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ORIGINAL ARTICLE – BREAST ONCOLOGY

A Nomogram to Predict the Pathologic Complete Response of Neoadjuvant Chemotherapy in Triple-Negative Breast Cancer Based on Simple Laboratory Indicators

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ABSTRACT

Background. Triple-negative breast cancer (TNBC) patients who achieve a pathologic complete response (pCR) after neoadjuvant chemotherapy (NAC) have better prognoses.

Objective. This study aimed to develop an intuitive nomogram based on simple laboratory indexes to predict the pCR of standard NAC in TNBC patients.

Methods. A total of 80 TNBC patients who received eight cycles of thrice-weekly standard NAC (anthracycline and cyclophosphamide followed by taxane) and subsequently underwent surgery in Zhejiang Cancer Hospital were retrospectively enrolled, and data on their pretreatment clinical features and multiple simple laboratory indexes were collected. The optimal cut-off values of the laboratory indexes were determined by the Youden index using receiver operating characteristic (ROC) curve analyses. Forward stepwise logistic regression (likelihood ratio) analysis was applied to identify predictive factors for a pCR of NAC. A nomogram was then developed according to the logistic model, and internally validated using the bootstrap resampling method.

Results. pCR was achieved in 39 (48.8%) patients after NAC. Multivariate analysis identified four independent indicators: clinical tumor stage, lymphocyte to monocyte ratio, fibrinogen level, and D-dimer level. The nomogram established based on these factors showed its discriminatory ability, with an area under the curve (AUC) of 0.803 (95% confidence interval 0.706–0.899) and a bias-corrected AUC of 0.771. The calibration curve and Hosmer–Lemeshow test showed that the predictive ability of the nomogram was a good fit to actual observation.

Conclusions. The nomogram proposed in the present study exhibited a sufficient discriminatory ability for predicting pCR of NAC in TNBC patients.

Neoadjuvant chemotherapy (NAC) has become a common approach for the care of patients with triple-negative breast cancer (TNBC).[1–4] By using standard anthracycline plus cyclophosphamide- and taxane-based NAC, approximately 30–40% of patients with TNBC can achieve a pathologic complete response (pCR), and they have been proven to have much better outcomes than those who had residual invasive disease after NAC.[1,5] Thus, predicting the pCR rate of standard NAC is highly advantageous. TNBC patients who otherwise have a relatively low probability of

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achieving a pCR could receive a more aggressive regimen to help optimize the efficacy of NAC, such as the addition of platinum.[6]

Various methods have been reported to predict the pCR of NAC in patients with breast cancer, including the analysis of histomorphological factors,[7] analysis of molecular biomarkers,[8,9] and the use of medical imaging tests.[10,11] Based on gene expression profiles, Lehmann and colleagues classified TNBC into six subtypes; namely, two basal-like (BL1 and BL2) subtypes, a mesenchymal (M) subtype, a mesenchymal stem-like (MSL) subtype, an immunomodulatory (IM) subtype, and a luminal androgen receptor (LAR) subtype, and it was found that subtype was an independent predictor of a pCR. The BL1 subtype has the highest pCR rate with anthracycline- and taxane-based NAC, and BL2 and LAR have the lowest pCR rate.[12,13] However, implementing these methods into routine clinical practice is still challenging. Currently, inflammation-based prognostic scores, namely the neutrophil to lymphocyte ratio (NLR), platelet to lymphocyte ratio (PLR), lymphocyte to monocyte ratio (LMR), and C-reactive protein/albumin ratio (CAR), have gained the attention of many researchers.[14–16] These parameters are simple, conventional, objective, and inexpensive laboratory indexes, and the prognostic value of each has been verified in many types of cancer;[17] however, their value for predicting the efficacy of NAC in TNBC patients has rarely been studied, and no study has investigated them together.

A nomogram is an intuitive graphical predictive model that can be used to predict the probability of different events.[18] Based on pretreatment clinical factors and simple laboratory indexes, the present study is the first effort towards developing a nomogram to predict the pCR of NAC in patients with TNBC.

