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ORIGINAL RESEARCH

Development and Validation of a Prognostic Nomogram for HR+ HER- Breast Cancer

Jie-Yu Zhou[1], Cheng-Geng Pan[1], Yang Ye[1], Zhi-Wei Li[1], Wei-Da Fu[2], Bin-Hao Jiang[3]

[1]Department of Thyroid and Breast Surgery, The Wenzhou Central Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China; [2]Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Ningbo University, Ningbo, Zhejiang, 315000, People's Republic of China; [3]Department of Urinary Surgery, Yueqing People's Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China

Correspondence: Bin-Hao Jiang, Department of Urinary Surgery, Yueqing People's Hospital, Wenzhou, Zhejiang, 325000, People's Republic of China, Tel/Fax +86-577-15157765226, Email jbh0370@126.com

Purpose: We aimed to develop a nomogram to predict prognosis of HR+ HER2- breast cancer patients and guide the application of postoperative adjuvant chemotherapy.

Methods: We identified 310 eligible HR+ HER- breast cancer patients and randomly divided the database into a training group and a validation group. The endpoint was disease free survival (DFS). Concordance index (C-index), area under the curve (AUC) and calibration curves were used to evaluate predictive accuracy and discriminative ability of the nomogram. We also compared the predictive accuracy and discriminative ability of our nomogram with the eighth AJCC staging system using overall data.

Results: According to the training group, platelet-to-lymphocyte ratio (PLR), tumor size, positive lymph nodes and Ki-67 index were used to construct the nomogram of DFS. The C-index of DFS was 0.708 (95% CI: 0.623–0.793) in the training group and 0.67 (95% CI: 0.544–0.796) in the validation group. The calibration curves revealed great consistencies in both groups.

Conclusion: We have developed and validated a novel and practical nomogram that can provide individual prediction of DFS for patients with HR+ HER- breast cancer. This nomogram may help clinicians in risk consulting and guiding the application of postoperative adjuvant chemotherapy.

Keywords: nomograms, prognosis, prediction, HR+ HER- breast cancer, chemotherapy

Introduction

Breast cancer has an incidence rate higher than any other malignant tumor in women worldwide. According to the American Cancer Society, 290,560 new cases occurred in 2022, representing 30% of diagnosed female cancer cases, and the number is growing at an annual rate of about 0.5%.[1] In China, the age at diagnosis of breast cancer is trending downward. Some immunohistochemical markers are used to classify breast tumors into subtypes.[2] Hormone receptors (HRs), including estrogen receptor (ER) and progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) are important immunohistochemical markers. According to the molecular classification, breast cancer is divided into luminal A, luminal B, HER2+, and triple-negative breast cancer (TNBC).[3] HR+ HER2-breast cancer including Luminal A and Luminal B subtypes is defined as breast cancer with positive HRs and negative HER2 status accounting for approximately 70% of all cases.[4] HR+ HER2- breast cancer shows sensitivity to anti-hormone therapy but is resistant to anti-HER2 treatment or immunotherapy and has a better prognosis compared with other types of breast cancer. About half of recurrences occur after 5 years after primary diagnosis in HR+ HER2- breast cancer patients.[5] However, patients with HR+ HER2- breast cancer still have a sustained risk of disease recurrence and death for at least 15 years from diagnosis after receiving 5 years of adjuvant hormonal therapy.[6] Recurrences occur at a steady rate throughout the period from 5 to 20 years and the long-term risk of recurrence is about 1–2% per year.[7]

Most HR+ HER2- breast cancers without lymphatic metastasis have been treated with adjuvant chemotherapy, according to a report that indicates individuals with invasive breast cancer measuring more than 1 cm gain a significant benefit from adjuvant chemotherapy regardless of ER and nodal status published in 2000.[8] However, HR+ HER2- breast cancers without lymphatic metastasis have a less aggressive phenotype, and approximately 85% of the patients may not experience recurrence even if they are treated with adjuvant hormone therapy alone.[9] It is indicated

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that a significant proportion of HR+ HER2-breast cancer patients without lymphatic metastasis are overtreated with unnecessary adjuvant chemotherapy. Many studies have focused on the development of a prognostic indicator that can select patients with a very low risk of recurrence and not require adjuvant chemotherapy. Prognostic indicators based on multigene assays (MGA), which measure the mRNA expression of multiple genes in tumor tissue, have been developed and implemented in clinical practice for HR+ HER2- breast cancer patients without lymphatic metastasis. The most extensively investigated MGA is Oncotype DX, which is a RT-PCR-based mRNA expression analysis of 21 genes.[9] Besides, MammaPrint is also recommend to determine whether adjuvant chemotherapy is necessary for HR+ HER2− early breast cancer.[10,11] However, these methods have the disadvantages of high price and are not covered by rural health insurance, which is the most common insurance in China. As a result, some patients refuse to accept these examinations. Thus, it is meaningful to build a predictive model with conventional clinicopathological parameters to select out patients with a low risk of late recurrence and a better prognosis so that precision medical treatments can be applied.

Nomograms can integrate several important variables in a graphical representation. One of the advantages of nomograms is the ability to predict personalized risks and prognosis according to the disease conditions of different cancer patients, and promote the development of personalized clinical treatments.[12] There are few nomograms predicting the prognosis of HR+ HER2- breast cancer and biomarkers associated with inflammatory response are not included in these nomograms.[13–15] Only one nomogram was developed to screen out low-risk HR+ HER2- breast cancer patients who were exempt from adjuvant chemotherapy.[14] Based on the Surveillance, Epidemiology, and End Results (SEER) database that contains a small number of Asians, the applicability of this nomogram for Chinese population remains to be considered. Meanwhile, this nomogram was built to predict breast cancer specific survival (BCSS) among patients without adjuvant chemotherapy.[14] For the above reasons, we aimed to develop a nomogram to predict the prognosis of HR+ HER2- breast cancer patients with clinicopathological and molecular variables including neutrophil-to-lymphocyte ratio (NLR), platelet-to-lymphocyte ratio (PLR) and systemic immune inflammation index (SII) from 310 HR+ HER- breast cancer patients treated at the Wenzhou Central Hospital in China.

Patients and Methods

Patient Selection and General Information

In this retrospective study, we collected clinicopathological data of patients with invasive HR+ HER2- breast cancer who meet the inclusion criteria diagnosed and treated at the Wenzhou Central Hospital from February 2012 to November 2017. Inclusion criteria were as follows: (1) female patients who were age 18 years or older; (2) all patients were diagnosed with primary HR+ HER2- breast cancer and confirmed by pathological test; (3) unilateral breast cancer; (4) no history of previous malignancies; (5) no recent inflammatory disease; (6) patients with complete clinical and laboratory data; (7) availability of tumor samples. Exclusion criteria were as follows: (1) carcinoma in situ; (2) metastatic invasive breast cancer; (3) inflammatory breast cancer; (4) history of critical basic diseases including acute or chronic liver disease or kidney disease, serious heart and lung diseases; (5) patients with hematological diseases, autoimmune diseases; (6) patients who had used anticoagulant drugs within 3 months before surgery; (7) patients who were under adjuvant chemotherapy or radiotherapy before surgery. The criteria for determining HR+ HER2- breast cancer were as follows: ER and/or PR positive status as defined by the American Joint Committee on Cancer (AJCC) (thresholds for defining ER/PR positive were set at more than 1% using immunohistochemical staining). HER2 status was defined by the Guidelines of Chinese Society of Clinical Oncology (CSCO). HER2 negative or low expression denoted HER2 negative and HER2 high expression was considered HER2 positive. HER2 expression between the two above statuses required further evaluation through fluorescence in situ hybridization, which can determine the presence of overexpression. The positive result of fluorescence in situ hybridization was considered to be HER2 positive, and the opposite was considered to be negative. The study was approved by the Ethics Committee of the Wenzhou Central Hospital (approval number: 20230715072800032333). All study patients signed written informed consent.

