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ORIGINAL ARTICLE

Preoperative systemic inflammation response index: Clinicopathologic predictor of pathological complete response in HER2-positive breast cancer patients receiving neoadjuvant systemic therapy

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Abstract

Background: Multiple pretreatment systemic inflammatory markers (SIMs) have been reported as predictors of pathological complete response (pCR) after neoadjuvant systemic therapy (NST) in patients with breast cancer (BC). However, the most significant SIM remains to be conclusively identified, and variations among different molecular subtypes remain unknown. The objective of the study was to identify the most significant SIM in patients with human epidermal growth factor receptor 2 (HER2) positive BC, to construct a pCR-predictive nomogram combining it with other clinicopathologic factors, and to evaluate its prognostic value on survival.

Methods: We retrospectively reviewed the findings for 240 patients with stage I-III HER2-positive BC who underwent NST and subsequent surgery at Kaohsiung and Taichung Veterans General Hospital from 2011 to 2021. Clinicopathologic factors were analyzed by stepwise logistic regression with backward selection. The data were used to construct a nomogram plot for determining the pCR probability. Kaplan-Meier curves and log-rank test were used to evaluate disease-free survival (DFS) and overall survival (OS).

Results: Among the pretreatment SIMs, only the systemic inflammation response index (SIRI) was significantly related to pCR, with an optimal cutoff value of 1.27×10^9/L. Stepwise logistic analyses indicated that clinical N stage, HER2 immunohistochemistry score, hormone receptor status, targeted therapy regimen, and SIRI were independent predictors of pCR, with an area under the curve of 0.722. The Hosmer-Lemeshow test and calibration curve revealed that the predictive ability was a good fit to actual observations. A nomogram was constructed based on the logistic model. The external validation of the model also revealed satisfactory discrimination and calibration. Kaplan-Meier analysis showed that patients with SIRI <1.27 had longer DFS and OS.

Conclusion: Pretreatment SIRI <1.27 is predictive of pCR, DFS, and OS in HER2-positive BC. Our nomogram could efficiently predict pCR and facilitate clinical decision-making before neoadjuvant treatment.

Keywords: Breast neoplasms; Neoadjuvant therapy; Nomograms

1. INTRODUCTION

Neoadjuvant systemic therapy (NST) is increasingly being used for treating early-stage breast cancer (BC). It not only improves breast-conserving surgery rates and reduces surgical morbidity, but also enables the prediction of long-term prognosis on the basis of pathological response.[1–3] Pathological complete response (pCR), defined as ypT0/isN0, is strongly associated with disease-free survival (DFS) and overall survival (OS) in patients with triple-negative BC (TNBC) and human epidermal growth factor receptor 2 (HER2)-enriched tumors receiving HER2-targeted therapy. These two subtypes also exhibit the highest pCR rates.[3]

To facilitate clinical decision-making before NST, many nomograms combining multiple clinicopathologic factors have been developed to estimate pCR probability.[4–6] Because most nomograms have been designed for populations containing all molecular subtypes, Jankowski et al discovered that patients with HER2-positive (HER2+) tumors require a specifically designed nomogram and built the Centre Georges-François Leclerc

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(CGFL)/Curie nomogram combining T stage, hormone receptor status, and Ki-67 levels.[7,8] Meanwhile, Fujii et al[9] used estrogen receptor (ER) and progesterone receptor (PR) expression levels, HER2/CEP17 ratio, inflammatory BC, and the NST regimen in their HER2+-tumor-specific nomogram.

Inflammation has been recognized to play important roles in cancer development, progression, and response to chemotherapy.[10] The immune and inflammatory cells, such as neutrophils, lymphocytes, and monocytes, that can be detected in systemic circulation, may have crucial interaction with cancer cells in the tumor microenvironment.[11–13] Many pretreatment systemic inflammation markers (SIMs) based on these peripheral blood cell counts have been reported to be associated with pCR in BC. Cullinane et al[14] found that a lower neutrophil-lymphocyte ratio (NLR) was associated with a greater rate of pCR in a 2020 meta-analysis. In a study by Ma et al,[15] patients with low lymphocyte-monocyte ratio (LMR) had higher pCR rates. A low systemic inflammation response index (SIRI, defined as neutrophil count × monocyte count/lymphocyte count) was found predictive of pCR in a study by Dong et al.[16] Absolute lymphocyte count (ALC) and platelet-lymphocyte ratio (PLR) have also been reported.[17,18] Nevertheless, the SIM showing the greatest correlation with pCR in patients with BC has not been conclusively identified, and the variations among molecular subtypes are unknown.

The primary objective of this study was to investigate the pCR-predictive ability of multiple pretreatment SIMs in patients with HER2+ BC treated with NST. The second objective was to construct an HER2+-tumor-specific nomogram based on clinicopathologic factors, including the SIMs that were significantly associated with pCR. The third objective was to evaluate the prognostic value of the pCR-associated SIMs on DFS and OS.

2. METHODS

2.1. Patients

We retrospectively enrolled female patients with primary stage I-III HER2+ invasive BC who underwent NST followed by surgical resection at Kaohsiung Veterans General Hospital and Taichung Veterans General Hospital between January 2011 and May 2021. This study was approved by the Kaohsiung and Taichung Veterans General Hospital Institutional Review Board.

The inclusion criteria were as follows: (1) diagnosis of HER2+ BC by core-needle biopsy with immunohistochemistry (IHC) staining; (2) peripheral blood samples collected after BC diagnosis and before NST administration; (3) all patients received NST with both chemotherapy and HER2-targeted therapy; and (4) all patients underwent surgical treatment after NST. The exclusion criteria were as follows: (1) distant metastases, (2) history of other malignant diseases, (3) bilateral BC, and (4) incomplete pathological or laboratory results.