METHODS

Patients and Factors

Breast cancer patients who underwent NAC and surgery in Zhejiang Cancer Hospital between January 2016 and December 2018 were retrospectively enrolled. Eligible patients were female, histologically and molecularly confirmed to have TNBC before NAC, and received four cycles of anthracycline (epirubicin or adriamycin) and cyclophosphamide followed by four cycles of taxane every 3 weeks before surgery. Patients were ineligible if they had previous or concurrent cancer, bilateral breast cancer, or distant metastases. Informed consent was obtained from each patient prior to surgery. This study was approved by the Institutional Review Board of Zhejiang Cancer Hospital.

TNBC was defined as estrogen receptor (ER)-negative, progesterone receptor (PR)-negative and human epidermal growth factor receptor 2 (HER2)-negative breast cancer. An ER and PR expression level of $< 1\%$ by immunohistochemical staining was considered negative. HER2 status was determined based on the American Society of Clinical Oncology/College of American Pathologists (ASCO/CAP) guidelines.[19] pCR was defined as no residual invasive cancer in the breast and axillary lymph nodes after NAC. Clinical stage was determined in accordance with the 8th TNM staging system by the American Joint Committee on Cancer (AJCC),[20] and clinical tumor stage was based on the longest tumor diameter measured by ultrasound. A positive family history was defined on the basis of the criterion that the patient had at least one first- or second-degree relative with cancer. Body mass index (BMI) was calculated by dividing the patient's weight (kg) by height (m^2), and was categorized with a cut-off value of 24 kg/m^2. All clinical factors and laboratory indexes, including neutrophil count, lymphocyte count, platelet count, monocyte count, serum C-reactive protein (CRP) level, serum albumin level, plasma fibrinogen level, and plasma D-dimer level, were estimated before both the tumor biopsy and NAC.

Statistical Analyses

Among these factors, age and the longest tumor diameter were analyzed as continuous variables, while the other factors were analyzed as categorical variables. Ki-67 status, NLR, PLR, MLR, CAR, fibrinogen level, and D-dimer level were divided into two groups according to the optimal cut-off values determined by maximizing the Youden index (sensitivity + specificity − 1) using receiver operating characteristic (ROC) curve analyses.[21] The correlations between pCR and clinical factors were analyzed using Chi square tests or Mann–Whitney *U* tests. Forward stepwise logistic regression (likelihood ratio) analyses were performed to identify predictive factors for pCR of NAC, and a nomogram was then established based on the logistic model. Calibration of the nomogram was carried out by internal validation using the bootstrap resampling approach, and was displayed using a calibration curve. The goodness of fit for the model was checked using the Hosmer–Lemeshow test. Discrimination of the nomogram was graphically shown using an ROC curve and quantified using the area under the curve (AUC). Statistical analyses were performed using IBM SPSS Statistics 24.0 software (IBM Corporation, Armonk, NY, USA) and R version 3.3.3 software (The R Foundation for Statistical Computing, Austria, Vienna). A p value ≤ 0.05 was deemed statistically significant.

RESULTS

A total of 80 patients with TNBC were retrospectively enrolled; their clinical characteristics are summarized in Table 1. The median age was 49.5 years (range 28–68), 37 (46.3%) patients were premenopausal, 21 (26.3%) patients had a family history of cancer, 30 (37.5%) patients had a BMI $\geq$ 25, and the median longest tumor diameter was 32 mm (range 8–86). Based on the 8th TNM staging system recommended by the AJCC, among 80 patients before NAC, 20.0% (16 cases) were classified as cT1, 60.0% (48 cases) were classified as cT2, 16.3% (13 cases) were classified as cT3, 3.8% (3 cases) were classified as cT4, 12.5% (10 cases) were classified as cN0, 50.0% (40 cases) were classified as cN1, 22.5% (18 cases) were classified as cN2, and 15.0% (12 cases) were classified as cN3. Additionally, 39 (48.8%) patients achieved a pCR after NAC. The optimal cut-off values were 37.5 for Ki-67 status, 1.71 for NLR, 129.7 for PLR, 5.37 for LMR, 0.047 for CAR, 2.92 for fibrinogen level, and 67.5 for D-dimer level. Data on grade and germline BRCA mutation status were unavailable for the majority of this cohort.

