Nomogram for predicting axillary upstaging in clinical node-negative breast cancer patients receiving neoadjuvant chemotherapy

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Abstract

Purpose

The prediction of axillary lymph node status after neoadjuvant chemotherapy (NAC) becoming critical because of the advocation of the de-escalation of axillary management. We investigate associated factors of axillary upstaging in clinical node-negative(cN0) breast cancer patients receiving NAC to develop and validate an accurate prediction nomogram;

Methods

We retrospectively analyzed 2101 breast cancer patients with stage of cT1-3N0 treated by NAC and subsequent surgery between 2010 and 2020 in twenty hospitals across China. Patients randomly divided into a training set and validation set (3:1). Univariate and multivariate logistic regression analysis were performed, after which a nomogram was constructed and validated;

Results

In total, pathologic node negativity (ypN0) achieved in 1552 (73.9%) patients and another 549(26.1%) patients upstaged to pathologic node positive (ypN+). Breast pathologic complete response (bpCR) was achieved in 499 (23.8%) patients and non-bpCR in 1602 (76.3%) patients. A nomogram was established by ER, tumor histology, NAC regimen, cycle of NAC treatment, and the bpCR, which were confirmed by multivariate logistic analysis as independent predictors of nodal upstaging in the training cohort (n = 1576). The area under the receiver operating characteristic curve (AUC) of the training cohort and validation cohort were 0.74 (95%CI, 0.64–0.71) and 0.76 (95% CI, 0.63–0.75) respectively;

Conclusion

We present a nomogram with a nationwide large sample data which can effectively predict axillary upstaging after neoadjuvant chemotherapy to give better advice for individualized axillary lymph node management of breast cancer.

Introduction

The administration of neoadjuvant chemotherapy (NAC) has evolved from a strategy for patients with inoperable breast cancer to an option for those with operable breast cancer (Montemurro et al. 2020). NAC provide accurate prognostic estimates based on the extent of tumor response, which can also guide adjuvant therapy, and provide frequent tumor down-stage, which can lead to smaller surgeries in patients with larger tumors at diagnosis(Gu et al. 2022). Based on these benefits, more patients with clinical node negative (cN0), not just clinical node positive (cN+) breast cancer receiving NAC (Foldi et al. 2021;

Pilewskie et al. 2017; Feng et al. 2022). Pathologic complete response (pCR) was more common in axillary lymph nodes than in the primary tumor, thus it has raised questions about the optimal approach to the axilla after the use of NAC (Barron et al. 2018,;Tadros et al. 2017,;Barrio et al. 2016).

Traditionally, axillary lymph node dissection (ALND) has been the standard management for all breast cancer surgery (Andersson et al. 2018). However, because of the morbidities like lymphedema, restriction of shoulder joint motions, seroma formation in the armpit, numbness, which have deleterious long-term effects on the quality of life, there have been increasing efforts to investigate the feasibility of sentinel lymph node biopsy (SLNB) with fewer complications and did not affect the accuracy of diagnosis or prognosis (Fisher et al. 2020; Krag et al 2007; Giuliano et al. 2016). NCCN (National Comprehensive Cancer Network) guideline(Gradishar et al. 2022) for breast cancer recommended SLNB for cN0 patients before NAC and cN + patients that turned to cN0 after NAC, however the false negative rate of SLNB is over 10% even though three lymph nodes detected, moreover, for patients who do not have lymph node metastases, SLNB still bring unnecessary complications(Foldi et al. 2021; Pilewskieet al. 2022). Currently, prospective randomized surgical trials investigating the omission of SLNB in patients who are clinically node negative after NAC (ycN0)(Reimer et al. 2020; Hersh et al.2022).

There is a clinical need to identify the subgroup of patients with very low risk of axillary disease in whom SLNB might be omitted(Kong et al. 2022). Thus, recently there were extensive literature exists predicting axillary pathological compelete response after NAC in clinically cN + patients(Weiss et al. 2021; Montagna et al. 2020; Chen et al. 2021). However, for patients with cN0 disease prior to NAC, there is still some patients upstage to positive nodal disease after NAC(ypN+) and there is no good data to advise them of residual potential disease risk at the time of surgery. The primary purpose of our study was to identifying risk factors that associated with nodal upstaging after NAC and present a novel nomogram which can effectively predict nodal upstaging in lymph nodes. The secondary purpose was to identify patients who might be avoiding axillary surgery if the ypN + rate was low.