Following NST, all patients underwent mastectomy or breast-conserving surgery plus radiation therapy. Either sentinel lymph node biopsy or axillary lymph node dissection was performed depending on the clinical nodal (cN) stage, results of intraoperative frozen section analysis, and surgeon's experience. We collected the following information from the patients' medical records: clinical factors, including age, body mass index (BMI), clinical tumor (cT), and cN stage based on breast sonography and/or computed tomography, pretreatment SIMs, NST regimens, and NST duration; pathologic factors determined in the core-needle biopsy specimen, including ER and PR statuses, HER2 IHC score, Ki-67 level, histologic type, histologic grade, and pathological response determined in the definitive surgery specimen.

2.2. Pathologic evaluation

ER and PR positivity were defined by staining of at least 1% of the tumor cell nuclei in the sample. The HER2 IHC score was determined according to the criteria of the American Society of Clinical Oncology/College of American Pathologists 2018 guidelines.[19] Samples with HER2 IHC scores of 2+ were further tested using fluorescence in situ hybridization (FISH). HER2 positivity was defined as IHC 3+ or IHC 2+ with FISH amplification. A cutoff point of 20% for the Ki-67 level was used.[20] Histological grade was assessed using the Nottingham combined grading system. pCR was defined as no evidence of residual invasive cancer in the breast or regional lymph nodes at the time of definitive surgery, regardless of the presence of residual ductal carcinoma in situ (ypT0/isN0).

2.3. Pretreatment SIMs

We calculated pretreatment ALC, NLR, PLR, LMR, and SIRI using peripheral venous blood samples collected after BC diagnosis and before the start of the NST regimen. More than 70% of the patients received the first cycle of NST within 2 weeks of blood sample collection. The longest interval between blood sample collection and the first NST cycle was two months. All complete blood cell counts with differential tests were performed at our institutional laboratories.

2.4. NST regimen

All patients were treated with neoadjuvant cytotoxic chemotherapy combined with HER2-targeted therapy. Chemotherapy regimen was classified as either taxane-based or sequential taxane-based plus anthracycline-based regimens. Taxane-based regimens included weekly paclitaxel for 12 weeks (12 cycles), triweekly docetaxel for 12 weeks (four cycles), or triweekly docetaxel with concurrent or sequential carboplatin or cyclophosphamide (six cycles when combined with carboplatin). Anthracycline-based regimens included epirubicin or liposomal doxorubicin + cyclophosphamide every 2 to 4 weeks, either combined with 5-fluorouracil or not. However, some patients who could not tolerate the adverse effects of chemotherapy may have undergone NST for durations shorter than 12 weeks. HER2-targeted therapy was administered with either trastuzumab alone or trastuzumab plus pertuzumab. Hormone therapy including tamoxifen or aromatase inhibitors could also be given to patients with positive hormone receptor.

2.5. Follow-up and survival

All patients' follow-up record from surgery date to August 2023 were reviewed. Laboratory tests, breast sonography, mammography, and any specific examination for suspected distant metastases were checked as the follow-up assessments. DFS was defined as the time from the date of the first NST cycle to the date of local recurrence, distant metastases, death from any cause, or last follow-up. OS was defined as the time from the date of the first NST cycle to the date of death from any cause or last follow-up.

2.6. Statistical analysis

Statistical analyses were performed using SPSS version 20 (SPSS Inc., Chicago, IL) and SAS version 9.4 (SAS Institute Inc., Cary, NC). Age and SIMs were analyzed as continuous variables, whereas the other factors were analyzed as categorical variables. The difference of clinicopathologic factors between pCR and non-pCR group were analyzed using chi-square tests, Fisher exact test, or Student's *t* tests. Receiver operating characteristic (ROC) curve analysis was used to determine the optimal cutoff value for continuous variables that were significantly associated with pCR. The point with the highest Youden

index (sensitivity + specificity – 1) was defined as the optimal cutoff point. Univariable logistic regression and backward stepwise selection for the multivariable model were performed to identify the independent predictors of pCR. A nomogram was established based on the multivariable logistic model. The goodness of fit for the model was checked using the Hosmer-Lemeshow test (HL test) and graphically shown by a calibration curve. The area under the ROC curve (AUC) was used to demonstrate the discriminatory capability of the model. Survival analysis was performed by the Kaplan-Meier method and log-rank test. Statistical significance was set at $p < 0.05$.

2.7. Nomogram construction

SAS was used for nomogram plot construction by using a method described by Yang.[21] First, the multivariable logistic model was built. Second, scoring of each predictor based on the estimated coefficients was done, whereas the biggest impact predictor was identified as a reference. Then, we could calculate total points and project onto the probability scale from 0 to 1. Finally, a nomogram plot could be constructed using SGPLOT procedure or graph template language.

2.8. External validation

A validation cohort was enrolled at Taichung Tzu Chi Hospital between January 2020 and August 2023. The inclusion and exclusion criteria were identical to our development cohort. Information on all variables was reviewed from the patients' medical records. The nomogram total score of each case was calculated for analysis. The calibration of the model is evaluated by HL test. Evaluation of model discrimination was reported by AUC of ROC analysis.

3. RESULTS

3.1. Patient characteristics

A total of 287 patients with HER2+ BC who underwent NST were identified, and 240 patients were ultimately included (Fig. 1). A total of 119 patients (49.6%) achieved pCR after NST. The clinical characteristics are presented in Table 1. All patients were women. The mean patient age was 53 years old (range, 25-79 years old), and 79 (33%) patients had BMI ≥25 kg/m^2. A total of 195 patients had cT1-2 tumors (81%) and 45 patients had cT3-4 tumors (19%). A total of 72.5% of the patients were classified as cN1-3 (n = 174). Twenty-five cases (10%) showed HER2 IHC 2+ tumors and 215 (90%) showed HER2 3+ tumors. Hormone receptor status was negative (ER–/PR–) in 104 patients (43%), positive (ER+/PR+) in 89 patients (37%), and dissociated (ER+/PR– or ER–/PR+) in 47 patients (20%). The Ki-67 level was below 20% in 16 cases (7%), greater than 20% in 214 cases (89%), and unknown in 10 cases (4%). Most tumors were diagnosed as invasive ductal carcinomas, while only 18 patients (7.5%) had other histological diagnoses. A total of 119 cases (50%) had grade 1-2 tumors, 107 (45%) had grade 3 tumors, and 14 (6%) had no available data regarding histologic grade. Most patients received a sequential taxane-based plus anthracycline-based regimen (n = 179; 75%). Only 10 patients (4%) had an NST duration of <12 weeks due to intolerance to the side effects of chemotherapy. Eighty-four patients received dual HER2-targeted blockade with trastuzumab plus pertuzumab, whereas 156 patients received trastuzumab only.