The correlations between pCR and clinical factors are displayed in Table 1. pCR was significantly associated with age, clinical tumor stage, PLR, LMR, fibrinogen level, and D-dimer level ($p \leq 0.05$), and borderline was significantly associated with the longest tumor diameter ($p = 0.052$). Similar results were demonstrated in the univariate logistic analyses, in which TNBC patients with a younger age, early clinical tumor stage, low LMR, low fibrinogen level, high PLR, and high D-dimer level had a higher rate of pCR (Table 2). Furthermore, in the multivariate logistic regression analysis, clinical tumor stage, LMR, fibrinogen level, and D-dimer level were indicated as independent predictors for pCR of NAC in TNBC patients. Patients with cT3-4 and cT2 TNBC were less likely to achieve pCR than those with cT1 TNBC (adjusted odds ratio [OR] 0.15, 95% confidence interval [CI] 0.02–0.90, $p = 0.038$ for cT3-4; adjusted OR 0.11, 95% CI 0.02–0.51, $p = 0.005$ for cT2). TNBC patients with high LMRs and fibrinogen levels had more difficulty achieving a pCR (adjusted OR 0.18, 95% CI 0.05–0.59, $p = 0.005$ for LMR; adjusted OR 0.14, 95% CI 0.04–0.48, $p = 0.002$ for fibrinogen). The proportion of TNBC patients with high D-dimer levels who achieved pCR was 8.13-fold higher than that of TNBC patients with low D-dimer levels (95% CI 1.16–56.85, $p = 0.035$).

A nomogram was developed, based on clinical tumor stage, LMR, fibrinogen level, and D-dimer level, to predict the pCR rate of NAC among TNBC patients (Fig. 1a). To calculate the probability of pCR, the points for the four factors were summed up, and the total points and the bottom risk scale were referenced. The calibration curve (Fig. 1b), based on internal validation with a bootstrap resampling frequency of 1000 and a Hosmer–Lemeshow Chi square value of 7.67 ($p = 0.363$), showed a satisfactory fit between the prediction and the actual observation. The ROC curve of the nomogram is shown in Fig. 1c; the AUC was 0.803 (95% CI 0.706–0.899). Furthermore, internal validation revealed a bias-corrected AUC of 0.771, which indicated that the nomogram had quite a good discriminatory capability.

DISCUSSION

Due to the diverse efficacy of NAC among TNBC patients, accurate methods for predicting pCR make great sense for understanding patient outcomes. The present study developed a nomogram to predict the pCR of thrice-weekly standard NAC in TNBC patients based on four pretreatment indictors; namely, clinical tumor stage, LMR, fibrinogen level, and D-dimer level. The nomogram indicated that TNBC patients with an early clinical tumor stage, low LMR, low fibrinogen level, and high D-dimer level before NAC were more likely to achieve a pCR. With an AUC of 0.803 (95% CI 0.706–0.899) and a bias-corrected AUC of 0.771 via internal validation using the bootstrap resampling method, the model exhibited sufficient ability to predict the pCR of NAC among TNBC patients. Notably, all patients in this study received a standard regimen of NAC, i.e. four cycles of anthracycline (epirubicin or adriamycin) and cyclophosphamide followed by four cycles of taxane every 3 weeks; thus, the applicability and representativeness of this nomogram will be stronger.

Accumulative evidence demonstrates that the systemic inflammatory response leads to tumor development by fostering multiple cancer hallmark functions.[22] Inflammation by innate immune cells, which are designed to maintain homeostasis, can instead inadvertently provided assist tumor initiation and progression in multiple ways, including causing genomic instability, blocking recognition by immune cells, stimulating proliferation, facilitating invasion and migration, and altering sensitivity to chemotherapy and radiotherapy.[22–24] Four inflammation-based prognostic scores have been reported to be more or less related to the curative effect of chemotherapy in different types of cancer, and were subsequently included in this study. When they were evaluated together to predict the pCR of NAC in TNBC patients, the forward stepwise logistic regression (likelihood ratio) analysis only identified the LMR as an optimal predictor. It is speculated that the LMR may perform better in the prediction of pCR than the NLR, PLR, or CAR.

