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Development of predictive models for pathological response status in breast cancer after neoadjuvant therapy based on peripheral blood inflammatory indexes

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Abstract

Background Achieving a pathological complete response (pCR) after neoadjuvant therapy (NAT) is considered to be a critical factor for a favourable prognosis in breast cancer. However, discordant pathological complete response (DpCR), characterised by isolated responses in the breast or axillary, represents an intermediate pathological response category between no response and complete response. This study aims to investigate predictive factors and develop models based on peripheral blood inflammatory indexes to more accurately predict NAT outcomes.

Method A total of 789 eligible patients were enrolled in this retrospective study. The patients were randomized into training and validation cohort according to a 7:3 ratio. Lasso and uni/multivariable logistic regression analysis were applied to identify the predictor variables. Two Nomograms combining clinico-pathologic features and peripheral blood inflammatory indexes were developed.

Result Molecular Subtype, HALP, P53, and FAR were used to construct the predictive models for traditional non pCR (T-NpCR) and total-pCR (TpCR). The T-NpCR group was divided into DpCR and non pCR (NpCR) subgroups to construct a new model to more accurately predict NAT outcomes. cN, HALP, FAR, Molecular Subtype, and RMC were used to construct the predictive models for NpCR and DpCR. The receiver operating characteristic (ROC) curves indicate that the model exhibits robust predictive capacity. Clinical Impact Curves (CIC) and Decision Curve Analysis (DCA) indicate that the models present a superior clinical utility.

Conclusion HALP and FAR were identified as peripheral blood inflammatory index predictors for accurately predicting NAT outcomes.

Keywords Breast cancer, Neoadjuvant therapy, Pathological response, FAR, HALP, Nomogram

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Introduction

Lymph node metastasis constitutes a pivotal determinant in the recurrence and metastatic progression of breast cancer. Neoadjuvant therapy (NAT) has become the preferred treatment for node-positive breast cancer [1]. Total-pathological complete response (TpCR) is defined as the absence of significant residual tumor in both the breast and lymph nodes by post-NAT pathological examination, serving as a critical indicator of favorable prognosis [2]. However, previous studies have indicated the potential for discrepancies in the response of breast lesions and lymph nodes to neoadjuvant therapy. The American College of Surgeons Oncology Group (ACOSOG) reported a pCR rate of 27.8% in the breast and axilla in the Z1071 study, compared with only 5.7% in the breast alone and 13.1% in the lymph nodes alone [3]. This phenomenon, where the tumor disappears in only one part of the breast and axillary lymph nodes, while remaining in another part, is known as a discordant pathological complete response (DpCR). Previous studies have generally considered DpCR as not having achieved complete pathological remission and therefore classified them into the NpCR group. However, in fact, patients with DpCR represent a unique prognostic group whose prognosis is intermediate between that of TpCR and non-pathological complete remission (NpCR) group [4, 5]. DpCR is a transitional state which could partly response to neoadjuvant therapy. It suggests that it may be possible to convert DpCR to TpCR [6]. Therefore, DpCR patients should be studied in isolation from traditional NpCR (T-NpCR) [7–9]. A more precise estimation of the pathological response of breast cancer prior to NAT has significant implications for the assessment of disease risk and the development of therapeutic strategies. Research on the clinic features and prediction model for DpCR status is currently insufficient, requiring further scientific investigations to address this deficiency.

Breast cancer cells can interact with peripheral stromal and inflammatory cells to form inflammatory tumor microenvironment, which contributes to tumorigenesis, progression, invasion and chemoresistance, affecting patient prognosis [10]. Peripheral blood inflammatory index including platelet-to-lymphocyte ratio (PLR), neutrophil-to-lymphocyte ratio (NLR), lymphocyte-to-monocyte ratio (LMR), and systemic immune-inflammatory index (SII) exhibit a significant correlation with the prognosis of BC patients [11–15]. Numerous retrospective clinical trials in breast cancer have used peripheral blood inflammatory indices to predict TpCR in NAT [16]. However, there is a lack of research investigating the predictive potential of peripheral blood inflammatory index for DpCR.

This study aimed to identify clinic features and peripheral blood inflammatory indexes that could be used to predict pathological response degree following NAT. We developed two prediction models and validated the predictive ability of the models.

Methods and materials

Patient selection

Female patients with breast cancer who were treated with NAT from January 2011 to December 2023 at Harbin Medical University Cancer Hospital were recruited into this retrospective study. The inclusion criteria are as follows: (1) all patients underwent ultrasound-guided aspiration biopsy of the breast and associated lymph nodes before NAT. The biopsy pathology confirmed the presence of tumour metastases in these lymph nodes; (2) received standard neoadjuvant treatment program. All neoadjuvant regimens are based on NCCN guidelines; (3) Surgical treatment was performed 21 days after the completion of the last NAT. (4) Received surgical resection and axillary lymph node dissection or sentinel lymph node biopsy. This study included invasive ductal carcinoma, lobular carcinoma, and triple-negative breast cancer. Patients with either of the following situations were excluded: (1) history of prior or concurrent breast cancer; (2) evidence of distant metastasis; (3) receiving less than two cycles of NAT; (4) abandoning NAT in the middle of process due to intolerable side-effects.

This study was approved by the Clinical Research Ethics Committee of the Harbin Medical University Cancer Hospital. This research complies with the 1964 World Medical Association Declaration of Helsinki and subsequently amended versions. Patients were informed upon admission that their clinical data might be used for research purposes, and written informed consent was obtained. Prior to establishing the retrospective study cohort, informed consent was reconfirmed from all patients.

Definition of different pathological reaction statuses after NAT

All samples were evaluated using the AJCC ypTNM criteria. Total pCR was defined as postoperative pathology in which no evidence of tumor residue was found in either the breast lesion or the lymph node (ypT0/ypN0). Discordant pCR was defined as postoperative pathology in which tumor residue was found in one of the two, but not the other, in either the breast lesion or the lymph node (ypT≥1/ypN0 or ypT0/ypN≥1). Breast pCR or lymph node pCR are collectively known as DpCR, as previous studies have shown that they have the same survival [7]. Non pCR was defined as postoperative pathology in which tumor residue was found in both the breast lesion and the lymph node. The combination of DpCR and NpCR was described as Traditional non pCR, which is the traditional meaning of not achieving pCR after

NAT. In addition, previous studies have demonstrated that survival rates for ductal carcinoma in situ (DCIS) or minimal residual disease (MRD) in the breast or lymph nodes show no significant difference from those observed for TpCR. Consequently, these two conditions have been included in the TpCR group [6, 17].