Materials And Methods

Study population

We used data from CSBrS-012 database of Chinese Society of Breast Surgery which covers twenty hospitals across China. It included breast cancer patients who completed standard breast and axillary surgery after NAC between January 2010 and December 2020. This study was approved by the Ethics Committee of The First Affiliated Hospital of Xi An Jiao Tong University. The need for informed consent was waived. The inclusion criteria of our study were (1) cT1-3N0 breast cancer patients diagnosed based on pre-NAC physical examination and core needle biopsy or fine-needle aspiration (2) NAC prior to surgery (3) complete clinical and pathological information, and (4) successful mastectomy or breast-conserving surgery and ALND or SLNB after NAC. Patients who were changed NAC regimen midway, patients received neoadjuvant endocrine therapy were excluded.

Clinical/pathological Parameters

Clinical/pathological parameters analyzed were include age, tumor diameter before NAC measured by ultrasound, histology, ER positivity (defined as ≥ 1% positive cells by immunohistochemistry(IHC)), PR positivity (defined as ≥ 1% positive cells), HR positivity (ER and/or PR positivity), HER2 status (3 + by IHC or 2 + by IHC and positive by in-situ hybridization defined as positive; 0 or 1 + by IHC or 2 + and negative by in-situ hybridization defined as negative), Ki-67 index was detected by IHC, biologic subtypes was performed by referring to the 2011 St.Gallen Consensus(Goldhirsch et al. 2011): HR+/HER2-, HR+/HER2+, HR-/HER2+, TNBC. The clinical tumor response was measured according to Response Evaluation Criteria in Solid Tumors (RECIST)(Eisenhauer et al. 2009). pCR in the breast was defined as the absence of any residual both invasive and in situ cancer in breast after NAC. ypN0 was defined as the absence of any tumor cells in the axillary lymph node after NAC. NAC was provided in accordance with National Comprehensive Cancer Network breast cancer guidelines. In our study, we divided NAC regimens into 4 category (1) AC-TH/TCbH, (2) TAC/AC-T/TA, (3) TC/TX/TP/AC, (4) TCbHP/ THP/ AC-THP.

Statistical Analysis

All the included patients were assigned into a training cohort and a validation cohort randomly according to a ratio of 3:1. Pearson's $\chi 2$ test was applied to compare baseline differences in clinical/pathological parameters between training and validation cohort. We performed the univariate logistic regression analysis to test the characteristics that related to axillary upstaging in patients with cN0 prior to NAC, and used multivariable logistic regression analysis to identify the independent predictors. A predictive nomogram of axillary lymph node upstaging after NAC was established based on the independent predictors determined by multivariate analysis. The ROC (receiver operating characteristic) curve and calibration curve were drawn and AUC (area under the ROC curve) was calculated to verify the performance of the nomogram. Statistical calculations were performed in SPSS version 21.0 (Inc., Chicago, IL, USA) and R 4.2.2 (R Project for Statistical Computing) software.

Results

Patient characteristics

Clinicopathological characteristics of patients in the training and validation cohorts are described in Table 1. A total of 2101 cN0 patients with an average age of 48 years enrolled in the study. The distribution of clinical T stages included 241 patients of T1, 1546 patients of T2, and 314 patients of T3. The most frequently encountered histology was invasive ductal carcinoma (1971, 93.8%). Presenting subtypes included ER+/HER2- (898, 42.7%), ER+/HER2+ (471, 22.4%), ER-/HER2+(322,15.3%), and TNBC (410, 19.5%). Among those with HER2 + tumors, 381 patients (48.0%, 381/793) underwent molecular targeted treatment. 1528 patients received mastectomy, while 504 patients received breast conserving surgery. The number of patients received axillary surgery of ALND, SLNB, and SLNB + ALND were 1252, 684, and 165 respectively.

Table 1
Clinicopathological characteristics of patients with cN0 breast cancer in the training set and validation set.

Characteristic	Trainning set(n = 1576)	Validation set(n = 525)	p value	ypN0 (n = 1552)	ypN+ (n = 549)
Age			0.709		
<=35	175 (11.1)	52 (9.9)		166	61
>=56	342 (21.7)	121 (23.0)		412	138
36–45	407 (25.8)	143 (27.2)		633	288
46–55	652 (41.4)	209 (39.8)		341	122
cT			0.528		
T1	181 (11.5)	60 (11.4)		177	64
T2	1162 (73.7)	384 (73.1)		1145	401
T3	233 (14.8)	81 (15.4)		230	84
Histology			0.137		
IDC	1478 (93.8)	493 (93.9)		1437	534
ILC	20 (1.3)	13 (2.5)		23	10
Invasive carcinoma	65 (4.1)	17 (3.2)		79	3
Others	13 (0.8)	2 (0.4)		13	2
ER			0.725		
Negative	613 (38.9)	199 (37.9)		701	111
Positive	963 (61.1)	326 (62.1)		851	438
PR			0.185		
Negative	763 (48.4)	236 (45.0)		832	167
Positive	813 (51.6)	289 (55.0)		720	382
HR			0.641		
Negative	554 (35.2)	178 (33.9)		633	99
Positive	1022 (64.8)	347 (66.1)		919	450
HER2			0.034		
Negative	1002 (63.6)	306 (58.3)		919	389