TABLE 1 Clinical features of 80 TNBC patients and their correlations with pCR of NAC

Factors	Total	pCR	Non-pCR	*p* value
Age, years [median (5–95%)]	49.5 (33.1–64.0)	48.0 (34.0–63.0)	52.0 (29.4–66.7)	**0.028**
Menopausal status				0.379
Premenopausal	37 (46.3)	20 (54.1)	17 (45.9)	
Peri/postmenopausal	43 (53.8)	19 (44.2)	24 (55.8)	
Family history				0.698
Negative	59 (73.8)	28 (47.5)	31 (52.5)	
Positive	21 (26.3)	11 (52.4)	10 (47.6)	
Body mass index, kg/m^2				0.773
< 25	50 (62.5)	25 (50.0)	25 (50.0)	
≥ 25	30 (37.5)	14 (46.7)	16 (53.5)	
Longest tumor diameter, mm [median (5–95%)]	32.0 (11.1–67.6)	30.0 (10.0–57.0)	34.0 (15.0–78.8)	0.052
Clinical tumor stage				**0.025**
cT1	16 (20.0)	12 (75.0)	4 (25.0)	
cT2	48 (60.0)	22 (45.8)	26 (54.2)	
cT3	13 (16.3)	5 (38.5)	8 (61.5)	
cT4	3 (3.8)	0 (0)	3 (100)	
Clinical nodal stage				0.531
cN0	10 (12.5)	3 (30.0)	7 (70.0)	
cN1	40 (50.0)	19 (47.5)	21 (52.5)	
cN2	18 (22.5)	10 (55.6)	8 (44.4)	
cN3	12 (15.0)	7 (58.3)	5 (41.7)	
Ki-67, %				0.100
< 37.5	21 (26.3)	7 (33.3)	14 (66.7)	
≥ 37.5	59 (73.8)	32 (54.2)	27 (45.8)	
NLR				0.274
< 1.71	23 (28.8)	9 (39.1)	14 (60.9)	
≥ 1.71	57 (71.3)	30 (52.6)	27 (47.4)	
PLR				**0.022**
< 129.7	35 (43.8)	12 (34.3)	23 (65.7)	
≥ 129.7	45 (56.3)	27 (60.0)	18 (40.0)	
LMR				**0.026**
< 5.37	37 (46.3)	23 (62.2)	14 (37.8)	
≥ 5.37	43 (53.8)	16 (37.2)	27 (62.8)	
CAR				0.167
< 0.047	45 (56.3)	25 (55.6)	20 (44.4)	
≥ 0.047	35 (43.8)	14 (40.0)	21 (60.0)	
Fibrinogen, g/L				**0.003**
< 2.92	30 (37.5)	21 (70.0)	9 (30.0)	
≥ 2.92	50 (62.5)	18 (36.0)	32 (64.0)	
D-dimer, ng/mL				**0.043**
< 67.5	13 (16.3)	3 (23.1)	10 (76.9)	
≥ 67.5	67 (83.8)	36 (53.7)	31 (46.3)	

Data are expressed as *n* (%) unless otherwise specified

The age and tumor diameter *p* values were determined by Mann–Whitney *U* tests, while other *p* values were determined by Chi square tests

Bold values indicate statistical significance ($p \leq 0.05$)

pCR pathologic complete response, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LMR* lymphocyte to monocyte ratio, *CAR* C-reactive protein/albumin ratio, *TNBC* triple-negative breast cancer, *NAC* neoadjuvant chemotherapy

TABLE 2 Predictive factors for pCR of NAC in 80 TNBC patients, estimated by univariate and multivariate logistic regression analyses

Factors	Univariate analysis			Multivariate analysis		
	OR	95% CI	*p* value	OR	95% CI	*p* value
Age, years	0.95	0.90–1.00	**0.048**			
Menopausal status						
Premenopausal	1					
Peri/postmenopausal	0.67	0.28–1.63	0.379			
Family history						
Negative	1					
Positive	1.22	0.45–3.30	0.698			
Body mass index, kg/m^2						
< 25	1					
≥ 25.0	0.88	0.35–2.17	0.773			
Longest tumor diameter, mm	0.97	0.95–1.00	0.072			
Clinical tumor stage						
cT1	1		**0.050**	1		**0.017**
cT2	0.28	0.08–1.00	**0.050**	0.11	0.02–0.51	**0.005**
cT3-4	0.15	0.03–0.71	**0.017**	0.15	0.02–0.90	**0.038**
Clinical nodal stage						
cN0	1		0.547			
cN1	2.11	0.48–9.35	0.325			
cN2	2.92	0.57–15.05	0.201			
cN3	3.27	0.55–19.25	0.191			
Ki-67, %						
< 37.5	1					
≥ 37.5	2.37	0.84–6.72	0.104			
NLR						
< 1.71	1					
≥ 1.71	1.73	0.65–4.63	0.277			
PLR						
< 129.7	1					
≥ 129.7	2.88	1.15–7.20	**0.024**			
LMR						
< 5.37	1			1		
≥ 5.37	0.36	0.15–0.89	**0.028**	0.18	0.05–0.59	**0.005**
CAR						
< 0.047	1					
≥ 0.047	0.53	0.22–1.31	0.169			
Fibrinogen, g/L						
< 2.92	1			1		
≥ 2.92	0.24	0.09–0.64	**0.004**	0.14	0.04–0.48	**0.002**
D-dimer, ng/mL						
< 67.5	1			1		
≥ 67.5	3.87	0.98–15.34	0.054	8.13	1.16–56.85	**0.035**