Pathologic features

Referring to the 2020 edition of the ASCO guidelines, an IHC score of ≥1% for ER or PR was defined as positive. IHC score of 0 or 1+for HER2 was considered negative. In cases with an IHC score of 2+, fluorescence in situ hybridization (FISH) must be performed in addition to IHC. IHC score of 3 (>10% of cells showing high-intensity periplasmic staining) or FISH positivity was considered positive. Ki-67 was defined as low expression if the proportion of positively stained cells was less than 15%. It was defined as moderate expression when the percentage of positively stained cells was between 15 and 29%. The high expression was defined when the percentage of positively stained cells was ≥29%.

Peripheral blood inflammation index

All peripheral blood inflammation index were calculated based on the haematology of the patients 7 days before they underwent NAT. The calculation of each index of peripheral blood inflammation was as follow: NLR (Neutrophil count/ Lymphocyte count), Pan-Immune-Inflammation-value (PIV, Platelet count ×Neutrophil count × Monocytes count/ Lymphocyte count), Systemic inflammatory response index (SIRI, Neutrophil count ×Monocyte count/ Lymphocyte count), the Hemoglobin, Albumin, Lymphocyte, Platelet Score (HALP, Hemoglobin count × Albumin × Lymphocyte count/ Platelet count), the Fibrinogen-Albumin Ratio (FAR, Fibrinogen×100/ Albumin), the Fibrinogen-Platelet Ratio (FPR, Fibrinogen/ Platelet count), the Systemic Immunoinflammatory Index (SII, Platelet count × Neutrophil count/ Lymphocyte count), LMR (Lymphocyte count/ Monocyte count), PLR (Platelet count/ Lymphocyte count).

Follow-up

All patients received regular follow-up after completing treatment according to clinical guidelines. The follow-up programme was conducted at the following intervals: every three to four months for the initial two years, every six months for the subsequent three years, and annually thereafter. Participants were defined as having lost to follow-up if there was an interval of more than two years between the last visit and the final follow-up. All patients were followed up until 30 January 2024. Disease-Free Survival (DFS) is defined as the period during which a patient survives from the time they are first confirmed to be free of disease until the recurrence of cancer or death. Similarly, overall survival (OS) was defined as the time from diagnosis to either death or the date of the final follow-up.

Statistical analysis

This study applied RStudio (version 4.3.2; https://www.r-project.org/) software for statistical analysis. Shapiro-Wilk test is used to assess the normality of continuous variables, Mann-Whitney U test is used for hypothesis testing of differences between groups. Chi-square test was used for hypothesis testing of differences between groups for categorical variables. The patients were randomly divided into a training and validation set in a 7:3 ratio. Lasso regression analysis, uni/multivariable logistic regression analysis were performed to identify factors associated with pCR status after NAT. The optimal parameter (lambda) selection in the Lasso model was cross-validated ten-fold based on the minimum criterion. The receiver operating characteristic curve (ROC) was employed to determine the best cut-off value. Kaplan-Meier curves and log-rank tests were employed to plot and compare the DFS and OS curves. The area under the receiver operating curve (AUC), sensitivity and specificity were employed to assess the performance of the model. Calibration curve were employed to evaluate the degree of consistency between observed and predicted results. Decision curve analysis (DCA) and clinical impact curves (CIC) were then used to assess the net clinical benefit. $P<0.05$ was considered a statistically significant.

Results

Baseline of patients achieve T-NpCR and TpCR

A total of 789 patients were included in the study. Of 207 (26.24%) achieved total PCR, while 582 (73.76%) were evaluated for traditional non pCR. The baseline clinic features and peripheral blood inflammatory indexes of patients are presented in Table 1. A chi-square test was performed for all variables. Molecular Subtype, Ki67, P53, NAT cycle, NAT regimen, HER2 Targeted Therapy, Carboplatin, SII, NLR, PLR, PIV, REC, RNC, RMC, FPR, FAR, HALP was found to be significantly different between the two groups. Therefore, these 17 variables were included in the screening process of predictors.

Identification of predictors of the T-NpCR and TpCR group

All patients were randomly divided into validation set ($n=267$) and training set ($n=522$) according to a 7:3 ratio. Four parameters (molecular subtypes, P53, FAR, and HALP) were identified as potential predictors by Lasso (Fig. 1A-B) and uni/multivariable (Fig. 1C) logistic regression analysis. Based on these predictors, nomogram were constructed (Fig. 1D).

Table 1 Clinical baseline characteristics between T-NpCR and TpCR patient

Characteristic	Levels	T-NpCR (*N* = 582)	TpCR (*N* = 207)	*P*
Age	Median ± IQR	52 ± 13	52 ± 11	0.647
BMI	Median ± IQR	24.2 ± 4.3	24 ± 4	0.987
Menstrual state	Menopause	320 (55%)	106 (51.2%)	0.393
	Premenopause	262 (45%)	101 (48.8%)	
Lesion number	Mono	462 (79.4%)	171 (82.6%)	0.368
	Multi	120 (20.6%)	36 (17.4%)	
cT	1 + 2	476 (81.8%)	179 (86.5%)	0.151
	3 + 4	106 (18.2%)	28 (13.5%)	
cN	1 + 2	381 (65.5%)	126 (60.9%)	0.271
	3	201 (34.5%)	81 (39.1%)	
Molecular Subtype	HR(+)HER2(-)	343 (58.9%)	26 (12.6%)	< 0.001
	HR(+)HER2(+)	74 (12.7%)	37 (17.9%)	
	HR(-)HER2(+)	66 (11.3%)	68 (32.9%)	
	HR(-)HER2(-)	99 (17%)	76 (36.7%)	
Ki67	≥ 30%	287 (49.3%)	147 (71%)	< 0.001
	15 − 30%	172 (29.6%)	41 (19.8%)	
	< 15%	123 (21.1%)	19 (9.2%)	
P53	0	247 (42.4%)	141 (68.1%)	< 0.001
	1	219 (37.6%)	21 (10.1%)	
	2	53 (9.1%)	15 (7.2%)	
	3	63 (10.8%)	30 (14.5%)	
NAT cycle	> 6	182 (31.3%)	74 (35.7%)	0.273
	≤ 6	400 (68.7%)	133 (64.3%)	
HER2 Targeted Therapy	Yes	110 (18.9%)	72 (34.8%)	< 0.001
	No	472 (81.1%)	135 (65.2%)	
PDW	> 13.45	257 (44.2%)	84 (40.6%)	0.417
	≤ 13.45	325 (55.8%)	123 (59.4%)	
SIRI	> 1.08	130 (22.3%)	54 (26.1%)	0.317
	≤ 1.08	452 (77.7%)	153 (73.9%)	
SII	> 839.22	112 (19.2%)	20 (9.7%)	0.002
	≤ 839.22	470 (80.8%)	187 (90.3%)	
NLR	> 1.51	437 (75.1%)	139 (67.1%)	0.034
	≤ 1.51	145 (24.9%)	68 (32.9%)	
PLR	> 162.59	201 (34.5%)	49 (23.7%)	0.005
	≤ 162.59	381 (65.5%)	158 (76.3%)	
LMR	> 3.12	521 (89.5%)	191 (92.3%)	0.313
	≤ 3.12	61 (10.5%)	16 (7.7%)	
PIV	> 462.21	63 (10.8%)	12 (5.8%)	0.048
	≤ 462.21	519 (89.2%)	195 (94.2%)	
REC	> 0.87	349 (60%)	145 (70%)	0.013
	≤ 0.87	233 (40%)	62 (30%)	
RLC	> 37	134 (23%)	60 (29%)	0.106
	≤ 37	448 (77%)	147 (71%)	
RNC	> 57.69	373 (64.1%)	111 (53.6%)	0.010
	≤ 57.69	209 (35.9%)	96 (46.4%)	
RMC	> 6.32	227 (39%)	102 (49.3%)	0.013
	≤ 6.32	355 (61%)	105 (50.7%)	
FPR	> 1.11	322 (55.3%)	76 (36.7%)	< 0.001
	≤ 1.11	260 (44.7%)	131 (63.3%)	
FAR	> 6.6	363 (62.4%)	63 (30.4%)	< 0.001
	≤ 6.6	219 (37.6%)	144 (69.6%)	