Totally, there were 310 primary HR+ HER2- breast cancer patients enrolled. Clinical information, including age at HR+ HER2- breast cancer diagnosis, menstrual status, body weight and height was collected. Treatment information including surgery type, adjuvant chemotherapy and adjuvant endocrinotherapy were also recorded. Laboratory data from

blood routine examination was obtained up to 2 weeks prior to surgery. Information related to histopathological type, pathology grade, tumor size, positive lymph nodes and Ki-67 index was obtained from pathology reports. Body mass index (BMI) was calculated as the weight in kg divided by the square of height in m (kg/m2). Albumin-to-globulin ratio (AGR) was calculated by dividing albumin value by globulin value. Neutrophil-to-lymphocyte ratio (NLR) was calculated by dividing the absolute neutrophil count by the absolute lymphocyte count, platelet-to-lymphocyte ratio (PLR) was calculated by dividing the absolute platelet count by the absolute lymphocyte count, similarly. Systemic immune inflammation index (SII) was calculated by dividing the product of the absolute platelet count and the absolute neutrophil count by the absolute lymphocyte count. Postoperative adjuvant therapy was performed routinely according to the Chinese treatment guidelines at that time.

Follow-Up and Endpoints

The end points were disease-free survival (DFS) defined as time from date of diagnosis to local, regional recurrence, distant metastasis, contralateral breast cancer, death, or last follow-up and overall survival (OS) defined as the time from diagnosis to death or last follow-up. The deadline for follow-up was October 2023.

Statistical Analysis

The R software was used to randomly divide all 310 patients (66%, seed 90) into two groups. Pearson chi-square test and Mann–Whitney *U*-test were used to evaluate the relationship of clinicopathological characteristics between the training group and the validation group. Log rank test and Cox univariate analysis were used to identify the univariate predictors. Based on the results of the univariate analysis ($P < 0.05$), further multivariate analysis using the Cox risk regression model with backward elimination was performed to identify variables ($P < 0.05$) to be included in the final nomogram. All P-values were two-sided and a P-value <0.05 was considered to be statistically significant. Statistical analysis was performed using the SPSS statistical software package, version 26.0 (IBM Corporation, Armonk, NY, USA). The nomogram was constructed using the R software (version R-3.5.3 https://www.r-project.org/). The cutoff values of the variables referenced to relevant studies or were determined by the X-tile software program (Yale University, New Haven, CT, USA version 3.6.1). Internal validation was performed with the validation cohort. The predictive accuracy and discriminative ability of the nomogram were determined by concordance index (C-index), area under the curve (AUC) and calibration curves. AUC was calculated basing on the 5-year and 8-year DFS predicted by our nomogram and the eighth AJCC staging system to compare the performance.

Results

Study Population Characteristics

The flowchart of the patient selection process is shown in Figure 1. A total of 310 primary HR+ HER2- breast cancer patients were included in this study. The median follow-up time was 96 months (range: 11–140 months). There were 59 recurrences, and 27 deaths during the follow-up period. The DFS rate was 80.97% and the OS rate was 91.29%. The median age of patients was 52 years (range: 27–87 years). The median BMI was 23.34 (range: 17.12–34.17). 51.61% of the patients were postmenopausal, and the others were premenopausal. The median preoperative NLR was 1.63 (range: 0.64–6.25), median preoperative PLR was 117.69 (range: 47–449.33), median preoperative SII was 378.32 (range: 102.13–1540), and median preoperative AGR was 1.61 (range: 1.06–2.96). A total of 202 (65.16%) patients were admitted to mastectomy and the others underwent breast-conserving surgery. For pathological types, invasive ductal carcinoma presented the majority (89.68%), while the others were invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma, invasive cribriform carcinoma, metaplastic carcinoma, invasive tubular carcinoma and phyllodes carcinoma. Among the pathological grades, 103(33.23%) patients presented with grade III, 167 (53.87%) with grade II, 40(12.9%) with grade I. 273(88.06%) patients presented with a tumor size <4cm and the others presented with a tumor size ≥ 4cm. A total of 117(37.74%) patients had lymph node metastasis (LNM) and 52(16.77%) patients presented with a LNM >3. Besides, 116(37.42%) patients represented with a Ki-67 index ≥30% and the others represented with a Ki-67 index <30%. A total of 193(62.26%) patients received postoperative adjuvant chemotherapy.

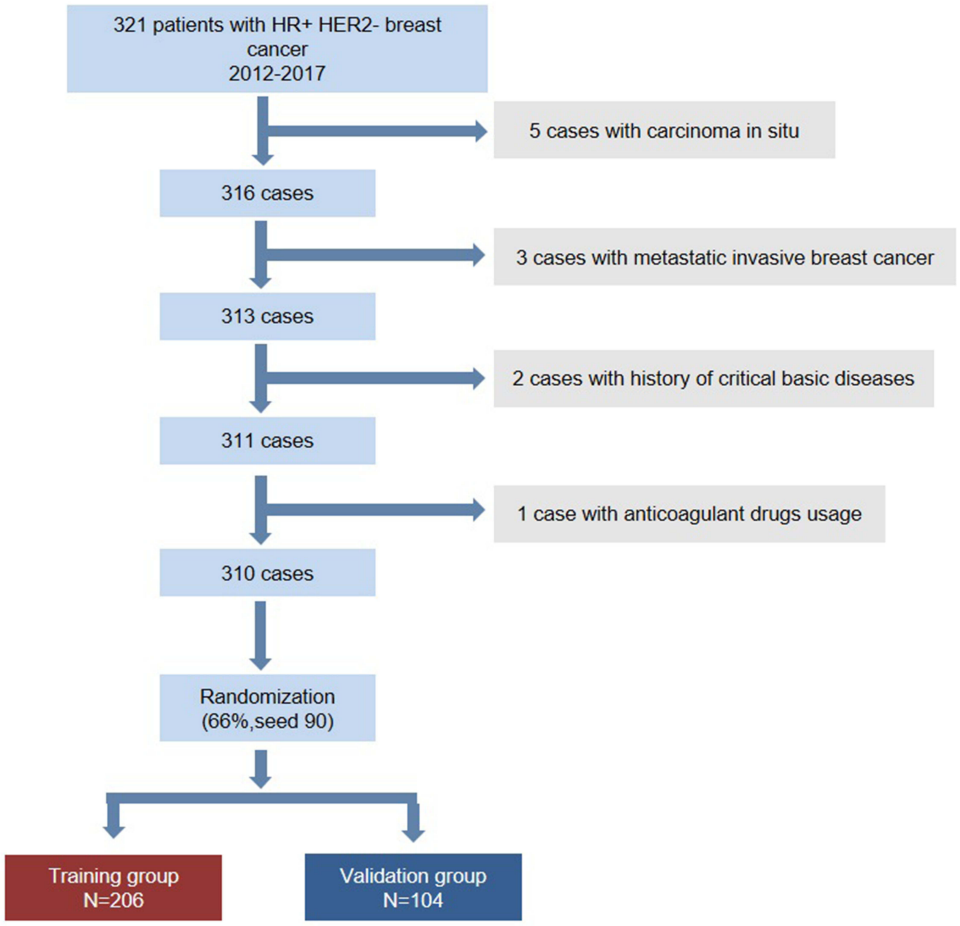

Figure 1 Patient selection flowchart.

