Clinics of Surgery

Research Article

ISSN: 2638-1451 | Volume 6

Development and Validation of a Nomogram for Predicting Response to Neoadjuvant Chemotherapy in Patients with Breast Cancer

Jie Dong[1], Qingqing Sun[1], Shuaikang Pan[2], Hongwei Jin[2], Nannan Lu[2], Yueyin Pan[2], Qiong Zhou[3] and Xinghua Han[1*]

[1]Department of Oncology, Anhui Provincial Hospital affiliated to Anhui Medical University, Hefei, Anhui Province, China

[2]Department of Oncology, The First Affiliated Hospital of USTC, Division of Life Sciences and Medicine, University of Science and Technology of China, Hefei, Anhui Province, China

[3]Department of Oncology, Anhui No.2 Provincial People's Hospital, Hefei, Anhui Province, China

***Corresponding author:**

Xinghua Han,
Department of Oncology, Anhui Provincial Hospital Affiliated to Anhui Medical University, Hefei, Anhui Province, China,
E-mail: hxhmail@ustc.edu.cn

Received: 15 Nov 2021
Accepted: 16 Dec 2021
Published: 21 Dec 2021
J Short Name: COS

Keywords:

Breast cancer; Neoadjuvant chemotherapy; Pathological complete response; SIRI, PLR

Citation:

Xinghua Han, Development and Validation of a Nomogram for Predicting Response to Neoadjuvant Chemotherapy in Patients with Breast Cancer.
Clin Surg. 2021; 6(13): 1-9

1. Abstract

1.1. Purpose: The objective of our study is to construct and validate a nomogram for predicting NAC efficacy in breast cancer patients.

1.2. Methods: Retrospective analysis of clinical data on female patients with breast cancer was performed. Model 1 was developed by entering variables from the univariate analysis ($P < 0.1$) into a multivariate logistic regression analysis. Model 2 was developed via the stepwise forward-backward variable selection technique in partial least squares regression. For model 3, the least absolute shrinkage and selection operator (LASSO) method was used to choose suitable variables, followed by the multivariate logistic regression analysis. Harrell's C-index, calibration curves, and decision curve analyses (DCA) were used to compare the performance of the models. In the validation cohort, these results were validated.

1.3. Results: The training and validation cohorts had 315 and 103 patients, respectively. Model 2 had a higher C-index than the other models. The decision curve analysis of the three prediction models indicated that model 2 could achieve the maximum net benefit. Compared with the other two models, the integrated discrimination improvement showed that model 2 had improved prediction. Model 2's calibration curve functioned well in the validation cohort, with a C-index of 0.758. The positive and negative predictive values of the nomogram in the training cohort were 47.0% (38.0%-57.0%) and 96.0% (92.0%-98.0%). The positive and negative predictive values in the validation cohort were 40.0% (24.0%-58.0%) and 88.0% (78.0%-94.0%).

1.4. Conclusions: The nomogram proposed in the study showed good performance for predicting response to NAC in breast cancer patients.

2. Introduction

In patients with breast cancer, neoadjuvant chemotherapy (NAC) was initially introduced to treat locally advanced diseases and make inoperable tumors operable. And then, its application expanded to breast cancer in the early stage, which extraordinarily enhances the number of breast-conserving surgeries (BCS) [1,2]. BCS also improves psychosocial and cosmetic outcomes of patients after breast cancer surgery over mastectomy [3]. It has been known that pathologic complete response (pCR) can be a surrogate endpoint for breast cancer patients receiving NAC [4]. Acquiring pCR is related to improved survival outcomes. However, most patients cannot achieve pCR and over 50% of them will remain residual invasive carcinoma after NAC [5]. Hence, we need to filter out the non-pCR patients and formulate the optimal treatment strategy for them. It has been reported that gene expression profiles, liquid

biopsy, and medical imaging tests can predict the response to NAC in patients with breast cancer [6-8]. However, it is still challenging to implement these testing methods in routine clinical practice. In recent years, inflammation markers based on peripheral venous blood cells, including systemic inflammatory response index (SIRI), platelet to lymphocyte ratio (PLR), neutrophil to monocyte ratio (NMR), systemic immune inflammation index (SII), neutrophil to lymphocyte ratio (NLR), and lymphocyte to monocyte ratio (LMR) have been studied in patients with breast cancer receiving NAC [9-14]. These parameters are simple, conventional, objective, and inexpensive laboratory indexes. However, no study has investigated them together for predicting pCR.

The goal of our present study is to construct and evaluate a nomogram for the pCR prediction based on clinicopathological characteristics and inflammatory markers in patients with breast cancer receiving NAC.