Characteristic	Trainning set(n = 1576)	Validation set(n = 525)	p value	ypN0 (n = 1552)	ypN+ (n = 549)
Positive	574 (36.4)	219 (41.7)		633	160
Ki67			0.747		
< 20	221 (14.0)	70 (13.3)		201	90
>=20	1355 (86.0)	455 (86.7)		1351	459
Biologic subtype			0.097		
HR-/HER2+	231 (14.7)	91 (17.3)		274	48
HR+/HER2-	679 (43.1)	219 (41.7)		560	338
HR+/HER2+	343 (21.8)	128 (24.4)		359	112
TNBC	323 (20.5)	87 (16.6)		359	51
NAC regimen			0.462		
AC-TH/ TCbH	192 (12.2)	72 (13.7)		228	36
TCbHP/ THP/ AC-THP	85 (5.4)	32 (6.1)		978	387
TAC/ AC-T/ TA	1020 (64.7)	345 (65.7)		98	48
TC/TX/TP/AC	114 (7.2)	32 (6.1)		102	15
Others	165 (10.5)	44 (8.4)		146	63
NAC Cycle			0.551		
4	252 (16.0)	68 (13.0)		224	96
6	626 (39.7)	218 (41.5)		604	240
8	390 (24.7)	137 (26.1)		408	119
> 8	167 (10.6)	54 (10.3)		189	32
Others	141 (8.9)	48 (9.1)		127	62
RECIST			0.994		
CR	141 (8.9)	47 (9.0)		162	26
PD	25 (1.6)	9 (1.7)		19	15
PR	1291 (81.9)	428 (81.5)		1269	450
SD	119 (7.6)	41 (7.8)		102	58

Characteristic	Trainning set(n = 1576)	Validation set(n = 525)	p value	ypN0 (n = 1552)	ypN+ (n = 549)
bpCR			0.023		
No	1182 (75.0)	420 (80.0)		1095	507
Yes	394 (25.0)	105 (20.0)		457	42
Operation			0.715		
BCS	371 (23.5)	133 (25.3)		431	73
Breast reconstruction	50 (3.2)	17 (3.2)		56	11
Mastectomy	1153 (73.2)	375 (71.4)		1065	463
Others	2 (0.1)	0 (0.0)		0	2

ypN0, pathologic node negative NAC; ypN0+, pathologic node positive after NAC; cT, clinical tumor stage before NAC; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; bpCR, breast pathologic complete response BCS, breast conservation surgery; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease.

The pathological results of operation after NAC showed that bpCR was achieved in 499 (23.8%) patients and non-bpCR in 1602 (76.3%) patients, ypN0 in 1552 (73.9%) patients and axillary upstaging (ypN+) in another 549 (26.1%) patients. Among patients who achieved bpCR the rate of ypN0 was 91.6%, while in the non-bpCR subgroup it was 68.4%. ER-/HER2 + and TNBC subtype patients achieved more ypN0 rate than HR positive subtypes (86.5% vs. 67.1%), conversely, HR+/HER2- patients have more risk of axillary upstaging than other subtypes (Fig. 1). Among 268 bpCR patients with ER-/HER2 + or TNBC subtypes, there was only 14 patients upstaged to ypN + after NAC, the rate of nodal negativity was 94.8%.

Prediction of lymph node upstaging

Univariate analysis revealed that ER positive, tumor histology, biological subtypes, NAC regimen, cycle of NAC treatment, and bpCR ($p < 0.05$) had statistical significance for ypN0. Apart from biological subtypes, all the other factors were confirmed as independent predictors of axillary upstaging in multivariate logistic regression analysis (Table 2).

Table 2
Univariate and multivariate logistic analysis of factors predict the lymph node positivity after NAC in the training cohort.