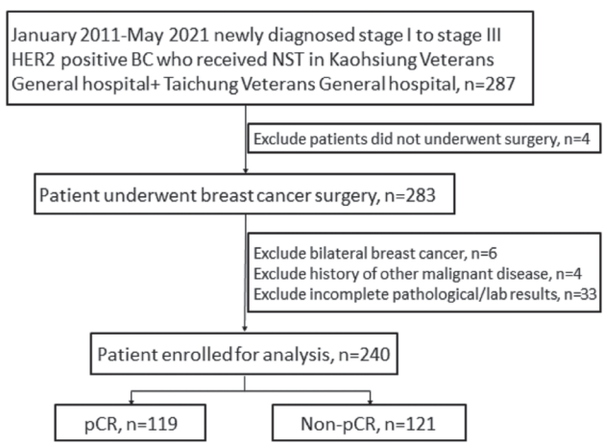

Fig. 1 The flow diagram of patient enrollment. BC = breast cancer; HER2 = human epidermal growth factor receptor 2; NST = neoadjuvant systemic therapy; pCR = pathological complete response.

3.2. Associations between clinicopathologic parameters and pCR

Statistical group analysis was performed between pCR and non-pCR patients (Table 1). Lower cT stage, cN0, HER2 IHC 3+, and SIRI were significantly associated with pCR. The pCR group had more negative hormone receptors ($p = 0.057$) and more dual HER2-targeted therapy ($p = 0.086$); however, this difference was not statistically significant. No obvious differences were observed in age, BMI, Ki-67 level, histologic type, histologic grade, chemotherapy regimen, NST duration, ALC, NLR, PLR, or LMR. The optimal cutoff value was 1.27 for SIRI, as determined by ROC curve analysis.

Univariable logistic regression analysis demonstrated that cT3-4, cN1-3, ER+/PR+, and SIRI ≥1.27 were associated with a lower pCR rate; HER2 IHC 3+ was associated with a higher pCR rate (Table 2). For hormone receptors, there was a significant difference between negative and positive status but not between negative and dissociated status. In successive stepwise multivariable logistic regression with backward selection, cN stage, HER2 IHC score, hormone receptor status, targeted therapy regimen, and SIRI were identified independent predictors in the model for pCR of NST in HER2+ patients with BC. cT stage was eliminated by the backward selection process. It was the last variable that can be deleted without a statistically significant loss of fit.

3.3. Nomogram for predicting pCR

The ROC curve of the multivariable regression model is shown in Fig. 2; the AUC was 0.722 (95% CI, 0.658-0.786). On the basis of this model, cN stage, HER2 IHC score, hormone receptor status, targeted therapy regimen, and SIRI were included to construct a nomogram to predict the pCR probability of NST in patients with HER2+ BC (Fig. 3). The score for each factor is listed as follows: 9.1 points for cN0; 0 points for cN1-3; 10 points for HER2 IHC 3+; 0 points for IHC 2+, FISH+; 4.5 points for ER–/PR+, ER+/PR– and ER–/PR–; 0 points for ER+/PR+; 4 points for trastuzumab + pertuzumab; 0 points for trastuzumab; 3.9 points for SIRI <1.27; 0 points for SIRI ≥1.27. HL test showed a chi-square value of 6.669 ($p = 0.464$), and the calibration curve showed a satisfactory fit between the prediction and the actual observation (Fig. 4).

3.4. External validation

A total of 48 patients with HER2+ BC who underwent NST were enrolled at Taichung Tzu Chi Hospital as the validation cohort. The clinical characteristics are presented in Table 3. The nomogram total score of each case was calculated for analysis. A

Table 1

Clinicopathologic parameters of 240 HER2-positive breast cancer patients and their correlations with pathological complete response of neoadjuvant systemic therapy

Variables	Total, n = 240	pCR, n = 119	Non-pCR, n = 121	*p*
Age, y, mean ± SD	53.1 ± 10.0	52.4 ± 9.8	53.8 ± 10.2	0.273
BMI, kg/m^2, n (%)				0.155
<25	161 (67)	85 (71)	76 (63)	
≥25	79 (33)	34 (29)	45 (37)	
Clinical T stage, n (%)				0.016
cT1-2	195 (81)	104 (87)	91 (75)	
cT3-4	45 (19)	15 (13)	30 (25)	
Clinical N stage, n (%)				<0.001
cN0	66 (27.5)	47 (39.5)	19 (16)	
cN1-3	174 (72.5)	72 (60.5)	102 (84)	
HER2, n (%)				0.002
IHC 2+, FISH +	25 (10)	5 (4)	20 (16.5)	
IHC 3+	215 (90)	114 (96)	101 (83.5)	
Hormone receptor, n (%)				0.057
ER–/PR–	104 (43)	60 (50)	44 (36)	
ER+/PR– or ER–/PR+	47 (20)	23 (19)	24 (20)	
ER+/PR+	89 (37)	36 (30)	53 (44)	
Ki-67, n (%)				0.857
<20%	16 (7)	9 (8)	7 (6)	
≥20%	214 (89)	105 (88)	109 (90)	
Unknown	10 (4)	5 (4)	5 (4)	
Histologic type, n (%)				0.345
Invasive ductal carcinoma	222 (92.5)	112 (94)	110 (91)	
Others	18 (7.5)	7 (6)	11 (9)	
Histologic grade, n (%)				0.669
1-2	119 (50)	61 (51)	58 (48)	
3	107 (45)	50 (42)	57 (47)	
Unknown	14 (6)	8 (7)	6 (5)	
Chemotherapy regimen, n (%)				0.823
Taxane	61 (25)	31 (26)	30 (25)	
Taxane + Anthracycline	179 (75)	88 (74)	91 (75)	
NST duration, n (%)				0.537
<12 wk	10 (4)	6 (5)	4 (3)	
≥12 wk	230 (96)	113 (95)	117 (97)	
Targeted therapy regimen, n (%)				0.086
Trastuzumab	156 (65)	71 (60)	85 (70)	
Trastuzumab + pertuzumab	84 (35)	48 (40)	36 (30)	
ALC, 10^9/L, mean ± SD	1.80 ± 0.56	1.78 ± 0.55	1.81 ± 0.58	0.705
NLR, mean ± SD	2.84 ± 2.02	2.65 ± 1.22	3.02 ± 2.57	0.156
PLR, mean ± SD	164.9 ± 77.3	157.2 ± 59.8	172.4 ± 90.9	0.128
LMR, mean ± SD	4.79 ± 2.12	5.01 ± 2.20	4.58 ± 2.03	0.117
SIRI, 10^9/L, mean ± SD	1.21 ± 1.12	1.06 ± 0.65	1.36 ± 1.43	0.035