3. Methods

3.1. Patient Population

Retrospective cohorts with breast cancer patients receiving NAC diagnosed at the First Affiliated Hospital of Anhui Medical University and the First Affiliated Hospital of USTC were analyzed. Patients were eligible if: (1) They were female primary breast cancer patients, (2) They were confirmed to have breast cancer before NAC by needle core biopsy; (3) They received breast-conserving surgery or modified radical mastectomy. Patients were ineligible if: (1) They have incomplete pathology report or laboratory examination results; (2) They were diagnosed with inflammatory breast cancer, bilateral breast cancer, or other inflammatory conditions. (3) They had distant metastases; Patients diagnosed at the First Affiliated Hospital of USTC between June 2015 and June 2021 were recruited in the training cohort, whereas patients diagnosed at the First Affiliated Hospital of Anhui Medical University between September 2020 and September 2021 were enrolled in the validation cohort. The study contained patients receiving NAC with regimens based on anthracyclines and/or taxanes. Anti-HER-2 targeted drugs were used to treat all patients who overexpressed human epidermal growth factor receptor 2 (HER-2). All clinical data were obtained from the medical records system. The project was authorized by the ethics committees of the First Affiliated Hospital of Anhui Medical University and the First Affiliated Hospital of USTC, and informed consent was waived.

3.2. Body Mass Index

The breast cancer patients' body weight and height were measured during their first round of neoadjuvant treatment. Body mass index (BMI) is determined by dividing patients' weight (kg) by their height (m2) and the cutoff value of BMI is 24 kg/m2.

3.3. Blood Samples

The peripheral vein blood test was performed in all patients before NAC initiation. NMR was defined as the neutrophil count divided by the monocyte count. NLR was calculated as the neutrophil count divided by the lymphocyte count. LMR was calculated by dividing the lymphocyte count by the monocyte count. PLR was defined as follows: the platelet count divided by the lymphocyte count. SIRI was defined as the monocyte count multiplied by neutrophil count divided by lymphocyte count. SII was defined as platelet count multiplied by neutrophil count divided by lymphocyte count.

3.4. Pathology

All patients' clinical stages were determined using the eighth edition of the American Joint Committee on Cancer staging guidelines. The absence of invasive tumors in breast tissue and axillary lymph nodes (ypT0/ypTis and ypN0) was regarded as pCR [15]. Immunohistochemistry (IHC) and fluorescence in situ hybridization (FISH) were used to determine the HER-2 status. This study contains the criteria for defining positive HER-2 status [16]. Expressions of estrogen receptor (ER) and progesterone receptor (PR) were determined by immunohistochemistry, and ER and PR positivity were defined as at least 1% of tumor cell nuclei staining in the sample. According to the expression of hormonal receptors (HR) and HER-2, patients were classified into 3 subtypes: HR-positive (HR+/HER-2–), Triple-negative (HR−/HER-2−), and HER-2–positive (HR±/HER-2+).

3.5. Statistical Methods

The Mann-Whitney U test was used to compare continuous variables presented as medians with interquartile ranges. Categorical variables were listed as whole numbers and proportions and compared using the $\chi 2$ test. The most appropriate cutoffs of inflammatory markers (NLR, PLR, LMR, SII, NMR, and SIRI) and age were determined by the receiver operating characteristic (ROC) curve.

Model 1 was created by incorporating variables from the univariate analysis ($P < 0.1$) into the multivariate logistic regression. Model 2 was developed via the stepwise forward-backward variable selection technique in partial least squares regression. For model 3, the least absolute shrinkage and selection operator (LASSO) method was performed to choose suitable variables, and variables were enclouded in multivariate logistic regression.

Calibration curves and Harrell's C-index and were constructed to evaluate the concordance between predicted and observed outcomes of the model in the training cohort and verified in the validation cohort. To assess the fitness of the nomogram, the Hosmer-Lemeshow test was also performed. To further evaluate the models' performance, integrated discrimination improvement (IDI) was calculated.

To estimate the clinical usefulness and benefits of the predictive models, decision curve analyses (DCA) were used. The total scores of the patients were obtained by the nomogram. The ap-

propriate cutoff value was determined via ROC curve analysis. The sensitivity, specificity, predictive values, and likelihood ratios were calculated to assess the accuracy of the best cutoff value. The R software (version 4.1.0) was used for all statistical analyses. Statistical significance is achieved if $p < 0.05$.

4. Results

4.1. Baseline Characteristics

There were 315 breast cancer patients in the training cohort and 103 patients in the validation cohort, respectively. In the training cohort, the best cutoff values for SIRI, PLR, LMR, NMR, SII, NLR, and age were 0.72, 119.25, 5.38, 8.74, 416.51, 1.77, and 34.5 years, respectively. The baseline characteristics were similar for the two cohorts. The pCR rate of the two cohorts was found in 19.05% and 21.40%, respectively. Table 1 showed the complete baseline characteristics of the primary and validation groups.