Variables	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Age						
<=35	reference					
36–45	0.73	0.47–1.13	0.16			
46–55	0.94	0.63–1.42	0.78			
>=56	0.87	0.56–1.37	0.55			
cT						
T1	reference					
T2	1.17	0.80–1.76	0.43			
T3	1.08	0.66–1.77	0.77			
Histology						
IDC	reference					
ILC	1.06	0.37–2.85	0.91	1.09	0.39–2.38	0.86
Invasive carcinoma	0.16	0.04–0.46	**0.00**	0.16	0.04–0.46	**0.00**
Others	0.43	0.06–1.73	0.29	0.42	0.06–0.69	0.28
ER						
Negative	reference					
Positive	3.24	0.85–1.77	**0.00**	3.09	1.50–7.24	**0.00**
PR						
Negative	reference					
Positive	1.22	0.85–1.77	0.29			
HR						
Negative	reference					
Positive	0.87	0.326–2.11	0.12			
HER2						
Negative	reference					

Variables	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
Positive	1.42	0.86–2.45	0.21			
Ki67						
< 20	reference					
>=20	1.07	0.76–1.51	0.69			
Biologic Subtype						
TNBC	reference					
HR+/HER2+	0.55	0.30–1.01	**0.05**	0.78	0.31–1.81	0.58
HR+/HER2-	0.67	0.57–1.32	0.06	1.02	0.41–2.25	0.97
HR-/HER2+	0.43	0.16–1.73	0.31	1.36	0.79–2.34	0.27
NAC regimen						
AC-TH/ TCbH	reference					
TAC/ AC-T/ TA	2.04	1.21–3.51	**0.01**	2.08	1.25–3.56	**0.01**
TC/TX/TP/AC	2.73	1.40–5.39	**0.00**	2.75	1.42–5.41	**0.00**
TCbHP/ THP/ AC-THP	1.20	0.50–2.70	0.67	1.26	0.53–2.81	0.58
Others	2.68	1.48–4.93	**0.00**	2.65	1.47–4.86	**0.00**
Cycle						
> 8	reference					
4	1.64	0.97–2.82	0.07	1.85	1.10–3.15	**0.02**
6	2.32	1.47–3.78	**0.00**	2.49	1.58–4.04	**0.00**
8	1.56	0.96–2.60	0.08	1.64	1.02–2.71	**0.05**
Others	1.79	1.00-3.23	**0.05**	1.95	1.10–3.51	**0.02**
RECIST						
CR	reference					
PD	1.80	0.65–4.93	0.25			
PR	0.89	0.52–1.56	0.68			
SD	1.46	0.76–2.88	0.26			
bpCR						

Variables	Univariate Analysis			Multivariable Analysis		
	OR	95% CI	P-value	OR	95% CI	P-value
No	reference					
Yes	0.24	0.15–0.35	**0.00**	0.23	0.15–0.34	**0.00**

cT, clinical tumor stage before NAC; ER, estrogen receptor; PR, progesterone receptor; HR, hormone receptor; HER2, human epidermal growth factor receptor 2; TNBC, triple-negative breast cancer; IDC, invasive ductal carcinoma; ILC, invasive lobular carcinoma; bpCR, breast pathologic complete response BCS, breast conservation surgery; CR, complete response; PD, progressive disease; PR, partial response; SD, stable disease. OR, odds ratio; 95% CI, 95% confidence interval. Only variables with P values < .05 were included in the multivariate analysis.

Construction And Validation Of The Nomogram

Based on independent predictors determined by multivariate logistic regression analysis, a predictive nomogram of axillary lymph node upstaging after NAC was established. We can assign a point value to each variable by draw a vertical line between each variable value and the first row. By summing up the scores of each variable we can calculate the total nomogram score. Then, a probability of axillary upstaging after NAC in cN0 patients can be determined by drawing a vertical line from the total score to the bottom row (Fig. 2).

We used ROC curve and calibration curve to quantify the performance of the nomogram. The ROC curve was constructed using the ER, tumor histology, NAC regimen, cycle of NAC treatment, and bpCR. The AUC was 0.74 in the training cohort and 0.76 in the validation cohort (Fig. 3). The calibration curve showed a good and satisfactory agreement between the predicted and actual probabilities both in the training and validation cohorts (Fig. 4).

Discussion

NAC aims to preoperatively downstage breast as well as axillary nodal in breast cancer patients(Samiei et al. 2021). However, with the more recognization to clinical value of the response of the breast tumor or lymph node to NAC, NAC is increasingly used for early-stage breast cancer with cN0(Feng et al. 2022). Risk of axillary nodal upstaging in primary cN0 breast cancer patients receiving NAC are unknown. In the current study, we focused on the pathological nodal status of cN0 patients who were underwent surgery followed by NAC, and analyzed parameters which could be a prediction factors of axillary upstaging in this kind of patients. Among 2101 patients who were cN0 prior to NAC, there was approximately 74% of patients still maintain negative axillary lymph node and another 23% patients upstaged to ypN+. We included 13 clinical/pathological features as potential predictors. ER status, tumor histology, biological

subtypes, NAC regimen, cycle of NAC treatment, and bpCR associated with axillary upstaging according to the univariate analysis.