All patients received postoperative adjuvant endocrinotherapy. A total of 140(45.16%) patients received aromatase inhibitors (AI), 90(29.03%) patients received tamoxifen, 5(1.61%) patients received AI and releasing hormone analogues (GnRHa), 75(24.19%) patients received tamoxifen and GnRHa. AI includes anastrozole, letrozole and exemestane. GnRHa includes goserelin and leuprorelin. The R software was used to randomly divide all 310 patients (66%, seed 90) into two groups: the training group (206 patients) and the validation group (104 patients). Demographic and clinicopathological characteristics of patients in the training and validation cohorts are shown Table 1. In the training group, 37 patients relapsed and 17 patients died. In the validation group, 22 patients relapsed and 10 patients died. There was no statistical difference between the two groups in terms of demographic and clinicopathological characteristics.

Table 1 Clinicopathological Characteristics of the Training and Validation Groups

Characteristic	Training Group (N=206) No. (%)	Validation Group (N=104) No. (%)	Chi-Square Value	P-value
Age, yr			0.894	0.640
≤47	74(35.92)	35(33.65)		
48–56	58(28.16)	26(25)		
>56	74(35.92)	43(41.35)		
BMI, kg/m2			3.042	0.081
≤21	47(22.82)	15(14.42)		
>21	159(77.18)	89(85.58)		

(*Continued*)

Table 1 (Continued).

Characteristic	Training Group (N=206) No. (%)	Validation Group (N=104) No. (%)	Chi-Square Value	P-value
Menstrual status			0.163	0.686
Premenopausal	98(47.57)	52(50)		
Postmenopausal	108(52.43)	52(50)		
NLR			0.028	0.867
≤2.3	168(81.55)	84(80.77)		
>2.3	38(18.45)	20(19.23)		
PLR			0.110	0.74
≤178	181(87.86)	90(86.54)		
>178	25(12.14)	14(13.46)		
SII			0.011	0.917
≤660	185(89.81)	93(89.42)		
>660	21(10.19)	11(10.58)		
AGR			3.327	0.068
≤1.8	155(75.24)	68(65.38)		
>1.8	51(24.76)	36(34.62)		
Surgery type			0.097	0.756
Mastectomy	133(64.56)	69(66.35)		
BCS	73(35.44)	35(33.65)		
Histopathological type			0.471	0.493
IDC	183(88.83)	95(91.35)		
Others*	23(11.17)	9(8.65)		
Pathology grade			1.828	0.401
I	30(14.56)	10(9.62)		
II	111(53.88)	56(53.85)		
III	65(31.55)	38(36.54)		
Tumor size, cm			2.897	0.089
<4	186(90.29)	87(83.65)		
≥4	20(9.71)	17(16.35)		
Positive lymph nodes			3.198	0.074
≤3	177(85.92)	81(77.88)		
>3	29(14.08)	23(22.12)		
Ki-67,%			1.597	0.206
<30	134(65.05)	60(57.69)		
≥30	72(34.95)	44(42.31)		
Multiple tumor foci			2.521	0.112
No	180(87.38)	97(93.27)		
Yes	26(12.62)	7(6.73)		
Endocrine therapy strategy			2.602	0.457
AI**	92(44.66)	48(46.15)		
Tamoxifen	60(29.13)	30(28.85)		
AI±GnRHa***	5(2.43)	0(0)		
Tamoxifen±GnRHa	49(23.79)	26(25)		

Notes: Statistical significance was tested by Pearson chi-square test and Mann–Whitney *U*-test. *Other histopathological types include invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma, invasive cribriform carcinoma, metaplastic carcinoma, invasive tubular carcinoma and phyllodes carcinoma. **Aromatase inhibitors include anastrozole, letrozole and exemestane. ***Gonadotropin releasing hormone analogues include goserelin and leuprorelin.

Abbreviations: BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; AGR, albumin to globulin ratio; BCS, breast conserving surgery; IDC, invasive ductal carcinoma; AI, aromatase inhibitor; GnRHa, gonadotropin releasing hormone analogues.

Prognostic Nomogram for DFS

In the training group, univariate analysis showed that preoperative PLR, tumor size, positive lymph nodes and Ki-67 index were related to recurrence. The final Cox multivariate analysis showed that preoperative PLR, tumor size, positive lymph nodes, and Ki-67 index were independent prognostic factors of DFS (Table 2). A nomogram that incorporated these four prognostic variables was then developed (Figure 2). Each subtype of these variables was assigned a score. The scores of these variables were added to get a total score. According to the total score, we may predict the 5 year- and 8 year-DFS for an individual. The C-index of DFS was 0.708 (95% CI: 0.623–0.793). The calibration curves revealed relatively good consistencies, as shown in Figure 3. Internal validation was performed with the validation group. In the validation group, the C-index of DFS was 0.67 (95% CI: 0.544–0.796), and the calibration curves are also shown in Figure 3.

Table 2 Univariate and Multivariate Analyses of DFS in the Training Group

Characteristics	Univariate Analysis of DFS		Multivariate Analysis of DFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Age, yr		0.085		
≤47	1			
48–56	0.43(0.18–1.02)	0.055		
>56	0.55(0.26–1.16)	0.117		
BMI, kg/m2		0.32		
≤21	1			
>21	1.55(0.65–3.72)	0.324		
Menstrual status		0.17		
Premenopausal	1			
Postmenopausal	0.64(0.33–1.22)	0.174		
NLR		0.159		
≤2.3	1			
>2.3	1.68(0.81–3.46)	0.164		
PLR		0.015		
≤178	1		1	
>178	2.56(1.17–5.62)	0.019	2.47(1.11–5.49)	0.026
SII		0.113		
≤660	1			
>660	2(0.83–4.79)	0.121		
AGR		0.587		
≤1.8	1			
>1.8	1.22(0.6–2.46)	0.589		
Surgery type		0.163		
Mastectomy	1			
BCS	0.59(0.28–1.25)	0.168		
Histopathological type		0.5		
IDC	1			
Others*	0.67(0.21–2.18)	0.503		
Pathology grade		0.268		
I	1			
II	0.65(0.25–1.66)	0.365		
III	1.14(0.44–2.93)	0.793		
Tumor size, cm		0.002		
<4	1		1	
≥4	3.29(1.5–7.21)	0.003	3.19(1.44–7.08)	0.004

(*Continued*)

Table 2 (Continued).

Characteristics	Univariate Analysis of DFS		Multivariate Analysis of DFS	
	HR (95% CI)	P-value	HR (95% CI)	P-value
Positive lymph nodes		0		
≤3	1		1	
>3	3.28(1.65–6.53)	0.001	2.97(1.48–5.96)	0.002
Ki-67,%		0.007		
<30	1		1	
≥30	2.38(1.25–4.55)	0.009	2.03(1.05–3.93)	0.035
Multiple tumor foci		0.472		
No	1			
Yes	1.38(0.57–3.3)	0.475		
Endocrine therapy strategy		0.177		
AI**	1			
Tamoxifen	1.57(0.88–2.8)	0.127		
AI±GnRHa***	2.56(0.61–10.85)	0.202		
Tamoxifen±GnRHa	0.86(0.42–1.75)	0.672		

Notes: Statistical significance was tested by Log rank test, Cox univariate analysis and Cox risk regression model. *Other histopathological types include invasive lobular carcinoma, invasive papillary carcinoma, mucinous carcinoma, invasive cribriform carcinoma, metaplastic carcinoma, invasive tubular carcinoma and phyllodes carcinoma. **Aromatase inhibitors include anastrozole, letrozole and exemestane. ***Gonadotropin releasing hormone analogues include goserelin and leuprorelin.

Abbreviations: DFS, disease free survival; HR, hazard ratio; CI, confidence interval; BMI, body mass index; NLR, neutrophil to lymphocyte ratio; PLR, platelet to lymphocyte ratio; SII, systemic immune inflammation index; AGR, albumin to globulin ratio; BCS, breast conserving surgery; IDC, invasive ductal carcinoma; AI, aromatase inhibitor; GnRHa, gonadotropin releasing hormone analogues.