4.2. Construction and Comparison of the Predictive Model in the Training Cohort

For model 1, Chi-square tests were performed (Supplementary Table 1). Multivariate analysis showed that clinical Tumor and Nodal stages, SIRI and age were statistically associated with pCR (Table 2). For model 2, the stepwise forward-backward variable selection technique in partial least squares regression was performed, and the results indicated that SIRI, PLR, clinical Tumor and Nodal stages and age were statistically correlated with pCR (Table 2). For model 3, we performed the LASSO method to select suitable variables, and the results of multivariate logistic regression showed that age, clinical Nodal stage, and SIRI remained their importance (Figure 1 and Table 2). Model 2 had a higher C-index than the other models. Besides, the DCA curves of the three prediction models showed that model 2 could achieve the maximum net benefit (Figure 2D). The calibration curve of the three models was shown in Figures 2A, B, and C. The IDI was -0.0162 ($p = 0.146$) between model 1 and 3. The IDI between model 2 and 3 was -0.0336 ($p = 0.024$). The IDI was 0.0174 ($P = 0.125$) between model 1 and 2. Hence, model 2 had a trend of improved prediction performance compared with model 1 and 3. In summary, model 2 performed better than model 1 and 3.

Table 1: Baseline characteristics.

	Training cohort		**Validation cohort**		
Characteristics	**Number**	**Percent (%)**	**Number**	**Percent (%)**	***P-value***
Age					
<34.5	33	10.50	9	8.70	
≥34.5	282	89.50	94	91.30	0 .610
BMI					
<24	160	50.80	48	46.60	
≥24	155	49.20	55	53.40	0.460
Grade					
1	4	1.30	2	1.90	
2	165	52.40	43	41.70	
3	85	27.00	23	22.30	
4	61	19.40	35	34.00	0.020
Clinical T stage					
1	32	10.20	12	11.70	
2	218	69.20	71	68.90	
3-4	65	20.60	20	19.40	0.895
Clinical N stage					
N0	116	36.80	37	35.90	
N1-N3	199	63.20	66	64.10	0.869
Ki67					
<20	78	24.80	18	17.50	
≥20	237	75.20	85	82.50	0.127
Phenotype by IHC					
HR	128	40.60	46	44.70	
Her-2+	123	39.00	45	43.70	
TNBC	64	20.30	12	11.70	0.141
NAC regimens					
Anthra based	50	15.90	11	10.70	

Tax based	41	13.30	20	19.40	
Anthra + Tax based	224	71.10	72	69.90	0.163
NLR					
<1.77	64	20.30	21	20.40	
≥1.77	251	79.70	82	79.60	0.988
PLR					
<119.25	123	39.00	42	40.80	
≥119.25	192	61.00	61	59.20	0.755
LMR					
<5.38	257	81.60	64	62.10	
≥5.38	58	18.40	39	37.90	0.000
NMR					
<8.74	154	48.90	16	15.50	
≥8.74	161	51.10	87	84.50	0.000
SII					
<416.51	121	38.40	31	30.10	
≥416.51	194	61.60	72	69.90	0.128
SIRI					
<0.72	88	27.90	29	28.20	
≥0.72	227	72.10	74	71.80	0.966
Neutrophil	3.63 (2.93-4.65)		4.11 (3.24-4.69)		0.097
Lymphocyte	1.58 (1.31-1.90)		1.67 (1.32-2.07)		0.168
Monocyte	0.42 (0.31-0.52)		0.35 (0.27-0.42)		0.000
Platelet	211(170- 262)		224 (191-260)		0.081
Response to NAC					
pCR	60	19.05	22	21.40	
Non-pCR	255	80.95	81	78.60	0.608

Abbreviations: pCR, pathologic complete response; BMI, Body Mass Index; HR, hormone receptor; IHC, Immunohistochemistry; HER-2, Human Epidermal Growth Factor Receptor 2; NAC, neoadjuvant chemotherapy; Anthra, Anthracyclines; Tax, taxanes; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; LMR, lymphocyte to monocyte ratio; NMR, neutrophil to monocyte ratio; SII, systemic immune inflammation index; SIRI, systemic inflammatory response index

Table 2: Predictive factors for pCR in multivariate analysis.