Table 1 (continued)

Characteristic	Levels	T-NpCR (*N* = 582)	TpCR (*N* = 207)	*P*
HALP	> 37.32	336 (57.7%)	160 (77.3%)	< 0.001
	≤ 37.32	246 (42.3%)	47 (22.7%)	

T-NpCR: traditional non-pathologic complete response, TpCR: total-pathologic complete response, BMI: body mass index, PDW: platelet distribution width, REC: relative eosinophilic count, RLC: relative lymphocyte count, RNC: relative neutrophil count, RMC: relative macrophage cell count

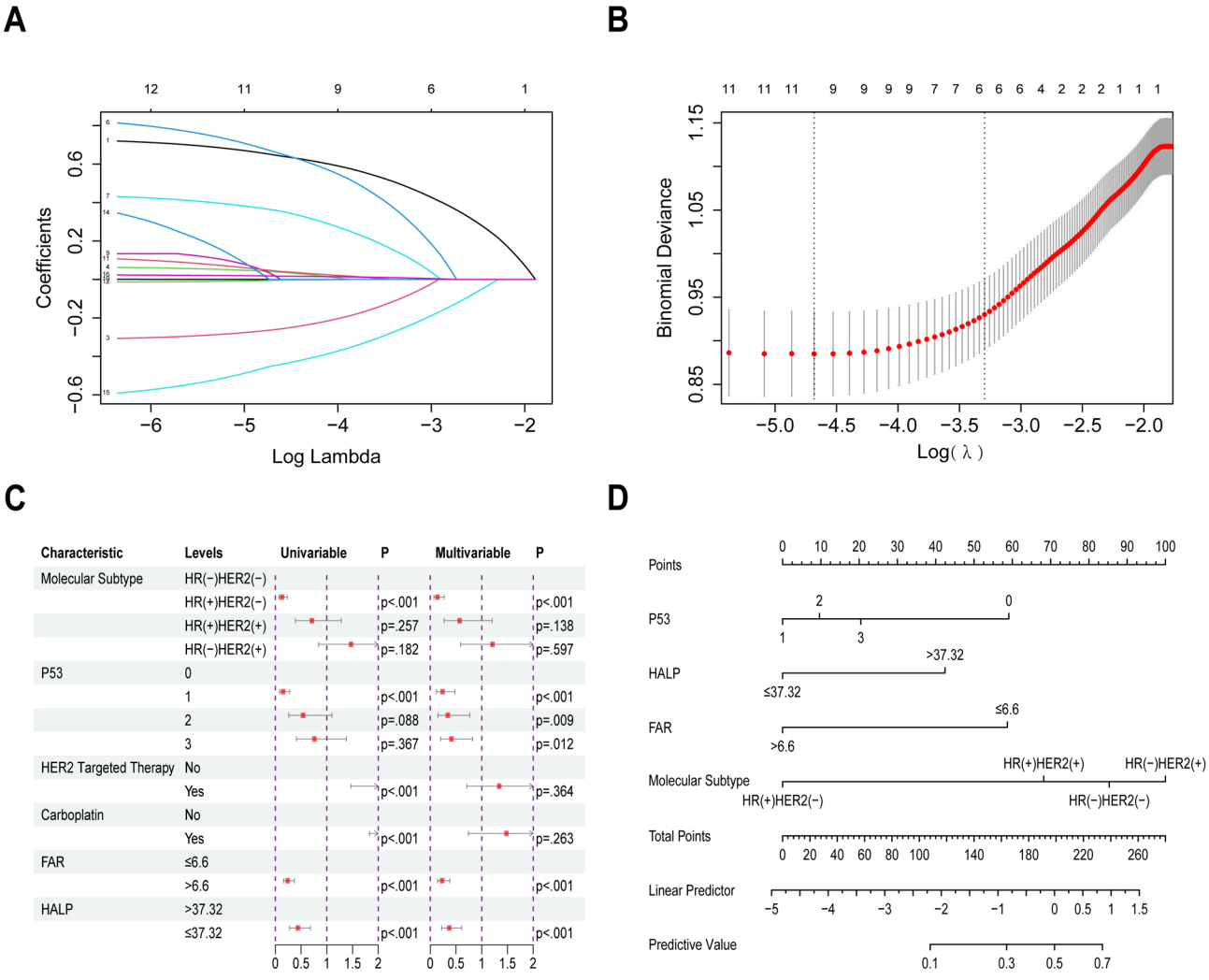

Fig. 1 Identification of key predictors of T-NpCR and TpCR. (**A**-**B**) Distribution of coefficients of cross-validation and lasso regression between traditional NpCR and TpCR group. (**C**) univariable and multivariable logistic regression analyses between traditional NpCR and TpCR group. (**D**) Nomogram that predict whether breast cancer patient will achieve traditional NpCR or TpCR status after NAT

Evaluating the prediction performance of T-NpCR and TpCR group model in train set

The ROC curve showed that AUC value of the model was 0.803 (95% CI: 0.761–0.846), and the AUC values of Molecular Subtype, FAR, HALP and P53 were 0.728 (95%CI: 0.684–0.772), 0.701 (95%CI: 0.653–0.749), 0.612 (95%CI: 0.56–0.664), 0.602 (95%CI: 0.549–0.656) (Fig. 2A). The calibration curve demonstrated that the average absolute error of the model was 0.014, indicating that the model exhibited enhanced predictive capability (Fig. 2B). To assess the clinical utility and predictive capacity of nomograms, DCA and CIC were plotted. The models in the T-NpCR and TpCR group exhibited superior clinical utility when the threshold probability values were within the range of 0.35 to 0.77 (Fig. 2C-D).