Comparison with the Eighth AJCC Staging System

We compared predictive accuracy and discriminative ability of our nomogram with the eighth AJCC staging system using the overall data. The C-index for our model to predict DFS was 0.699 (95% CI: 0.631–0.767) and was significantly better than that of the eighth AJCC TNM staging system (0.624, 95% CI 0.546–0.672, P = 0). The AUC for 5-year and 8-year DFS for our model was 0.717 and 0.612 which was larger than the AUC of 0.701 and 0.628 for the eighth AJCC TNM staging system (Figure 4).

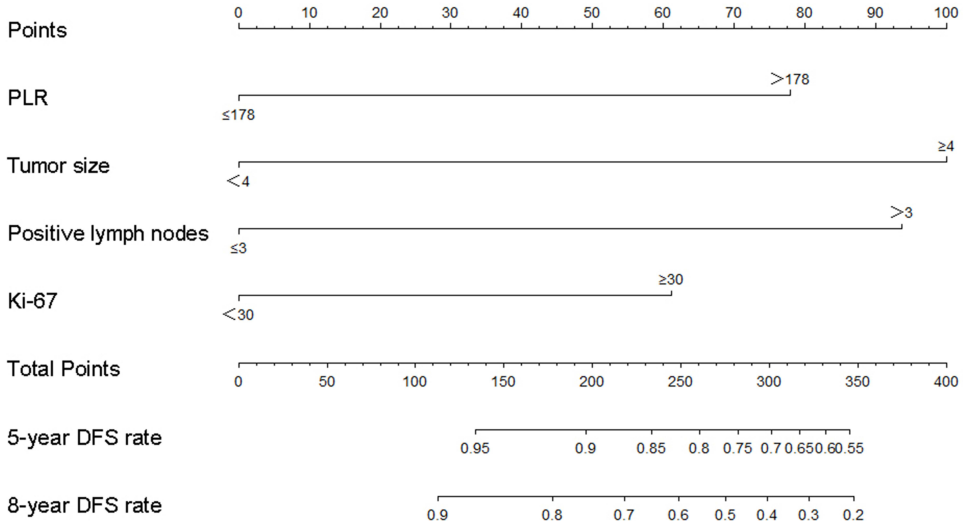

Figure 2 Nomogram for the prediction of DFS in HR+ HER2- breast cancer.

Abbreviations: PLR, platelet to lymphocyte count ratio; DFS, disease free survival.

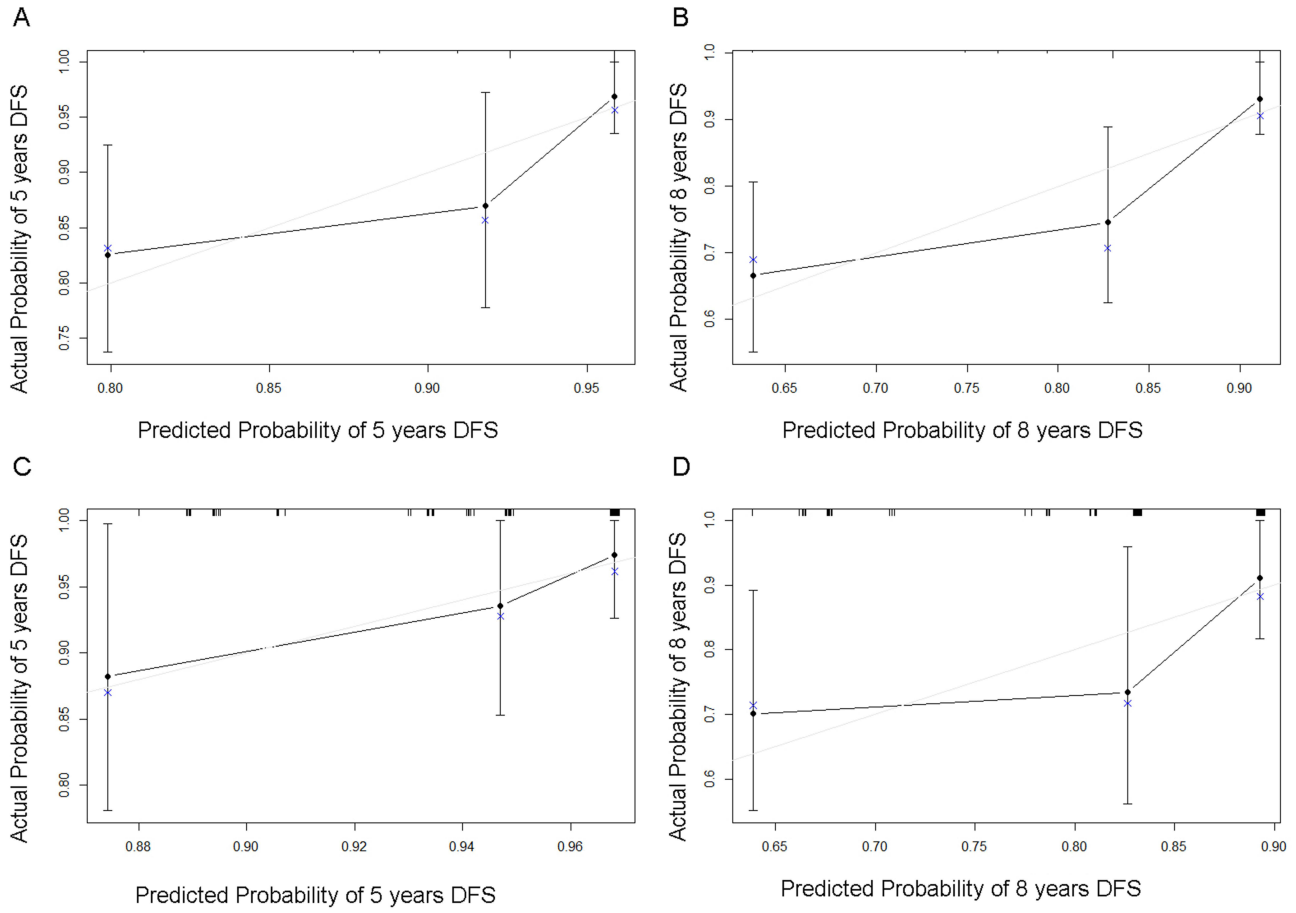

Figure 3 Calibration curves for predicting the DFS for patients with HR+ HER2- breast cancer in the training group at (**A**) 5 years and (**B**) 8 years and in the validation group at (**C**) 5 years and (**D**) 8 years. Nomogram-predicted probability is plotted on the x-axis and the actual survival is plotted on the y-axis.
Abbreviation: DFS, disease-free survival.

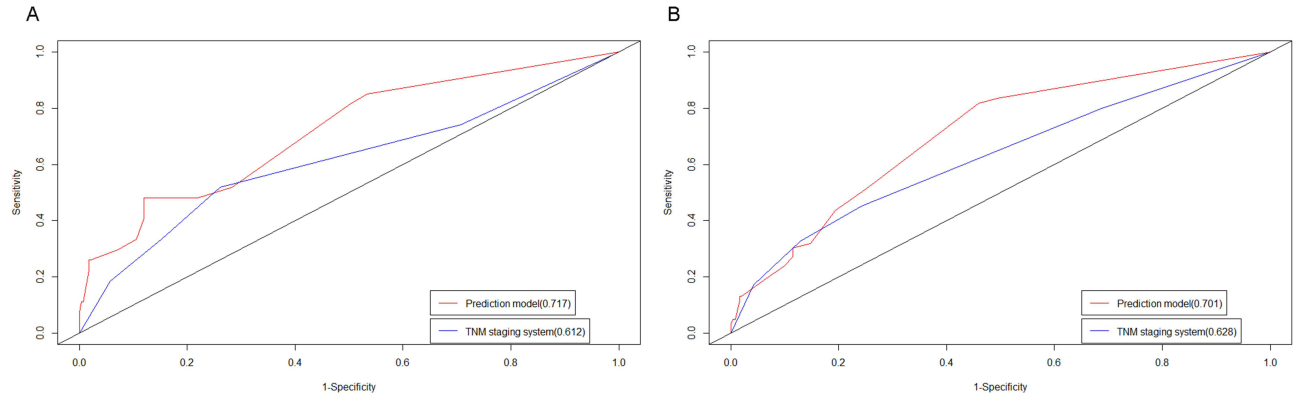

Figure 4 5 years (**A**) and 8 years (**B**) ROC curves for DFS.
Abbreviation: DFS, disease-free survival.