	Model 1		**Model 2**		**Model 3**	
Variable	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***	**OR (95%CI)**	***P***
Age						
<34.5	1		1		1	
≥34.5	0.263(0.085-0.798)	0.019	0.260(0.087-0.759)	0.014	0.333(0.114-0.960)	0.041
cT						
T1	1		1			
T2	0.371(0.117-1.193)	0.092	0.292(0.094-0.915)	0.033	NA	NA
T3-4	0.170(0.041-0.668)	0.013	0.163(0.039-0.631)	0.010	NA	NA
cN						
N0	1		1		1	
N1-N3	0.051(0.023-0.143)	0.000	0.059(0.023-0.134)	0.000	0.066(0.025-0.156)	0.000

SIRI						
<0.72	1		1		1	
≥0.72	0.120(0.034-0.421)	0.001	0.213(0.083-0.528)	0.001	0.145(0.039-0.511)	0.003
PLR						
<119.25			1			
≥119.25	NA	NA	3.066(1.261-8.143)	0.018	NA	NA

Abbreviations: pCR, pathologic complete response; OR, Odds Ratio; cT, clinical Tumor stage; cN, clinical Nodal stage, SIRI, systemic inflammatory response index; PLR, platelet to lymphocyte ratio.

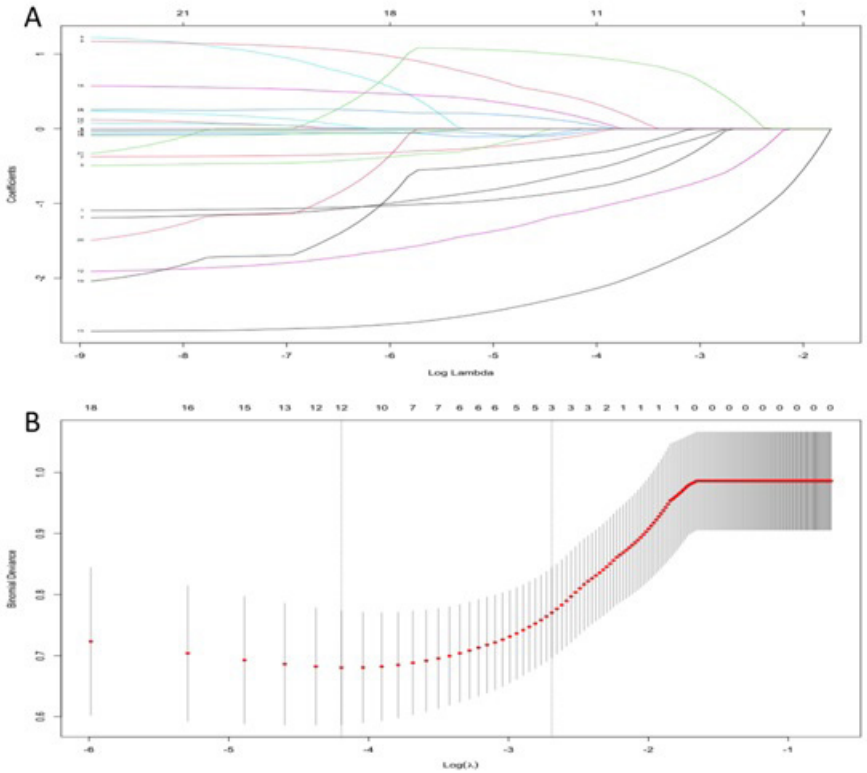

Figure 1. Tuning parameter selection for pCR (A) and LASSO coefficient profiles of the texture features (B) in the LASSO model, an optimal λ (0.000137) resulted in 17 variables.

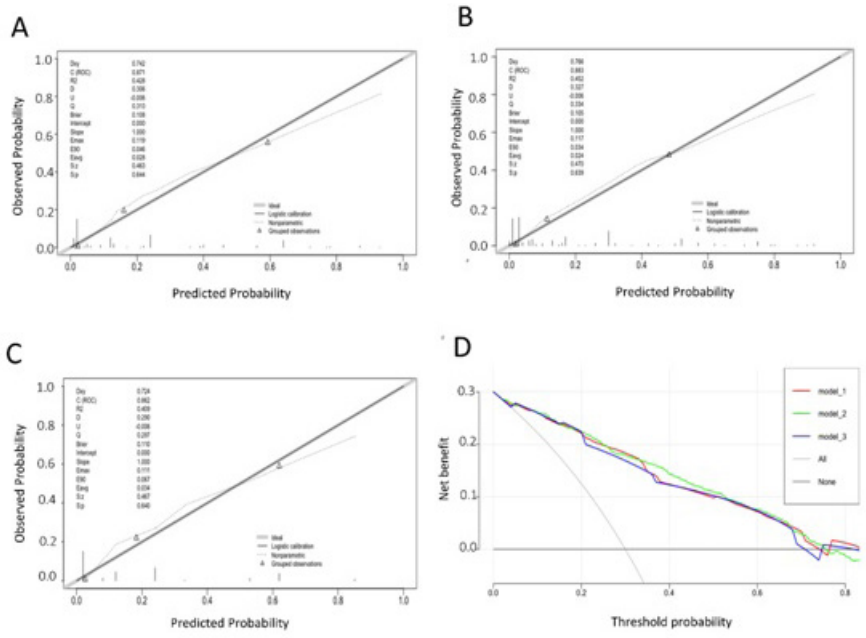

Figure 2. Validity of the predictive performance of model 1 (A), model 2 (B), and model 3 (C) and DCA curve for the three models (D).