The rate of breast and axillary response is significantly associated with biological subtypes and bpCR. TNBC and HER2 positive breast cancers can achieve axillary pCR rates greater than other types (Samiei et al. 2021; Samiei et al. 2020; Haque et al.2018). Is that parallel in upstaging? Researchers from Mayo Clinic have investigated nodal upstaging in 228 cN0 patients receiving NAC and neoadjuvant endocrine therapy and found that ER+/HER2- subtype carries higher risk for nodal upstaging rather than other subtypes (Hammond et al. 2022). In our study, biological tumor subtype is an influencing factor of nodal upstaging in univariate analysis but not independent predictor. As it showed in histogram (Fig. 1), HR+/HER2- subtype appears more risk of axillary upstaging than TNBC and HER2 positive subtypes. HER2 status is not predict nodal upstaging in our study, and we ascribed it to that among those with HER2 + tumors, only nearly half underwent molecular targeted treatment because targeted drugs were not covered by medical insurance in the early years. Moreover, it had been confirmed before that the response of patients with HR positive disease to NAC was relatively low(Lopez-Tarruella et al. 2022) but we find that HR positive status is not the indicator of nodal upstaging but ER is. Among patients who achieved bpCR the rate of axillary upstaging was 8.4%, while in the non-bpCR group, it was 31.6%. In reverse, it consistent with studies that evaluating downstaging. Among 268 bpCR patients with ER-/HER2 + and TNBC subtypes there was only 14 patients upstaged to ypN + after NAC, the rate of nodal negativity was approximately 95%. Unfortunately, surgical axillary management is a routine procedure for all these patients, even it is a SLNB, patients suffer unnecessary complications like Lymphedema, paraes-thesia, arm and shoulder impairment, and pain(Verbelen et al. 2019; Gebruers et al. 2015).

A nomogram based on patients information can identify patients with very low risk of axillary disease in whom SLNB might be omitted(Moorman et al. 2022). Resent years, several nomograms have been developed to predict the axillary pathological complete response of patients who underwent NAC(Gu et al. 2022; Guo et al. 2020; Jin et al. 2016; Kang et al.2022; Hwang et al. 2019), but there was few research which discussed axillary lymph node upstaging during the NAC. To the best of our knowledge, the present nomogram is the first to predict axillary lymph node upstaging in cN0 patients who received NAC that based on real world data from a large number of multicenter patients. Apart from the ER positive status and breast pCR, tumor histology, NAC regimen, and treatment cycle are involved in our predicted nomogram. As we can see, invasive lobular carcinoma get more score than other subtypes in the possibilities of axillary upstaging. Steffi et al.(2022) reported that diagnosis of ILC was associated with larger tumors, ER and PR positivity, and lower expression of HER2, and our findings are in agreement with data from those prior study. Axillary metastasis also be controlled by targeted therapy for HER2 positive disease, NAC regimen types that didn’t include targeted therapy like TAC/ AC-T/ TA, TC/TX/TP/AC get more score for axillary upstaging in the nomogram. Interestingly if a patient receive 6 cycle of NAC, the likelihood of axillary up staging is higher than those of 8 cycle, 8 cycle, 4 cycle. It may because of that in some occasion patients receive surgery after 6 cycles of NAC due to the poor response. For patients received only 4 or less cycle NAC, surgery may cut the damage in time.

Our nomogram has additional value for the selection of cN0 patients who are not good candidates for axillary de-escalation. But it still have some limitations: (1) Chi-Chang Yu et al(Yu et al. 2022) found that Lymphovascular invasion was the strongest(OR: 29.37,95%CI:7.15–120.68)independent risk predictor of axillary metastasis in cN0 patients undergoing NAC. Unfortunately, in our study we couldn't analyze this factor because it was not included in the initial database. (2) This study used a retrospective method, which makes it prone to potential bias compared with a prospective study. (3) No external validation was set up in this study.

Conclusions

The ER status, tumor histology, biological subtypes, NAC regimen, cycle of NAC treatment, and bpCR were positively associated with axillary upstaging in initial cN0 breast cancer patients. Furthermore, we constructed a nomogram model that could accurately predict the risk of axillary upstaging.

Declarations

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Ethics approval and consent to participate: The study was performed in accordance with the Declaration of Helsinki and was approved by the Ethical Review Committee of the First Hospital of Jilin University (No. 2021-066). Since this study was retrospective and all data analysis was conducted anonymously, there was no informed consent of patients.