ALC = absolute lymphocyte count; BMI = body mass index; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; LMR = lymphocyte-monocyte ratio; NLR = neutrophil-lymphocyte ratio; NST = neoadjuvant systemic therapy; pCR = pathological complete response; PLR = platelet-lymphocyte ratio; PR = progesterone receptor; SIRI = systemic inflammation response index.

HL test showed a chi-square value of 12.4 (p = 0.136). The ROC curve of the external validation is shown in Fig. 5; the AUC was 0.755 (95% CI, 0.621-0.889, p = 0.004).

3.5. Survival analysis

The mean DFS and OS times in patient with SIRI <1.27 was 120.63 months (95% CI, 109.32-131.95) and 131.78 months (95% CI, 125.80-137.75), respectively. Patients with SIRI ≥1.27 had mean survival times of DFS and OS of 109.21 months (95% CI, 96.87-121.55) and 121.31 months (95% CI, 110.01-132.61), respectively. The log-rank test revealed that patients with SIRI <1.27 had longer DFS and OS time compared to patients with SIRI ≥1.27 (chi-square = 10.324, p = 0.001; and chi-square = 6.535, p = 0.011), as shown in Figs. 6, 7. The cause of the drop of DFS probability after 120 months was a patient whose lung metastasis was found after a 10-year follow-up.

3.6. Subgroup analysis for neoadjuvant hormone therapy

Among 136 patients with positive hormone receptor, a total of 59 patients (43.4%) achieved pCR. Only nine patients had neoadjuvant hormone therapy, either tamoxifen or an aromatase inhibitor. There was no CDK4/6 inhibitor used. Chi-square test revealed that there was no significant difference in usage of hormone therapy between pCR and non-pCR group (p = 0.299), as shown in Supplementary Table 1, http://links.lww.com/JCMA/A226.

3.7. Subgroup analyses according to single or dual HER2 blockade

Multivariable logistic regression analyses in trastuzumab + pertuzumab subgroup and trastuzumab only subgroup are shown in Supplementary Tables 2 and 3, http://links.lww.com/JCMA/A226.

Table 2

Univariable and multivariable analyses for predictive factors of pathological complete response

	Univariable analysis		Multivariable analysis	
Variables	**OR (95% CI)**	***p* value**	**OR (95% CI)**	***p***
Age, y	0.99 (0.96-1.01)	0.272		
BMI, kg/m^2				
<25	1			
≥25	0.68 (0.39-1.16)	0.156		
Clinical T stage				
cT1-2	1		Eliminated by backward	
cT3-4	0.44 (0.22-0.86)	0.017	Stepwise regression	
Clinical N stage				
cN0	1		1	
cN1-3	0.29 (0.16-0.53)	<0.001	0.25 (0.13-0.48)	<0.001
HER2				
IHC 2+, FISH+	1		1	
IHC 3+	4.52 (1.64-12.47)	0.004	4.60 (1.54-13.78)	0.006
Hormone receptor				
ER–/PR–	1		1	
ER+/PR– or ER–/PR+	0.70 (0.35-1.40)	0.32	0.94 (0.44-2.00)	0.870
ER+/PR+	0.50 (0.28-0.89)	0.02	0.49 (0.26-0.93)	0.028
Ki-67				
<20%	1			
≥20%	0.75 (0.27-2.09)	0.580		
Unknown	0.78 (0.16-3.80)	0.756		
Histologic type				
Invasive ductal carcinoma	1			
Others	0.63 (0.23-1.67)	0.349		
Histologic grade				
1-2	1			
3	0.83 (0.49-1.41)	0.496		
Unknown	1.27 (0.42-3.88)	0.677		
Chemotherapy regimen				
Taxane	1			
Taxane + anthracycline	0.94 (0.52-1.67)	0.823		
NST duration				
<12 wk	1.55 (0.43-5.65)	0.504		
≥12 wk	1			
Targeted therapy				
Trastuzumab	1		1	
Trastuzumab + pertuzumab	1.60 (0.94-2.73)	0.087	1.85 (1.03-3.32)	0.040
ALC, 10^9/L	0.92 (0.58-1.44)	0.704		
NLR	0.90 (0.77-1.05)	0.181		
PLR	0.997 (0.994-1.001)	0.135		
LMR	1.10 (0.97-1.25)	0.121		
SIRI, 10^9/L	0.69 (0.49-0.98)	0.038		
<1.27	1		1	
≥1.27	0.54 (0.31-0.93)	0.026	0.55 (0.30-0.996)	0.048
		HL test	Chi-square = 6.669	0.464

Multivariable analysis was based on backward stepwise logistic regression (likelihood ratio) analysis.

ALC = absolute lymphocyte count; BMI = body mass index; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; HL test = Hosmer-Lemeshow test; IHC = immunohistochemistry; LMR = lymphocyte-monocyte ratio; NLR = neutrophil-lymphocyte ratio; NST = neoadjuvant systemic therapy; OR = odds ratio; PLR = platelet-lymphocyte ratio; PR = progesterone receptor; SIRI = systemic inflammation response index.