Performance of the Nomogram in Stratifying Risk of Patients

We grouped patients in the total cohort into three risk groups after sorting by total DFS score. Patients in the training and validation cohort were grouped in the same way. The cutoff values of total DFS score were defined by X-tile software program. Each risk group showed significantly different survival outcomes in three different cohorts. (Table 3, Figure 5).

Table 3 Univariate Analyses of DFS by Total DFS Score

Univariate Analysis of DFS						
Characteristics	**Total Group (N=310)**		**Training Group (N=206)**		**Validation Group (N=104)**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Total DFS Score		0		0		0.008
Low Risk Group (≤90)	1		1	1		
Medium Risk Group (90–100)	4.2(2.04–8.64)	0	4.32(1.82–10.28)	0.001	4.08(1.1–15.12)	0.035
High Risk Group (>100)	6.7(3.15–14.23)	0	6.94(2.69–17.9)	0	6.29(1.73–22.88)	0.005

Note: Statistical significance was tested by Log rank test and Cox univariate analysis.
Abbreviations: DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

These cutoff values also well-differentiated patients to low risk, medium risk, and high risk groups with extremely distinct prognosis.

Performance of the Nomogram in Guiding Postoperative Adjuvant Chemotherapy

Patients who received postoperative adjuvant chemotherapy showed better survival outcomes compared with patients who did not receive postoperative adjuvant chemotherapy in medium risk group and high risk group. (Table 4, Figure 6). Therefore, postoperative adjuvant chemotherapy is recommended to patients in medium risk group and high risk group.

Discussion

HR+ HER2- breast cancer is the most common subtype in women diagnosed with early-stage breast cancer.[16] The widespread use of breast cancer screening, the improvement in loco-regional and systemic (neo)adjuvant therapies allow a cure for most patients with early-stage breast cancers and have declined the risk of mortality by more than one-third in the past 4 decades. Nevertheless, breast cancer recurrence still occurs.[5] Patients with HR+ HER2- breast cancer have a sustained risk of disease recurrence and death for at least 15 years from diagnosis after receiving 5 years of adjuvant hormonal therapy.[6] In addition, HR+ HER2-breast cancer includes a group of highly heterogeneous breast cancers, and the prognosis of each patient is extremely variable.[17] Therefore, it is meaningful to stratify patients with HR+ HER2- breast cancer based on their individual characteristics to better assess prognosis. It has been proven that PLR, tumor size, positive lymph nodes and Ki-67 index are independent prognostic factors of patients with HR+ HER2- breast cancer and was confirmed in this study.[18,19] It is reported that pathological grade is related to prognosis of breast cancer. High pathological grade is associated with poor prognosis in breast cancer patients. However, pathological grade is not an independent predictor in this study. The result can be explained by short follow-up period and limited cases.

It has been widely acknowledged that the immune system plays an important role in the pathogenesis and progression of several types of cancers including breast cancer.[20,21] Researches show that the pretreatment index or systemic inflammation score can predict prognosis in patients with multiple malignancies.[22–24] Biologically, the activation of

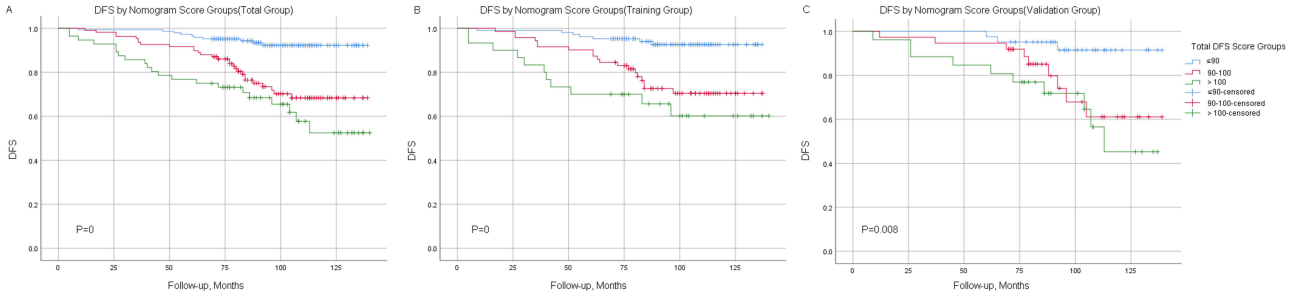

Figure 5 Risk group stratification in the total, training and validation group. DFS curves of patients in the total group (**A**), training group (**B**) and validation group (**C**) by nomogram score groups.
Abbreviation: DFS, disease-free survival.

Table 4 Univariate Analyses of DFS in Different Risk Groups by Postoperative Adjuvant Chemotherapy

Univariate Analysis of DFS								
Characteristics	**Low Risk Group (≤90)**		**Medium Risk Group (90–100)**		**High Risk Group (>100)**		**Total Group**	
	HR (95% CI)	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**	**HR (95% CI)**	**P-value**
Postoperative Adjuvant Chemotherapy		0.182		0.041		0.001		0.135
No	1		1		1		1	
Yes	0.41(0.11–1.59)	0.197	0.47(0.22–0.99)	0.046	0.24(0.09–0.59)	0.002	0.68(0.4–1.13)	0.138

Note: Statistical significance was tested by Log rank test, Cox univariate analysis.
Abbreviations: DFS, disease free survival; HR, hazard ratio; CI, confidence interval.

systemic inflammation is associated with changes in circulating white blood cells. White cell counts and their combinations such as NLR, PLR and SII have been highlighted because hematological tests are routinely performed for cancer patients in clinical practice. Therefore, information about these variables can be easily obtained in routine work.[25] Unfortunately, only PLR was proved to be an independent predictor of prognosis in this study. High PLR level is associated with poor DFS in HR+ HER2- breast cancer patients. PLR was suggested as a prognostic biomarker in several types of malignancies, including gastric, ovarian, colorectal and pancreatic cancer.[26–29] In a meta-analysis, a high PLR was associated with worse OS for several solid malignancies.[24] Meanwhile, it has been proven that preoperative PLR is an independent prognostic factor for OS and DFS in breast cancer. High PLR was an independent adverse prognostic factor for breast cancer, and low PLR could improve the sensitivity of patients to neoadjuvant chemotherapy.[30] Prognostic value of PLR in each molecular subtype of breast cancer is not well known. In a meta-analysis, there was