Consent for publication：Not applicable.

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Conflict of interest statement: The authors have declared that no competing interest existed.

Availability of data and material All data during the study are proprietary in nature and may only be provided with restrictions (e.g. anonymized data).

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Figures

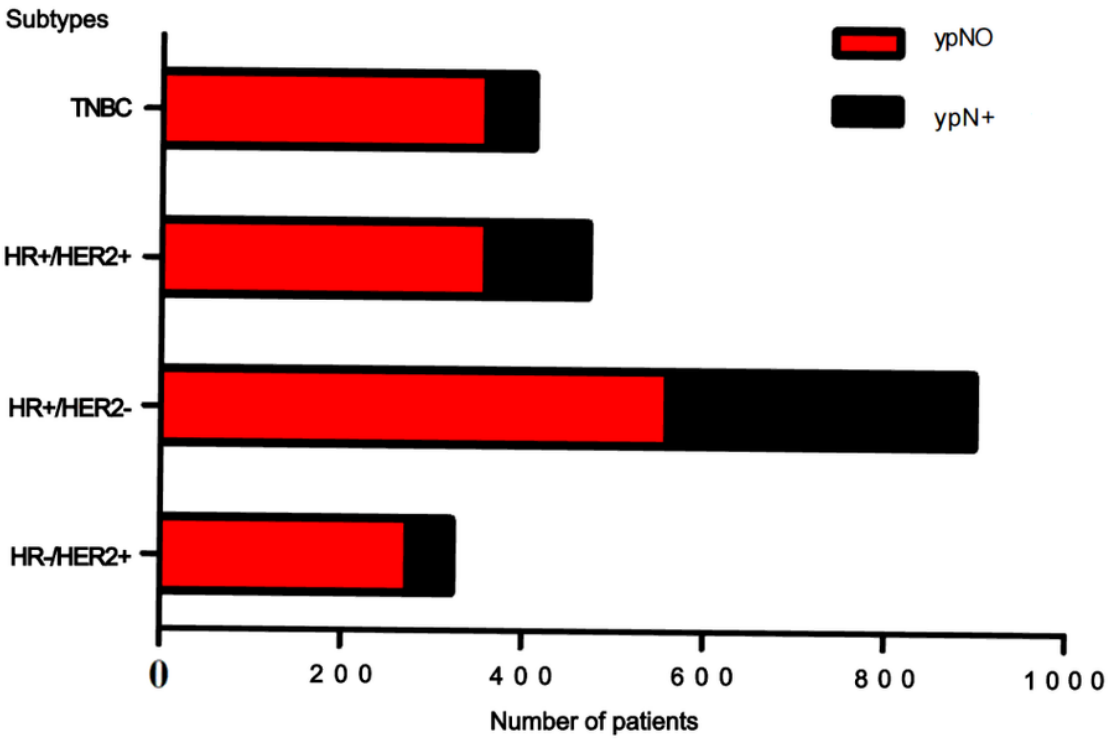

Figure 1

Pahologic lymph node status after NAC in different subtype patients with primary cN0 status.