Baseline and prognosis of patients achieve NpCR and DpCR

To further understand the prognosis of patients with different extent of pathological response after NAT for breast cancer, the T-NpCR cohort was divided into two subgroups: non pCR and discordant pCR. The mean

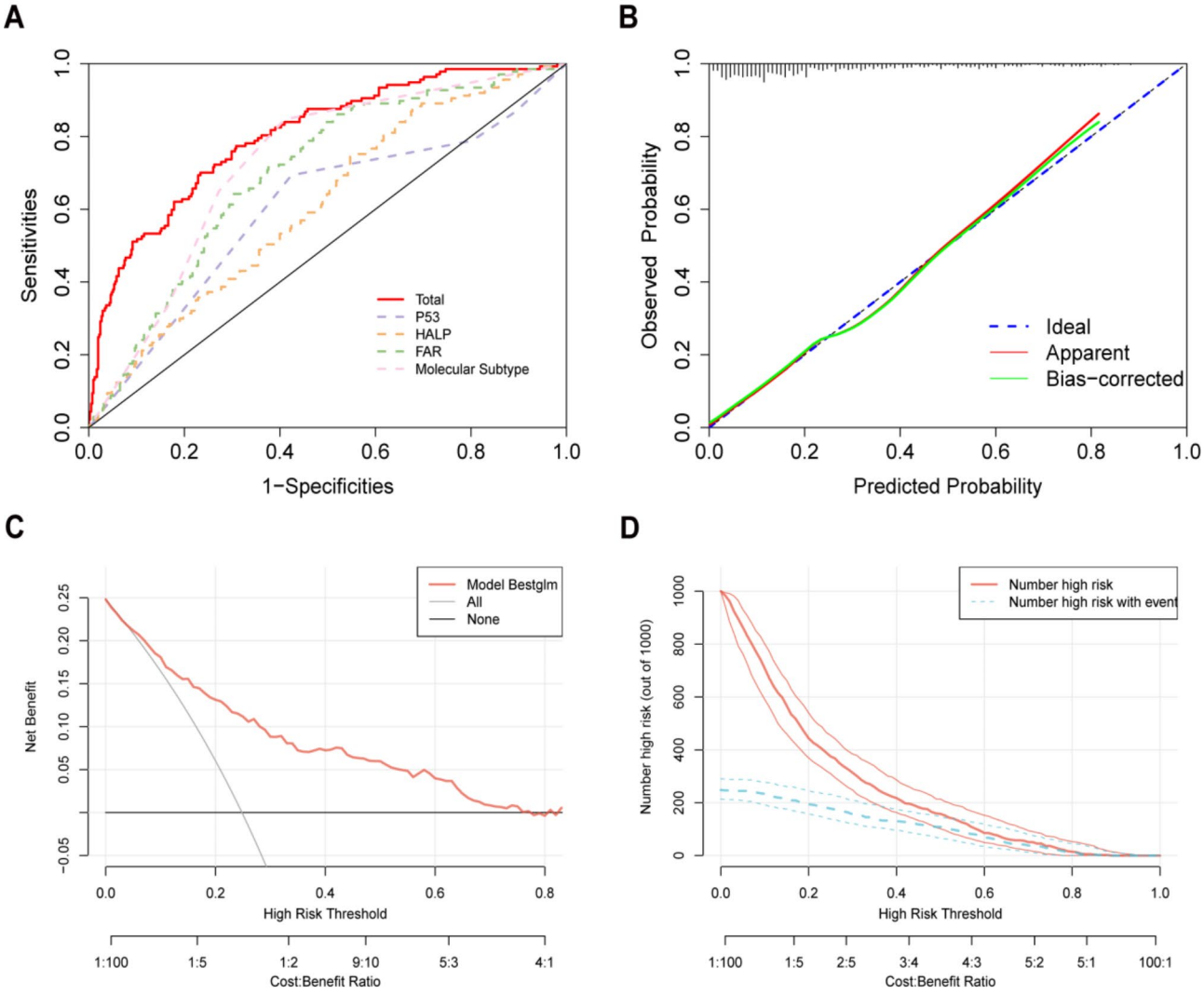

Fig. 2 Evaluation of the prediction model of traditional NpCR and TpCR in training set. (**A**) ROC curves; (**B**) Calibration curves; (**C**) Decision curve analysis (DCA) and (**D**) Clinical Impact Curve (CIC)

follow-up period for the entire cohort was 49 months (3–88 months). Based on the follow-up data, Kaplan-Meier curves were plotted for patients in the three groups (Fig. 3A-B). The result demonstrated that patients in the TpCR group exhibited the best OS and DFS, followed by the DpCR group, and the NpCR group proved to be the worst. Log-rank test was performed for OS in each of the two groups of patients in the different groups. The P value for the NpCR and DpCR groups was 0.035, the NpCR and TpCR groups was less than 0.001, the DpCR and TpCR groups was 0.011. Log-rank test was performed for DFS in each of the two groups of patients in the different groups. The P value for the NpCR and DpCR groups was 0.048, the NpCR and TpCR groups was less than 0.001, the DpCR and TpCR groups was 0.012. Thus, DpCR represents a subgroup with a distinct prognosis, making it scientifically meaningful to study it separately from T-NpCR. The baseline clinical characteristics of the NpCR and DpCR groups are shown in Table 2. Among them, 314 patients were assessed as NpCR, and 268 patients were assessed as DpCR. Chi-square tests revealed statistically significant differences between the groups for the variables Lesion number, cN, Molecular Subtype, P53, NAT regimen, HER2 targeted therapy, RMC, FPR, FAR, and HALP. These 10 variables were included in the predictor selection process for model construction. Five parameters (cN, Molecular Subtype, RMC, HALP and FAR) were identified as potential predictors by Lasso (Fig. 3C-D) and uni/multivariable (Fig. 3E) logistic regression analysis. Based on these predictors, nomogram were constructed (Fig. 3F).

