability of achieving axillary pCR.

Abbreviations

pCR

Pathological complete response

ALN

axillary lymph nodes

ALND

axillary lymph node dissection

NAC

neoadjuvant chemotherapy

AUC

Adjusted area under the characteristic curve

SLNB

Sentinel lymph node biopsy

OR

Odds ratio

CI

Confidence interval

ER

Estrogen receptor

PR

Progesterone receptor

HER2

Human epidermal growth factor receptor 2

Declarations

Ethics approval and consent to participate

The study was approved by the institutional review board (IRB) of Cancer Hospital, Chinese Academy of Medical Sciences and IRB of Beijing Tiantan Hospital affiliated to Capital Medical University.

Consent for publication

Not applicable.

Availability of data and materials

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

Competing interests

The authors declare that they have no competing interests.

Funding

This research was supported by Grants from the Capital Health Specialized Development Research, Beijing Municipal Health Bureau (Grants No. 2016-4-4026), CAMS Innovation Fund for Medical Sciences (CIFMS) (Grant No.2016-I2M-1-001 and Grant No.2017-I2M-3-004), National Natural Science Foundation of China (Grant No. 81602343) and Youth Research Fund of Beijing Tiantan Hospital (Grant No. 2017-YQN-09)

Authors' Contributions

WYW offered the idea of this study, analyzed the patient data, and drafted the manuscript. XW and WYW performed the statistical analysis and revised the manuscript. XW revised the manuscript and did a lot of

work in data collection. XW and PLW was the supervisor of this study and was a major contributor in writing the manuscript. All authors read and approved the final manuscript.