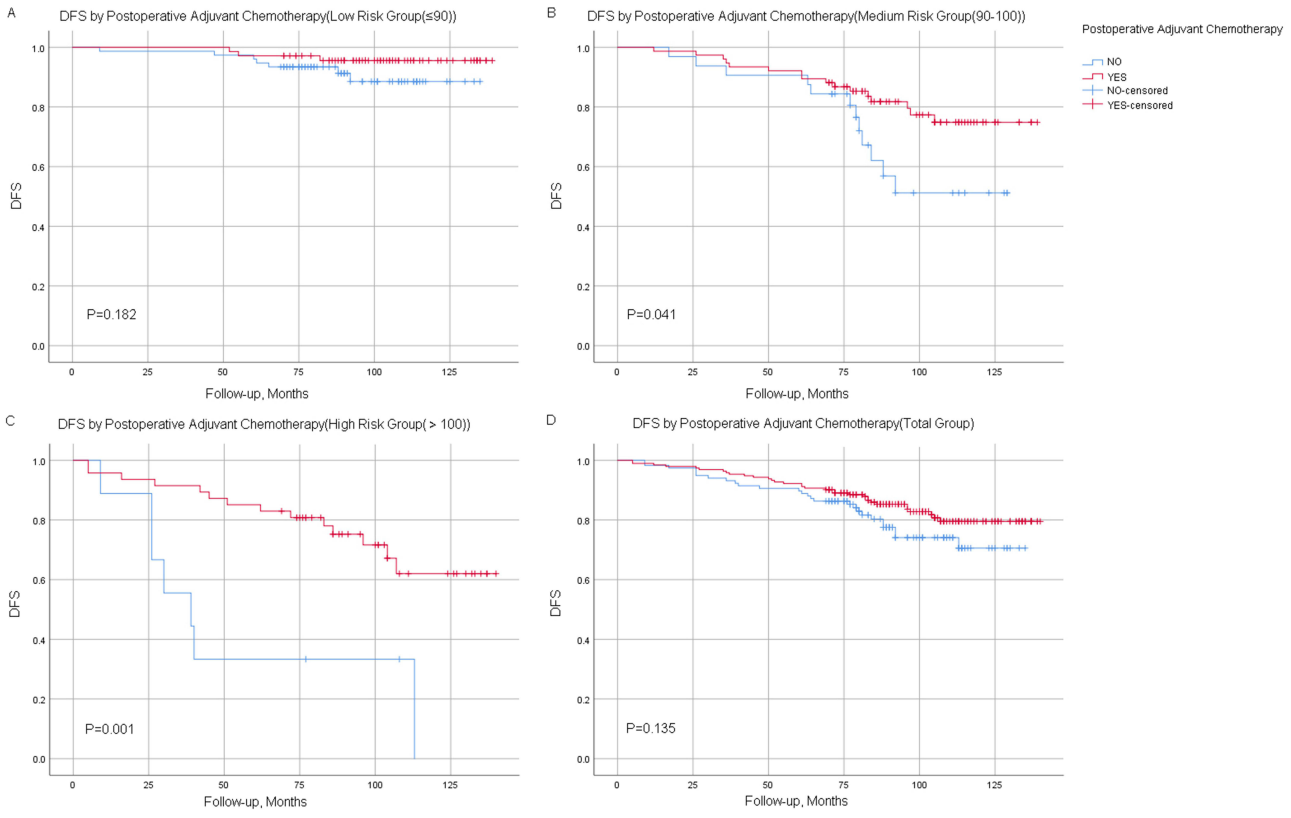

Figure 6 Risk group stratification in the low risk, medium risk, high risk and total group. DFS curves of patients in the low risk group (**A**), medium risk group (**B**), high risk group (**C**) and total group (**D**) by different postoperative adjuvant chemotherapy strategy.
Abbreviation: DFS, disease-free survival.

a significant difference in the incidence of high levels of PLR between HER2 statuses, but not between ER or PR receptor statuses.[31] High PLR tended to have a lower effect of DFS on HR- and HER2+ breast cancer but statistical significance was not reached. Moreover, a study by Cho et al showed the PLR as a significant prognostic marker predicting poor prognosis in patients with luminal subtypes.[18] Recent researches have revealed the role of platelets in the pathogenesis and progression of malignant tumors. Platelets contribute to sustaining proliferative signals. Platelets secrete platelet chemotactic growth factor (platelet factor 4), transforming growth factor-beta and vascular endothelial growth factor to stimulate tumor differentiation and proliferation.[32–34] In the contrary, lymphocyte was proven to play a major role in the prevention of tumor growth and immunity.[35] Lymphocytopenia indicates compromised anti-tumor immunity that provides a favorable environment for tumor cell growth.[36] The balance between anti-tumor immunity and inflammation was broken in the pathogenesis and progression of tumors. Lymphocytes decrease and platelets increase, leading to the high level of PLR.

Ki-67 is a protein encoded by the MKI67 gene that is expressed in G1, S, G2, and M cell cycle phases representing a robust biomarker of cellular proliferation.[37] Assessed by immunohistochemistry, Ki-67 index is regarded as a reliable indicator of the proliferative activity of breast cancer. In addition to this, Ki-67 index may play an important role in assessing response to systemic therapeutic strategies and can act as a prognostic biomarker.[38] The role of Ki-67 index in determining the risk of breast cancer is widely acknowledged. Ki-67 index is able to discriminate Luminal A (low Ki-67) versus Luminal B (high Ki-67) breast cancers and to drive the choice between endocrine therapy versus chemotherapy. However, its limited reproducibility, which stems from a lack of standardization of procedures, inter-observer variability, and preanalytical and analytical variabilities, has restricted the use of Ki-67 index in clinical practice. At present, there is no international consensus on the cut-off of ki-67 index. According to recommendations from the International Ki-67 in Breast Cancer working group, Ki-67 index <10% is defined as low and >30% is considered high.[39] St Gallen guidelines states that tumors with Ki-67 index ≤5% have no need for chemotherapy, and tumors with Ki-67 index >30% are recommended to receive chemotherapy. However, as most ER+ HER2- early-stage breast cancers have an intermediate Ki-67 index between these two extremes, the therapeutic choice should be based on other parameters. The presence of pathologists specialising in breast cancer is recommended to optimise the quality of Ki-67 determination so as to improve the analytical validity of Ki-67 and minimize the differences between laboratories and observers.[40] Besides, the importance of the median Ki-67 index assessed by each laboratory to correctly assess the risk is also highlighted. The Ki-67 decrease is a marker of good response to preoperative endocrine therapy, in combination with other parameters, may help in identifying those patients with favorable prognosis who do not require chemotherapy.[41] The cut-off of Ki-67 index was determined by X-tile software program in the current study. A Ki-67 index ≥30% was considered high and <30% was defined as low. A high Ki-67 index is associated with poor DFS in HR+ HER2- breast cancer patients in this study.

The nomogram developed in this study was constructed using the training group, and internal validation was performed with the validation cohort. The C-index of DFS was 0.708 (95% CI: 0.623–0.793) in the training group and 0.67 (95% CI: 0.544–0.796) in the validation group. The calibration curve showed good consistencies between the predicted DFS rate and the actual DFS rate in both groups. In addition, our nomograms showed significantly higher C-index and larger AUCs than that of the eighth AJCC TNM staging system in predicting DFS. There are few nomograms predicting the prognosis of HR+ HER2- breast cancers and biomarkers associated with the inflammatory response are not included these nomograms[13–15] and many nomograms focused on OS or BCSS but not DFS. Our study made up for these shortcomings. To the best of knowledge, this study is the only one study that incorporates biomarkers associated with the inflammatory response into clinicopathological variables in predicting prognosis for HR+ HER2- breast cancer patients.