4.3. The Creation and Validation of a pCR-Predicting Nomogram.

According to the results of model 2 in the training cohort, a nomogram was created for predicting pCR (Figure 3), which showed that the clinical Nodal stage had the most important impact on achieving pCR, followed by SIRI, clinical Tumor stage, PLR, and age. The C-index of the nomogram for predicting pCR was 0.884 (95% CI: 0.844–0.924). The calibration curves showed good consistency on the existence of pCR between the possibility estimation using the nomogram and pathological confirmation (Figure 4A). The results of the Hosmer–Lemeshow test also indicated good calibration (Chi-square 7.3641, p = 0.9085). The C-index of our nomogram for the pCR prediction was 0.758 (95% CI: 0.649-0.868) in the validation cohort. The calibration curves also performed well (Figure 4B).

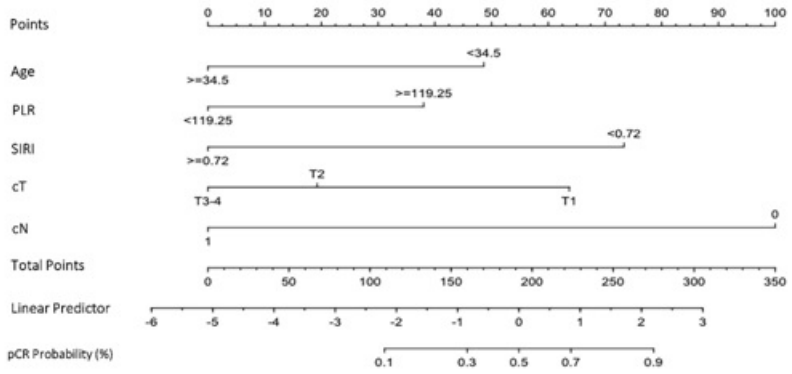

Figure 3. Nomogram for predicting pCR in patients treated with NAC.

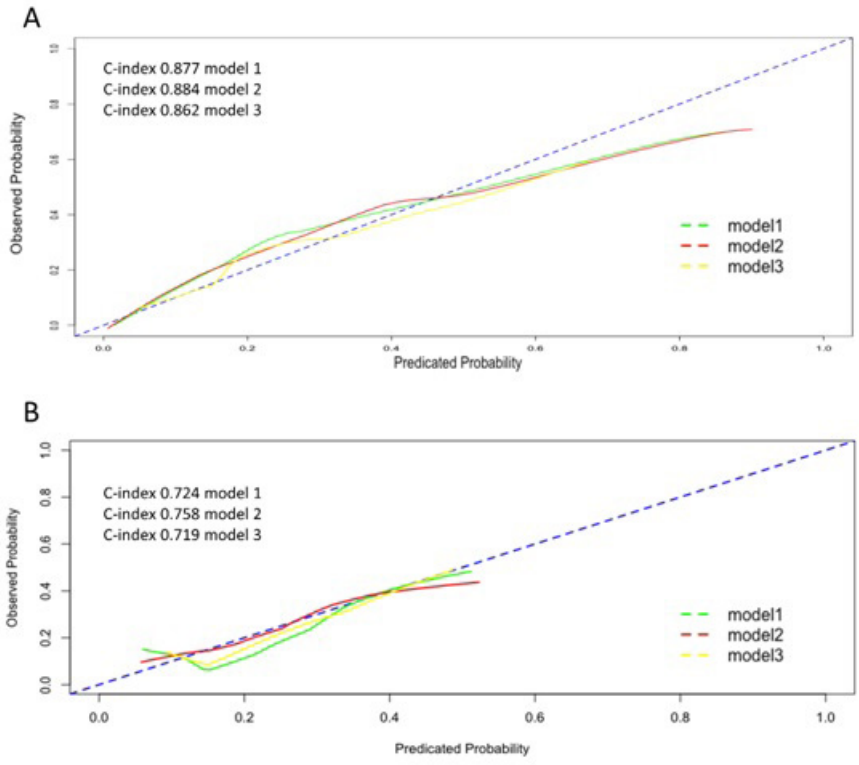

Figure 4. Calibration curves for the nomogram in the training cohort (A) and validation cohort (B).