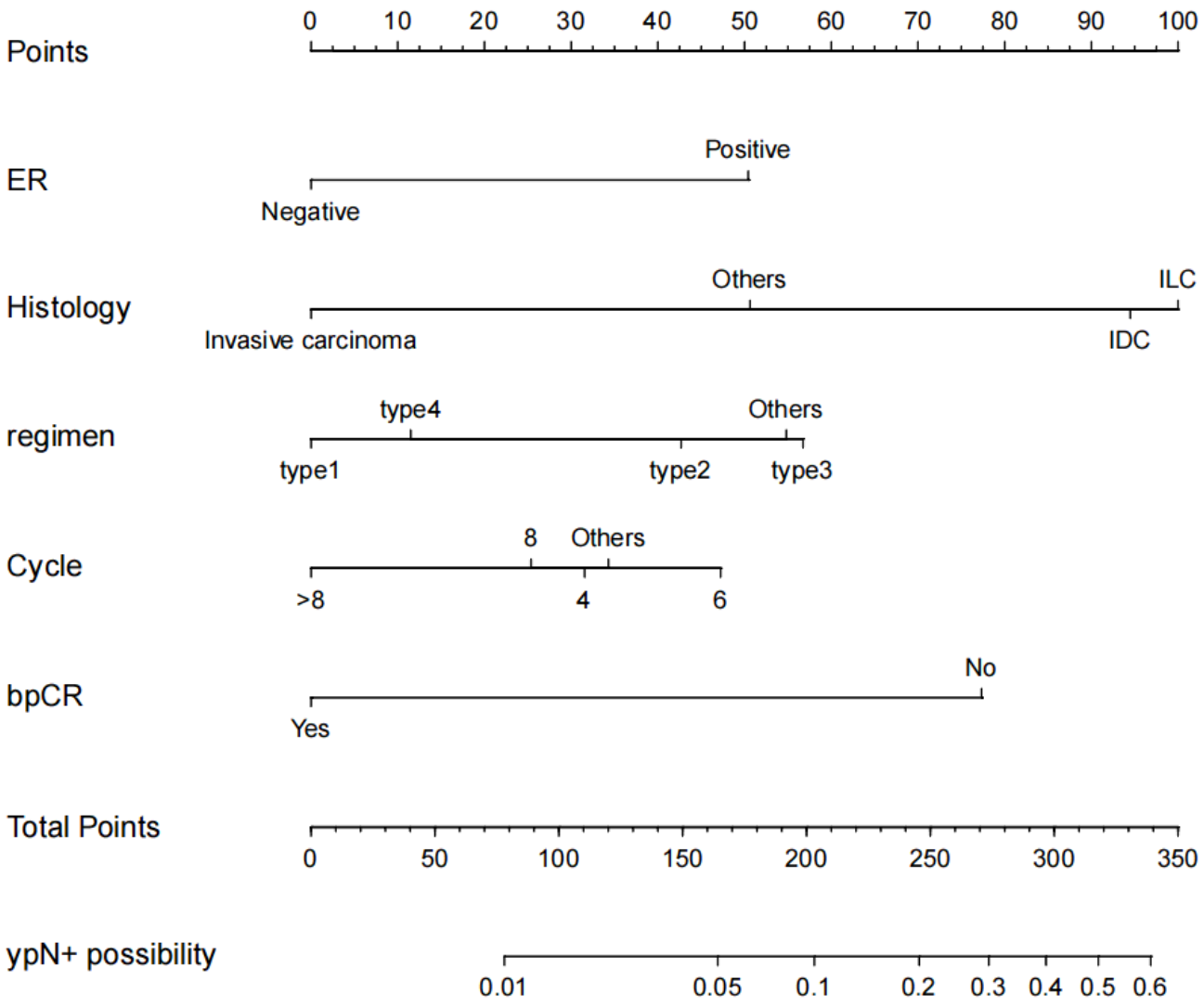

Figure 2

Nomogram to predict the probability of ypN+ in cN0 patients before NAC. NAC regimen: type1:AC-TH/ TCbH, type2: TAC/ AC-T/ TA, type3:TC/TX/TP/AC, type4: TCbHP/ THP/ AC-THP.