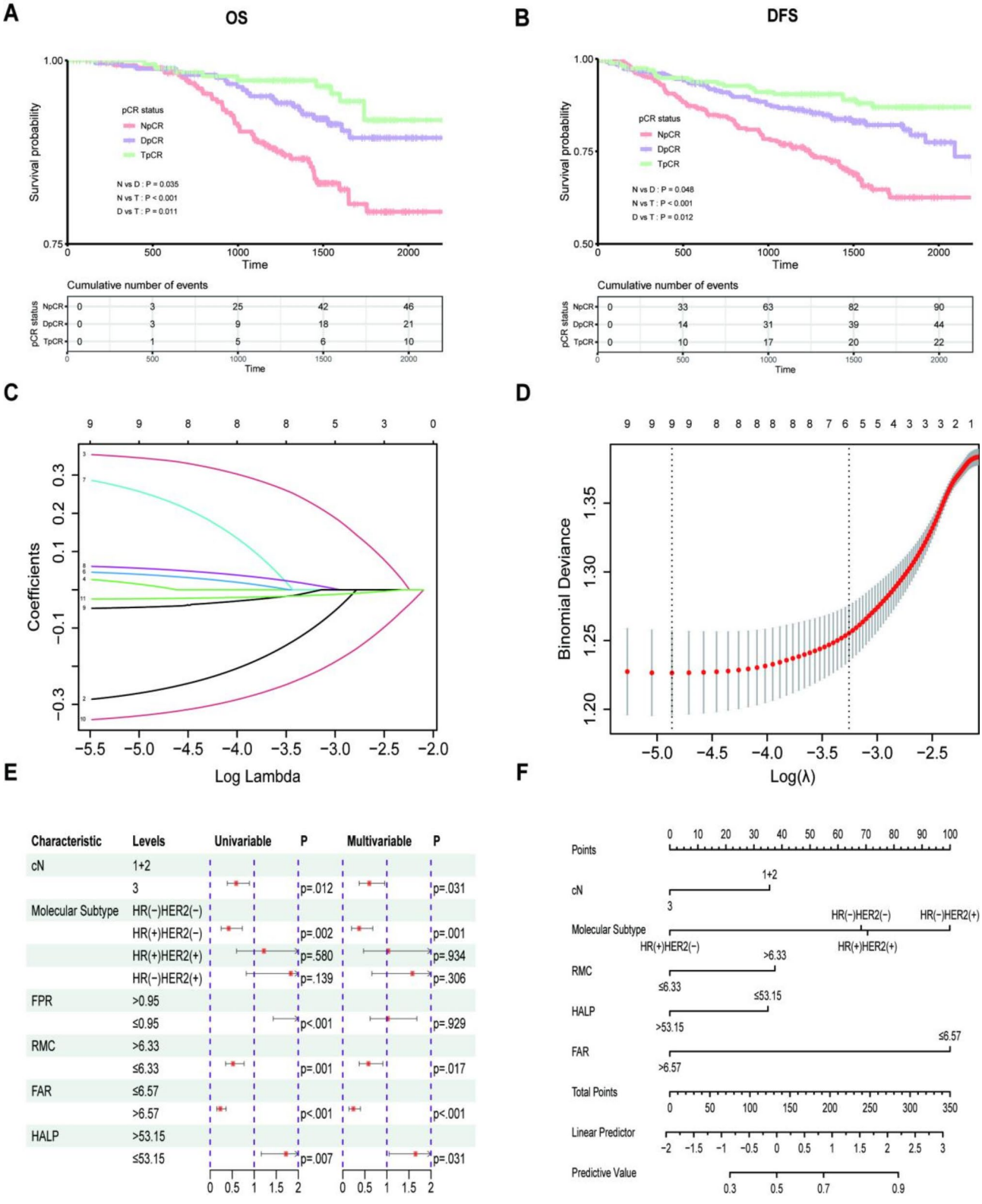

Fig. 3 Survival of breast cancer patients with different pathological response status and identification of key predictors of NpCR and DpCR. (**A**) Kaplan–Meier curve of OS. (**B**) Kaplan–Meier curve of DFS. (**C**-**D**) Distribution of coefficients of cross-validation and lasso regression between NpCR and DpCR group. (**E**) univariable and multivariable logistic regression analyses between NpCR and DpCR group. (**F**) Nomogram that predict whether breast cancer patient will achieve NpCR or DpCR status after NAT

Table 2 Clinical baseline characteristics between NpCR and DpCR group

Characteristic	Levels	NpCR (*N* = 314)	DpCR (*N* = 268)	*P*
Age	Median ± IQR	52 ± 12	51 ± 14	0.440
BMI	Median ± IQR	24.2 ± 4.2	24.2 ± 4.3	0.561
Menstrual state	Menopause	182 (58%)	138 (51.5%)	0.139
	Premenopause	132 (42%)	130 (48.5%)	
Lesion number	Mono	234 (74.5%)	228 (85.1%)	0.002
	Multi	80 (25.5%)	40 (14.9%)	
cT	1	255 (81.2%)	221 (82.5%)	0.778
	2	59 (18.8%)	47 (17.5%)	
cN	1 + 2	190 (60.5%)	191 (71.3%)	0.008
	3	124 (39.5%)	77 (28.7%)	
Molecular Subtype	HR(+)HER2(-)	218 (69.4%)	125 (46.6%)	< 0.001
	HR(+)HER2(+)	27 (8.6%)	47 (17.5%)	
	HR(-)HER2(+)	22 (7%)	44 (16.4%)	
	HR(-)HER2(-)	47 (15%)	52 (19.4%)	
Ki67	≥ 30%	144 (45.9%)	143 (53.4%)	0.192
	15 – 30%	100 (31.8%)	72 (26.9%)	
	< 15%	70 (22.3%)	53 (19.8%)	
P53	0	133 (42.4%)	114 (42.5%)	0.003
	1	127 (40.4%)	84 (31.3%)	
	2	20 (6.4%)	41 (15.3%)	
	3	34 (10.8%)	29 (10.8%)	
NAT cycle	> 8	70 (22.3%)	86 (32.1%)	0.010
	≤ 8	244 (77.7%)	182 (67.9%)	
HER2 targeted therapy	Yes	51 (16.2%)	64 (23.9%)	0.028
	No	263 (83.8%)	204 (76.1%)	
PDW	> 13.05	138 (43.9%)	119 (44.4%)	0.979
	≤ 13.05	176 (56.1%)	149 (55.6%)	
SIRI	> 0.54	74 (23.6%)	56 (20.9%)	0.502
	≤ 0.54	240 (76.4%)	212 (79.1%)	
SII	> 406.8	62 (19.7%)	50 (18.7%)	0.821
	≤ 406.8	252 (80.3%)	218 (81.3%)	
NLR	> 1.96	236 (75.2%)	201 (75%)	1.000
	≤ 1.96	78 (24.8%)	67 (25%)	
PLR	> 137.55	107 (34.1%)	94 (35.1%)	0.869
	≤ 137.55	207 (65.9%)	174 (64.9%)	
LMR	> 6.01	281 (89.5%)	240 (89.6%)	1.000
	< 6.01	33 (10.5%)	28 (10.4%)	
PIV	> 130.77	34 (10.8%)	29 (10.8%)	1.000
	≤ 130.77	280 (89.2%)	239 (89.2%)	
REC	> 1.14	185 (58.9%)	164 (61.2%)	0.636
	≤ 1.14	129 (41.1%)	104 (38.8%)	
RLC	> 44.82	75 (23.9%)	59 (22%)	0.663
	≤ 44.82	239 (76.1%)	209 (78%)	
RNC	> 61.26	204 (65%)	169 (63.1%)	0.695
	≤ 61.26	110 (35%)	99 (36.9%)	
RMC	> 6.33	110 (35%)	117 (43.7%)	0.041
	≤ 6.33	204 (65%)	151 (56.3%)	
FPR	> 0.95	198 (63.1%)	124 (46.3%)	< 0.001
	≤ 0.95	116 (36.9%)	144 (53.7%)	
FAR	> 6.57	242 (77.1%)	121 (45.1%)	< 0.001
	≤ 6.57	72 (22.9%)	147 (54.9%)	
HALP	> 53.15	195 (62.1%)	141 (52.6%)	0.026
	≤ 53.15	119 (37.9%)	127 (47.4%)	