4.4. The Clinical Usefulness Evaluation of the Nomogram

The best cutoff value for total scores was determined to be 133.5 using the nomogram by ROC curve analysis. In the training and validation cohorts, we calculated the sensitivity, specificity, positive and negative predictive values, and positive and negative likelihood ratio to assess the ability of the nomogram for distinguishing the presence from lack of pCR. Table 3 shows the specific value in the training and validation cohorts.

Table 3: Clinical usefulness of the Nomogram for predicting pCR.

	Value (95% CI)	
Variable	**Training Cohort**	**Validation Cohort**
Area under ROC curve	0.884 (0.844–0.924)	0.758 (0.649-0.868)
Cutoff value	133.5	133.5
Sensitivity, %	0.85 (0.73-0.92)	0.64 (0.41-0.82)
Specificity, %	0.78 (0.72-0.83)	0.74 (0.63-0.83)
Positive predictive value, %	0.47 (0.38-0.57)	0.40 (0.24-0.58)
Negative predictive value, %	0.96 (0.92-0.98)	0.88 (0.78-0.94)
Positive likelihood ratio	3.80 (2.95-4.89)	2.45 (1.51-3.99)
Negative likelihood ratio	0.05 (0.02-0.09)	0.49 (0.28-0.86)

Abbreviations: pCR, pathologic complete response.

5. Discussion

NAC is becoming more popular in breast cancer patients. However, most patients cannot achieve pCR after NAC. For patients with the non-pCR disease, they would need upgraded therapeutic regimens. Therefore, we need to filter out the patients with a low probability of achieving pCR. In the present study, we compared three statistical methods to obtain a better predictive model and developed a nomogram based on clinicopathological parameters and inflammation indicators for predicting pCR in breast cancer patients receiving NAC. Inflammation markers, such as SII, PLR, SIRI, NLR, LMR, and NMR, have been studied in breast cancers receiving NAC. However, there remains unclear whether the predictive value of those indicators for pCR would change when evaluating them together. In our study, the six inflammation-based indicators were included. When they were evaluated to predict pCR, the multivariate analysis identified the SIRI and PLR as independent predictors, which means SIRI and PLR may perform better in predicting pCR than the NLR, LMR, NMR, and SII. Inflammation cells, such as neutrophils, lymphocytes, and monocytes, may exert important anti-tumor effects. Neutrophils exhibit an anti-tumor phenotype directly through antibody-dependent cytotoxicity and indirectly through the secretion of pro-inflammatory cytokines [17]. Lymphocytes can mediate cytotoxicity to suppress tumor growth [18]. Monocytes perform anti-tumor functions, by contributing to antitumoral immunity, including phagocytosis and promotion of angiogenesis [19]. Platelets can also work as active players in tumor metastasis [20]. The concentration of the cells may indicate the host immune responses against tumors. SIRI and PLR have been studied in many cancer types, including breast cancer, and high SIRI and PLR are associated with worse outcomes, generally [21-24]. In our study, we found that patients with high SIRI were less likely to achieve pCR, which is consistent with our previous finding [25]. And patients with high PLR were associated with better NAC response, which contradicted the finding of Xu J et al [26]. However, in their study, they only performed $\chi 2$ tests to evaluate the association between PLR and NAC efficacy. Besides, the better NAC efficacy in our study was defined as pCR, which was different from their study. These reasons may explain the contradictory conclusion. The underlying mechanism of inflammation indicators for predicting pCR needs further exploration.

In addition, in our present study, age, clinical Nodal and Tumor stage were also identified as independent predictors for the pCR. In our cohort, the young age was associated with a high pCR rate, which is consistent with the findings of Chou HH et al [27]. Choi HJ et al. found that a higher clinical tumor stage was related to a lower pCR rate [28]. And Hwang HW et a. reported that a low clinical Nodal stage was associated with a high pCR rate [29]. All of these findings matched ours. It is reported that TIL, PET-CT, and gene expression profiles can predict pCR [29-31]. However, these methods cannot be routinely performed in actual clinical practice. Hence, we need to find more appropriate methods. Based on the multivariate analysis results in the training cohort, we integrated the independent predictive factors, such as age, clinical Tumor and Nodal stage, PLR, and SIRI to construct the nomogram. The nomogram's C-index and calibration curve demonstrated good performance in predicting pCR. The model was also shown to have strong stability in the validation cohort. For evaluating the clinical usefulness of the model, the specificity, sensitivity, negative and positive predictive values were calculated in estimating the chance of achieving pCR (Table 3). Patients with a score < 133.5 were less likely to obtain pCR (negative predictive value, 96.0%). As a result, the nomogram might be used to identify non-pCR patients. This method helped to save the limited medical resources for society and reduce the medical costs for patients.