Multivariate analysis was based on forward stepwise logistic regression (likelihood ratio) analysis

Bold values indicate statistical significance ($p \leq 0.05$)

OR odds ratio, *CI* confidence interval, *NLR* neutrophil to lymphocyte ratio, *PLR* platelet to lymphocyte ratio, *LMR* lymphocyte to monocyte ratio, *CAR* C-reactive protein/albumin ratio, *pCR* pathologic complete response, *NAC* neoadjuvant chemotherapy, *TNBC* triple-negative breast cancer

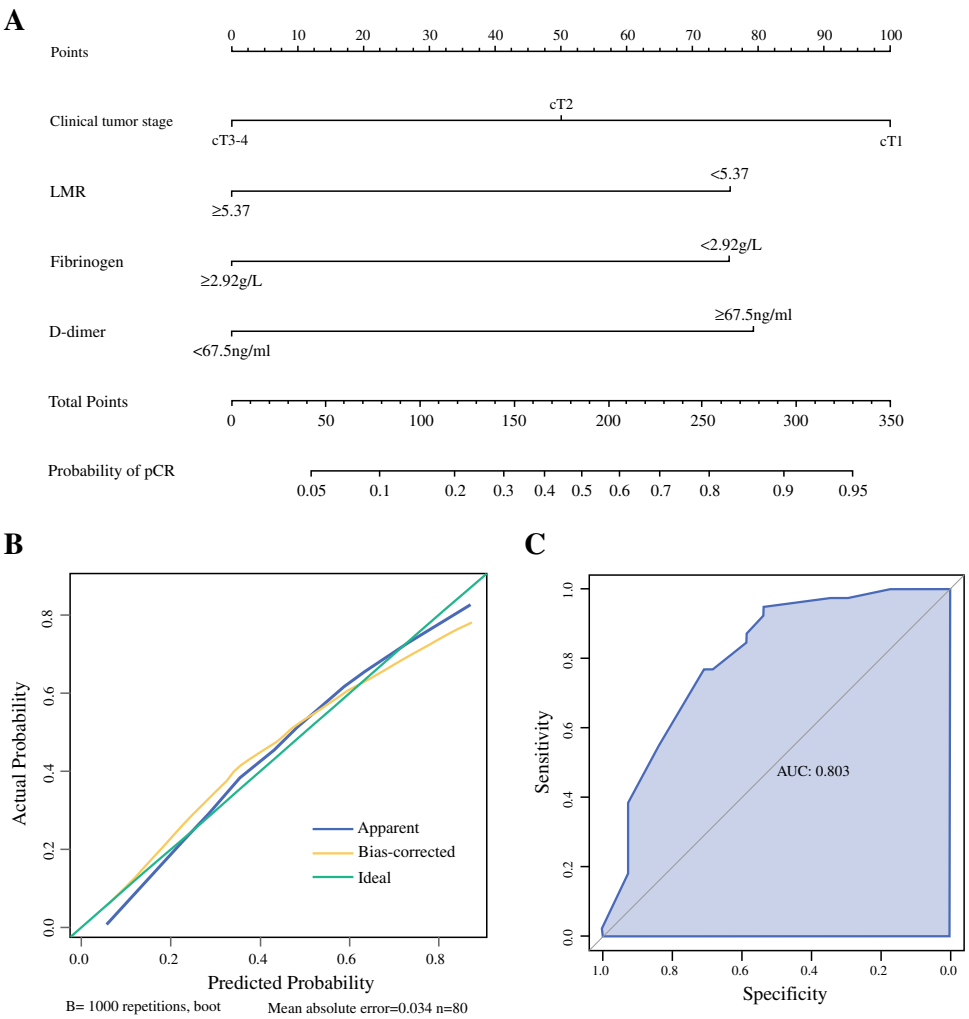

FIG. 1 The nomogram and its calibration and discrimination. **a** The nomogram for predicting the pCR of NAC in TNBC patients. **b** The calibration curve based on internal validation with a bootstrap resampling frequency of 1000. **c** The ROC curve with an AUC of 0.803 to demonstrate the discriminatory ability of the nomogram in predicting the pCR of NAC in TNBC patients. *LMR* lymphocyte to monocyte ratio, *pCR* pathologic complete response, *AUC* area under the curve, *NAC* neoadjuvant chemotherapy, *TNBC* triple-negative breast cancer, *ROC* receiver operating characteristic

The LMR has been studied in various types of cancer, including breast cancer, and low LMRs are generally associated with aggressive behaviors and worse outcomes.[15,25] Our study was the first to investigate the relationship between the LMR and the efficacy of NAC in TNBC patients. Interestingly, patients with low LMRs were more likely to achieve a pCR. This phenomenon might be explained by the fact that a low LMR correlates with aggressive behavior, which is known to be an important factor of chemosensitivity. The underlying mechanism needs further exploration. Additionally, long-term follow-up of patients in this study is needed to determine the relevance between the LMR and patient outcomes.

In addition, two coagulation-related parameters, i.e. fibrinogen and D-dimer levels, were used in the present study. In breast cancer, elevated levels of fibrinogen and D-dimers have been correlated with enhanced malignancy and a worse prognosis.[26–28] In our study, both were found to be related to the pCR of NAC in TNBC patients. An increasing number of studies have described a strong connection between hemostasis activation and cancer development. As a reliable biomarker of coagulation activation, the concentration of D-dimers may reflect the relationship between hemostasis and tumor progression, which may explain why D-dimers can be used to predict NAC efficacy and patient outcomes.[28,29]