In trastuzumab + pertuzumab subgroup, while HER2 IHC 3+ (OR = 8.99), ER+/PR+ (OR = 0.20), and SIRI ≥1.27 (OR = 0.23) were correlated with pCR, cN stage did not reach statistical significance (p = 0.062). On the contrary, cN stage (OR = 0.22) was the only one predictor of pCR in Trastuzumab only subgroup.

4. DISCUSSION

Cancer-related inflammation is associated with the development and progression of tumors and resistance to chemotherapy.[22] Several studies have investigated the pCR-predictive roles of SIMs, but there was no consensus on the optimal indicator. As BC is a heterogeneous disease, different subtypes are amenable to different therapies. This study focused on patients with HER2+ BC treated with neoadjuvant chemotherapy and targeted therapy to avoid the bias among subtypes and find the optimal predictors in this subgroup.

In the present study, clinical N stage, the HER2 IHC score, hormone receptor status, targeted therapy regimen, and SIRI were independent predictors of pCR in patients with HER2+

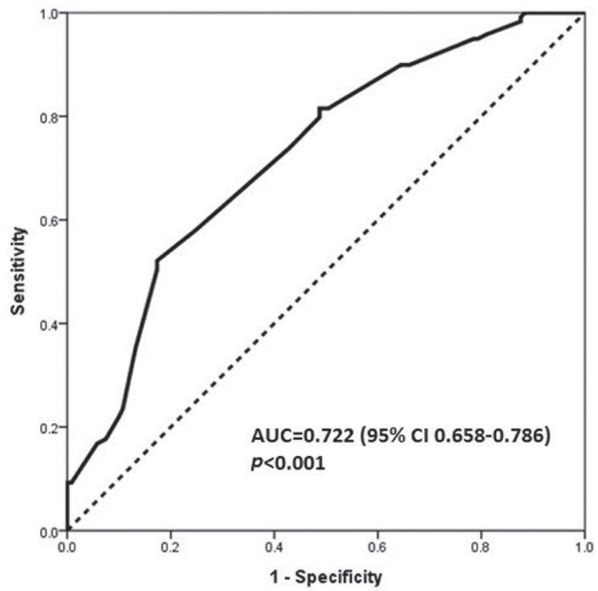

Fig. 2 The receiver operating characteristic curve to demonstrate the discriminatory ability of the multivariable logistic model. AUC = area under the curve.

BC treated with NST. A nomogram based on these factors was developed to predict the pCR probability after NST in patients with HER2+ BC. The nomogram demonstrated an acceptable discriminatory capability, with an AUC of 0.722, and good calibration (p = 0.464). The discrimination and calibration were also satisfactory in the external validation. Besides SIRI, the other independent predictors identified in this study were consistent with those of previous studies.[5,8,9,23,24] Jankowski et al[8] found that Ki-67 level was a predictor of pCR in HER2+ BC, but our study failed to support this finding. The CGFL/Curie model developed by Jankowski et al[8] was also compared to our model in our study population. The CGFL/Curie nomogram total points of each case were calculated for analysis. The AUC of their model was 0.642 (95% CI, 0.570-0.714, p < 0.001) (Fig. 8). The HL test revealed a significant difference between the predicted probabilities and the observations (p = 0.027), indicating poor calibration of the model. The compromised accuracy of CGFL/Curie model when applying to our cohort may result from different ethnicity and era, or an inadequate statistical power. However, this comparison still showed the importance of developing our own model for Taiwanese patients with HER2+ BC treated with NST.

Dual HER2-targeted therapy is an independent predictor of pCR and the only clinically controllable variable in our nomogram. Although the addition of pertuzumab increased the pCR rate, it also increased the incidence and severity of treatment-related diarrhea.[24] It is not always easy in daily practice to