Postoperative adjuvant chemotherapy is an important and effective treatment for breast cancers. For high-risk breast cancer with poor prognosis, such as TNBC, HER2+ breast cancer, breast cancers with larger tumor, and more positive lymph nodes, postoperative adjuvant chemotherapy can significantly improve DFS and OS. However, the effect of postoperative adjuvant chemotherapy remains controversial in HR+ HER- early-stage breast cancer. At present, most guidelines recommend that patients with HR+ HER2− early breast cancer should be tested for Oncotype DX or MammaPrint to determine whether postoperative adjuvant chemotherapy is necessary.[10,11] However, the high price

and low popularity in both developing and developed countries limit the extension of gene testing.[42] Furthermore, the time taken to obtain results of genomic tests is long, and patients are unable to receive therapy until the test results are obtained. Besides, neither Oncotype DX nor MammaPrint can solve the problem of all patients receiving the test. The results of oncotype DX are divided into three groups: high, medium, low-risk. Endocrine therapy alone is effective for low-risk patients and endocrine therapy followed by postoperative adjuvant chemotherapy should be used for high-risk patients, according to the guidelines. However, the systematic treatment for the medium-risk population (26–30 points) presenting about 22–36% of patients is still unclear.[10,43,44] Based on the above reasons, constructing a simple clinical prediction model to predict the prognosis of HR+ HER2- breast cancer and guide postoperative adjuvant chemotherapy is important. In this study, patients who received postoperative adjuvant chemotherapy in the high- and medium-risk groups had a better DFS while DFS showed no differences in the low-risk group. The result indicated that our nomogram effectively screened out patients who need postoperative adjuvant chemotherapy. As far as we know, there is only one nomogram that was developed to screen out low-risk HR+ HER2- breast cancer patients who are exempt from adjuvant chemotherapy.[14] However, this nomogram was built to predict BCSS among patients who did not receive adjuvant chemotherapy.[14] Meanwhile, the data was based on the SEER database, which contains a small number of Asians. As we known, the clinicopathological features and prognosis of breast cancer may vary by race/ethnicity.[45] Therefore, the nomogram may not be generalizable to external populations such as the Chinese population for the potential referral and therapeutic bias it may bring. Based on the Chinese population, our nomogram solved the problem.

Despite above strengths, this study had some limitations. Firstly, due to the short follow-up period, there were only a small number of death cases. As a result, no independent prognostic indicator other than tumor size and positive lymph nodes was screened out in this study. Therefore, OS was not predicted in this study. Secondly, this was a retrospective study and could only generate hypothesis generating results, which needed a prospective study to confirm. Thirdly, the data was collected in a single center with a relatively small sample size. As a result, some of the calibration plots were less than ideal. Fourthly, the nomogram in this study is based on Chinese HR+ HER2- breast cancer patients, and it is still unclear whether it can be applied to western patient cohorts. Fifthly, we intended to create a universal and practical nomogram. Therefore, several predictive factors, especially those associated with high cost were not included in this study, such as BRCA1/2 mutation. Further efforst on prospective and multi-center data collection with a longer follow-up period are needed to improve our nomogram.

Conclusion

We have developed and validated a novel and practical nomogram that can provide individual prediction of DFS for Chinese patients with HR+ HER2- breast cancer by including PLR for the first time. This nomogram may help clinicians in predicting the prognosis of patients with HR+ HER2- breast cancer and guiding the application of postoperative adjuvant chemotherapy.

Abbreviations

HR, hormone receptor; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor-2; TNBC, triple-negative breast cancer; MGA, multigene assay; SEER, Surveillance, Epidemiology, and End Results; BCSS, breast cancer specific survival; NLR, neutrophil-to-lymphocyte ratio; PLR, platelet-to-lymphocyte ratio; SII, systemic immune inflammation index; AJCC, American Joint Committee on Cancer; CSCO, Guidelines of Chinese Society of Clinical Oncology; BMI, body mass index; AGR, albumin-to-globulin ratio; DFS, disease free survival; OS, overall survival; C-index, concordance index; AUC, area under the curve; LNM, lymph node metastasis; AI, aromatase inhibitor; GnRHa, gonadotropin releasing hormone analogues.

Key Points

Significant findings of the study: We have developed and validated a novel and practical nomogram that can provide individual prediction of DFS for Chinese patients with HR+ HER2- breast cancer by including PLR for the first time. This nomogram may help clinicians in predicting the prognosis of patients with HR+ HER2- breast cancer and guiding the application of postoperative adjuvant chemotherapy.

What this study adds: Our study incorporates platelet-to-lymphocyte ratio into the construction of the nomogram predicting prognosis of HR+ HER2- breast cancer patients for the first time with a sample size of 310 cases and may help screening out patients who need postoperative adjuvant chemotherapy.

Ethics Approval

All clinical investigations were conducted according to the principles expressed in the Declaration of Helsinki. The study was approved by the Ethics Committee of the Wenzhou Central Hospital (approval number: 202307150728000323333).

Consent to Participate

All study patients signed written informed consent.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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References

1. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2022. *CA Cancer J Clin*. 2022;72(1):7–33. doi:10.3322/caac.21708
2. Callagy G, Cattaneo E, Daigo Y, et al. Molecular classification of breast carcinomas using tissue microarrays. *Diagn Mol Pathol*. 2003;12(1):27–34. doi:10.1097/00019606-200303000-00004
3. Goldhirsch A, Wood WC, Coates AS, et al. Strategies for subtypes--dealing with the diversity of breast cancer: highlights of the St. Gallen International Expert Consensus on the Primary Therapy of Early Breast Cancer 2011. *Ann Oncol*. 2011;22(8):1736–1747. doi:10.1093/annonc/mdr304
4. Waks AG, Winer EP. Breast cancer treatment: a review. *JAMA*. 2019;321(3):288–300. doi:10.1001/jama.2018.19323
5. Dowling RJO, Sparano JA, Goodwin PJ, et al. Toronto workshop on late recurrence in estrogen receptor-positive breast cancer: part 2: approaches to predict and identify late recurrence, research directions. *JNCI Cancer Spectr*. 2019;3(4):pkz049. doi:10.1093/jncics/pkz049
6. Early Breast Cancer Trialists' Collaborative G. Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. *Lancet*. 2005;365(9472):1687–1717. doi:10.1016/S0140-6736(05)66544-0
7. Pan H, Gray R, Braybrooke J, et al. 20-year risks of breast-cancer recurrence after stopping endocrine therapy at 5 years. *N Engl J Med*. 2017;377(19):1836–1846. doi:10.1056/NEJMoa1701830
8. Adjuvant therapy for breast cancer. *NIH Consens Statement*. 2000;17:1–35.
9. Paik S, Shak S, Tang G, et al. A multigene assay to predict recurrence of tamoxifen-treated, node-negative breast cancer. *N Engl J Med*. 2004;351(27):2817–2826. doi:10.1056/NEJMoa041588
10. Gradishar WJ, Anderson BO, Abraham J, et al. Breast cancer, version 3.2020, NCCN clinical practice guidelines in oncology. *J Natl Compr Canc Netw*. 2020;18(4):452–478. doi:10.6004/jnccn.2020.0016
11. Krop I, Ismaila N, Andre F, et al. Use of biomarkers to guide decisions on adjuvant systemic therapy for women with early-stage invasive breast cancer: American Society of Clinical Oncology Clinical Practice Guideline Focused Update. *J Clin Oncol*. 2017;35(24):2838–2847. doi:10.1200/JCO.2017.74.0472
12. Doll KM, Rademaker A, Sosa JA. Practical guide to surgical data sets: Surveillance, Epidemiology, and End Results (SEER) Database. *JAMA Surg*. 2018;153(6):588–589. doi:10.1001/jamasurg.2018.0501
13. Hwang YS, Kim HJ, Kim J, et al. Validation study of a nomogram for predicting probability of low risk of MammaPrint results in women with clinically high-risk breast cancer. *Discov Oncol*. 2022;13(1):141. doi:10.1007/s12672-022-00604-z
14. Wen N, Qiu J, Xu L, et al. Adjuvant chemotherapy guidance for pT1-3N0-1 breast cancer patients with HR(+), HER2(-) subtype: a cohort study based on the SEER database. *Ann Transl Med*. 2021;9(24):1779. doi:10.21037/atm-21-5937
15. Zhu Y, Wang J, Xu B. A novel prognostic nomogram for predicting survival of hormone receptor-positive and HER2 negative advanced breast cancer among the han-population. *Front Oncol*. 2022;12:918759. doi:10.3389/fonc.2022.918759
16. Pellegrino B, Hlavata Z, Migali C, et al. Luminal breast cancer: risk of recurrence and tumor-associated immune suppression. *Mol Diagn Ther*. 2021;25(4):409–424. doi:10.1007/s40291-021-00525-7