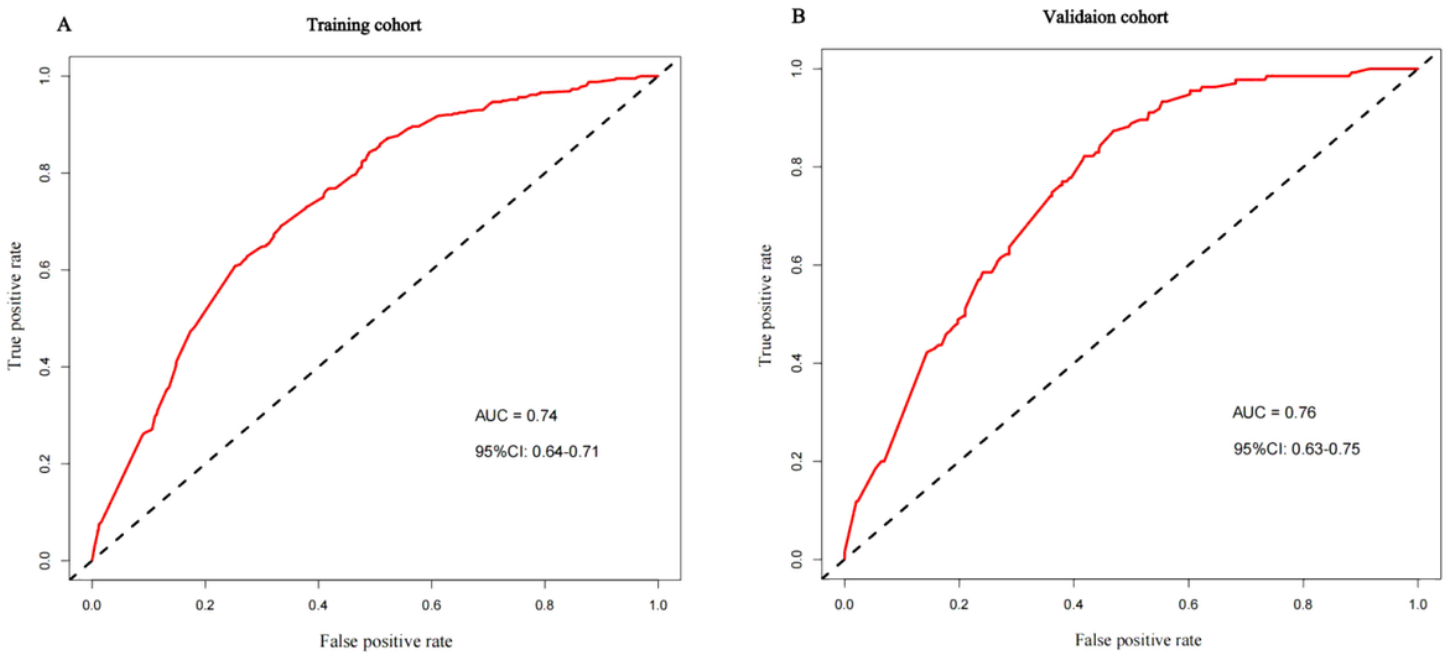

Figure 3

The ROC (receiver operating characteristic curves curve) for prediction model of ypN+ inpatients with cN0 prior to NAC. (A) is the training cohort and (B) is the validation cohort. AUC: area under the curve.

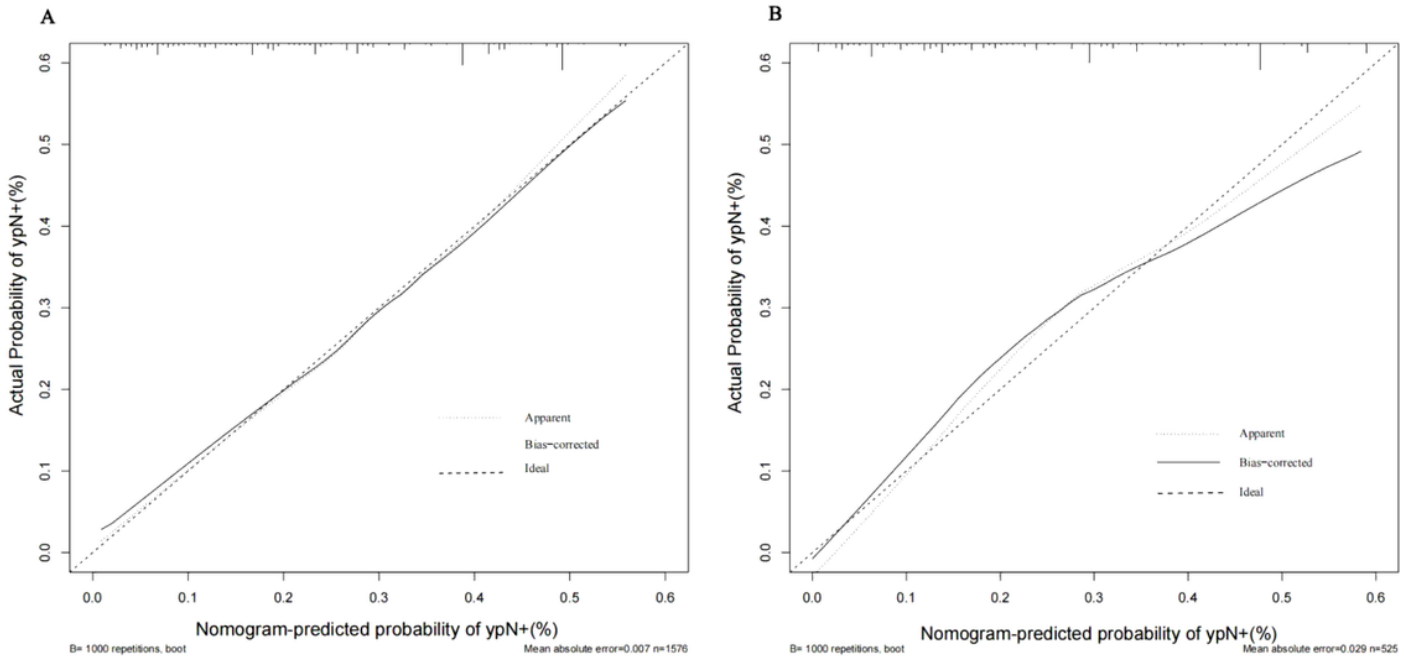

Figure 4

The calibration curve for prediction model of ypN+ in patients with cN0 prior to NAC. (A) is the training cohort and (B) is the validation cohort.