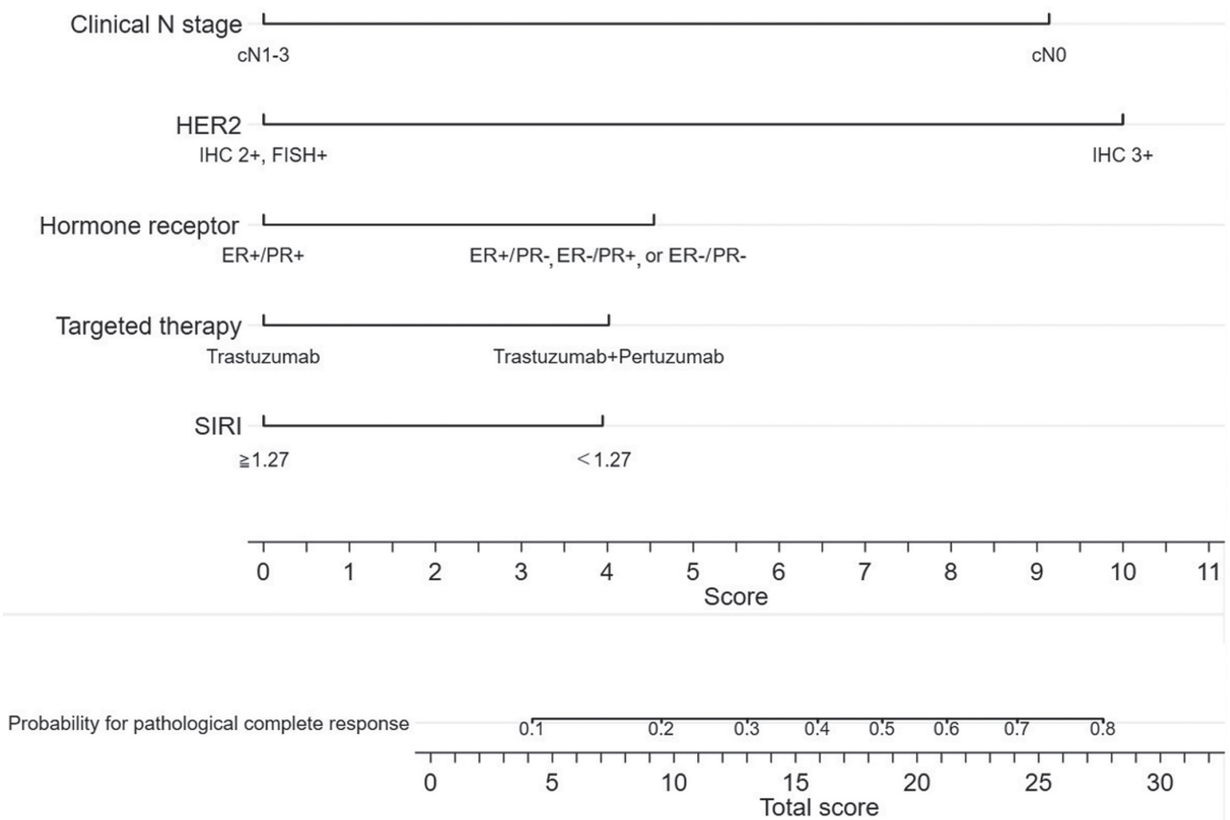

Fig. 3 The nomogram for predicting pathological complete response probability in patients with HER2-positive breast cancer. The score for each factor is listed as follows: 9.1 points for cN0; 0 points for cN1-3; 10 points for HER2 IHC 3+; 0 points for IHC 2+ with fluorescence in situ hybridization amplification; 4.5 points for ER–or PR–; 0 points for ER+/PR+; 4 points for trastuzumab + pertuzumab; 0 points for trastuzumab; 3.9 points for SIRI <1.27; 0 points for SIRI ≥1.27. ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PR = progesterone receptor; SIRI = systemic inflammation response index.

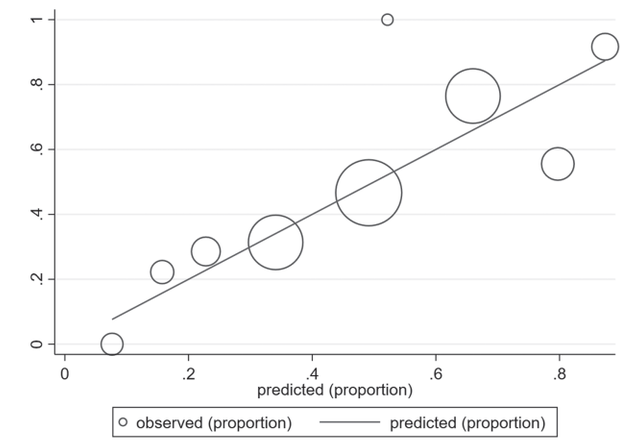

Fig. 4 The calibration curve of the model.

determine the marginal benefit of pertuzumab and whether it outweighs the possible adverse effects. Our nomogram could be used to estimate the benefit of adding pertuzumab, by comparing the predicted pCR probability of trastuzumab alone and of dual HER2 blockade. Thus, it may provide more information to clinicians and patients, and help them make decisions accordingly. In subgroup analyses according to single or dual HER2 blockade, while the HER2 IHC score, hormone receptor status, and SIRI were pCR-predictors in trastuzumab + pertuzumab subgroup, cN is the only one in trastuzumab only subgroup. This finding may result from a lower response rate of single HER2 blockade in nodal positive disease, which was also observed in clinical nodal positive subgroup analysis (shown in Supplementary Table 4, http://links.lww.com/JCMA/A226). These results may provide some evidence for current indication of neoadjuvant pertuzumab in patients with nodal positive disease. However, due to reduced sample size in each subgroup, the findings need to be verified in a larger cohort.

Although neoadjuvant hormone therapy is seldom used in patients with HER2+ BC, there were about 6.6% of hormone-receptor-positive patients had neoadjuvant hormone therapy in our cohort. Subgroup analysis revealed no significant association between hormone therapy and pCR.

While ALC, NLR, PLR, and LMR were not associated with pCR in our study, SIRI was the optimal SIM for HER2+ BC. SIRI was first described by Qi et al[25] as a prognostic marker for predicting the survival of patients with pancreatic cancer after chemotherapy. Since then, SIRI has been reported to correlate closely with prognosis in many tumors, including lung, gastric, liver, and BC.[26–30] Dong et al[16] found that SIRI <0.72 is predictive of pCR in patients with BC undergoing NST. Chen et al[31] found that patients with BC receiving NST with SIRI <0.85 had longer DFS and OS. In the present study, we found a higher cutoff value. SIRI <1.27 is predictive of pCR, DFS and OS in patients with HER2+ BC. A possible explanation for this might be the differences in the study populations. The present study focused on patients with HER2+ BC, while the two abovementioned studies included all BC subtypes. We noticed a slightly greater number of patients with high SIRI in HER2+ group in the study by Chen et al, although the differences were not significant. Further studies are needed to clarify the association between SIRI and HER2 status.

The pathophysiological functions of neutrophils, monocytes, and lymphocytes may explain the prognostic significance of SIRI in patients with BC. Neutrophils secrete cytokines, chemokines, reactive oxygen species, and matrix-degrading proteinases to influence the tumor microenvironment. These substances promote tumor growth and invasiveness by modifying tumor immune surveillance, proliferation, angiogenesis, and metastasis.[11] Monocytes can differentiate into tumor-associated macrophages (TAMs), which play a major role in tumor initiation, growth, development, and metastasis. Besides, growing evidence has shown that TAMs can enhance cancer cells' resistance against chemotherapy and radiotherapy by producing cytokines and survival factors.[10,12] Lymphocytes have the ability to recognize tumor cells and rapidly initiate an antitumor response through direct cytotoxicity, activating other components of the immune response, inhibiting angiogenesis, and facilitating