Our research also has some limitations. This was a retrospective study using a relatively small number of patients and the results may be biased. And then, there might be deviations in the evaluation of the patient's inflammatory status. Many comorbidities can influence the value of the inflammation markers. More importantly, the relationship of SIRI and PLR with disease-free survival and overall survival cannot be assessed in the study because of the missing follow-up data. Therefore, prospective and multicenter investigations are necessary to confirm the study's conclusions.

In conclusion, our nomogram is convenient and reliable. We can filter out the non-pCR patients and formulate the optimal treatment strategy for them by the nomogram.

6. Acknowledgement

This work was supported by the Anhui Province Natural Science Foundation (1908085MH286) and China Postdoctoral Science Foundation (2020M682050).

References

1. Rubens RD, Sexton S, Tong D, Winter PJ, Knight RK, Hayward JL. Combined chemotherapy and radiotherapy for locally advanced breast cancer. Eur J Cancer. 1980; 16(3): 351-6.
2. Colomer R, Saura C, Sanchez-Rovira P, Pascual T, Rubio IT, Burgues O, et al. Neoadjuvant Management of Early Breast Cancer: A Clinical and Investigational Position Statement. Oncologist. 2019; 24(5): 603-11.
3. Cochrane RA, Valasiadou P, Wilson AR, Al-Ghazal SK, Macmillan RD. Cosmesis and satisfaction after breast-conserving surgery correlates with the percentage of breast volume excised. Br J Surg. 2003; 90(12): 1505-9.
4. Prowell TM, Pazdur R. Pathological complete response and accelerated drug approval in early breast cancer. N Engl J Med. 2012; 366(26): 2438-41.
5. Cortazar P, Zhang L, Untch M, Mehta K, Costantino JP, Wolmark N, et al. Pathological complete response and long-term clinical benefit in breast cancer: the CTNeoBC pooled analysis. The Lancet. 2014; 384(9938): 164-72.
6. Braman NM, Etesami M, Prasanna P, Dubchuk C, Gilmore H, Tiwari P, et al. Intratumoral and peritumoral radiomics for the pretreatment prediction of pathological complete response to neoadjuvant chemotherapy based on breast DCE-MRI. Breast Cancer Res. 2017; 19(1): 57.
7. Han Y, Wang J, Xu B. Novel biomarkers and prediction model for the pathological complete response to neoadjuvant treatment of triple-negative breast cancer. J Cancer. 2021; 12(3): 936-45.
8. Magbanua MJM, Swigart LB, Wu HT, Hirst GL, Yau C, Wolf DM, et al. Circulating tumor DNA in neoadjuvant-treated breast cancer reflects response and survival. Ann Oncol. 2021; 32(2): 229-39.
9. Graziano V, Grassadonia A, Iezzi L, Vici P, Pizzuti L, Barba M, et al. Combination of peripheral neutrophil-to-lymphocyte ratio and platelet-to-lymphocyte ratio is predictive of pathological complete response after neoadjuvant chemotherapy in breast cancer patients. Breast. 2019; 44: 33-8.
10. Hu Y, Wang S, Ding N, Li N, Huang J, Xiao Z. Platelet/Lymphocyte Ratio Is Superior to Neutrophil/Lymphocyte Ratio as a Predictor of Chemotherapy Response and Disease-free Survival in Luminal B-like (HER2(-)) Breast Cancer. Clin Breast Cancer. 2020; 20(4): e403-e9.
11. Ma Y, Zhang J, Chen X. Lymphocyte-to-Monocyte Ratio is Associated with the Poor Prognosis of Breast Cancer Patients Receiving Neoadjuvant Chemotherapy. Cancer Manag Res. 2021; 13: 1571-80.
12. Peng Y, Chen R, Qu F, Ye Y, Fu Y, Tang Z, et al. Low pretreatment lymphocyte/monocyte ratio is associated with the better efficacy of neoadjuvant chemotherapy in breast cancer patients. Cancer Biol Ther. 2020; 21(2): 189-96.
13. Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pre-treatment systemic immune-inflammation index is a useful prognostic indicator in patients with breast cancer undergoing neoadjuvant chemotherapy. J Cell Mol Med. 2020; 24(5): 2993-3021.
14. Chen L, Kong X, Wang Z, Wang X, Fang Y, Wang J. Pretreatment Systemic Inflammation Response Index in Patients with Breast Cancer Treated with Neoadjuvant Chemotherapy as a Useful Prognostic Indicator. Cancer Manag Res. 2020; 12: 1543-67.
15. von Minckwitz G, Untch M, Blohmer JU, Costa SD, Eidtmann H, Fasching PA, et al. Definition and impact of pathologic complete response on prognosis after neoadjuvant chemotherapy in various intrinsic breast cancer subtypes. J Clin Oncol. 2012; 30(15): 1796-804.
16. Wolff AC, Hammond MEH, Allison KH, Harvey BE, Mangu PB, Bartlett JMS, et al. Human Epidermal Growth Factor Receptor 2 Testing in Breast Cancer: American Society of Clinical Oncology/ College of American Pathologists Clinical Practice Guideline Focused Update. Arch Pathol Lab Med. 2018; 142(11): 1364-82.
17. Brandau S, Dumitru CA, Lang S. Protumor and antitumor functions of neutrophil granulocytes. Semin Immunopathol. 2013; 35(2): 163-76.
18. Morrow ES, Roseweir A, Edwards J. The role of gamma delta T lymphocytes in breast cancer: a review. Transl Res. 2019; 203: 88-96.
19. Olingy CE, Dinh HQ, Hedrick CC. Monocyte heterogeneity and functions in cancer. J Leukoc Biol. 2019; 106(2): 309-22.
20. Schlesinger M. Role of platelets and platelet receptors in cancer metastasis. J Hematol Oncol. 2018; 11(1): 125.
21. Van Berckelaer C, Van Geyt M, Linders S, Rypens C, Trinh XB, Tjalma WAA, et al. A high neutrophil-lymphocyte ratio and platelet-lymphocyte ratio are associated with a worse outcome in inflammatory breast cancer. Breast. 2020; 53: 212-20.
22. Wang L, Zhou Y, Xia S, Lu L, Dai T, Li A, et al. Prognostic value of the systemic inflammation response index (SIRI) before and after surgery in operable breast cancer patients. Cancer Biomark. 2020; 28(4): 537-47.