NpCR: non-pathologic complete response, DpCR: discordant-pathologic complete response

Evaluating the prediction performance of NpCR and DpCR subgroups model in train set

The ROC curve demonstrated that the overall AUC value of the model was 0.74 (95% CI: 0.691–0.788). The AUC values for the variables cN, HALP, FAR, Molecular Subtype, and RMC were 0.559 (95% CI: 0.514–0.604), 0.623 (95% CI: 0.575–0.672), 0.566 (95% CI: 0.511–0.622), 0.602 (95% CI: 0.548–0.657), and 0.667 (95% CI: 0.613–0.72), respectively (Fig. 4A). The calibration curve showed that the average absolute error of the model was 0.044, indicating a relatively reliable predictive capability (Fig. 4B). The DCA and CIC analysis demonstrated that the model exhibited good clinical utility for the NpCR and DpCR subgroups when the threshold probability was larger than 0.43 (Fig. 4C-D).

Evaluation of models prediction performance in validation set

The formulas for the two multivariable logistic regression models were derived and their predictive performance was evaluated in the validation set. The ROC curve demonstrated an AUC of 0.744 (95% CI: 0.664–0.824) for the T-NpCR vs. TpCR group and 0.798 (95% CI: 0.727–0.87) for the NpCR vs. DPCR group (Fig. 5A, E). Calibration curves based on the validation set data showed that the observed value curves were close to the actual values (Fig. 5B, F). Additionally, DCA and CIC curves indicated that nomograms of the models of T-NpCR vs. TpCR group (Fig. 5C, D) and NpCR vs. DpCR group (Fig. 5J, H) provided high predictive accuracy for the pathological response status of patients treated with NAT.