Table 3

Clinicopathologic parameters of the external validation cohort

Variables	Total, n = 48
pCR, n (%)	
Yes	17 (35)
No	31 (65)
Age, y, mean ± SD	52.9 ± 11.6
BMI, kg/m^2, n (%)	
<25	32 (67)
≥25	16 (33)
Clinical T stage, n (%)	
cT1-2	35 (73)
cT3-4	13 (27)
Clinical N stage, n (%)	
cN0	15 (31)
cN1-3	33 (69)
HER2, n (%)	
IHC 2+, FISH +	10 (21)
IHC 3+	38 (79)
Hormone receptor, n (%)	
ER–/PR–	16 (33)
ER+/PR– or ER–/PR+	8 (17)
ER+/PR+	24 (50)
Ki-67, n (%)	
<20%	6 (12.5)
≥20%	42 (87.5)
Unknown	0 (0)
Histologic type, n (%)	
Invasive ductal carcinoma	44 (92)
Others	4 (8)
Histologic grade, n (%)	
1-2	22 (46)
3	26 (54)
Unknown	0 (0)
Chemotherapy regimen, n (%)	
Taxane	22 (46)
Taxane + anthracycline	26 (54)
NST duration, n (%)	
<12 wk	2 (4)
≥12 wk	46 (96)
Targeted therapy regimen, n (%)	
Trastuzumab	24 (50)
Trastuzumab + pertuzumab	24 (50)
SIRI, n (%)	
<1.27	36 (75)
≥1.27	12 (25)

BMI = body mass index; ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; NST = neoadjuvant systemic therapy; pCR = pathological complete response; PR = progesterone receptor; SIRI = systemic inflammation response index.

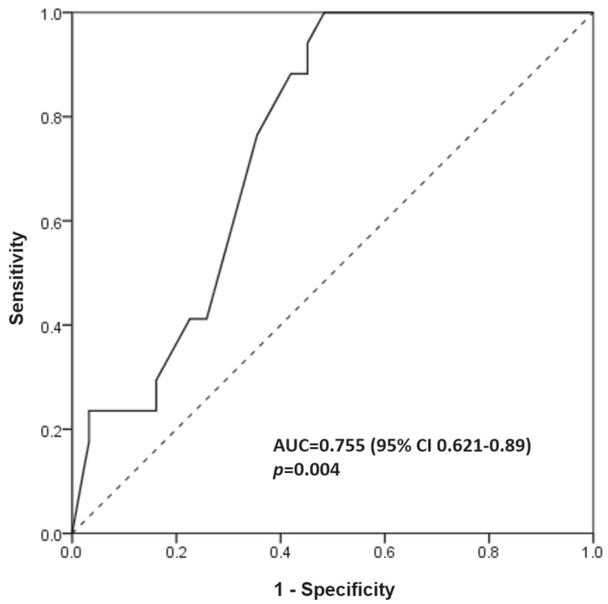

Fig. 5 The receiver operating characteristic curve of external validation. AUC = area under the curve.

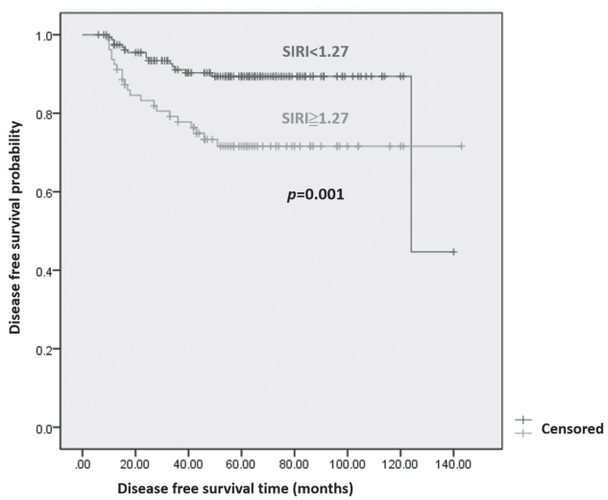

Fig. 6 Kaplan-Meier curve of disease-free survival. SIRI = systemic inflammation response index.

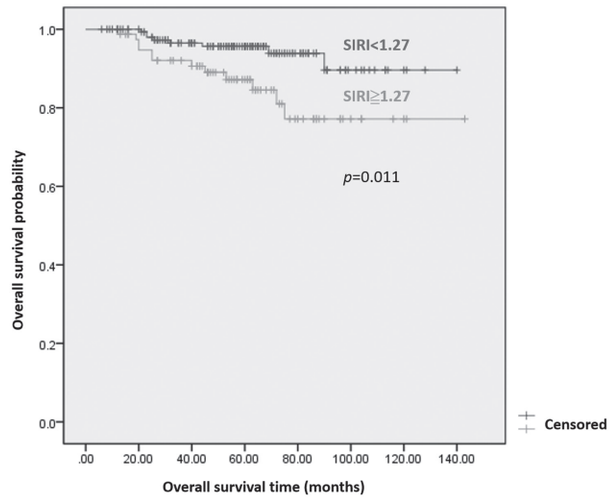

Fig. 7 Kaplan-Meier curve of overall survival. SIRI = systemic inflammation response index.

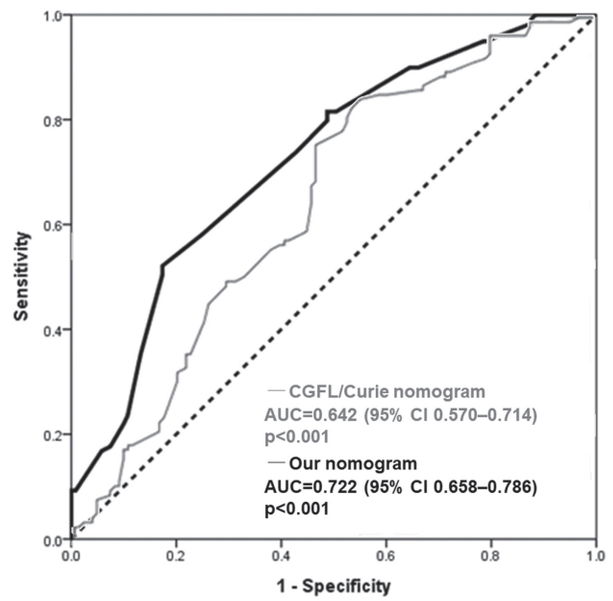

Fig. 8 Comparison of the receiver operating characteristic curve between our model and the CGFL/Curie model applied to our cohort. AUC = area under the curve.

antigen presentation.[13] In short, the levels of these cells indicate the host immune response to malignant tumors. These mechanisms may explain why patients with a lower SIRI had a higher pCR rate. In addition, we found an association between SIRI and cT stage (Table 4). In a meta-analysis for patients with all kinds of cancer, Zhou et al[30] also found correlation between SIRI and cancer stage. Change in the immune response to tumor may be another measurement of tumor development besides stage, though additional studies are warranted.