Fibrinogen is a multifunctional protein that is mainly synthesized by the liver epithelium.[30] The secretion of cytokines by cancer cells can stimulate the production of fibrinogen, and, notably, some cancer cells can synthesize fibrinogen themselves.[31,32] Fibrinogen regulates many cellular processes, such as cellular adhesion, proliferation, and migration.[30] In tumors, fibrinogen can protect cells from natural killer cytotoxicity.[33] Additionally, it was reported that fibrinogen can induce the epithelial-mesenchymal transition by restraining the expression of adherent junction protein E-cadherin and increasing the

levels of the mesenchymal marker vimentin, which might be responsible for the resistance of tumor cells to chemotherapeutic agents.[34]

In addition, in this study, clinical tumor stage was identified as an independent predictor for the pCR of NAC, a result that is consistent with those of previous studies.[7,35] In this cohort, 75% of patients who were classified as cT1 TNBC, 45.8% of patients who were classified as cT2 TNBC, and only 31.3% of patients who were classified as cT3-4 TNBC achieved a pCR, which suggested the importance of taking clinical tumor stage into account when estimating the probability of pCR. Some studies also found that clinical nodal stage and Ki-67 were predictors of pCR in breast cancer,[36,37] while our analysis failed to support these findings in this cohort.

This was a retrospective study and we could not account for unknown factors associated with pCR. Many factors not examined in the present study, such as tumor grade, BRCA mutation status, and tumor-infiltrating lymphocytes, would also likely be related to pCR of TNBC.[36,38,39] Additionally, morphological changes in the tumor during NAC that were estimated by sonography or magnetic resonance imaging constitute a good predictor of pCR.[40] Morphological assessment can reflect the early response of the tumor to NAC and is able to guide subsequent NAC to improve patient outcomes.[41]

CONCLUSIONS

To our knowledge, no nomograms for predicting the pCR of NAC in TNBC patients have been published to date. Based on four simple, easily accessible, inexpensive, and objective factors, the present study established the first nomogram to predict the pCR of standard NAC in TNBC patients. The nomogram demonstrated its discriminatory capability with a fairly high AUC in our cohort; however, the applicability of this model still needs to be externally validated in multicenter, large-scale studies.

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DISCLOSURE Fanrong Zhang, Minran Huang, Huanhuan Zhou, Kaiyan Chen, Jiaoyue Jin, Yingxue Wu, Lisha Ying, Xiaowen Ding, Dan Su, and Dehong Zou declare no potential conflicts of interest.

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