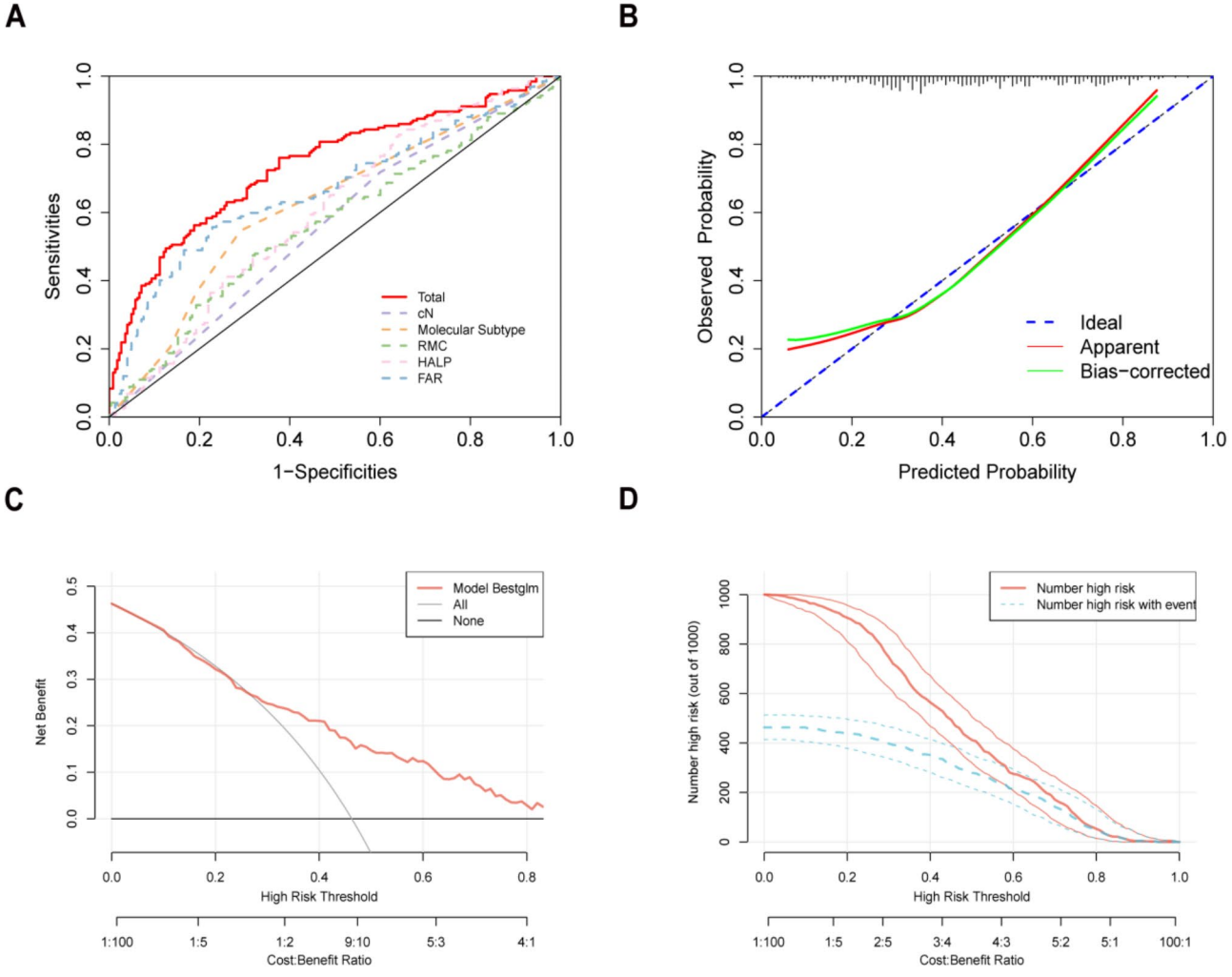

Fig. 4 Evaluation of the prediction model of NpCR and DpCR in training set. (**A**) ROC curves; (**B**) Calibration curves; (**C**) DCA and (**D**) CIC

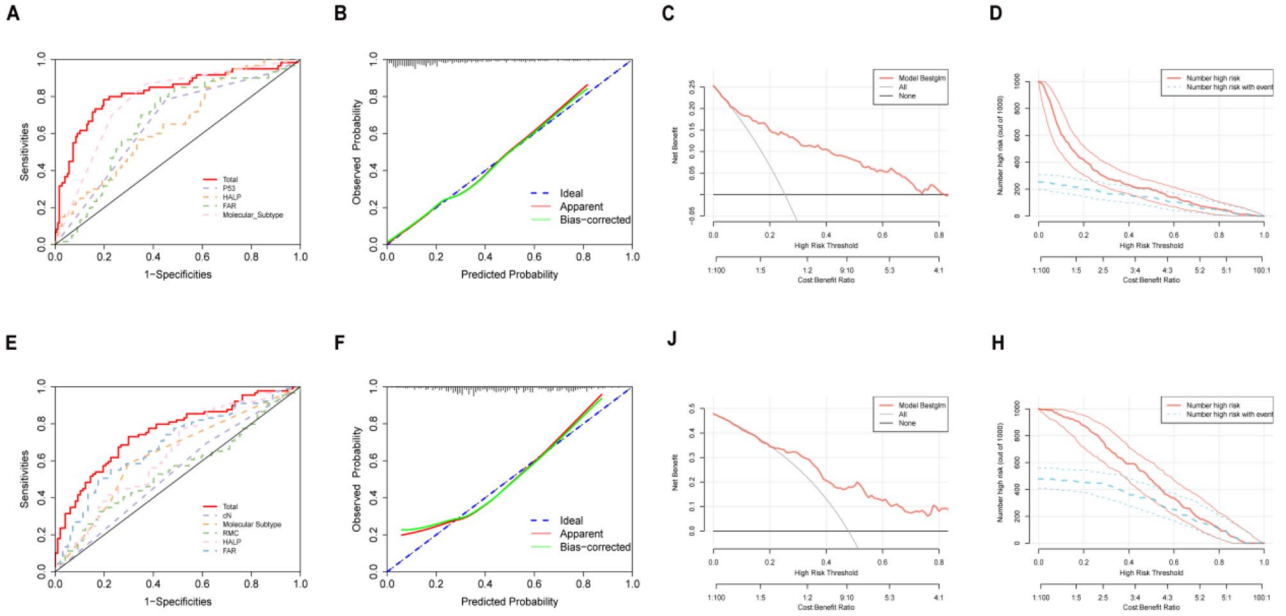

Fig. 5 Evaluating the two prediction models separately in the validation set using ROC curves, calibration curves, DCA and CIC. (**A**-**D**) T-NpCR and TpCR model; (**E**-**H**) NpCR and DpCR model

Discussion

This study included 789 patients with breast-related lymph node metastases at baseline status who underwent NAT. Molecular Subtype, HALP, P53, and FAR were identified as predictors of traditional non pCR and total pCR groups by regression analysis, and prediction models were constructed and validated. The T-NpCR group was divided into two subgroups, non pCR and discordant pCR, for subgroup analyses. Kaplan-Meier curves demonstrated that the TpCR group had the greatest survival for OS and DFS, followed by the DpCR group, while the NpCR group had the worst. NpCR and DpCR prediction models based on cN, HALP, FAR, molecular subtype and RMC were constructed and their predictive performance was verified in the training and validation sets.

Chen et al. showed that HR(-)HER2(+) subtype of breast cancer had the highest rate of breast pCR and nodal pCR, and HR(+)HER2(-) subtype had the lowest rate of breast pCR [18]. This indicates that the heterogeneity of different subtypes of tumors, different biological behaviors, and NAT regimens contributing to DpCR. It has been suggested that cancer cells in lymph nodes may have a tumor immune tolerance, and potential explanations include differences in chemotherapy sensitivity of metastatic tumor cells or the protective effect of the lymph node microenvironment on the tumor [19]. A study by Rene et al. showed that lymphatic dysfunction were more likely to have DpCR [20]. Previous studies have indicated that fibrinogen deposition, diminished immune response, or combination of chronic systemic diseases (e.g., diabetes mellitus) may contribute to lymphatic dysfunction. This ultimately results in the inadequate delivery of NAT drugs within the lymphatic system, or in the failure of to interact with tumor foci [21, 22]. In our study, elevating peripheral blood fibrinogen was associated with a worse pathological response status. The two predictive models developed in our study indicated that molecular subtype of breast cancer was associated with different pathological response status. The analysis of the baseline characteristics revealed that patients with HER2-positive or triple-negative types were more likely to have better pathological response. Nevertheless, the precise mechanism remains to be elucidated through further investigation. To ascertain the mechanisms underlying DpCR, more in-depth studies are needed to identify which neoadjuvant treatment strategies may transform DpCR into TpCR status. Additionally, the axillary lymph node management strategies employed for patients undergoing NAT prove pivotal in enhancing long-term survival and reducing recurrence in breast cancer patients [23].