Tumor-infiltrating lymphocytes (TILs) are biomarkers that may reflect local antitumor inflammatory responses. An association between high levels of TILs and an increased pCR rate in the neoadjuvant setting of BC has been observed in previous studies.[32–34] Hwang et al[5] developed a nomogram to predict pCR based on pretreatment TILs level, cN stage, and ER status. In comparison with their nomogram, we used pretreatment SIRI instead of TILs. The addition of the HER2 IHC score and targeted therapy regimen in our nomogram was reasonable because we focused on HER2+ BC patients. There is limited literature on the relationship between TILs and SIMs. Lee et al[35] found that CD8+ TILs, a subset of TILs, were associated with ALC, absolute monocyte count, and LMR in patients with BC. However, the association between TILs and SIRI remains unknown. TIL evaluation in core-needle biopsy was not performed at Taichung Veterans General Hospital and was started at Kaohsiung Veterans General Hospital in 2019; thus, the present cohort includes only 19 cases with data on TILs. The analysis of TILs was not performed due to insufficient statistical power. While

Table 4

Relationship between the SIRI and other prognostic variables in 240 patients with HER2-positive breast cancer

Variables	Total, n = 240	SIRI <1.27, n = 161	SIRI ≥1.27, n = 79	*p*
Clinical T stage, n (%)				0.001
cT1-2	195 (81)	140 (87)	55 (70)	
cT3-4	45 (19)	21 (13)	24 (30)	
Clinical N stage, n (%)				0.078
cN0	66 (27.5)	50 (31)	16 (20)	
cN1-3	174 (72.5)	111 (69)	63 (80)	
HER2, n (%)				0.729
IHC 2+, FISH +	25 (10)	16 (10)	9 (11)	
IHC 3+	215 (90)	145 (90)	70 (89)	
Hormone receptor, n (%)				0.132
ER– or PR–	151 (63)	96 (60)	55 (70)	
ER+/PR+	89 (37)	65 (40)	24 (30)	
Targeted therapy, n (%)				0.293
Trastuzumab	156 (65)	101 (63)	55 (70)	
Trastuzumab + pertuzumab	84 (35)	60 (37)	24 (30)	

ER = estrogen receptor; FISH = fluorescence in situ hybridization; HER2 = human epidermal growth factor receptor 2; IHC = immunohistochemistry; PR = progesterone receptor; SIRI = systemic inflammation response index.

TILs are evaluated by pathologists, SIRI might demonstrate advantages on its reproducibility and cost-effectiveness because it is machine-measured and might act as an alternative or supplement to TILs. More studies are necessary to validate this assumption.

As patients with a low pCR probability predicted by our nomogram may have higher risk of residual disease after standard NST, they could be suitable candidates in future investigation of new NST regimen. Trastuzumab emtansine (T-DM1) is recommended in the adjuvant setting for those with residual disease after NST because it improved DFS compared to trastuzumab.[36] However, it could not replace standard NST because the results from randomized studies were controversial.[37,38] Trastuzumab deruxtecan (T-DXd), a novel antibody–drug conjugate with bystander effect, was superior to T-DM1 in patients with HER2+ metastatic BC in the DESTINY-Breast03 trial.[39] Whether T-DXd might have a role in the neoadjuvant setting is yet to be discovered. Neoadjuvant immunotherapy may be another investigational option. While neoadjuvant pembrolizumab and chemotherapy for TNBC has been approved by US Food and Drug Administration based on the results of the KEYNOTE-522 trial,[40] the role of immunotherapy for HER2+ BC remains unknown.

The present study had several limitations. First, although we enrolled patients from two medical centers in Taiwan, this was a retrospective study with a relatively small sample size. Large prospective multicenter studies are required. Second, data for some possible confounding factors of SIRI, such as chronic inflammation, inflammatory BC, smoking, and lifestyle, could not be collected. Third, in this study, we found no significant difference in pCR rate between taxane-based and sequential taxane-based plus anthracycline. The result is consistent with a 2023 meta-analysis by Zhu et al.[41] However, the two chemotherapy groups were actually heterogeneous, as there were differences in drug intensity and addition of drug combination. We have attempted to analyze different regimens categorized by taxane intensity, addition of carboplatin, and anthracycline intensity. The proportion of detailed chemotherapy regimens is shown in Supplementary Table 5, http://links.lww.com/JCMA/A226. There was no significant difference in detailed chemotherapy regimens between pCR group and non-pCR group (p = 0.780). We also did the chi-square tests for any two regimens and no significant difference was found. The statistical power may not be achieved due to small sample size in each regimen group. Furthermore, as a retrospective real-world study, variation of actual received dosage and cycles existed in each regimen group and were difficult to be categorized. In short, further prospective trial is needed to clarify the efficacy of different neoadjuvant chemotherapy regimens.

In conclusion, this study revealed the pCR-predictive and prognostic value of SIRI in patients with HER2+ BC treated with NST. To our knowledge, this study is the first to generate a nomogram for predicting pCR of NST based on SIRI and other clinicopathologic factors in patients with HER2+ BC. We believe that in addition to assisting clinicians and patients predict prognoses and make choices accordingly, the nomogram can also help future research for the development of new NST regimens for patients with HER2+ BC.

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APPENDIX A. SUPPLEMENTARY DATA

Supplementary data related to this article can be found at http://links.lww.com/JCMA/A226.

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