17. Cheang MC, Chia SK, Voduc D, et al. Ki67 index, HER2 status, and prognosis of patients with luminal B breast cancer. *J Natl Cancer Inst*. 2009;101(10):736–750. doi:10.1093/jnci/djp082
18. Cho U, Park HS, Im SY, et al. Prognostic value of systemic inflammatory markers and development of a nomogram in breast cancer. *PLoS One*. 2018;13(7):e0200936. doi:10.1371/journal.pone.0200936
19. Zambelli A, Gallerani E, Garrone O, et al. Working tables on Hormone Receptor positive (HR+), Human Epidermal growth factor Receptor 2 negative (HER2-) early stage breast cancer: defining high risk of recurrence. *Crit Rev Oncol Hematol*. 2023;191:104104. doi:10.1016/j.critrevonc.2023.104104
20. Koh CH, Bhoo-Pathy N, Ng KL, et al. Utility of pre-treatment neutrophil-lymphocyte ratio and platelet-lymphocyte ratio as prognostic factors in breast cancer. *Br J Cancer*. 2015;113(1):150–158. doi:10.1038/bjc.2015.183
21. Mantovani A, Allavena P, Sica A, Balkwill F. Cancer-related inflammation. *Nature*. 2008;454(7203):436–444. doi:10.1038/nature07205
22. Guthrie GJ, Charles KA, Roxburgh CS, Horgan PG, McMillan DC, Clarke SJ. The systemic inflammation-based neutrophil-lymphocyte ratio: experience in patients with cancer. *Crit Rev Oncol Hematol*. 2013;88(1):218–230. doi:10.1016/j.critrevonc.2013.03.010
23. Szkandera J, Absenger G, Liegl-Atzwanger B, et al. Elevated preoperative neutrophil/lymphocyte ratio is associated with poor prognosis in soft-tissue sarcoma patients. *Br J Cancer*. 2013;108(8):1677–1683. doi:10.1038/bjc.2013.135
24. Templeton AJ, Ace O, McNamara MG, et al. Prognostic role of platelet to lymphocyte ratio in solid tumors: a systematic review and meta-analysis. *Cancer Epidemiol Biomarkers Prev*. 2014;23(7):1204–1212. doi:10.1158/1055-9965.EPI-14-0146
25. Gabay C, Kushner I, Epstein FH. Acute-phase proteins and other systemic responses to inflammation. *N Engl J Med*. 1999;340(6):448–454. doi:10.1056/NEJM199902113400607
26. Asher V, Lee J, Innamaa A, Bali A. Preoperative platelet lymphocyte ratio as an independent prognostic marker in ovarian cancer. *Clin Transl Oncol*. 2011;13(7):499–503. doi:10.1007/s12094-011-0687-9
27. Lee S, Oh SY, Kim SH, et al. Prognostic significance of neutrophil lymphocyte ratio and platelet lymphocyte ratio in advanced gastric cancer patients treated with FOLFOX chemotherapy. *BMC Cancer*. 2013;13(1):350. doi:10.1186/1471-2407-13-350
28. Smith RA, Bosonnet L, Raraty M, et al. Preoperative platelet-lymphocyte ratio is an independent significant prognostic marker in resected pancreatic ductal adenocarcinoma. *Am J Surg*. 2009;197(4):466–472. doi:10.1016/j.amjsurg.2007.12.057
29. Zou ZY, Liu HL, Ning N, Li SY, Du XH, Li R. Clinical significance of pre-operative neutrophil lymphocyte ratio and platelet lymphocyte ratio as prognostic factors for patients with colorectal cancer. *Oncol Lett*. 2016;11(3):2241–2248. doi:10.3892/ol.2016.4216
30. Asano Y, Kashiwagi S, Onoda N, et al. Platelet-lymphocyte ratio as a useful predictor of the therapeutic effect of neoadjuvant chemotherapy in breast cancer. *PLoS One*. 2016;11(7):e0153459. doi:10.1371/journal.pone.0153459
31. Zhang M, Huang XZ, Song YX, Gao P, Sun JX, Wang ZN. High platelet-to-lymphocyte ratio predicts poor prognosis and clinicopathological characteristics in patients with breast cancer: a meta-analysis. *Biomed Res Int*. 2017;2017:9503025. doi:10.1155/2017/9503025
32. Ishii Y, Hamashima T, Yamamoto S, Sasahara M. Pathogenetic significance and possibility as a therapeutic target of platelet derived growth factor. *Pathol Int*. 2017;67(5):235–246. doi:10.1111/pin.12530
33. Jain S, Harris J, Ware J. Platelets: linking hemostasis and cancer. *Arterioscler Thromb Vasc Biol*. 2010;30(12):2362–2367. doi:10.1161/ATVBAHA.110.207514
34. Sabrkhany S, Griffioen AW, Oude Egbrink MG. The role of blood platelets in tumor angiogenesis. *Biochim Biophys Acta*. 2011;1815(2):189–196. doi:10.1016/j.bbcan.2010.12.001
35. Dunn GP, Old LJ, Schreiber RD. The immunobiology of cancer immunosurveillance and immunoediting. *Immunity*. 2004;21(2):137–148. doi:10.1016/j.immuni.2004.07.017
36. Kitayama J, Yasuda K, Kawai K, Sunami E, Nagawa H. Circulating lymphocyte number has a positive association with tumor response in neoadjuvant chemoradiotherapy for advanced rectal cancer. *Radiat Oncol*. 2010;5(1):47. doi:10.1186/1748-717X-5-47
37. Davey MG, Hynes SO, Kerin MJ, Miller N, Lowery AJ. Ki-67 as a prognostic biomarker in invasive breast cancer. *Cancers*. 2021;13(17):4455. doi:10.3390/cancers13174455
38. Louis DM, Nair LM, Vallonthaiel AG, Narmadha MP, Vijaykumar DK. Ki 67: a promising prognostic marker in early breast cancer-a review article. *Indian J Surg Oncol*. 2023;14(1):122–127. doi:10.1007/s13193-022-01631-6
39. Nielsen TO, Leung SCY, Rimm DL, et al. Assessment of Ki67 in breast cancer: updated recommendations from the international Ki67 in Breast Cancer Working Group. *J Natl Cancer Inst*. 2021;113(7):808–819. doi:10.1093/jnci/djaa201
40. Penault-Llorca F, Radosevic-Robin N. Ki67 assessment in breast cancer: an update. *Pathology*. 2017;49(2):166–171. doi:10.1016/j.pathol.2016.11.006
41. Cardoso F, Kyriakides S, Ohno S, et al. Early breast cancer: ESMO clinical practice guidelines for diagnosis, treatment and follow-updagger. *Ann Oncol*. 2019;30(8):1194–1220. doi:10.1093/annonc/mdz173
42. Turner BM, Skinner KA, Tang P, et al. Use of modified Magee equations and histologic criteria to predict the Oncotype DX recurrence score. *Mod Pathol*. 2015;28(7):921–931. doi:10.1038/modpathol.2015.50
43. Chin-Lenn L, De Boer RH, Segelov E, et al. The impact and indications for Oncotype DX on adjuvant treatment recommendations when third-party funding is unavailable. *Asia Pac J Clin Oncol*. 2018;14(6):410–416. doi:10.1111/ajco.13075
44. McVeigh TP, Kerin MJ. Clinical use of the Oncotype DX genomic test to guide treatment decisions for patients with invasive breast cancer. *Breast Cancer*. 2017;9:393–400. doi:10.2147/BCTT.S109847
45. Fan L, Strasser-Weippl K, Li JJ, et al. Breast cancer in China. *Lancet Oncol*. 2014;15(7):e279–e289. doi:10.1016/S1470-2045(13)70567-9