Peripheral blood immune cells can partially respond to the inflammatory state in the immune microenvironment, which is the theoretical basis for the hypothesis that peripheral blood inflammatory markers may predict tumor prognosis [24]. Abnormalities in coagulation can increase the risk of thrombosis and have a pro-tumorigenic effect, and indicators such as albumin and haemoglobin can reflect the overall nutritional status of the patient [25–27]. Peripheral blood inflammatory indexes have been shown in several studies to potentially predict prognostic status or NAT outcome in breast cancer [28,

29]. However, the capability of these peripheral blood parameters to predict between the three different pCR status of NpCR, DpCR, and TpCR is still unclear. Our study screened peripheral blood inflammatory indexes and clinico-pathological features that might predict pathological response status after NAT by lasso regression, univariable and multivariable regression analyses, and screened parameters that had good ability to predict the three pathological response statuses two by two. Based on these parameters we plotted nomograms, and the AUC values of the two model groups were as follows: in the T-NpCR vs. TpCR group: 0.803 (95% CI: 0.761–0.846) and in the NpCR vs. DpCR group: 0.74 (95% CI: 0.691–0.788). In addition, we noticed that HALP and FAR appeared in both predictive models and had a longer share of the scoring axis in the nomogram compared to other predictors in the same group. This suggests that the combination of HALP and FAR may have a better ability to predict the extent of tumor remission after NAT in breast cancer.

The HALP integrates four routinely collected indicators of immune and nutritional status and has been used as a new prognostic biomarker to predict many clinical outcomes in a variety of tumors. A meta analysis that included tumors such as gastric and cervical cancers showed that low HALP at baseline status was associated with poor prognosis of the tumor [30]. Lou et al. demonstrated that baseline HALP could be a predictor of whether or not to pCR after NAT in breast cancer. Using a cut-off value of 24.14, the OR for low HALP was 0.518 (95% CI: 0.365–0.734), and the area under the ROC curve for HALP was 0.847 [31]. Another 2022 study discussed whether HALP could be used as a predictor for the presence or absence of axillary lymph node involvement, and demonstrated that the rate of axillary lymph node involvement for HALP less than 29.01 was 67.7% and 53.3% for HALP greater than or equal to 29.01 ($p=0.038$) [32]. In our study, the level of HALP was significantly lower in the NpCR group than in the TpCR group (45.7±19.2 VS 56.6±24.2). This phenomenon is consistent with previous studies. Interestingly, the HALP level in the DpCR group were lower than which in the NpCR group (45.7±19.2 VS 40.9±14.7) and the difference was statistically significant. The results of univariable and multivariable regression analyses also matched this trend. This suggests that the relationship between HALP score and prognosis may not be strictly positive. Also, we noted that platelets were highest in the DpCR group, followed by the NpCR group, and smallest in the TpCR group. The peripheral blood inflammation indexes associated with platelets were broadly consistent with this trend. Apart from platelets, haemoglobin, albumin and lymphocytes could not explain this trend. This implies that platelets and the coagulation system may play a role in the formation of DpCR, making neoadjuvant therapy less responsive in a subset of patients who may achieve TpCR or making oncological treatment slightly more effective in patients who may NpCR.

FAR is a coagulation-inflammation-nutritional indicator of prognosis in a variety of solid tumors [33–37]. Since infection, blood coagulation, and so on affect plasma fibrinogen values, fibrinogen can somewhat represent the degree of inflammatory response [38]. Hwang et al. showed that patients with high FAR (cut-off value of 7.1) had a worse prognosis, and that univariable (HR: 2.722, 95% CI: 1.659–4.468, $P<0.001$) and multivariable (HR: 2.622, 95% CI: 1.455–4.724, $P=0.001$) regression analyses also confirmed this [39]. Yang et al. set the cut-off value of FAR at 6.6 in their study, and survival analyses showed that high FAR implied worse OS and DFS [40]. In contrast, however, Zheng et al. reached the opposite result. The study concluded that low FAR (≤8.4) was protective for patients and that OS and DFS were worse with high FAR-PLR scores [41]. To date there are no studies discussing whether FAR can predict DpCR status after NAT. In our study, it was found that low FAR predict patients with better NAT responsiveness. The cut-off values of FAR were calculated from ROC curves to be 6.57 (NpCR vs. DpCR) and 5.51 (NpCR vs. TpCR) in the two groups, respectively. Unlike HALP, there was a more direct correlation between FAR and NAT outcome. That is, lower FAR indicate a better pathological response. Based on our findings, the coagulation system-related components, especially platelets and fibrinogen, may correlate with pathological response status after NAT. However, the mechanisms behind these findings still need to be supplemented and validated by further research.

In this study, we developed predictive models based on peripheral blood inflammatory indexes, discussed the unique prognosis of discordant pCR, and provided a more accurately tool for predicting the pathological response status after NAT in breast cancer patients. Despite the encouraging results, our study has several limitations: (1) There is a lack of an external validation cohort to test the conclusions; (2) The findings of this retrospective study should be validated by further prospective studies; (3) Some patients had interval censoring during the follow-up process. What's more, further validation in larger cohorts is required before the models can be applied in routine clinical practice.

Conclusion

In conclusion, this study identified potential factors affecting the outcome of NAT in breast cancer. FAR and HALP were found to be potential indicators that could be used to accurately predict pathological responses to NAT in breast cancer.

Abbreviations

pCR	Pathological complete response
NAT	Neoadjuvant therapy
T-NpCR	Traditional NpCR
TpCR	Total pathological complete response
DpCR	Discordant pathological complete response
NpCR	Non pCR
ACOSOG	American College of Surgeons Oncology Group
PLR	Platelet to-lymphocyte ratio
NLR	Neutrophil to-lymphocyte ratio
LMR	Lymphocyte to-monocyte ratio
SII	Systemic immuno inflammatory index
DCIS	Ductal carcinoma in situ
MRD	Minimal residual disease
FISH	Fluorescence in situ hybridization
PIV	Pan-Immune-Inflammation-value
SIRI	Systemic inflammatory response index
HALP	The Hemoglobin, Albumin, Lymphocyte, Platelet Score
FAR	Fibrinogen Albumin Ratio
FPR	Fibrinogen Platelet Ratio
DFS	Disease free survival
OS	Overall survival
ROC	Receiver operating characteristic curve
CIC	Clinical Impact Curves
DCA	Decision Curve Analysis
AUC	Area under the receiver operating curve

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Author contributions
Shuqiang Liu, Cong Jiang, Shiyuan Zhang, Kun Qiao and Yuanxi Huang contributed to the concept and design of the study. Danping Wu, Xiaotian Yang and Boqian Yu contributed to the acquisition and interpretation of data and drafting the article. All authors read and approved the final version of the article.

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Data availability
No datasets were generated or analysed during the current study.

Declarations

Ethical approval and consent to participate
This study was approved by the Clinical Research Ethics Committee of the Harbin Medical University Cancer Hospital. This research complies with the 1964 World Medical Association Declaration of Helsinki and subsequently amended versions. All patients were provided with written informed consent prior to participation.

Consent for publication
Not applicable.

Competing interests
The authors declare no competing interests.

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