Acknowledgement

Not applicable

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Figures

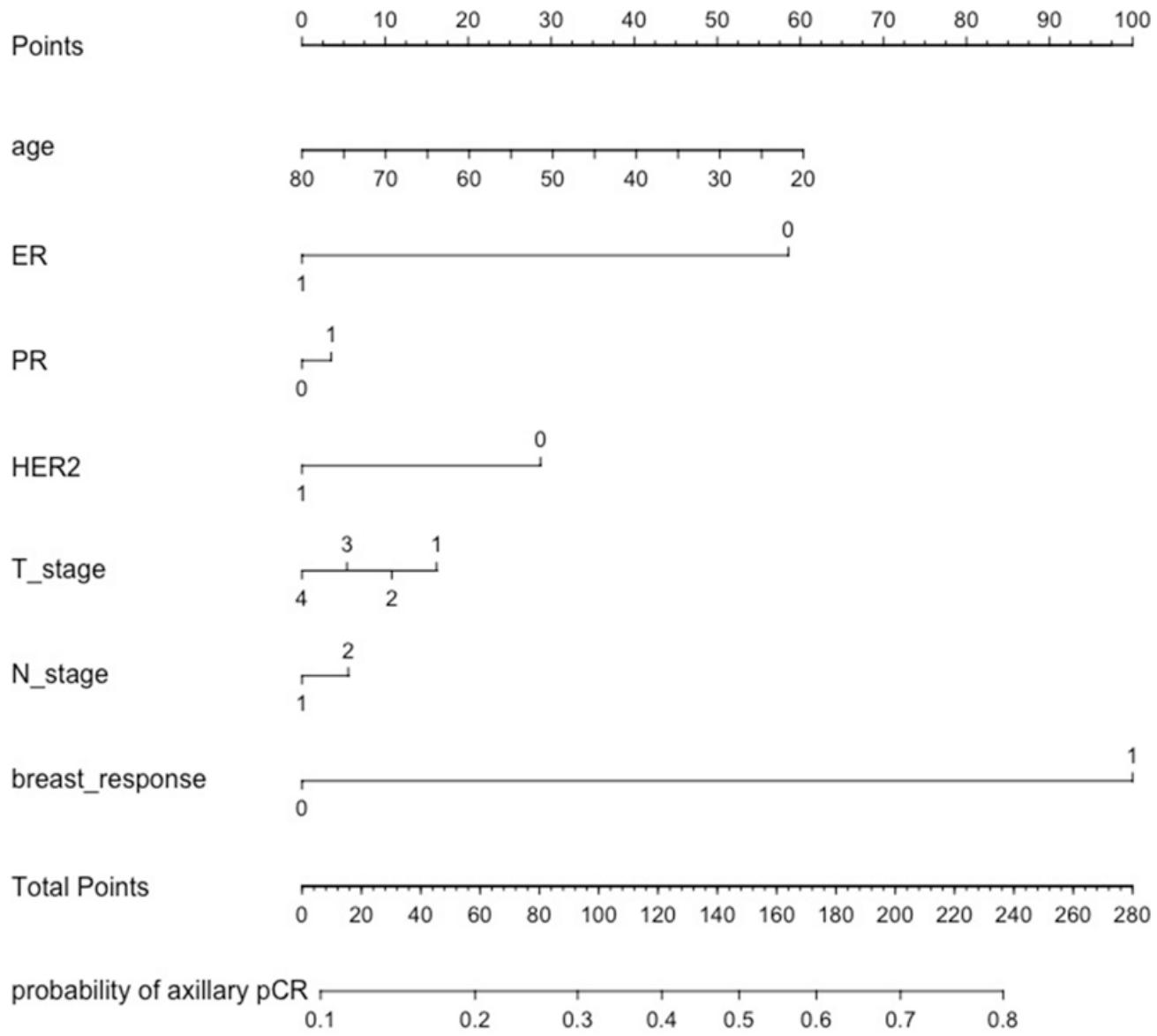


Figure 1

Nomogram to predict Axillary lymph node pathological complete response in patients with positive lymph node before NAC.