23. Sun L, Hu W, Liu M, Chen Y, Jin B, Xu H, et al. High Systemic Inflammation Response Index (SIRI) Indicates Poor Outcome in Gallbladder Cancer Patients with Surgical Resection: A Single Institution Experience in China. Cancer Res Treat. 2020; 52(4): 1199-210.
24. Diem S, Schmid S, Krapf M, Flatz L, Born D, Jochum W, et al. Neutrophil-to-Lymphocyte ratio (NLR) and Platelet-to-Lymphocyte ratio (PLR) as prognostic markers in patients with non-small cell lung cancer (NSCLC) treated with nivolumab. Lung Cancer. 2017; 111: 176-81.
25. Dong J, Sun Q, Pan Y, Lu N, Han X, Zhou Q. Pretreatment systemic inflammation response index is predictive of pathological complete response in patients with breast cancer receiving neoadjuvant chemotherapy. BMC Cancer. 2021; 21(1): 700.
26. Xu J, Ni C, Ma C, Zhang L, Jing X, Li C, et al. Association of neutrophil/lymphocyte ratio and platelet/lymphocyte ratio with ER and PR in breast cancer patients and their changes after neoadjuvant chemotherapy. Clin Transl Oncol. 2017;19(8):989-96.
27. Chou HH, Kuo WL, Yu CC, Tsai HP, Shen SC, Chu CH, et al. Impact of age on pathological complete response and locoregional recurrence in locally advanced breast cancer after neoadjuvant chemotherapy. Biomed J. 2019; 42(1): 66-74.
28. Choi HJ, Ryu JM, Kim I, Nam SJ, Kim SW, Yu J, et al. Nomogram for accurate prediction of breast and axillary pathologic response after neoadjuvant chemotherapy in node positive patients with breast cancer. Ann Surg Treat Res. 2019; 96(4): 169-76.
29. Hwang HW, Jung H, Hyeon J, Park YH, Ahn JS, Im YH, et al. A nomogram to predict pathologic complete response (pCR) and the value of tumor-infiltrating lymphocytes (TILs) for prediction of response to neoadjuvant chemotherapy (NAC) in breast cancer patients. Breast Cancer Res Treat. 2019; 173(2): 255-66.
30. Li P, Wang X, Xu C, Liu C, Zheng C, Fulham MJ, et al. (18)F-FDG PET/CT radiomic predictors of pathologic complete response (pCR) to neoadjuvant chemotherapy in breast cancer patients. Eur J Nucl Med Mol Imaging. 2020; 47(5): 1116-26.
31. Bownes RJ, Turnbull AK, Martinez-Perez C, Cameron DA, Sims AH, Oikonomidou O. On-treatment biomarkers can improve prediction of response to neoadjuvant chemotherapy in breast cancer. Breast Cancer Res. 2019; 21(1): 73.