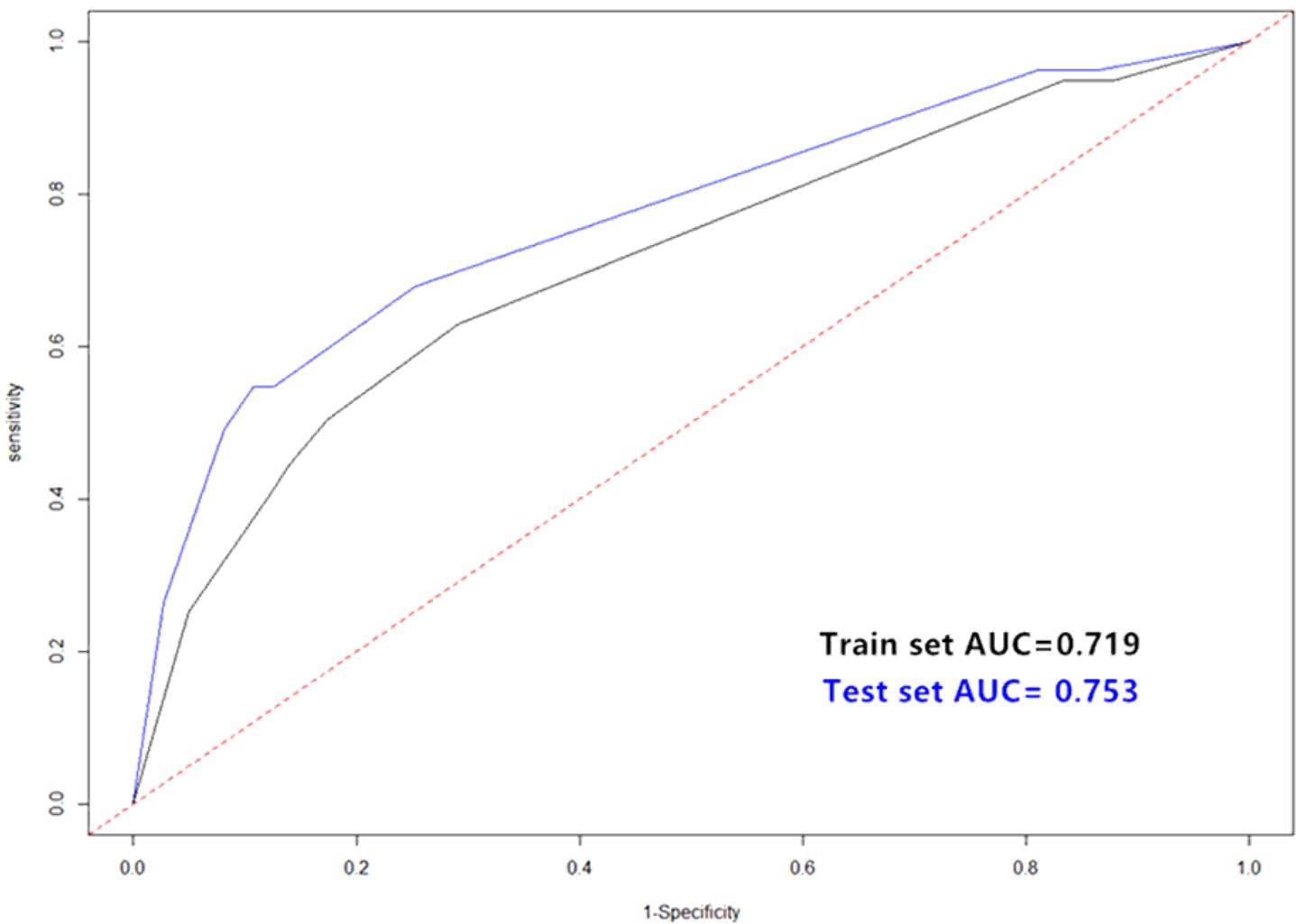


Figure 2

Receiver Operating Characteristics (ROC) Curve for Nomogram in the training and testing sets. The area under the curve (AUC) were 0.719 and 0.753 respectively.

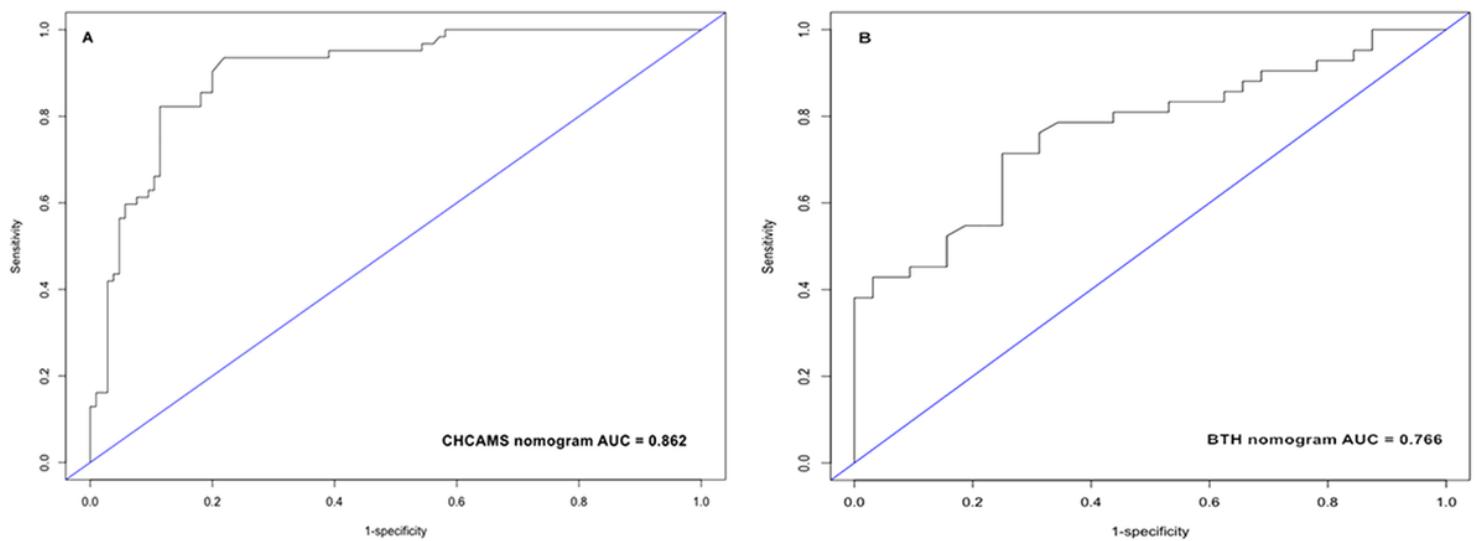


Figure 3

Receiver Operation characteristics (ROC) Curves for discrimination of External Validation sets. The areas under the curve (AUC) were 0.862 (95% CI 0.793-0.911) (Fig.3A) and 0.766 (95% CI 0.616-0.826) (Fig 3B) respectively.